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Carbohydrate Chemistry

Volume 21
Part I

A Specialist Periodical Report

Carbohydrate Chemistry

Volume 21

Part I
Monosaccharides, Disaccharides,
and Specific Oligosaccharides

A Review of the Recent Literature Published during 1987

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Preface

This report summarizes the literature for 1987 available to us by March 1988. The format of recent volumes has been retained.

I regret that an unusual combination of factors has led to the exceptional delay in bringing this volume to publication. We are well aware that the value of this report diminishes with time, and since this is the last report for which I will be responsible as Senior Reporter, I hope Professor Ferrier will have more success in expediting publication as he takes over.

I would like to thank all my colleagues for their contributions to this volume. We welcome Dr. Peter Tyler as a new member of the team, bringing an even stronger New Zealand flavour to the work. I would also like to thank Dr. P.G. Gardam and Mr A.G. Cubitt and their colleagues at the Royal Society of Chemistry for the production of this report from our submitted typescripts.

Neil R. Williams
July 1989

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.

Contents

Abbreviations

The following abbreviations have been used:

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

TMS	trimethylsilyl
TPP	triphenylphosphine
TPS	tri-isopropylbenzenesulphonyl
Tr	triphenylmethyl
Ts	toluene p-sulphonyl
U	uracil-1-yl

1
Introduction and General Aspects

We hope that the following chapters provide a fair summary of the large amount of carbohydrate chemistry published in 1987, and give an indication of the wide range of compounds reported and studied during the year. The report covers monosaccharides, disaccharides, and specific oligosaccharides (as defined in Chapter 4). As usual, the most extensive chapters cover glycosides and nucleosides, but several other chapters contain a large number of references, and over 1500 references altogether demonstrate the interest in this area of chemistry. The report reflects a particular surge of interest in C-glycosides in Chapter 3 and in inositol phosphates in Chapter 18.

The lack of a precise definition of a carbohydrate has led to somewhat arbitrary decisions as to whether border-line cases merit inclusion in our survey; we have tried to assess likely interest to carbohydrate chemists, or whether significant carbohydrate chemistry is discussed in work focussed as much if not more on aglycone units. We apologize if our judgement does not always meet with your approval.

Reviews of a more general nature not covered elsewhere in this report include a review on the evolution of a general strategy for the stereoselective construction of polyoxygenated natural products,[1] and a review of some miscellaneous topics involving synthetic reactions of carbohydrates, including syntheses of aminosugars, deoxysugars, glycosides, and the Ferrier ring synthesis.[2]

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2
Free Sugars

Reviews covering the structural determination of carbohydrates by chemical and spectroscopic means,[1] the uses of lithium aluminium hydride-aluminium chloride and acidic sodium cyanoborohydride in the reduction of carbohydrates and their derivatives,[2] and chemical and biological preparations of D-ribose[3] have appeared.

The hydrogenolysis of D-glucose in aqueous and non-aqueous solution using palladium, rhodium or ruthenium catalysts supported on carbon has been investigated. Of these, only the ruthenium catalyst at 200°C and a pressure of 50 bar allowed conversion of glucose into methanol.[4]

1. Theoretical Aspects

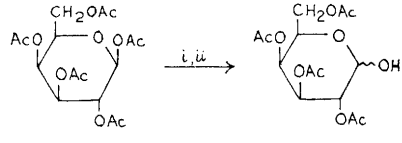
Calculations of the electronic structures of a series of carbohydrates using the CNDO/2 method have produced linear relationships between ^{13}C-n.m.r. chemical shifts and the atomic charges for the α- and β-D-glucose, α- and β-D-galactose and β-L-arabinose systems.[5] Model systems, treated by the RHF/STO-3G method, have been used to evaluate the anomeric and Δ^2 effects in simple and 1-O-methylpyranosides and hence derive their conformational and anomeric energies. 1,1-Dihydroxyethane and 1,1-dimethoxyethane were chosen as model systems for the anomeric effect while the Δ^2 effect was investigated using 1,1,2-trihydroxyethane and 2,2-dimethoxyethanol.[6] A theoretical study of the structure of D-glucopyranose in eleven solvents by a PCILO quantum mechanical method has been carried out. The stability of the individual conformers was compared using a method in which the total energy is divided into the energy of an isolated molecule and the solvation energy. The influence of the solvent on rotation of the pendant groups and on the stability of anomers was investigated; the results were found to be in good agreement with experiment.[7] The method was further extended to the anomeric pairs of all eight D-hexopyranoses.[8] The theoretical basis of distinguishing the configuration of the aldoses has been described using the concept of rotational symmetry. A comprehensive treatment of

aldose configurations was developed in symmetry terms and presented as dichotomous trees.[9]

A new kinetic model for the alkaline isomerization and degradation of monosaccharides has been presented. Computer simulations using the model fit the experimental data and allow determination of all relevant rate constants. The rate limiting step appears to be enolization for both isomerization and degradation.[10] The mechanism of redox reactions between lead hydroxide and 3-O-methyl-D-glucose has been studied by quantum mechanical calculations. The calculations show that there is a redistribution of electron density in both systems which favours the formation of a carboxyl group in the C(1)-C(3) part of the aldose.[11]

2. Synthesis

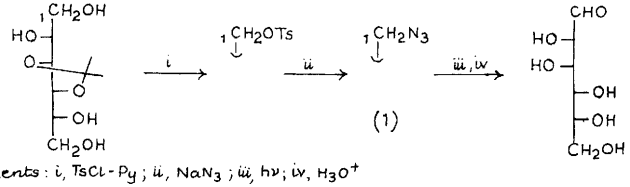
Peracetylated sugars treated with tributyltin methoxide gave products selectively deacetylated at the anomeric position (Scheme 1). Equatorial anomers were deprotected more rapidly and more selectively than their axial counterparts.[12] Anodic electrolysis has been used to deprotect aldose dithioacetals in good yield.



Reagents: i, Bu_3SnOMe; ii, H_2O

Scheme 1

Other acetals were found to be stable to the conditions. Thus 2,3,4,5,6-penta-O-acetyl-D-galactose diethyldithioacetal gave 2,3,4,5,6-penta-O-acetyl-D-galactose in 65% yield; other examples quoted gave the free sugar in higher yields.[13]



Reagents: i, TsCl-Py; ii, NaN_3; iii, hν; iv, H_3O^+

Scheme 2

D-Mannitol has been converted into D-mannose by the photolysis of the azide (1) as shown in Scheme 2.[14] Some [1-^{13}C]aldoses have been synthesized by conventional means and used to study their 75MHz

^{13}C-n.m.r. spectra.[15] A convenient method for preparing pure [^{11}C]glucose by photosynthesis from $^{11}CO_2$ using spinach leaf and hydrolysis of the labelled sucrose produced has been described.[16] References to the preparation of [1-^{13}C]-enriched 5-deoxypentoses and 5-*O*-methylpentoses are made in Chapters 5 and 12.

Sophorose has been easily prepared on an industrial scale from stevioside by partial acid hydrolysis.[17]

The formose reaction, carried out at room temperature in the presence of calcium hydroxide, has been studied.[18] The effects of the presence of oxygen and reducing sugars on the formose reaction using calcium hydroxide-methylene glycol have been described. The induction period was found to be shortened by reducing sugars but increased by oxygen, although the rate after induction remained the same; large quantities of added reducing sugar decreased the conversion rate. The progress of the reaction could be followed by measuring the pressure above the reaction mixture.[19] The same workers have carried out a detailed study of the pressure-volume changes in this reaction; the formation of the complex between calcium hydroxide and methylene glycol was accompanied by a volume contraction, which was followed by two stages of volume increase, corresponding to the induction period and the period during which sugars are formed.[20]

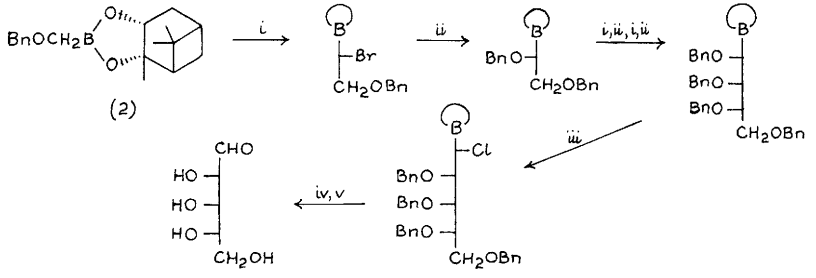
The isomerization of monosaccharides by aqueous potassium hydroxide under nitrogen has been monitored by liquid chromatography on cation(Pb^{2+}) exchange and reverse phase columns. The simple epimerization reaction of pentoses and hexoses accounts for about 90% of the saccharides found in the solution after one week. The remaining sugars were formed either by fragmentation or recombination; *e.g.*, glucose and sorbose are found in the isomerization mixtures of pentoses. The aldol reaction responsible for the formation of hexoses from glyceraldehyde at pH 11.5 was found to be fast, thus accounting for the rapid fragmentation and recombination observed.[21]

The previously reported rapid interconversion of D-glucose and D-mannose by nickel(II) and *N*,*N*,*N*'-trimethylethylenediamine (see Vol. 19, p.162) has been extended to other metal ions (cobalt(II), calcium, and strontium) and *N*,*N*,*N*',*N*'-tetramethylethylenediamine-(tetmen). The best system was found to be nickel(II)-tetmen.[22] The epimerization reaction was shown to involve a 1,2-carbon shift, *i.e.*, a skeletal rearrangement, by means of ^{13}C-n.m.r. of the products of the nickel(II)-*N*,*N*,*N*'-trimethylethylenediamine treatment of D-[1-^{13}C]glucose when the product was shown to be D-[2-^{13}C]mann-

ose.[23] Similar rearrangements were shown to occur in reactions with alkaline earth or rare earth metal ions and monoamines.[24] Molybdate catalyzed epimerization of D-erythro-L-manno-octose gave a mixture of D-erythro-L-gluco-octose and the starting sugar with the former predominating.[25]

The metal-ion catalyzed photoreactions of sugars which result in cleavage of carbon-carbon bonds have been reviewed.[26]

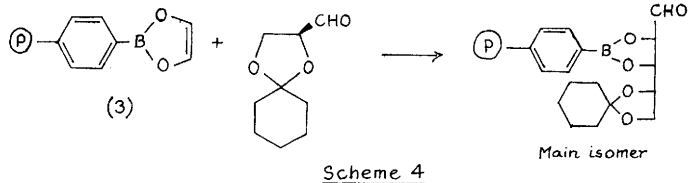
Chain extension using an insertion reaction of dichloromethyllithium or dibromomethyllithium with a cyclic chiral boronate derivative, (S)-pinanediol[(benzyloxy)methyl]boronate (2), has been used in a synthesis of L-ribose in 13% overall yield (Scheme 3).[27] A new



Reagents: i, Br_2HCLi; ii, BnOLi; iii, Cl_2HCLi; iv, H_2O_2; v, H_2-Pd

Scheme 3

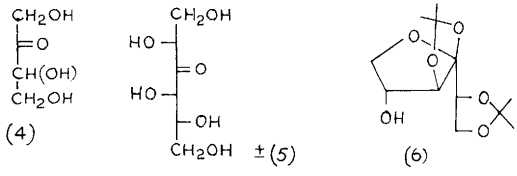
synthetic equivalent (3) of the glycolaldehyde anion has been used for the two carbon chain extension of aldehydes. Thus L-ribose was synthesized from 2,3-O-cyclohexylidene-L-glyceraldehyde and a boronate (3) by the addition shown in Scheme 4. Diaddition and higher addition reactions to yield polymers is alleviated by using a polymer-supported reagent as shown in the Scheme. The main product gave L-ribose after deprotection.[28] The observation that the proportions



Scheme 4

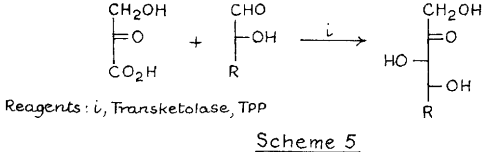
of diastereoisomers formed in the condensation of glycolaldehyde with DL-glyceraldehyde and in the triose aldol condensation vary little with changes in the metal hydroxide catalysis has been interpreted as evidence for a pericyclic transition state involving cis-enediolate attack on the aldehyde.[29] The earlier work on base-cat-

alyzed condensation of glycolaldehyde and hydroxyketones (see Vol. 18, p.7) has been extended to the reaction of the racemic tetrulose (4) which gives D,L-lyxo-3-hexulose (5) as the major product and its C-2 epimer as the minor one. The former was isolated as its 1,2:3,4-di-O-isopropylidene derivative (6).[30]

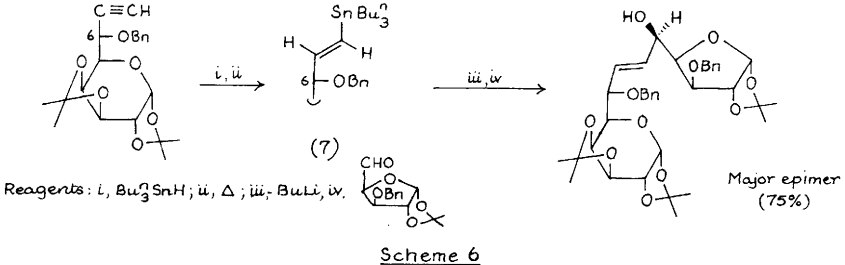


Ketoses have been prepared using transketolase catalysis. The enzyme, isolated from Saccharomyces cerevisiae (baker's yeast) or from spinach leaf was investigated for substrate specificity and it was shown that it was not necessary for the ketose to be phosphorylated. The general biosynthetic condensation shown in Scheme 5 was used in the preparation of L-erythrulose from glycolaldehyde, D-xylulose from D- or D,L-glyceraldehyde, and 5-deoxy-D-xylulose from D,L-lactaldehyde. L-Glyceraldehyde was not active as a substrate.[31]

A review on total synthesis of higher monosaccharides concentrates mainly on the author's work on the hetero-Diels Alder reaction between an aldehyde and an electron-rich diene.[32] Vinyltin derivatives (7) of simple monosaccharides, prepared as shown in Scheme 6, react with butyllithium to give the corresponding vinyllithium compound, which may be reacted with aldehydosugars to give the nigher sugars.[33]

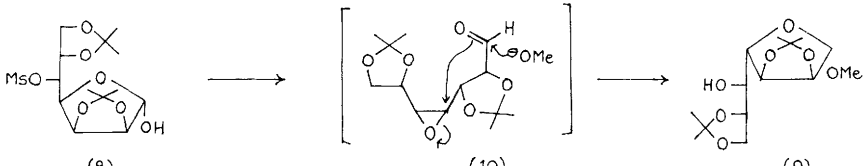


Scheme 5



Scheme 6

Osmylation of higher octenoses, previously reported (see Vol. 19, p.6; Vol. 20, p.6), has been used to synthesize β-L-threo-D-gluco- and -D-manno-octopyranoside.[34] Inversions at C4 and C5 of the heptose derivative (8) using sodium methoxide gave rise to 2,3:6,7-di-O-isopropylidene-β-L-glycero-L-allo-heptofuranoside (9) via the anhydrosugar (10) as shown in Scheme 7.[35]



(8) (10) (9)

Scheme 7

Carbon-labelled higher sugar phosphates of the pentose pathway are referred to in Chapter 7.

3. Physical Measurements

Enthalpies of combustion of D-ribose and 2-deoxy-D-ribose have been measured by bomb calorimetry.[36] Ultrasonic, volumetric and viscometric measurements have been performed on aqueous solutions of D-glucose and D-mannose at 20° and 30°C. These measurements were used to evaluate important ultrasonic and thermodynamic parameters including apparent and partial molal volume, apparent and partial molal compressibility, viscosity B-coefficients of the Jones-Dole equation, and changes in free energy, entropy, and enthalpy on dissolution. The parameters were used to explain the predominant solute-solvent interactions.[37]

Rate constants for the tautomerization of 5-hydroxypentanal have been determined by line shape ^{13}C-n.m.r. analysis.[38] The mutarotation of D-fructose to a five component equilibrium mixture of the two pyranose, two furanose and the open chain forms has been re-examined by g.c. and g.c.-m.s. of pertrimethylsilylated samples, the β-pyranose to β-furanose equilibrium being the major contributor.[39] The mutarotation of D-glucose in some mammalian body fluids has been measured using β-glucose oxidase-mutarotase and polarimetry. The mutarotation was more rapid than in distilled water in many cases.[40]

All six tautomers of D-glucose in aqueous solutions have been detected and quantified using high resolution ^{13}C n.m.r. on D-

[1-^{13}C]glucose.[41] ^{13}C-n.m.r. has also been used to determine the proportions of pyranose and furanose forms in aqueous solutions of thirteen monosaccharides.[42] Equilibrium tautomers of allose, altrose, gulose, idose, and talose have been analyzed as their trimethylsilyl ethers by capillary g.c. Aldopentoses were also examined. G.c.-m.s. and n.m.r. were used to identify the components.[43] The proportions of furanose and pyranose ring forms in DMSO solutions of glucose, galactose, arabinose and 3-O-(α- and β-D-galactopyranosyl)-D- and -L-arabinose have been determined by Hakamori methylation and g.c.-m.s. analysis of their derived methylated alditol acetates. The values would appear to represent those obtaining under the conditions of the methylation procedure.[44] N.m.r. studies support the idea that D-fructose exists mainly as the β-furanose in DMSO due in part to the OH-1 to OH-4 hydrogen bond, as previously suggested (see Vol. 19, p.9). However, an important factor, as the authors suggest, is the influence of the medium on the free energy of the β-pyranose form, which predominates in aqueous solution; changes in tautomeric composition in mixtures of DMSO and water indicate that specific solvation by water is the main factor in stabilization of the β-pyranose form.[45] Trehalulose (1-O-α-D-glucopyranosyl-D-fructose), isolated by preparative reversed-phase HPLC from the crystallization liquors of isomaltulose, has been shown by ^{13}C-n.m.r. to exist as a 2:1 mixture of the β-fructopyranoid and β-fructo-furanoid forms in water.[46] An ingenious examination of the ability of the anomers of the eight 2-aldohexoses to form hydrogen bonds to water has allowed a rationalization of their α:β ratios in aqueous solution.[47] By means of a kinetic study of standard amide hydrolyses in aqueous carbohydrate solution the carbohydrate-solvent interactions causing inhibitory kinetic effects have been evaluated. Whilst dilute solutions of several free sugars show almost ideal thermodynamic behaviour, other effects are attributed to sugar-induced alterations in the three-dimensional H-bonded structure of water.[48]

An *in situ* e.s.r. study of the formation and structure of radicals from D-ribose and 2-deoxy-D-ribose has shown that radicals are formed at C-1, C-2, and C-3 by hydrogen abstraction followed by regioselective α,β-water elimination, thus giving 2-deoxyribonolactonyl, 1-deoxypentopyranos-2-ulos-1-yl and 4-deoxypentopyranos-3-ulos-4-yl.[49]

Construction of an apparatus for measuring electrocapillary curves of the mercury-electrolyte interface based on the maximum

bubble pressure technique has allowed the study of the absorption of D-xylose, D-ribose, and sucrose at the mercury-0.7953M sodium fluoride interface.[50]

γ-Irradiation of α-D-glucose at 77-415K has been investigated by e.s.r. analysis, which showed that the chain reaction was propagated from initially formed radicals by decomposition to sugar acids and by dehydration to yield secondary radicals.[51]

4. Oxidation

The kinetics of the oxidation of D-galactose, D-glucose, D-mannose, D-fructose, L-sorbose, L-arabinose, D-ribose and D-xylose with cerium(IV) in perchloric acid showed that two complexes were formed in each case. The first forms in a pre-equilibrium reaction during mixing and is partly oxidized via Michaelis-Menton kinetics and partly dissociated to the second. The latter is oxidized more slowly than the former. The pseudo first order rate constant in 1.0M perchloric acid was almost constant over the range of sugar concentrations 0.1M to 1.0M, from which it was concluded that practically all the cerium(IV) was complexed.[52] Kinetic parameters for the oxidation of D-lyxose by iron(III) and cerium(IV) sulphates have been determined. Both reactions are first order in oxidant, and various organic acids are produced.[53] Thallium(III) in a twelve molar equivalent oxidizes D-fructose completely to carbon dioxide, formaldehyde and formic acid are formed as intermediate products, the rate of oxidation being strongly inhibited by the presence of chloride or acetate ions.[54] The kinetics and mechanism of oxidation of D-fructose by copper-pyridine complex in excess pyridine have been studied spectrophotometrically. The observation that the rate of oxidation was equal to the rate of enolization led to the proposal that the reaction species was the enediolate anion.[55] Ruthenium(III) catalyzed oxidation of aldoses by NBS has been studied in aqueous acetic acid in the presence of mercury(II) acetate and sulphuric acid. The reaction was first order in NBS but the order in aldose concentration changed from one to fractional in the presence of the catalysts. It was suggested that the reactive species is the α-anomer in the D-series; D-arabinose, D-xylose, D-galactose, D-mannose, and D-glucose were examined, the rate of oxidation decreasing in the order given.[56] Oxidation of D-xylose by potassium bromate in dilute sulphuric acid to give D-xylonic acid has been studied kinetically, and the thermodynamic constants

determined.[57] The changes in ascorbic acid induced by oxygen have been examined. It was found that the rate of oxidation increased with pH, decreased in the presence of glucose, was slightly increased by maltose, while the presence of tartaric acid caused little change.[58] Oxidation of ascorbic acid by molecular oxygen catalyzed by copper(II)[59] and by copper(II) glycine peptides[60] has been studied. The pertechnate ion oxidizes ascorbic acid to give a red species which comprises technetium(V)-dehydroascorbate complex. Kinetics of the reaction were measured and Arrhenius parameters were obtained.[61]

A cyclic voltammetric study of glucose oxidation on an oxide-covered platinum electrode in the presence of an underpotential-deposited thallium layer has been reported.[62] The interfacial mass-transfer of mediators of anodic oxidation of glucose using bromide and hypobromite ions as the redox mediators has been studied. Both the experimental results and the theoretical analysis indicate that the rate of oxidation is independent of the glucose concentration but is significantly affected by the intrafacial mass transfer and the initial concentration of mediator, the ratio of the surface area of the electrode to the volume of solution, and the rate of generation of active mediator.[63]

On the basis of a kinetic study, the mechanism of oxidation of lactose by Nessler's reagent in alkaline medium has been proposed. An enediol intermediate with mercury(II) triiodide ion as the reacting species were invoked.[64]

Reference to the degradation of some disaccharides by alkaline hydrogen peroxide is made in Chapter 3.

5. Other Reactions

A spectrophotometric method has been used to study the Lobry de Bruyn-Alberda van Ekenstein reaction of D-glucose, and the kinetics of interconversion of D-glucose, D-fructose, and D-mannose have been measured.[65] A detailed study of the mechanism of the alkaline degradation of monosaccharides has been carried out.[66]

A study of the bonding of sodium in the sodium chloride, bromide, and iodide adducts of sucrose has been undertaken using i.r. spectra.[67] Partially sulphonated polyvinyl alcohols have been shown to be better catalysts for the hydrolysis of sucrose than sulphuric acid. The hydrolysis rate was higher with syndiotactic PVA derivatives than with isotactic or atactic PVA partial sulphonates.[68]

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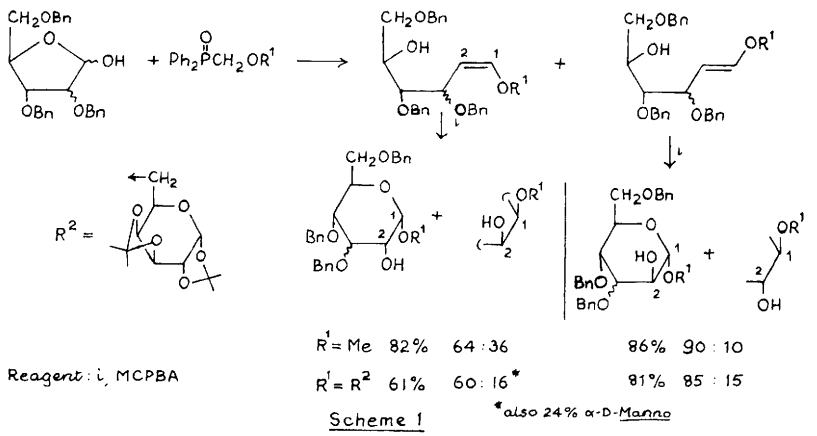
3
Glycosides and Disaccharides

1 O-Glycosides

1.1 Synthesis of Monosaccharide Glycosides.- A review has been published on the synthesis of glycopeptides which covers aspects of glycoside formation and the linkage between sugars and serine or serine-containing peptides.[1]

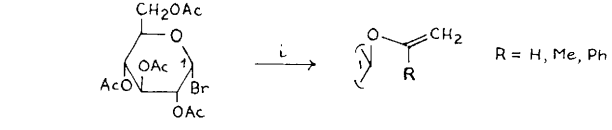
Tetra-O-benzyl-α-D-glucopyranosyl dimethylphosphinothiolate reacts with alcohols in the presence of silver perchlorate at room temperature to give good yields of mainly α-linked products.[2] Another novel approach to the preparation of hexopyranosides involves the use of alkoxymethylene Horner Wittig reagents applied to 2,3,5-tribenzylpentoses (Scheme 1). From the E-alkene products



Scheme 1

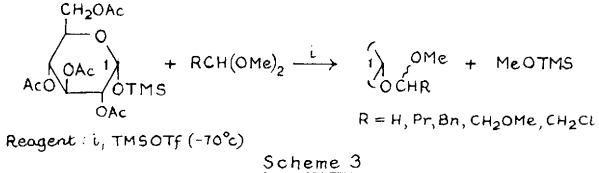
mixtures of 1,2-trans-related glycosides were obtained, whereas the Z-isomers led to 1,2-cis-glycosides. Simple or carbohydrate Horner Wittig reagents could be used.[3]

A simple and high-yielding synthesis of vinyl and substituted vinyl β-D-glucopyranosides is illustrated in Scheme 2,[4] and three reports have appeared on the preparation of related acetal glycosides which can be made in high yields and with good anomeric



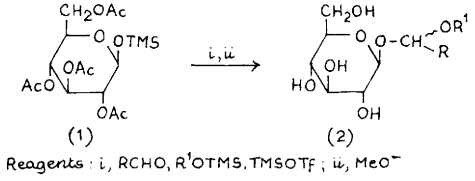
Scheme 2

selectivity as indicated in Scheme 3. The tetrabenzyl silyl α-glycoside can also be used, but it is less reactive and cannot be



Scheme 3

obtained anomerically pure. Diastereoisomers at the new asymmetric centre were formed in the approximate ratio of 3:1.[5] The reaction is also applicable to the β- isomer of the starting material and can be generalized by use of any acetals of any aldehyde; alternatively, the unprotected compounds (2) can be made from the silyl β-glycoside (1) as shown in Scheme 4.[6] The products can be



Scheme 4

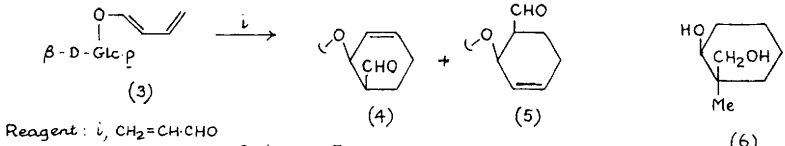
hydrolysed by acid or enzymically to release the aldehydes. Cytotoxic aldehydes which cannot themselves be used clinically because of binding to proteins can be administered in the acetal-glycosidic form. The aminated compounds (2), ($R=(CH_2)_nNH_2$, R^1=Me, n=1-4) have been made by acetal exchange from (1) via the ω-bromides and azides, giving potential β-glucosidase inhibitors. The amines were resistant to enzymolysis while their synthetic precursors - the bromo or azido analogues - were hydrolysed.[7]

The potentially useful observation has been made that while treatment of methyl α-D-glucopyranoside with benzoic acid, triphenylphosphine and diethyl azodicarboxylate is known to give the 6-benzoate, similar treatment of the β-anomer afforded, after

hydrolysis, only methyl β-D-allopyranoside; similarly, methyl β-D-xylopyranoside gave methyl β-D-ribopyranoside.[8]

Synthesis of n-alkyl β-D-mannofuranosides from C_{7-16} n-alkanols and 2,3:5,6-di-O-ethylboranediyl-α-D-mannofuranosyl bromide has given mesogenic compounds of potential value as liquid crystals.[9]

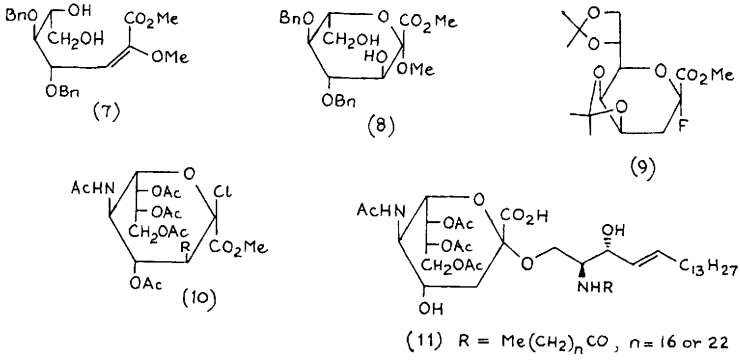
The cyclohexyl glycosides (4) and (5) have been made in the ratio 60:40 by condensation between the 1-butadienyl glycoside (3) and acrolein (Scheme 5). The reaction was carried out in water and



Scheme 5

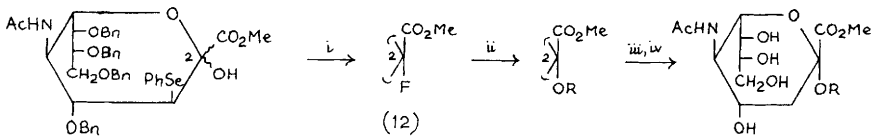
had rates and selectivities which were enhanced relative to those for the reaction of the corresponding tetra-O-acetate in non-polar solvents. The sugar was removed enzymically to allow access to optically pure cyclohexane derivatives, e.g., the new diol (6).[10]

Considerable attention has been paid to the further development of routes to glycosides of 2-ulosonic acids. Treatment of the alkene (7) with m-chloroperbenzoic acid gave (8) as the only glycoside formed (45%),[11] and the glycosyl fluoride (9) has been



applied to the preparation of α-glycosides, including disaccharides, of KDO.[12] Most attention, however, has gone into the synthesis of glycosides of neuraminic acid: the glycosyl chloride (10, R=H) has been used to obtain the p-nitrophenyl α-glycoside,[13] the corresponding allyl compound and hence the formylmethyl analogue required for reductive-amination coupling to proteins,[14] and the ceramides (11).[15] An alternative approach to α-glycosides of the series uses the

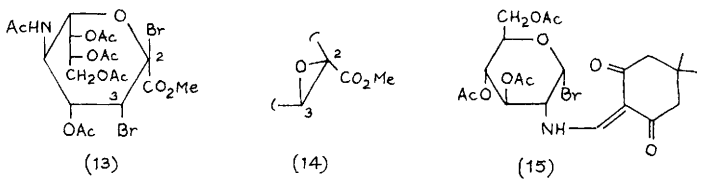
hydroxy compound (10, R=OH) and subsequent C-3 deoxygenation by way of the phenoxythiocarbonyl derivative,[16] and a further method employs the 3-selenoglycosyl fluoride (12), made from the 2-ene followed by epimerization of the seleno-group (Scheme 6).[17]



Reagents: i, DAST ; ii, ROH - $AgOTf - SnCl_2$; iii, Bu_3SnH ; iv, H_2-Pd/C

Scheme 6

Alternatively, β-glycosides have been obtained using the dibromide (13), the second bromine atom of which prevented elimination and provided steric hindrance on the α-face of the molecule,[18] and also the 2,3-epoxide (14), which preferentially undergoes cis-ring opening with alcohols in acid conditions. The hydroxyl group



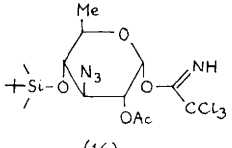
(13) (14) (15)

at C-3 was subsequently removed by radical methods.[19] In both these cases the strategies were applied in disaccharide syntheses. Peracetylated glycosyl chlorides or fluorides have been used to prepare steroidal glycosides of N-acetyl-D-neuraminic acid, and optimum conditions were found for forming both the α- and the β-linked products.[20]

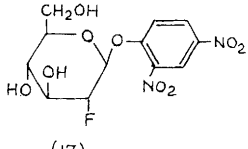
Several reports have appeared on the synthesis of glycosides of aminosugars. In the series of 2-amino-2-deoxy compounds, β-glycosides of glucosamine have been made using either the peracetylated glycosyl chloride with tin (II) triflate as catalyst,[21] or the peracetylated N-phthalimido sugar with tin (IV) chloride,[22] or the reasonably stable cystalline bromide (15) under Koenigs-Knorr conditions. The protecting group was removed using chlorine or base.[23] Further examples of the preparation of glycosides of 2-amino-2-deoxysugars are given in Chapters 9 and 19.

The 3-azido glycosylating agent (16), made from a methyl α-D-allopyranoside 3-triflate, has been used in the preparation of the β-glycoside Amphotericin B (Chapter 10),[24] and an indole analogue

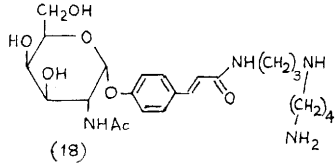
of daunomycin has been made using the glycosyl p-nitrobenzoate.[25] The synthesis of the four diastereomeric methyl 4-amino-2,4,6-trideoxy-L-hexopyranosides, also required for anthracycline work, is referred to in Chapter 9.



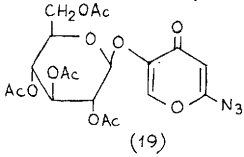
(16)



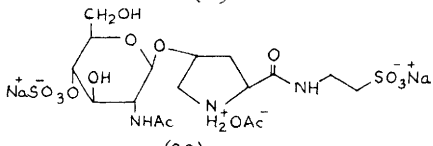
(17)



(18)



(19)



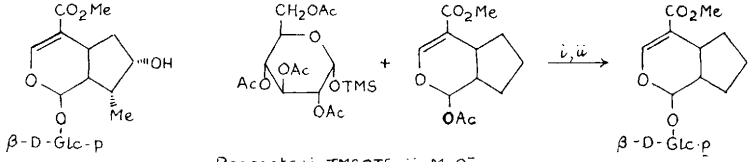
(20)

Considerable attention has been paid to the synthesis of aryl glycosides. One report advocates the use of tert-butyldimethylsilyl derivatives of the phenols together with acylated glycosyl acetates with boron trifluoride as catalyst.[26] Another used tetra-O-benzoyl-α-D-glucopyranosyl bromide and phenols in the two phase system of aqueous sodium hydroxide and dichloromethane in the presence of a phase transfer catalyst, giving moderate yields of aryl β-D-glucopyranosides.[27] Specific compounds synthesized include 4-O- β-D-glucopyranosylgallic acid 6-sulphate,[28] β-glucosides of dimethyl (hydroxymethyl)phenyl N-methylcarbamates (insecticide metabolites),[29] (thiazolylacetyl) resorcinols,[30] and the glycosides (17) and (18), the former being a powerful inhibitor of β-glucosidases[31] while the latter is related to naturally occurring spermidine conjugates.[32]

Likewise furanose and pyranose derivatives of the complex phenols 4-methylumbelliferone (made from 1,2-trans-related glycosyl fluorides),[33] xanthotoxol,[34] and 1,3,5,8-tetrahydroxy-2-methylanthraquinone[35] have been prepared.

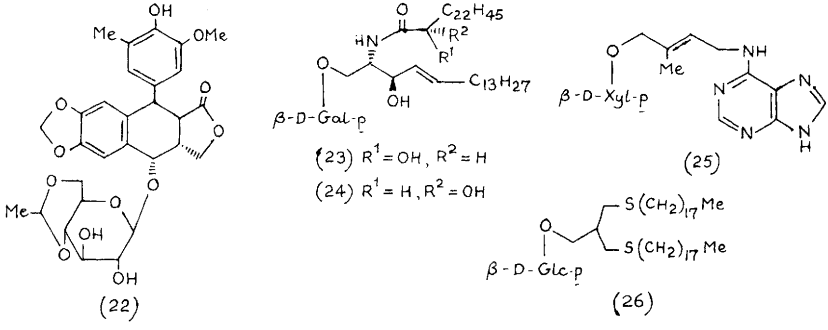
Further reports have appeared on standard syntheses of glucosylated[36] and glucuronosylated[37] steroids and of glucosylated dammarane triterpenes.[38,39] The kojic acid derivative (19)[40] and dehydroxymethylbulgecin A (20)[41] have also been described, the latter a product of using the oxazoline procedure.

Extension of work on acetal glycosides[5-7] has resulted in the synthesis of logamin (21), a key intermediate of biosynthesis, the work depending upon that illustrated in Scheme 7.[42] Etoposide (22),



Scheme 7

an antitumour agent, and related 2-amino-2-deoxy-and 3-amino-3-deoxy derivatives and enantiomers have been made using initially 2,3-di-*O*-chloroacetyl-4,6-*O*-ethylidene-D-glucose as glycosylating agent with catalytic boron trifluoride.[43] Pseudo-disaccharides which involve linkage between sugars and pseudo-sugars are referred to in Chapter 18.



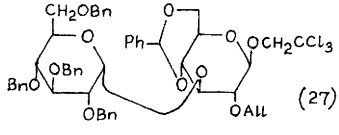
Other glycoside syntheses to be reported include those of α-L-rhamnopyranosides of the hydroxyamino acids serine and threonine[44] and 2-deoxy-α-D-*arabino*-hexopyranosyl derivatives of these compounds (by the acetylglycal-NIS method).[45]

The cerebrosides (23) and (24) have been made by the trichloroacetimidate method and the former was shown to be the natural product.[46] Compound (25), a cytokinin metabolite, has been obtained via the 4-amino-intermediate which was coupled with 6-chloropurine.[47]

The glycolipid compound (26) was made using the 1,3-dibromo-2-hydroxymethylpropane glycoside,[48] and the all *trans*-retinyl β-D-glucuronide was made by standard methods.[49]

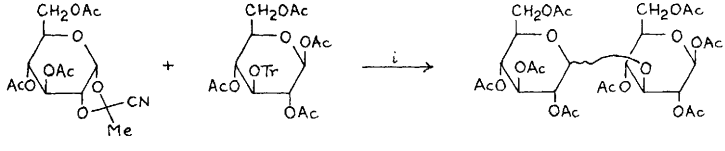
1.2 Synthesis of Disaccharides and their Derivatives.- As before, reducing disaccharides are treated according to their non-reducing moieties.

2-Pyridyl tetra-O-benzyl-β-D-glucopyranoside has been used to prepare a range of mainly 1,2-cis-related disaccharides,[50] and ethyl tetra-O-benzoyl- or tetra-O-benzyl-1-thio-β-D-glucopyranoside, activated by methyl triflate, give access mainly to β- and α-linked products, respectively. In this way the 1,3-linked D-glucobioses have been made,[51] and the α-isomer has also been made, using tetrabenzyl-α-D-glucopyranosyl bromide, as the derivative (27) which can be selectively deprotected for higher saccharide synthesis.[52] The effects of pressure on the Helferich glycosylation of methyl 2,4,6-tri-O-acetyl-β-D-glucopyranoside and the 2,3,6-substituted isomer have been examined; in both cases increase in



(27)

pressure favoured the formation of the β-linked isomers, the 1,4-linked isomer changing from an α,β-ratio of 80:20 at atmospheric pressure to 20:80 at 12 kbar.[53] A related examination of the reaction shown in Scheme 8 showed that increase in pressure could



Reagent: i $TrClO_4$

Scheme 8

change poor selectivity into specificity for the β-linked disaccharide.[54] It was proposed that at high pressures cyclic 1,2-acyloxonium ions were favoured as reaction intermediates over glycosyl carbonium ions.

Application of the trichloroacetimidate method has given good yields of 4- and 6-linked glucosyl glucoses and 2-linked glucosyl-galactose with good α-selectivity.[55]

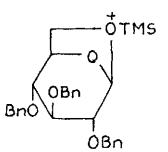
An efficient preparation of benzyl glycosides of lactose and cellobiose from the disaccharide peracetates has been reported,[56] and the eight possible monodeoxy analogues of methyl β-maltoside

and the 6,6'-and 1,2-dideoxy compounds have been tested as substrates for amyloglucosidase. Hydroxy groups were found to be required at C-3, 4' and 6' for activity.[57]

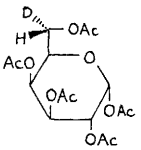
A synthesis of methyl 6-O-α-D-glucopyranosyl-α-D-glucopyranoside with good α-glucosylating activity resulting from the use of 2,3,4-tri-O-benzyl-6-O-trimethylsilyl-α-D-glucosyl bromide [which was assumed to react by way of ion (28)] has been described.[58]

Treatment of a 90% glucose solution with the β-glucosidase from almond can be made to yield 40% of mixed β-linked D-gluco-bioses.[59]

Disaccharides having D-glucose linked to the following other sugars have been reported: 2-acetylamino-2-deoxy-D-mannuronic acid (α-1→4),[60] D-galactose (α-1→6 and β-1→6),[51] formylmethyl 2,3-di-O-methyl-α-L-rhamnopyranoside (3,6-di-O-methyl-D-glucose β-1→4 linked),[61] and the corresponding benzyl and allyl glycosides[62] (these compounds required for immunological work). Other disaccharides having D-glucose bonded to a 6-amino-2,3,6-trideoxysugar and D-ribose of a nucleoside are referred to in Chapter 19.



(28)



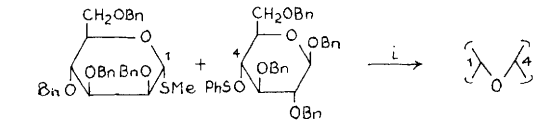
(29)

2,3,4-Tri-O-acetyl-6-O-tert-butyldiphenylsilyl-α-D-galactosyl chloride has been used in the synthesis of β-1→6 linked D-galactose di-, tri- and oligosaccharides,[63] and methyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-galactopyranoside used with nitrosyl tetrafluoroborate also gives good yields of β-linked disaccharides.[64] On the other hand, the trichloroacetimidate method has given high yields of 4- and 6-linked D-galactosylglucose and 2-linked D-galactosylgalactose with good α-selectivity.[55] The nature of the products formed by enzymic α-D-galactosyl transfer to D-galactose is dependent on glycosylation of the acceptor and its anomeric configuration. Glycosylation inhibits formation of 1→6 linked products.[65]

The 6- and 2'-O-methyl derivatives of N-acetyllactosamine have been prepared for biochemical studies,[66,67] and various lactosyl-ceramides have been made by the trichloroacetimidate route.[68] 6'-(S)-^{2}H-Methyl lactoside has been synthesized from the known specifically labelled compound (29) for use in enzymic syntheses of trisaccharides.[69]

A route to 1,6-anhydro lactose, maltose and cellobiose by use of glycosyl sulphones is reported in Chapter 5.

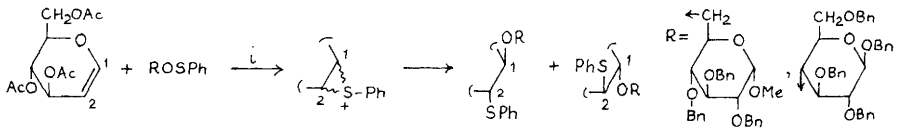
In the D-mannopyranosyl disaccharide set of compounds a novel route to mainly α-linked derivatives is illustrated in Scheme 9,[70] and of the D-mannobioses the α-1→6-linked compound has been prepared as the 6-phosphate ester of the α-methyl-9-methyl nonanoate glycoside.[71] By use of 4-uloside intermediates methyl 2-O-α-D-



Scheme 9

mannopyranosyl-α-D-talopyranoside and methyl 2-O-α-D-talopyranosyl-α-D-talopyranoside have been prepared,[72] as have the 3-linked isomers.[73]

In interesting use of sulphenate esters in a general synthetic route to 2-deoxy-D-arabino-hexopyranosyl disaccharides is illustrated in Scheme 10. The products illustrated were desulphurized, yields were >80% and β:α-ratios varied from 1.5-4:1.[74]

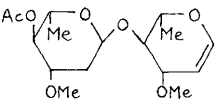


Scheme 10

In the reaction of 3,4-di-O-acetyl-1,2-O-endo-cyanoethylidene-6-deoxy-α-D-glucopyranose with tetra-O-acetyl-3-O-triphenylmethyl-β-D-glucose in the presence of tritylium perchlorate 14 kbar of pressure resulted in the formation of the β-linked product exclusively.[75] 3-O-Benzyl-6-deoxy-D-glucose has been used as the source of both components required in the synthesis of the disaccharide 2-O-(3-O-acetyl-6-deoxy α-D-glucopyranosyl)-4-O-acetyl-6-deoxy-D-glucose and the antitumor terpenoid compound phyllanthostatin of which it is a component.[76] The disaccharide is linked to a carboxylic acid in the natural product; synthetically this bond can be made by the Mitsunobu procedure.[77,78]

Disaccharides with α-L-rhamnopyranose linked to the 4-position of D-glucuronic acid[79] and separately to the 3,4 and 6 positions of 2-amino-2-deoxy-D-glucose have been reported,[80] as have compounds

with β-L-rhamnose bonded to the 2-positions of methyl β-D-glucopyranoside and methyl α-L-arabinopyranoside[81] and to the 3-position of (3',4'-dihydroxyphenyl)-2-ethyl-β-D-glucopyranoside. In this case the rhamnoside carried methyl groups at O-3 and O-4 and the product was required for comparison with a plant component.[82] The preparations of the disaccharides having 6-deoxy-4-O-methyl-D-glucose linked α- and β- to O-4 and β- to O-3 of 2,6-di-O-methyl-D-mannose have been reported, the β-1→4 compound being the disaccharide EF moiety of flambamycin.[83] The N-iodosuccinimide approach has been used in the synthesis of disaccharide derivative (30) and its linking to the aglycone of Avermectin A_{1a} in the total synthesis of the compound.[84]

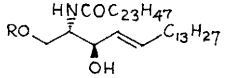


(30)

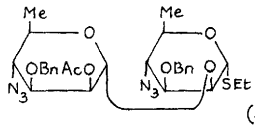
Preparation of the disaccharides having L-iduronic acid α- and β-1→3 linked to methyl 2-acetylamino-2-deoxy-β-D-galactoside 4-sulphate has been reported.[85]

Considerable attention has been given to the synthesis of disaccharides with ulosonic acid non-reducing compounds - particularly 3-deoxy-D-*manno*-octulosonic acid (KDO). The α-1→4 linked disaccharide with an α-allyl aglycone was made as a means of incorporating KDO into polyacrylamide copolymers,[86] but particular attention has been paid to the dimer having KDO α-1→6 linked to 2-amino-2-deoxy-D-glucose 4-phosphate in connection with studies of lipid A. Several analogues, some with anti-tumour activity, and having long linear substituents at N-2 and O-3, have been reported,[87-90] and a method of access to the dimer based on the use of a glycosyl fluoride has been described.[12] Disaccharides having α- or β- bonded N-acetylneuraminic acid as non-reducing units have been produced by a new method depending on the use of the α-glycosyl fluorides having a *cis*- or *trans* - phenylseleno group at C-3. These were obtained from the well known 2-ene.[17] A related method, also based on this ene, gives β-linked disaccharides by way of the 2,3-epoxide.[19] The α-2→9 disialic acid has been made,[91] as have compounds (31)-(34) with N-acetylneuraminic acid α- and β-2→3 linked to D-galactose.[92]

In the area of aminodeoxy-containing disaccharides main attention has been given to dimers of 2-amino-2-deoxy-D-glucose.



(31) R = α-NeuAc(2→3)β-Gal-p
(32) R = α- " α- "
(33) R = β- " β- "
(34) R = β- " α- "



(35)

With β-1→4 linked compounds two reports have described preparations of the basic unit of cell wall peptidoglycans of bacteria, i.e., the dimer having a muramic acid (3-lactyl ether) at the reducing end,[93,94] and one describes an analogue with a dipeptide bonded at O-3.[95] A set of disaccharides with muramic acid at the reducing end have also been described.[94]

Interest in β-1→6 linked compounds has focussed on bacterial lipid A having phosphate groups at O-1 and O-4' and fatty acid groups at O-3 and O-3'.[96-98] A basic route to compounds of this group has been defined[99] and a compound with muramic acid at the reducing position with a bonded dipeptide attached has been reported.[100]

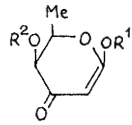
4,6-Dideoxy-4-formamido-D-mannose has been dimerized by α-1→2 linking, and the related trimer has been made in the course of immunological work.[101] An extension using the thioglycoside (35) gave di- to penta-saccharides of the series and also analogues having α-1→3 linkages.[102]

In the pentose series 2-O-β-D-xylopyranosyl-D-glucose has been bonded to a diterpene to produce the sweet baiyunoside,[103] and the 6-β-linked isomer has been made as its β-p-allylphenyl glycoside.[104]

Several disaccharides having L-arabinofuranose linked to O-4 of D-glucose, L-arabinose and D-xylose have been made using the 1,2-cyanoethylidene derivative and O-4 trityl ethers,[105] and β-D-ribofuranose linked β- to O-7 of KDO β-allyl glycoside has been reported.[86]

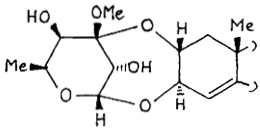
1.3 O-Glycosides Isolated from Natural Products.- As always, only compounds having notable features in the carbohydrate portions are recorded.

Helicidol, a compound isolated from the seeds of Helicia erratica, has been characterized as p-hydroxymethyl β-D-allopyranoside.[106] The hex-1-enosid-3-uloses (36) and (37) have also been isolated from a plant source[107] and the toxic principle from Urginea rubella has been found to contain the hexosid-3-ulose acetal structure (38).[108]



(36) R^1 = sesquiterpene, R^2 = angeloyl

(37) R^1 = " , R^2 = senecioyl



(38)

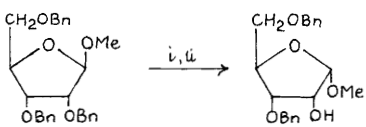
Steroidal glycosides from a gorgonian contain 3-O-β-D-arabinofuranosyl-β-D-glucose and the analogue with an acetyl ester group at C-2 of the pentose unit. They inhibit cell division of sea urchin eggs.[109]

1.4 Hydrolysis and Other Reactions and Features.- The effects of substituents in the aromatic rings of β-D-glucopyranosides on their rates and mechanisms of hydrolysis in concentrated potassium hydroxide (12.75 M) have been studied,[110] as have the reactions of some disaccharides with alkaline hydrogen peroxide. Five different paths were identified, including a newly proposed peroxy radical mechanism which is more rapid than the others.[111]

Invertase - catalysed hydrolysis of sucrose can occur to the extent of 99% in 1 min with retention of configuration at both anomeric centres.[112]

A specific method of deprotecting 2-chloroethyl glycosides (and presumably ethers) involves heating with sodium benzene sulphinate and potassium iodide in DMF. The reactions proceed by way of phenyl sulphones which then undergo β-elimination of the carbohydrate portions.[113] A specific method of cleaving natural products containing a component which is an allyl glycoside involving allylic bromination is described in Chapter 19.

The unusual reaction illustrated in Scheme 11 is proposed to involve tin-catalysed anomerization followed by chelation of tin species to O-1 and O-2 thus activating the 2-benzyl ether to give a 2-trichlorostannyl intermediate and leading to the first example of



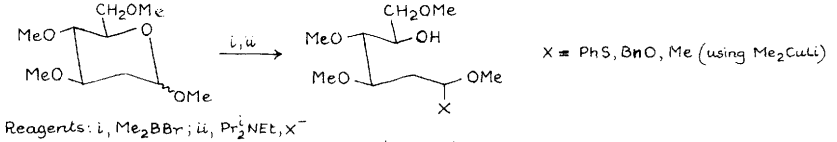
Reagents: i, $SnCl_4$; ii, H_2O

Scheme 11

selective debenzylation at a secondary position. See Chapter 5 for

examples of its application in the preparation of 2-substituted D-arabinose derivatives.[114] The selective acetolysis of methyl 2,3,4,6-tetra-O-benzyl-α-D-mannopyranoside is also referred to in Chapter 5.

Methyl glycosides, treated with boron trichloride at -78° in dichloromethane, afford the corresponding glycosyl chlorides in a reaction which is compatible with the presence of benzyl ethers, acetyl groups and other glycosyl linkages.[115] On the other hand, permethyl 2-deoxy-derivatives give high yields of acyclic products when treated with dimethylboron bromide followed by a nucleophile in basic conditions (Scheme 12). The results obtained from several



Scheme 12

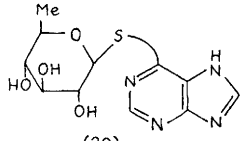
glycosides were rationalized on the basis of the operation of the anomeric and exo-anomeric effects.[116]

A theoretical study has been made of the stereochemistry of methyl α- and β-D-glucopyranoside in various solvents.[117]

2 S-Glycosides

Sugar peracetates treated with methylthiotrimethylsilane and boron trifluoride give the 1,2-trans-related 1-thioglycosides in a high yielding method which avoids smell,[118] and reaction of D-glucose and D-xylose with tert-butylthiol affords anomeric mixtures of the tert-butyl 1-thioglycopyranosides. Acetylated aldehydo-derivatives gave the corresponding dithioacetals.[119]

The arylthio glycosides (39) and (40) have been made, the former as a potential substrate for a glucuronidase[120] and the latter by an addition to tri-O-acetyl-D-glucal in the presence of



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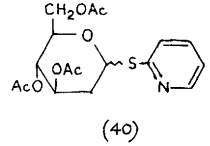


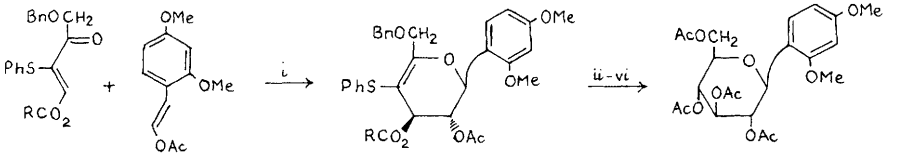
(40)

p-toluenesulphonic acid. No allylic rearrangement was observed.[121]

Cinnamyl 1-thioglycosides have been made from 1-thiourea analogues by use of 2-bromostyrene in a study of inhibition of delayed hypersensitivity reaction.[122]

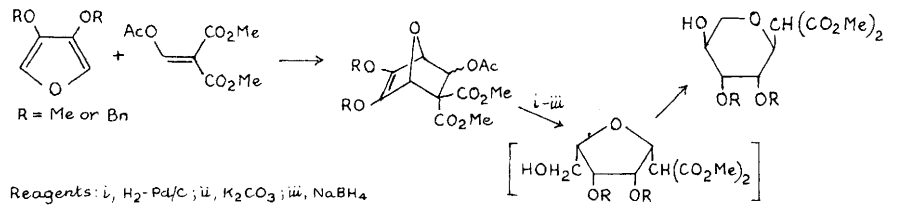
3 C-Glycosides

3.1 Pyranoid Compounds.- Two reports, both involving the hetero-Diels Alder reaction, have described the synthesis of racemic C-glycosides. The first (Scheme 13) develops a route to aryl C-glycosides with some optical induction obtained when R was chiral,[123] and the second (Scheme 14) an approach to lyxopyranosyl derivatives.[124]



Reagents: i, Δ ; ii, Raney Ni ; iii, $BH_3 \cdot SMe_2$; iv, H_2O_2 ; v, H_2-Pd/C ; vi, Ac_2O

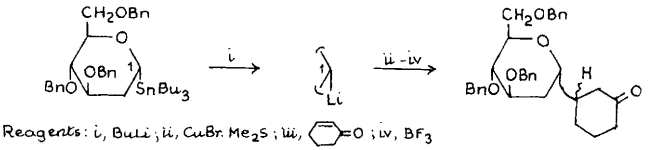
Scheme 13



Reagents: i, H_2-Pd/C ; ii, K_2CO_3 ; iii, $NaBH_4$

Scheme 14

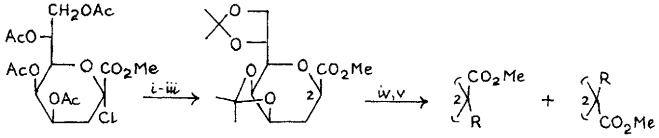
An extensive range of methods involving anomeric substitution reactions have been applied, several utilising glycosyl lithium intermediates, and Sinay and his coworkers have described fully their pioneering work in this area (c.f., Vol. 19, p.31 and 161).[125] Such nucleophilic intermediates take part in conjugate addition processes, α- and β-bonded precursors giving α- and β-C-glycosides (Scheme 15).[126] C-Glycosides of KDO are also readily made by way



Reagents: i, BuLi ; ii, CuBr·Me_2S ; iii, =O ; iv, BF_3

Scheme 15

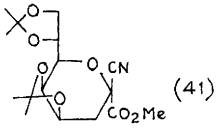
of anionic intermediates (Scheme 16), the β-products predominating with R=CN,CH_2OH,COMe; the X-Ray diffraction analysis of compound



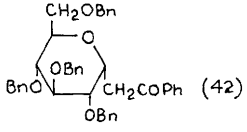
Reagents: i, H_2-Pd/C ; ii, MeO^- ; iii, Me_2CO-H^+ ; iv, LDA ; v, RX

Scheme 16

(41) was carried out to provide a reference compound for anomeric assignment.[127]



(41)



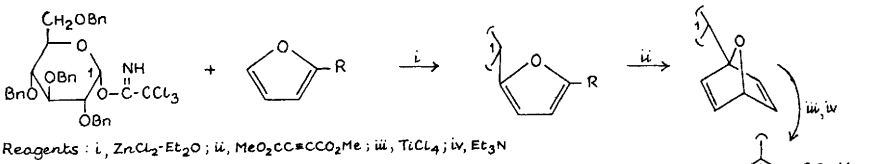
(42)

Other methods have depended upon nucleophilic attack at the anomeric centre; these include reaction of tetra-O-acetyl-α-D-glucopyranosyl chloride with lithium diaryl cuprates to give β-C-glycosides,[128] and reaction of tetra-O-benzyl-α-D-glucopyranosyl chloride with silyl enol ethers and silver triflate to give good yields of mainly 2-linked compounds e.g.,(42).[129] In related work a one-pot route from 2,3,4,6-tetra-O-benzyl-D-glucose proceeded by way of the β-trifluoroacetate which was treated with silyl enol ethers or allyltrimethylsilane to give β-products, or with aromatic hydrocarbons and BF_3 to give mainly α-derivatives.[130]

An improved procedure for making both pyranosyl and furanosyl cyanides involves the use of the glycosyl acetates and trimethylsilyl cyanide and boron trifluoride,[131] and a further method involves the treatment of compounds with the nitromethyl anomeric substituent with PCl_5. The method is particularly suited for giving 1,2-cis-related glycosyl cyanides.[132]

Trichloroacetimidates may also be used as indicated in Scheme 17; C-glycosylated thiophene and indole compounds may also be made by this approach.[133] An extension of this method has been used intramolecularly to give the bergenin derivative (43).[134]

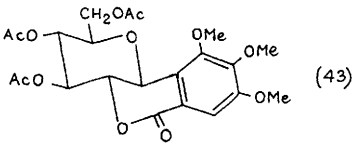
Silylated glycosides treated with allyltrimethylsilane and trimethylsilyl triflate give good yields of allyl C-glycosides in the furanoid and pyranoid and aldoside and ketoside series. With glucosides and ribofuranosides 1,2-cis-related products can be



Reagents: i, $ZnCl_2$-Et_2O; ii, $MeO_2CC{\equiv}CCO_2Me$; iii, $TiCl_4$; iv, Et_3N

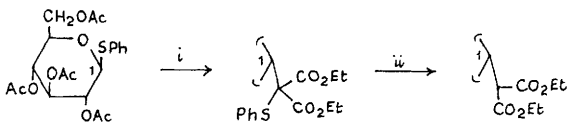
Scheme 17

obtained with high selectivity. Use of triethylsilane leads to good yields of anhydroalditols.[135] α-Mannopyranosides are obtained with good selectivity.[136]



(43)

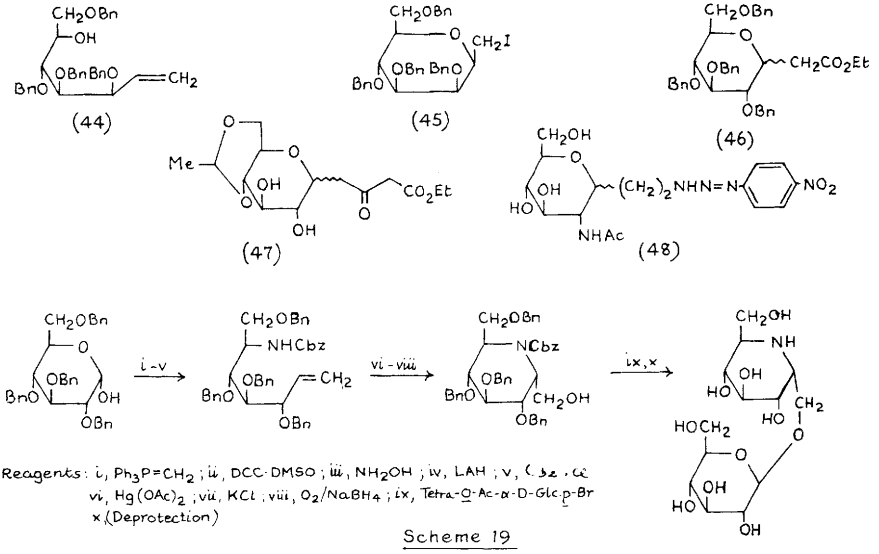
Suitably protected phenylthio glycosides treated with dialkyl zincs in di-iodomethane offer a new route to C-glycosides. Both α- and β-D-glucopyranose compounds gave products with a 3:1 α:β ratio.[137] Phenylthioglycosides can be used to give malonic acid C-glycosides (Scheme 18).[138]



Reagents: i, $N_2C(CO_2Et)_2$-$Rh(OAc)_2$; ii, Raney Ni

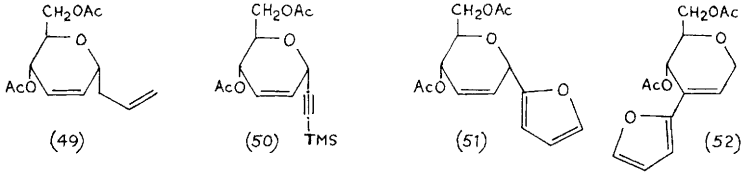
Scheme 18

Several approaches to C-glycosides have used alkenes produced from aldoses by Wittig or related procedures. The alkene (44) was obtained from 2,3,4,6-tetra-O-benzyl-D-mannose, giving mainly the β-product (45) on iodocyclization. The method was also applied in the furanoid series and again gave 1,2-trans-related products.[139] Both anomers of (46) can be made by use of $(EtO)_2POCHCO_2Et\ Na^+$.[140] Wittig procedures have been used to obtain equal proportions of compounds (47),[141] and the glucosamine derivatives (48), which are inhibitors of human β-D-hexosaminidase, have been made similarly.[142] The preparation of a nojirimycin C-glycosidic disaccharide, which is a potent α-glucosidase inhibitor, is outlined in Scheme 19.[143]



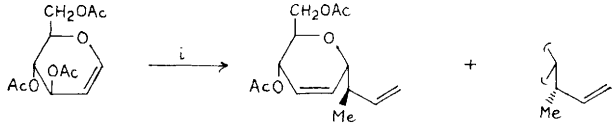
Scheme 19

Several additional reports have appeared on the use of unsaturated compounds in the synthesis of C-glycosides. The allylic rearrangement of glycal derivatives continues to receive attention. Tri-O-acetyl-D-glucal, treated with allyltrimethylsilane, 1,2-bis(trimethylsilyl)acetylene and furan in the presence of Lewis acid catalysts, gives compounds (49) - (51) respectively; (51) was obtained with an equal proportion of the isomer (52), which is an



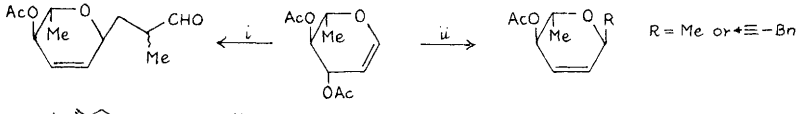
unusual type of product from this kind of reaction and was presumably formed from the 3-substituted glycal by a prototropic rearrangement.[144]

Scheme 20 illustrates the dependence upon the nature of the reagents of the products found using different but-2-enylsilanes in this type of reaction.[145] A related approach utilizes homoenol ethers,[146] and another substitution reaction uses organoaluminium reagents[147] (Scheme 21).



Reagents: i, BF_3 + RSiR$_3$ R = Me⟋⟍SiMe$_3$ 3 : 1
R = ⟋⟍SiMe$_3$ (Me) 1 : 3
R = ⟋⟍SiBu^{t}Ph$_2$ (Me) 1 : 7

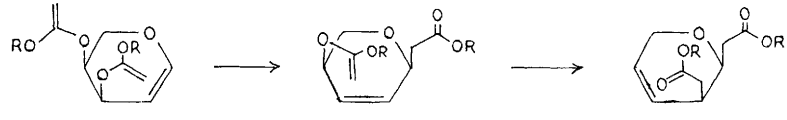
Scheme 20



Reagents: i, ⟋⟍OTHP, $SnCl_4$; ii, Me_3Al or Me_2Al-≡-Bn

Scheme 21

The first Claisen rearrangement of the pair shown in Scheme 22 is much the faster, and the processes can therefore be used to make 2-enes or 3-enes in this series. The rate difference, which was



R = SiBu^{t}Me$_2$

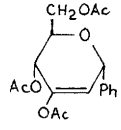
Scheme 22

not observable with cyclohexene derivatives, was ascribed to the weakening of the C-3-O bond by a "vinylogous anomeric effect". A thorough discussion of steric and stereoelectronic effects was given.[148]

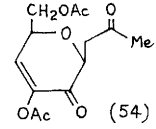
2,3-Unsaturated C-glycosides can be made by direct substitutions applied to other 2,3-unsaturated compounds. Thus, phenyl glycosides treated with ethyl nitroacetate, triphenylphosphine and a Pd(0) catalyst, give good yields of products having the $CH(NO_2)CO_2Et$ substituent, with retention of anomeric configuration.[149] Similarly, S-acetyl-1-thio-compounds with arylzinc chlorides and $Pd(PPh_3)_4$ give aryl C-glycosides, but with inversion of configuration.[150] An approach to aryl C-glycosides by way of phenyl 1-thio-2,3-unsaturated glycosides and derived C-1 lithio intermediates is noted in Chapter 13.

Two reports have utilized 3-ulose analogues of glycals. In the

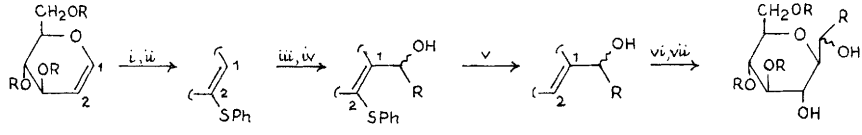
first, diphenylcopper complexes were used to obtain products such as (53) (following acetylation),[151] and in the second, enolsilyl ethers and Ti (IV) catalysts afforded the rearranged products (54).[152] A further approach to C-glycosides via 2-phenylthioglycals is illustrated in Scheme 23.[153]



(53)



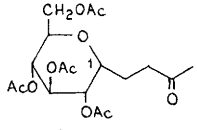
(54)



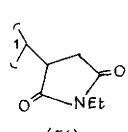
Reagents: i, PhSCl; ii, DBU; iii, BuLi; iv, RCHO; v, Raney Ni; vi, $BH_3.Me_2S$; vii, H_2O_2 R = Bn

Scheme 23

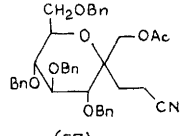
Glycosyl radicals added to electron-deficient alkenes afford access to C-glycosides, examples having been given in a review of "Radical Reactions in Organic Synthesis".[154] Compounds (55)-(57) were amongst compounds reported as having been made by addition of



(55)

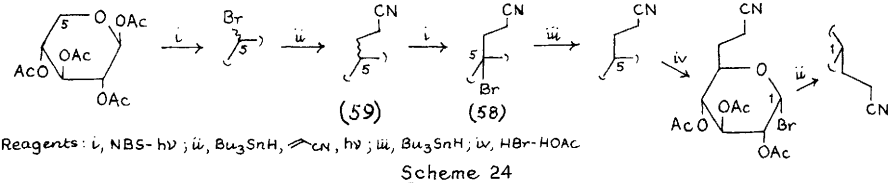


(56)



(57)

the tetra-O-acetyl-D-glucosyl radical to butenone[155] and N-ethylsuccinimide,[155] and addition of a hept-2-ulosyl radical to acrylonitrile.[156] An extension of this approach has allowed chain extension from C-1 and from C-5 of a D-xylopyranose ring to give access to a 4,8-anhydroundecanose derivative with good selectivity (Scheme 24). A key step was the production of a single bromide (58)



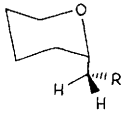
(59) (58)

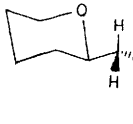
Reagents: i, NBS-hν; ii, Bu_3SnH, CN, hν; iii, Bu_3SnH; iv, HBr-HOAc

Scheme 24

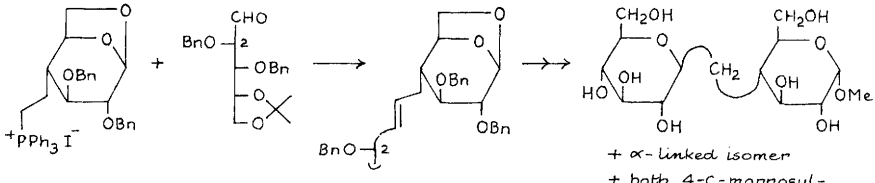
by photobromination of the epimeric nitriles (59) which can be accounted for by conformational control.[157]

A ^{1}H n.m.r. study of a series of α- and β-D-C-glucopyranosides has shown that the preferred rotamer states about the "glycosidic" bond are (60) and (61), i.e., they are analogous to those favoured by O-glycosides.[158] Related studies on the preferred conformations


(60)

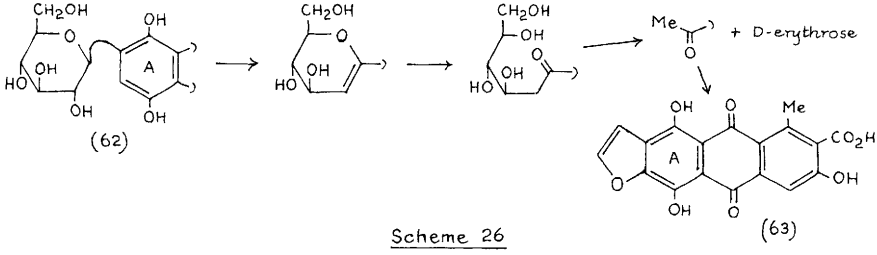

(61)

of C-linked analogues of the 1,4-α, 1,4-β, 1,6-α and 1,6-β linked methyl D-glucobioses are referred to in Chapter 21. The synthetic approach to the first two of these is outlined in Scheme 25.[159]



Scheme 25

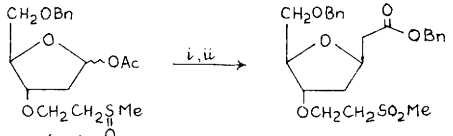
Degradation of carminic acid (62), the principal component of cochineal, with 60% sulphuric acid gave as a main product the anthrafuradione (63). A possible route involving a retroaldol step is indicated in Scheme 26.[160]



Scheme 26

3.2 Furanoid Compounds.- Reaction of substituted D-ribofuranosyl fluorides with silyl enol ethers and allyl trimethylsilane gives mainly α-C-glycosides.[161] Similar reaction of 2,3,5-tri-O-benzyl-β-D-ribosyl acetate with various silylated nucleophiles also affords

α-linked products.[162] In the area of 2-deoxy-D-*erythro*-pentose compounds, the glycosyl acetate (64) gives access to β-*C*-glycosides as indicated in Scheme 27.[163] A full paper on the intramolecular



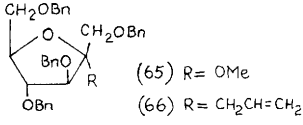
(64)

Reagents: i, $=\!<^{OSiR_3}_{OBn}$ - TMSOTf ; ii, oxidation

Scheme 27

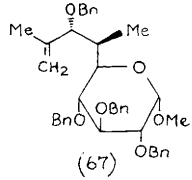
C-arylation of benzylated pentofuranosyl acetates has appeared.[164]

Various other means of obtaining furanosyl *C*-glycosides have been described. The fructofuranoside (65) afforded the *C*-allyl compound (66) from which α- and β-D-fructofuranosyl *C*-glycosides were produced;[165] compound (67), on treatment with *N*-bromosuccinimide, gave the product of *O*-5 participation (68);[166] and the 2-*O*-

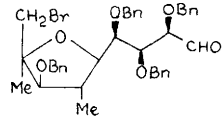


(65) R= OMe

(66) R= $CH_2CH{=}CH_2$

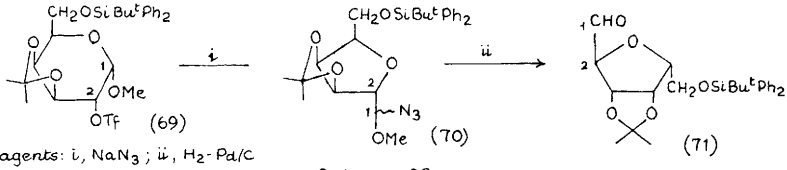


(67)



(68)

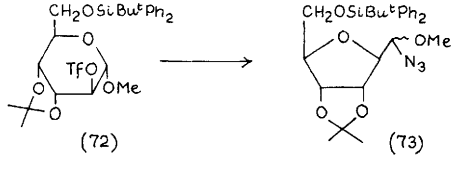
triflate (69), treated with sodium azide, gave the product of ring-contraction (70), which on reduction afforded the aldehyde (71) (Scheme 28). Likewise, compound (72) gave (73) in high yield on treatment with sodium azide.[167]



(69) (70) (71)

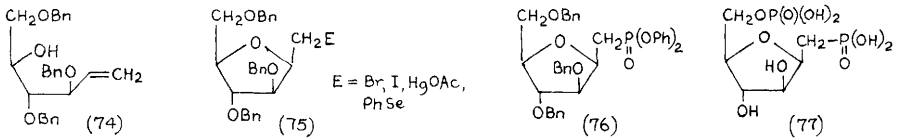
Reagents: i, NaN_3 ; ii, H_2-Pd/C

Scheme 28

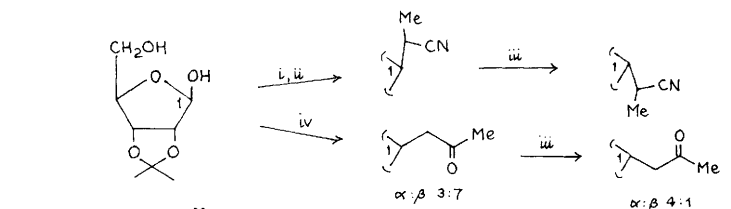


(72) (73)

The alkene (74), produced by Wittig chemistry from 2,3,5-tri-O-benzyl-D-arabinose, reacts with electrophiles to give the β-C-glycosides (75)[168] and the phosphonate (76)[169] from which the D-arabinose phosphonate isostere (77) of D-arabinose 1,5-diphosphate was made.

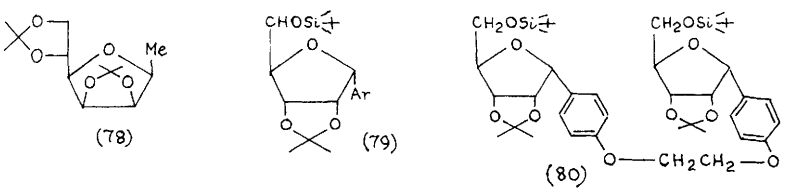


Reaction of 2,3-O-isopropylidene-D-ribose with Wittig reagents gives mainly β-products under kinetic control and α-products following equilibration with base (Scheme 29).[141]



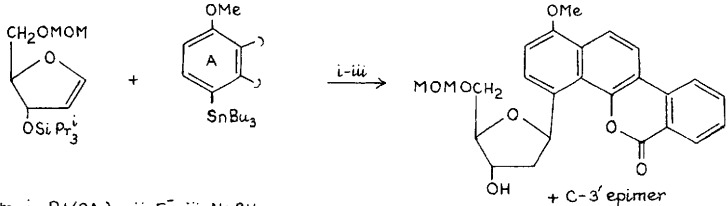
Scheme 29

2,3:5,6-Di-O-isopropylidene-D-mannono-γ-lactone treated with tris(dimethylamino)phosphine in carbon tetrachloride gave the exo-dichloromethylene product which on hydrogenation resulted in the 1-deoxyheptitol derivative (78).[170] In related work 2,3-O-isopropylidene-5-O-tert-butyldimethylsilyl-D-ribono-γ-lactone gave the α-products (79) on treatment with lithiumaryls, and an extension of this methodology gave the dimer (80) and hence, by linking C-5 to



C-5' by way of a diamide bridge, a water-soluble receptor for hydrophobic groups.[171]

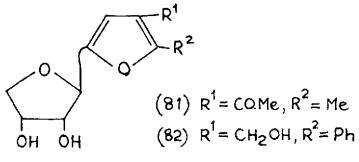
Synthesis of C-glycosides related to ravidomycin and related antibiotics by palladium - mediated coupling of furanoid glycals is illustrated in Scheme 30.[172]



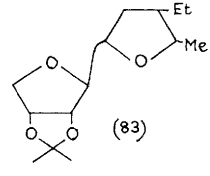
Reagents: i, $Pd(OAc)_2$; ii, F^-; iii, $NaBH_4$

Scheme 30

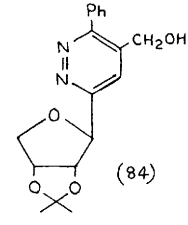
The known 2-C-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)furan has been converted into corresponding glycosyl-N-heterocycles which are C-nucleoside analogues,[173,174] and the related compounds (81) and (82), prepared from D-glucose and β-dicarbonyl derivatives, have been used to obtain (83)[175] and (84),[176] respectively. A C-glycosylnaphthalene has been prepared as outlined in Scheme 31.[177] Other furanosylheterocycles are noted in Chapter 9.



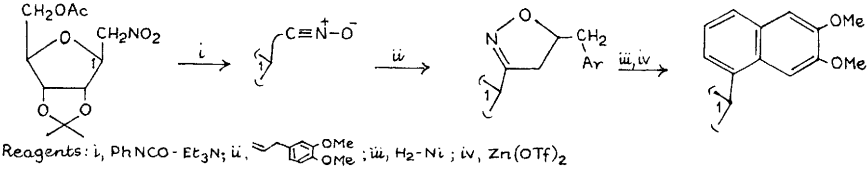
(81) R^1 = COMe, R^2 = Me
(82) R^1 = CH_2OH, R^2 = Ph



(83)



(84)



Reagents: i, PhNCO - Et_3N; ii, ; iii, H_2-Ni ; iv, $Zn(OTf)_2$

Scheme 31

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4
Oligosaccharides

1 General

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

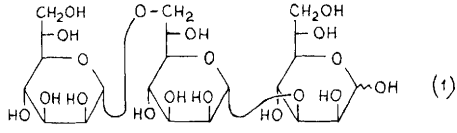
A review has appeared on the synthesis of oligosaccharides, glycopeptides and complex oligosaccharides of glycoproteins and on the conformational analysis of the oligosaccharide sequences.[1] Another has been published on chiral selection and chiral induction using regiospecifically di- and poly-substituted β-cyclodextrins.[2] 2,3,4-Tri-O-acetyl-6-O-tert-butyldiphenylsilyl-α-D-galactopyranosyl chloride has been applied in the synthesis of β-1→6 linked D-galactose oligosaccharides, and various substituted derivatives of the dimer and trimer were made.[3]

2 Trisaccharides

2.1 Linear Homotrisaccharides.- The α-(1→2)-linked trimer of D-glucopyranose (kojitriose) and the tetramer and pentamer have been synthesized,[4] as have the α-(1→4)-α-(1→3) and α-(1→3)-α-(1→4) isomers, in connection with studies of nigeran.[5] In the D-mannopyranose set of compounds the α-(1→2)-α-(1→2), α-(1→2)-α-(1→3) and the α-(1→2)-α-(1→6) trimers were made as their 6"-phosphates which are the end groups of oligosaccharide chains of lysosomal enzymes.[6] In the course of the same work the α-(1→2)-α-(1→3) and the α-(1→2)-α-(1→6) compounds were made with "spacer groups" attached at the

anomeric centres and phosphate groups at the non-reducing end group primary positions.[7]

The α-(1→4)-α-(1→4) linked D-galactose trimer has been made and has phytoalexin eliciting activity,[8] and the heptose trimer (1) of the core region of the Gram-negative bacterial polysaccharides has also been prepared.[9] The β-(1→4) linked-D-galactose trimer has been reported as one of a sequence of oligomers which can be made by a systematic approach.[10]

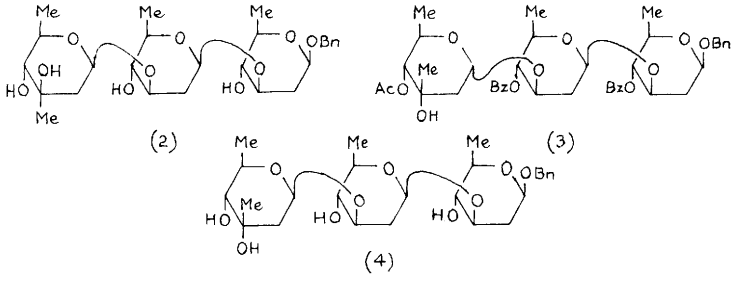


2.2 Linear Heterotrisaccharides.- The following trisaccharides having D-glucose at the reducing termini have been synthesized (the first two β-linked to ceramide): O-α-D-Galp-(1→4)-O-β-D-Galp-β-D-Glc,[11] O-α-D-Galp-(1→3)-O-β-D-Galp-β-D-Glc,[11] O-β-D-GlcpUA-(1→4)-β-D-Galp-D-Glc, (a Klebsiella polysaccharide constituent),[12] O-α-D-Neup5Ac-(2→6)-O-β-D-Galp-(1→4)-D-Glc (present in human milk),[13] O-α-D-Neup5Ac-(2→3)-O-β-D-Galp-(1→4)-D-Glc (part of a ganglioside chain).[14]

The following other hexose-terminating trimers have also been reported: O-β-D-GalpNAc-(1→4)-O-β-D-GlcpNAc-(1→2)-D-Man (and the 4"-sulphate),[15] O-α-D-Manp-(1→2)-O-α-D-Manp-(1→3)-D-Gal and O-α-D-Manp-(1→2)-O-β-D-Manp-(1→3)-D-Gal.[16,17]

Compounds terminating in 2-aminohexose units to have been synthesized are: O-α-D-KDOp-(2→6)-O-β-D-GlcNH$_2$p-(1→6)-D-GlcNH$_2$ (a lipid A analogue having both amino groups acylated with a long chain fatty acid),[18] O-α-D-KDOp-(2→4)-O-α-D-KDOp-(2→6)-D-GlcNH$_2$ (the repeating unit of the inner core of a lipopolysaccharide),[19] O-β-D-GlcpNAc-(1→3)-O-β-D-Galp-(1→4)-D-GlcNAc,[20] O-β-D-GlcpNAc-(1→3)-O-β-D-Galp-(1→3)-O-β-D-GlcpNAc-Ph-pNO$_2$,[20] O-β-D-GlcpNAc-(1→3)-O-β-D-Galp-(1→3)-O-α-D-GalpNAc-Ph-pNO$_2$,[20] O-α-D-Glcp-(1→3)-O-α-L-Rhap-(1→3)-ManpNAc.[21] The KDO-terminating trimer O-α-L-Rhap-(1→3)-O-α-L-Rhap-(1→8)-D-KDO has been isolated from an Acinetobacter,[22] and the following L-rhamnose-terminating compounds have been synthesized: O-β-D-ManpNAc-(1→4)-O-α-D-Glcp-(1→2)-L-Rha,[23] and O-β-D-Glcp-(1→4)-O-α-and β-L-Rhap-(1→2)-L-Rha (with O-methyl groups at O-3,-2',-3', -3" and -6").[24,25]

More unusual compounds to have been prepared are the deoxysugar



(2) (3) (4)

compounds (2), (3) and (4) which are components of auretoic acid,[26] a derivative of an isomer of the trisaccharide of mithramycin[26] and the E, D, C trisaccharide of the antibiotic respectively.[27]

2.3 Branched Heterotrisaccharides.- Compounds of this category to have been reported are: O-β-D-GlcpNAc-(1→4)-O-[β-D-GlcpNAc-(1→3)]-D-Gal,[28] O-α-D-Manp-(1→3)-O-[α-D-Glcp-(1→4)]-D-Gal,[16,29] O-α-D-Manp-(1→3)-O-[β-D-Glcp-(1→4)]-D-Gal[29] and O-β-D-GlcpNAc-(1→6)-O-[β-D-GlcpNAc-(1→3)]-D-Gal.[30]

3 Tetrasaccharides

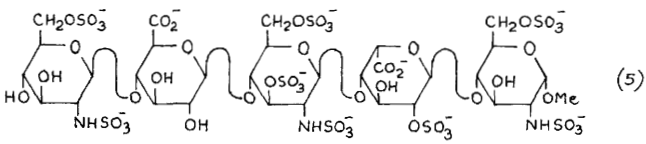
As with the trisaccharides, the following tetrasaccharides are classified according to whether they have linear or branched chains, and then by the nature of the sugars at the reducing ends.

3.1 Linear Tetrasaccharides.- Compounds of this group to have been isolated from natural products or synthesized are: O-β-D-Galp-(1→4)-O-β-D-GlcpNAc-(1→4)-O-β-D-Galp-(1→4)-D-Glc,[31] O-β-D-Galp-(1→4)-O-β-D-GlcpNAc-(1→3)-O-β-D-Galp-(1→4)-D-Glc,[31] (the repeating unit of the capsular polysaccharide of Streptococcus pneumoniae which has been made synthetically by way of a tetramer 1,2-O-cyanoethylidene derivative),[32] O-β-D-GlcpNAc-(1→3)-O-β-D-Galp-(1→3)-O-β-D-GlcpNAc-(1→3)-D-Gal,[28] O-β-D-Galf-(1→5)-O-β-D-Galf-(1→5)-O-β-D-Galf-(1→5)-D-Galf (a unit of the cell wall polysaccharide of Aspergillus niger)[33] and O-α-D-Manp-(1→6)-O-β-D-Manp-(1→4)-O-β-D-GlcpNAc-(1→4)-D-GlcpNAc (isolated from urine of calves with α-mannosidosis).[34] D-Quinovosyl-L-rhamnosyl-D-glucosyl-D-fucose tetramers which have been isolated from a plant root as cyclic esters are referred to in Chapter 7.

3.2 Branched Tetrasaccharides.- Compounds synthesized: O-α-D-Manp-(1→2)-O-α-D-Manp-(1→3)-O-[α-D-Glcp-(1→4)]-D-Gal,[16,29] O-α-D-Manp-(1→2)-O-α-D-Manp-(1→3)-O-[β-D-Glcp-(1→4)]-D-Gal,[16,29] O-β-D-Galp-(1→4)-O-β-D-Galp-NH_2-O-[β-D-Galp-(1→3)]-D-$GalNH_2$[35] and O-α-D-Manp-(1→6)-O-[α-D-Manp-(1→3)]-O-β-D-Talp-(1→4)-D-GlcNAc.[36]

4 Pentasaccharides

The α-(1→4) linked D-glucose pentasaccharide having a 2-pyridylamino group at C-6 of the non-reducing terminus and as an α-linked p-nitrophenyl glycoside has been prepared from amylose as a substrate for α-amylase.[37] O-α-L-Rhap-(1→2)-O-α-L-Rhap-(1→3)-O-α-L-Rhap-(1→3)-O-β-D-GlcpNAc-(1→2)-O-α-L-Rhap-OMe has been synthesized,[38] as has the methyl glycoside (5) which represents the sequence in heparin responsible for binding and activation of the anticoagulant protein.[39] The synthesis of the ceramide pentasaccharide(6, X hapten)



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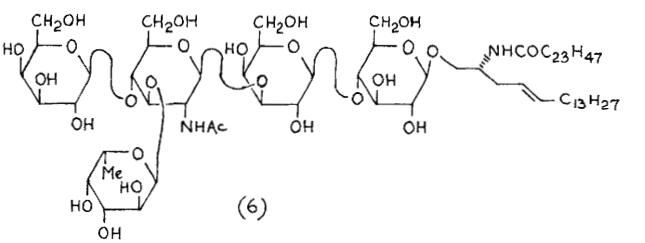

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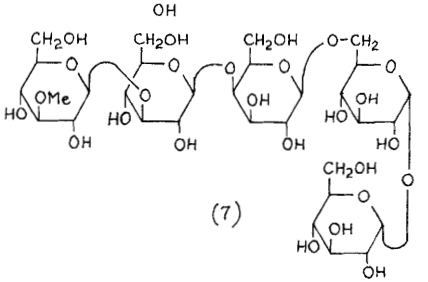

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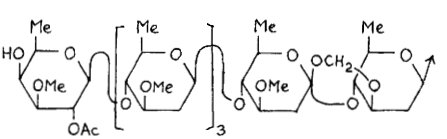


(8)

has been reported[40] as has that of the non-reducing pentasaccharide (7) which is a component of the glycolipid antigen of M. Smegmatis.[41]

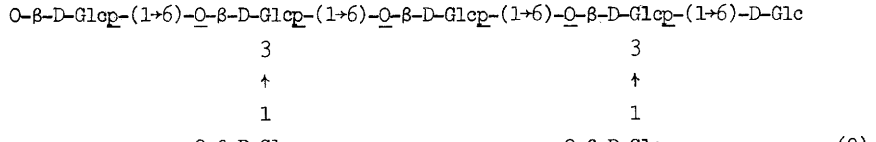
5 Hexasaccharides

Cyclomaltohexaose has been synthesized formally from maltose in a multistep process.[42,43]

The major constituent of a coaggregation polysaccharide of Streptococcus sangius has been characterized as: O-α-D-GalpNAc-(1→3)-O-β-L-Rhap-(1→4)-O-β-D-Glcp-(1→6)-O-β-D-Galf-(1→6)-O-β-D-GalpNAc-(1→3)-D-Galol[44] and the unusual hexasaccharide (8) has been identified as the carbohydrate portion of steroidal glycosides of toxic oriental medicines.[45]

6 Higher Saccharides

The β-(1→5) linked D-galactofuranose heptasaccharide linked to L-homoserine, which is similar to the extra-cellular galactomannan of Aspergillus species, has been synthesized by a solid-phase procedure,[46] and the phytoalexin elicitor of soyabean (9) has also been synthesized.[47]



(9)

The β-(1→3) linked tetramer of N-acetyllactosamine has been prepared by a block approach,[48] and the first total synthesis of cyclomalto-octaose (δ-cyclodextrin) has been developed from maltose.[49] Incubation of α-maltosyl fluoride with pullulanose gave 6-O-α-maltosylcyclomaltohexaose as well as other branched cyclomalto-oligosaccharides.[50]

The stereocontrolled synthesis of compound (10), which has phytoalexin elicitor activity, has been reported.[51]

(10)

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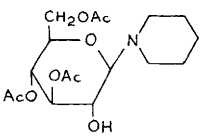
5
Ethers and Anhydro-sugars

1 Ethers

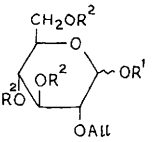
Methyl Ethers.- 4-O-Methyl-β-D-xylopyranoside has been identified as the sugar moiety in the new lignan glycoside cleistanthoside B from the heartwood of Cleistanthus collinus.[1]

A number of methyl ethers of methyl β-D-galactopyranoside have been prepared by standard partial methylation and chromatographic separation procedures.[2] The methylation of methyl α-D-hexopyranosides with diazomethane in the presence of small amounts of water has been described. Long reaction times with diazomethane in wet ether gave all the partially methylated derivatives. The presence of electrolytes such as sodium or potassium phosphates enhanced the degree of methylation resulting in the preferential formation of mixtures of the tri-O-methyl derivatives.[3] The synthesis of [1-^{13}C]-enriched 5-O-methyl pentoses has been achieved via [^{13}C] cyanide addition to the appropriate 4-O-methyl tetrose and separation of the C-2 epimers by chromatography.[4] Some phosphates of KDO, 3-deoxy-D-arabino-heptulosonic acid, and 3-deoxy-D-gluco-octulosonic acid have been converted into methylated derivatives to help the detection of such phosphates in lipopolysaccharides.[5]

Other Alkyl and Aryl Ethers.- The regioselective alkylation at O-3 of methyl 2,6-dideoxy-α- and β-L-lyxo- and α-L-arabino-hexopyranosides through activation as the dibutylstannylidene acetals has been described,[6] whereas phase transfer catalysed benzylation (Bu_4NBr, BnBr, NaOH) of benzyl 2,6-dideoxy-α-L-lyxo-hexopyranoside afforded a 3:1 mixture of the 4- and 3-O-benzyl ethers.[7] The adduct (1) obtained on treating penta-O-acetyl-β-D-glucopyranose with piperidine was used to synthesize some 2-O-alkyl-D-glucose derivatives (2).[8] A new approach to β-D-mannopyranoside derivatives selectively alkylated at O-3 and O-6 has been exemplified by the preparation of methyl 3,6-di-O-allyl-2,4-di-O-benzoyl-β-D-mannopyranoside from methyl β-D-galactopyranoside. The galactoside was selectively allylated at O-3 and O-6 via activation as a



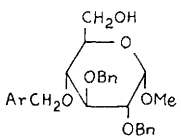
(1)



(2) R^1 = Ac or H
R^2 = Bn or Ac

dibutylstannylidene acetal. Inversion of configuration at C-2 and C-4 was effected by tetrabutylammonium benzoate mediated displacement of the O-2 and O-4 trifluoromethanesulphonyl esters.[9] A variety of 3-O-alkyl-, alkenyl-, ω-hydroxyalkyl- and ω-methoxyalkyl-D-glucoses and 3-O-alkyl-D-alloses have been synthesized conventionally by alkylation of the corresponding 1,2:5,6-di-O-isopropylidene-D-hexofuranoses, and their cytotoxicity against leukemia cells, antimicrobial activity, and plant growth inhibitory effects determined.[10] A number of partially benzylated derivatives of 6-deoxy-D-glucose have been prepared from the corresponding D-glucose ethers by a conventional 6-deoxygenation procedure.[11] Per-O-butylated methyl glycosides have been synthesized under phase transfer conditions.[12]

The cleavage of 4,6-O-benzylidene and 4,6-O-(p-methoxybenzylidene) acetals of hexopyranosides by diisobutylaluminium hydride has been reported.[13] D-Glucose derivatives gave predominantly the 4-O-benzyl or 4-O-p-methoxybenzyl ether, e.g., (3), as with LAH/$AlCl_3$. In the D-altro series the 6-O-benzyl ether, e.g., (4),



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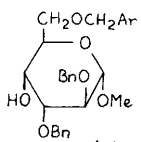
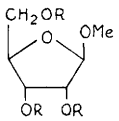


(4)

predominated, although the ratio of 6- to 4-ether was somewhat variable depending on the starting material. Using $LiEt_3BH/TiCl_4$, one altro derivative gave predominantly a 4-O-p-methoxybenzyl ether.

A novel selective debenzylation of β-D-ribofuranoside derivatives offers a route to partially protected ribofuranose compounds potentially useful for nucleoside synthesis. Thus treatment of the 4-chlorobenzyl ether (5) with stannic chloride and subsequent hydrolysis afforded (6).[14] It was proposed that tin-catalysed anomerization is followed by chelation of the tin species between O-1 and O-2 activating the 2-benzyl ether to give a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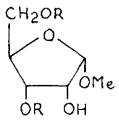
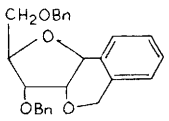

(6)

R = $CH_2C_6H_4Cl(p)$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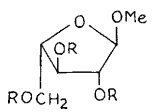
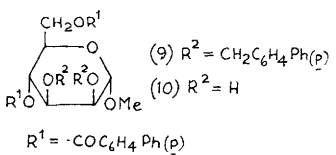
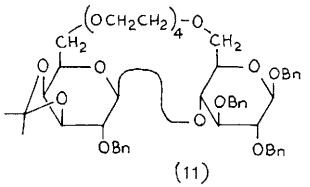

(8) R = $CH_2C_6H_4Cl(p)$

2-O-trichlorostannyl intermediate which is hydrolysed on work-up. The unsubstituted benzyl ether gave much more of the product of internal C-glycosidation (7). The reaction is not general though, since the arabinoside (8) under the same conditions reacted very slowly to give mainly the product of glycoside hydrolysis as well as some internal C-glycosidation. A chemoselective glycosidic debenzylation in the presence of another benzyl ether has been effected by hydrogenolysis (Pd/C, H_2, THF/EtOH 1:1).[15] In the selective acetolysis of methyl 2,3,4,6-tetra-O-benzyl-α-D-manno-pyranoside, the relative reactivity of groups was 1-OMe>6-OBn>4-OBn> 3-OBn≈2-OBn, and this permitted the synthesis of a range of partially benzylated acetylated mannopyranose derivatives required as mannopyranosylating synthons. The rate of acetolysis of various benzylated and acetalated methyl β-D-mannopyranosides was also studied.[16] Anhydrous ferric chloride in dichloromethane has been used to cleave benzyl and p-phenylbenzyl ethers. Methyl ethers and acyl groups were not affected. Thus the mannopyranoside derivative (9) afforded 82% of diol (10) after brief treatment with the reagent.[17] A full paper on the catalytic transfer hydrogenolysis of benzylated 1,6-anhydro-β-D-hexopyranoses to give partially O-benzoylated derivatives has been published.[18] (see Vol.20, p.55)


(9) $R^2 = CH_2C_6H_4Ph(p)$
(10) $R^2 = H$
$R^1 = -COC_6H_4Ph(p)$


(11)

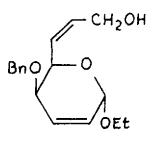
Acetonation of lactose with 2-methoxypropene/TsOH/DMF gave the 4′,6′-mono- and the 3,2′:4′,6′-di-acetal (54 and 21% isolated yields respectively, the latter after acetylation), and not the 6,2′:4′,6′-diacetal reported previously (SPR Vol.14, p.45). Studies with benzyl β-lactoside revealed initial formation of the 6,6′-bis-O-(1-methoxy-1-methylethyl) derivative, (45% yield using Py.TsOH as

catalyst), and this observation led to the conversion of benzyl 3′,4′-O-isopropylidene-lactoside into the macrocyclic ether (11) through 6,6′ protection.[19]

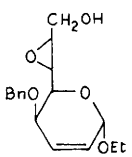
Silyl Ethers.- Use of the diphenylmethylsilyl ether protecting group has been reported.[20] This group generally has intermediate stability between the trimethylsilyl and the tert-butyldimethylsilyl ether groups. Studies on the selective silylation of methyl α- and β-D-aldohexopyranosides with tert-butyldimethylsilyl chloride have revealed some preparatively useful reactions.[21] Thus methyl 2,6-di-O-tert-butyldimethylsilyl-α-D-glucopyranoside is available in 70% yield from methyl glucoside. Similarly, the 2,6-disubstituted α-galactoside (84%), the 2,3,6-trisubstituted α-galactoside (57%), the 2,6-disubstituted α-mannoside (50%) and the 3,6-disubstituted α-mannoside (80%) were prepared from the parent methyl α-D-aldohexopyranosides. β-Glycosides did not give preparatively useful yields.

2 Intramolecular Ethers (Anhydro-sugars)

Oxirans.- Treatment of the cis-alkene (12) with MCPBA gave epoxide (13) and its isomer in a 1.8:1 ratio whereas Sharpless epoxidation using diethyl (S,S)-tartrate (1 month,-10°C) gave exclusively isomer



(12)



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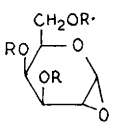
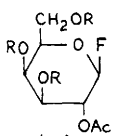


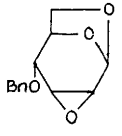
(14)

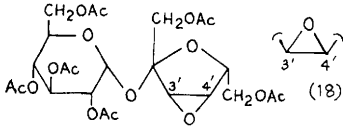


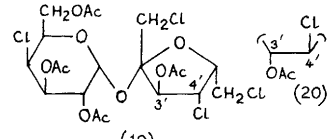
(15)

R = Bn or $CH_2C_6H_4Br(p)$

(13) which was required for the synthesis of antileukemia olguine analogues.[22] The crystalline 1,2-anhydro-α-D-galactopyranose derivatives (14) were prepared from the corresponding β-glycosyl fluorides (15) in good yield by treatment with potassium tert-butoxide in refluxing tetrahydrofuran.[23] An improved procedure has been described for the synthesis of epoxide (16) in 33% yield in five steps from levoglucosan. Nucleophilic opening of this epoxide occurred as expected with standard nucleophiles, although treatment with Me_2Mg in refluxing dioxan gave only 32% of the desired product,


(16)


(17) (18)


(19) (20)

presumably due to steric effects with the bulky nucleophile.[24] The sucrose epoxide derivatives (17) and (18) have been synthesized and their reactions with nucleophiles studied. Both epoxides incorporated the nucleophile (e.g., N_3^-, Cl^-, Br^-) at C-4′ on ring opening.[25]

The reaction of 6-O-acetylsucrose with sulphuryl chloride in chloroform/pyridine gave, after dechlorosulphation and acetylation, a mixture of (19) and (20). The chlorine atoms at C-4′ in these compounds were postulated to be derived from the chloride ion opening of the isomeric C-3′,4′ epoxides. Compound (20), after deacetylation, was reported to be 2,200 times sweeter than sucrose.[26]

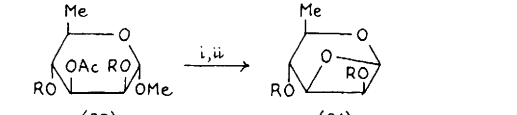
A 1,6;2,3-dianhydride, proposed as a useful intermediate for the chiral synthesis of polypropionate derived natural products, is mentioned in Chapter 14.

A comprehensive analysis of the ^1H and ^{13}C-n.m.r. data for the anomeric pairs of allo, manno- and talo-isomers of methyl 2,3-anhydro-4,6-O-benzylidene-D-aldohexopyranosides has been reported using 2-D homo- and hetero-correlation techniques,[27] and an analysis of the conformation in solution of benzyl 2,3-anhydro-4-azido-4-deoxy-pentopyranosides has been made using ^1H n.m.r. spectra.[28]

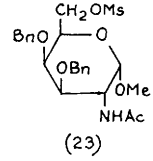
Other Anhydrides.- The synthesis of polysaccharides with a regular structure has been reviewed covering mostly the polymerization of anhydro-sugars.[29] 1,5-Anhydro-D-fructose has been discovered to be the precursor of microthecin in the fungus Morchella vulgaris. It exists as the 2,6-hemiketal in solution and its structure was confirmed by X-ray analysis of its derived oxime.[30]

An improved procedure for the preparation of 1,6-anhydro-β-D-glucopyranose has been described. Treatment of 1,2,3,4-tetra-O-acetyl-6-O-trityl-β-D-glucopyranose with Lewis acids ($SnCl_4$ or $TiCl_4$) afforded tri-O-acetyl-1,6-anhydro-β-D-glucopyranose in 78%

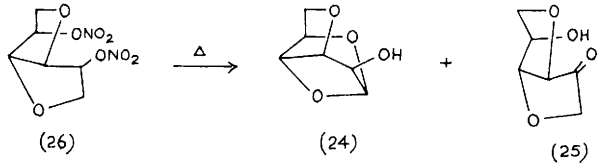
yield on a 0.1 mole scale.[31] The synthesis of some 1,6-anhydro-disaccharides by base treatment of the respective arylglycosyl sulphones has been reported.[32] The synthesis of 1,3-anhydro-β-D-rhamnopyranose ethers (21) from D-mannose has also been reported. The intermediate methyl glycoside (22) was transformed directly to a glycosyl chloride followed by 1,3-anhydride formation (Scheme 1).[33] The same group has also described[34] the preparation of the enantiomers of (21) from L-rhamnose by similar procedures.



Scheme 1

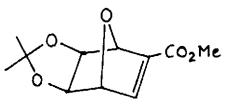


Reaction of 2,3,4-tri-O-benzyl-D-glucose with DAST gave mostly 3,6-anhydro-2,4-di-O-benzyl-β-D-glucopyranosyl fluoride, due to 3-O-benzyl participation, rather than the desired 1,6-difluoride.[35] Similarly treatment of (23) with cesium fluoride gave the corresponding 3,6-anhydride instead of the desired 6-fluoride.[36] 1,4:3,6-Dianhydro-α-D-mannopyranose (24), isolated as a stable crystalline solid, is formed in 75-80% yield along with 5-10% of 1,4:3,6-dianhydro-D-fructose (25) on flash vacuum thermolysis of isomannide dinitrate (26) (Scheme 2). Isosorbide dinitrate (the C-2 epimer of (26)) gives a 6:3:1 mixture of (25), (24) and the C-2 epimer of (24) in 80% yield.[37] A chiral product (27), derived from an asymmetric Diels-Alder reaction of furan, has been converted into 2,5-anhydro-3,4-O-isopropylidene-D-allose (28) by

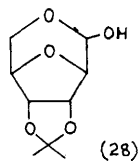


Scheme 2

standard methods.[38] The 2,6-anhydroheptose (29) has been obtained by reduction of the correponding glucosyl cyanide.[39] Depending upon the reaction solvent, 1,2-di-O-acetyl-3,5,6-tri-O-benzyl-D-allofuranose can be converted by reaction with $SnCl_4$ either to 2-O-acetyl-1,6-anhydro-3,5-di-O-benzyl-β-D-allofuranose (50%)



(27)



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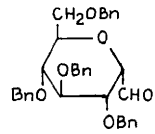
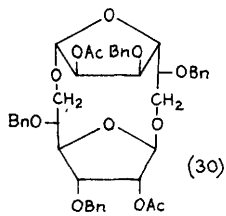


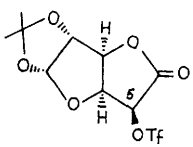
(29)

(in dichloromethane) as reported in the patent literature, or to the 1,6′;1′,6-dianhydride (30) (57%) (in toluene).[40] Sugar lactones (31) and (32) in the presence of benzyl-amine both gave rise to the



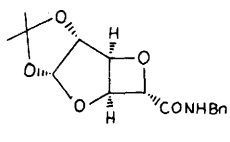
(30)

chiral oxetan (33).[41] When the benzyl-amine is replaced by K_2CO_3/MeOH a mixture of methyl esters analogous to (33) and its C-5 epimer is formed from both (31) and (32). The anhydrosucrose derivative (34) was obtained when, on deacetylation, the C-2



(31)

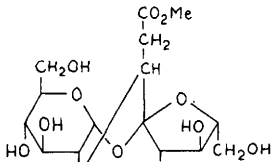
(32)



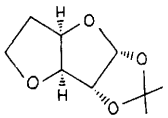
(33)

alkoxide added in Michael fashion to an α,β-unsaturated ester function at C-6′.[42] (1R, 5R)-2,6-Dioxabicyclo[3.3.0]octan-3-one has been synthesized from D-glucose by way of the 3,6-anhydro-5-deoxy-D-glucose derivative (35).[43] During a study of the behaviour of 3-deoxy-D-manno-oct-2-ulosonic acid (KDO) in dilute acid, the 2,7-anhydro-sugar (36) was isolated from the equilibrium mixture formed.[44]

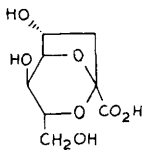
Further studies on the relative rates of $^1H/^2H$ exchange using Raney nickel in ^2H_2O have allowed the selective labelling of 1,6-anhydro-galactopyranose at C-3 and 1,6-anhydro-galactofuranose at



(34)



(35)



(36)

C-2.[45] The photobromination of 1,5-anhydropentofuranose derivatives and subsequent metal deuteride reduction of the resulting 5-exo-bromides gave C-5 chirally deuterated 1,5-anhydropentofuranoses. The stereochemistry of the reduction was discussed in terms of effects of C-2 and C-3 substituents. Products were mainly or exclusively the 5-S-^{2}H derivative.[46] Anodic oxidation of levoglucosan in MeOH/Bu_4NClO_4 gave methyl β-D-arabinopyranoside in 47% yield. At controlled pH(~7), D-arabinose was obtained. Levoglucosenone under the same conditions gave a mixture of polymers.[47]

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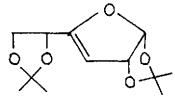
6
Acetals

1. Isopropylidene Acetals

A further paper on the determination of ring sizes of isopropylidene acetals by means of the ^{13}C-n.m.r. of the acetal carbon atoms has appeared.[1] An improved synthesis of 1,2:5,6-di-O-isopropylidene-D-galactofuranose by means of the treatment of the enose (1) with borane in DMS, followed by alkaline hydrogen peroxide, has been described.[2]



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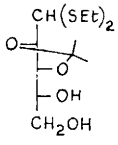
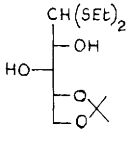


(2)



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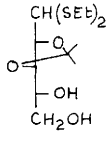

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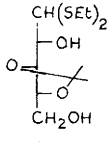
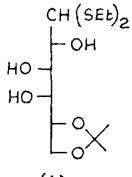


(5)



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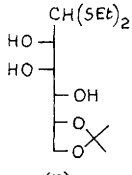

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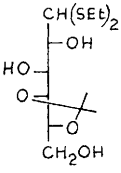

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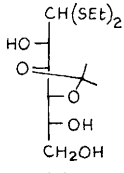
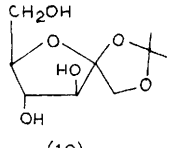


(9)

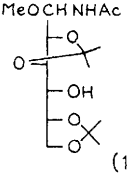
Tosic acid-catalyzed rearrangement of mono-O-isopropylidene derivatives of aldose diethyldithioacetals has been demonstrated by labelling experiments to proceed via an intramolecular process. The reactions always proceeded to yield the threo-acetal. Thus 4,5-O-isopropylidene-D-arabinose diethyldithioacetal, on treatment with tosic acid at 60° for 48 hours, gave the 2,3-O-isopropylidene derivative (2). Similar reactions with 4,5-O-isopropylidene-xylose (3) derivative gave an equimolar mixture of the rearranged 2,3- and 3,4-acetals, (4) and (5). In the same way the 5,6-acetals (6) and (7)

gave (8) and (9) respectively. The same paper described an improved synthesis of 2,3:5,6-di-O-isopropylidene-D-glucofuranose diethyldithioacetal.[3]

Treatment of D-fructose with 2-methoxypropene in the presence of stannous chloride in refluxing 1,2-dimethoxyethane gave the 1,2-acetal (10). Further reactions of (10) will be found in Chapter 15.[4]



(10)



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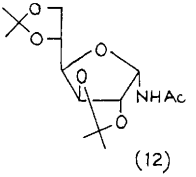


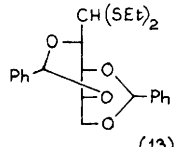
(12)

The purification of diisopropylidenesorbose using mixtures of benzene-petroleum instead of benzene alone results in a product with greatly reduced water content.[5]

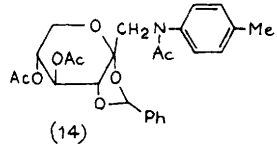
On treatment with dimethoxypropene-tosic acid N-acetyl-D-glucosylamine gives the two 2,3:5,6-acetals (11) and (12) in 43% and 10% yields respectively.[6] Acetonation of lactose with 2-methoxypropene-tosic acid in DMF has been shown to give the 4',6'-O-isopropylidene- and 3,2':4'6'-di-O-isopropylidene derivatives in 54% and 24% yields respectively, and not the 6,2':4'6'-diacetal as previously claimed (see Vol. 14, p. 45). Studies with benzyl β-lactoside revealed initial formation of the 6,6'-di-O-(methoxydimethyl)-methyl acetal. Uses of these observations in the synthesis of macrocyclic ethers are described in Chapter 5.[7]

2. Benzylidene Acetals

A new di-O-benzylidene derivative (13) of D-arabinose diethyl dithioacetal was obtained by benzylidenation with α,α-dimethoxytoluene. Its structure was confirmed by X-ray crystallography.[8] Treatment



(13)

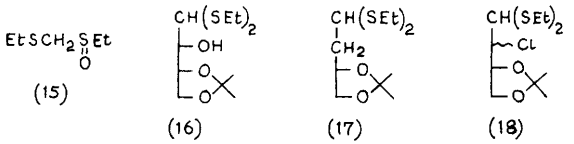


(14)

of 1-deoxy-1-p-toluidino-D-fructose with benzaldehyde in ethanol gave, after acetylation, the 2,3-benzylidene derivative (14).[9]

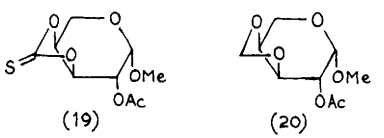
3. Other Acetals

Tetrose derivatives have been prepared via the intermediate sulphoxides obtained by treatment of 2,3-O-isopropylidene-D-glyceraldehyde with ethyl ethylthiomethyl sulphoxide (15). Thus lithium aluminium hydride reduction of the D-*erythro*-sulphoxides gave 3,4-O-isopropylidene-D-erythrose diethyl dithioacetals (16) and (17) and the same sulphoxide with triphenylphosphine-carbon tetrachloride gave the 2-chloro isomers (18).[10] Reaction of 3,4-O-thionocarbonyl-



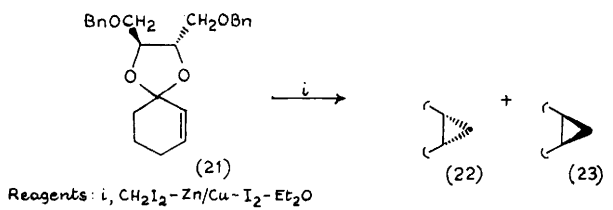
(15) (16) (17) (18)

β-L-arabinoside (19) with tributyltin hydride has been investigated in detail. Among the products found was the methylidene acetal (20) which became the major product when an excess of the tin reagent was used.[11] New acetals of adenine nucleosides[12] are described in



(19) (20)

Chapter 20. Diastereoselective cyclopropanation of 1,4-di-O-benzyl-L-threitol ketals of 2-cycloalken-1-ones using chelation-controlled reactions has been shown to be a general procedure. Thus the cyclohex-2-enyl acetal (21) gave a 9:1 ratio of the cyclopropane derivatives (22) and (23) (Scheme 1).[13]

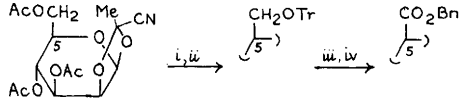


Scheme 1

1,2-O-Cyanoethylidene derivatives of alkyl mannopyranuronates have been synthesized via Jones oxidation of the corresponding 1,2-O-cyanoethylidene mannopyranoses (Scheme 2).[14]

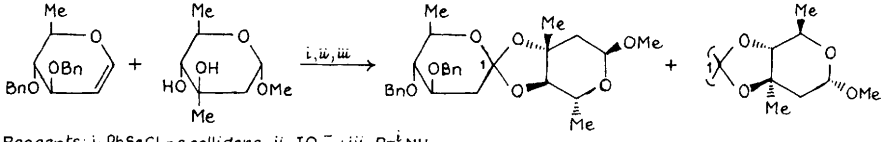
Reference to acyclic acetals at the anomeric centre will be found

in Chapter 3.



Reagents: i, NaOMe-MeOH; ii, TrCl-Py; iii, CrO_3; iv, BnOH

Scheme 2



Reagents: i, PhSeCl-s-collidene, ii, IO_4^-; iii, Pr^i_2NH

Scheme 3

Synthesis of two isomers of the spiro-ortholactone part of the C-D fragment of orthosomycins has been described (Scheme 3).[15]

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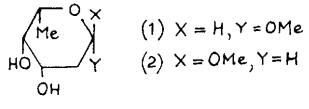
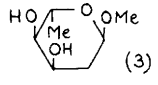
7
Esters

1 General Methods

Guanidine has been used for the very rapid deacetylation of sugar peracetates quantitatively; benzoyl and pivaloyl groups were unaffected.[1] Peracetylated sugars, on treatment with tributyltin methoxide, gave products selectively deacetylated at the anomeric centre. Equatorial anomers were deacetylated more quickly, and hence selectively, than their axial counterparts.[2] Lipases obtained from the porcine pancreas and Candida have been used to remove ester groups selectively; the 3-O-acetyl derivative of 1,2:5,6-di-O-isopropylidene-α-D-glucose was removed by the former but not the latter, while the butanoyl group was removed by both. Candida lipase was found to remove selectively the 6-O-acetyl group from methyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside and the 5-O-butanoyl group from 3-O-acetyl-1,2-O-isopropylidene-5-O-butanoyl-α-D-xylofuranose. Secondary debutanoylation was also achieved on 5-O-2,2-dimethylpropanoyl-1,2-O-isopropylidene-3-O-butanoyl-α-D-xylofuranose using Candida lipase.[3] Reversal of the normal action of lipases has been achieved in dry organic solvents when selective acylations at secondary positions were possible.[4] Dibutylstannylidene acetal activation of the 2,6-dideoxy-hexopyranosides (1) - (3) has been used to acylate, sulphonylate, or alkylate the 3-position regioselectively.[5] Various esterolytic enzymes have been in-



(1) X = H, Y = OMe
(2) X = OMe, Y = H



(3)

vestigated for carrying out partial deacetylation of 1,6-anhydro-2,3,4-tri-O-acetyl-β-D-glucopyranose; chymotrypsin and wheat germ lipase preferentially removed the O-3 acetyl group whereas liver esterase and pancreas lipase selectively removed the acetyl group from O-4, thus providing an improvement over regiochemical methods.[6] Among many examples of alcohol acylations with acid anhydrides under cobalt(II) chloride catalysis is a report of the

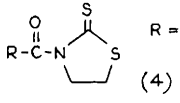
peracetylation of D-glucose in 95% yield. The reaction, conducted at 80°C, could not be used for selective acetylation.[7]

2 Carboxylic Esters

Highly purified N-acetyl-4-O-acetylneuraminic acid (Neu 4,5 Ac_2), Neu 5,7 Ac_2, and Neu 5,7,9 Ac_3 have been used to study spontaneous migrations of acetyl groups between hydroxy groups. At pH values where deacetylation does not take place it was shown that Neu 5,7 Ac_2 was easily converted into Neu 5,9 Ac_2, and Neu 5,7,9 Ac_3 yielded an equilibrium amount of Neu 5,8,9 Ac_3, while Neu 4,5 Ac_2 did not give rise to migrations. The results are of significance for the biosynthetic origins of O-acetylated sialic acids.[8] Sialic acid and N-glycolylneuraminic acid have been shown to be esterified at the 9-hydroxy group using orthoesters and catalytic tosic acid; selective 9-esterification was also applicable to N-acetyl α- and β-neuraminyl-oligosaccharides. The same paper reports the synthesis of 4-O-acetyl-N-acetylneuraminic acid.[9]

An improved procedure for the synthesis of sugar monochloroacetates uses monochloroacetic anhydride-sodium hydrogen carbonate in DMF as reagent mixture. The esters, obtained in up to 88% yield, were used in further chloro-substitution reactions to form, e.g., azidoacetates.[10] The 1-O-acyl group in 1,2-trans-acylated aldoses has been replaced by trifluoroacetyl by heating with trifluoroacetic anhydride-trifluoroacetic acid. Furanoses gave either β-anomers or mixtures of α- and β-anomers, whereas pyranoses gave only α-anomers. Hydrolyses giving the 1-hydroxy derivatives proceeded in good yields.[11]

The susceptibility of methyl 2,6-di-O-pivaloyl-α-D-glucopyranoside to esterases from rabbit sera has been examined; the 6-ester group was hydrolyzed much more readily.[12] The primary hydroxy group of α-D-glucose and methyl α-D-glucopyranoside were selectively esterified by treatment with N-acylthiazolidine-2-thiones (4) in pyridine-DMSO (free sugar) or pyridine alone (glycoside). Yields of esters were greater than 60%.[13]



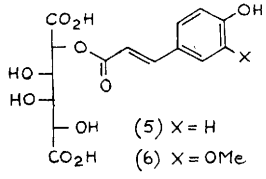
R = $Me(CH_2)_n$- , n = 6-16

(4)

2,3,4-Tri-O-acyl-D-glucoses have been found as lipid components in the leaves of the tomato Lycopersicon penelli. Nine compounds

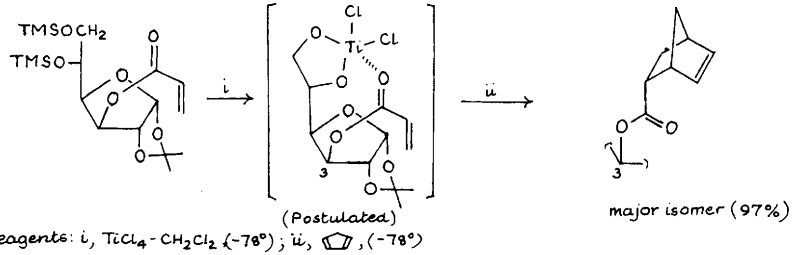
were isolated, the acyl moieties being primarily 2-methylpropanoyl, 2-methylbutanoyl, 3-methylbutanoyl, 8-methylnonanoyl and decanoyl.[14] The synthesis of sucrose and mannitol polystearic acid esters using a solvent-free system has been described, in which a modified Kizzi method of transesterification by ethyl stearate is employed. The method, with potassium soap as solubilizer and sodium-potassium alloy as catalyst, was carried out in a one-pot procedure, giving yields of up to 95%.[15]

Novel 2'-(E)-O-p-coumaroyl-(5) and -feruloyl-(6)-galactaric acids have been isolated from orange peel.[16] New acylated flavonol



(5) X = H
(6) X = OMe

glucosides have been isolated from leaves of Allium tuberosum, and shown to contain 2-O-feruloyl-β-D-glucopyranoside moieties. The migratory propensity of the feruloyl group from O-2 to O-6 was demonstrated at pH 7, 100°C or at pH 11 at room temperature.[17] An improved synthesis of cord factor analogues via the Mitsunobu reaction used trehalose with triphenylphosphine-diisopropylazodicarboxylate-β-O-tetrahydropyran-2-yl mycolic acid and tris(dimethylamino)phosphine oxide-dichloromethane as solvent. 6,6'-Dimicolyl trehalose was obtained in good yield under these mild conditions in which there is no protection of the carbohydrate required.[18] Two groups have carried out diastereoselective Diels Alder reactions on sugar acrylate esters as chiral auxiliaries via titanium complexes as shown in Scheme 1,[19] or uncatalyzed with a range of dienes, e.g., as shown in Scheme 2.[20] Arylpropanoic

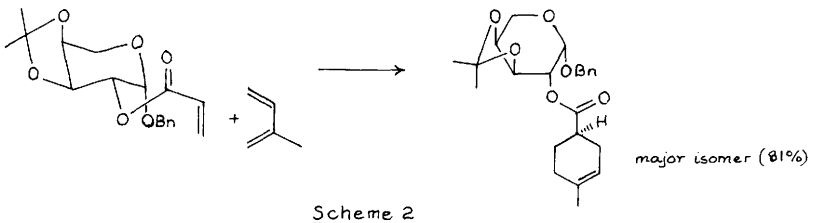


Reagents: i, $TiCl_4$-CH_2Cl_2 (-78°); ii, ⬠, (-78°)

Scheme 1

esters of di- and mono-acetone glucose have been prepared in an

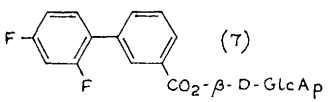
optically pure state. Hydrolysis or transesterification of the products yielded the optically pure arylpropanoic acids, or their methyl esters. Aryl groups used were 3-fluoro-diphenyl, 2-methyl-propyl-phenyl, and 6-methoxynaphth-2-yl.[21] Perbenzoyl-β-D-



Scheme 2

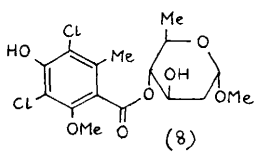
glucopyranosyl cinnamate has been prepared from the corresponding glycosyl bromide using phase transfer catalysis.[22]

The ester glucuronide (7) of diflunisal was found to be unstable particularly in neutral or basic solution, nine rearrangement or degradation products being detected by reversed-phase ion-pair HPLC.[23] The full paper on heterogeneous catalytic transfer hydro-



(7)

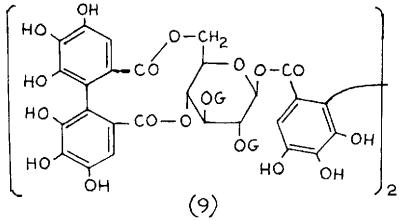
ginolyses of conformationally rigid molecules in which benzyl groups act as hydrogen donors to yield benzoate esters (see Vol. 20, p.71) has appeared.[24] Further studies on the selective esterification of methyl 4,6-di-O-benzyl-α-D-mannopyranoside have been reported (see Vol. 20, p.68). With benzoyl chloride or tosyl chloride in the two phase system, benzene-aqueous sodium hydroxide, in the presence of sodium benzenesulphonate-DMSO, the 2-esters were obtained. Selective acylation at O-3 was achieved by employing a copper complex of the substrate in THF.[25] The methyl glycoside (8) of curacin, the chromophoric terminus of several orthosomycin antibiotics, has been synthesized conventionally. The 3-O-acylated regioisomer was also prepared.[26]



(8)

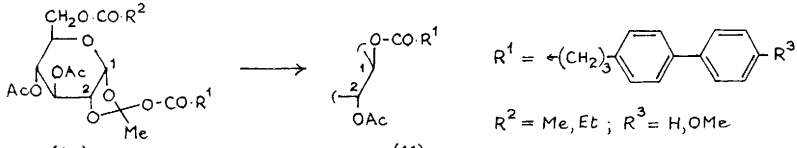
A new ellagitannin, liquidambin, from the leaves of Liquidambar

formosana, has been identified as 5-O-galloyl-2,3:4,6-di-O-(S)-hexahydroxydiphenoyl-D-glucose, which has a free aldehydo group, present in the hydrated form to a substantial extent.[27] Ellagitannins possessing a dimeric structure with several galloyl groups on the glucose core, e.g., coriariin A (9), display marked antitumour activity, apparently by potentiation of the immunity of the host.[28] Detailed studies using 2D ^{1}H-^{1}H and ^{1}H-^{13}C n.m.r.



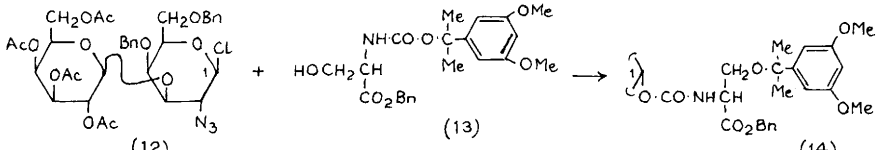
(9)

spectroscopy have demonstrated the oligomeric nature of several complex glucose-containing tannins.[29] Acyl ortho-esters (10) undergo a facile rearrangement to trans-diacyl derivatives of type (11) by an intramolecular pericyclic transition state similar to that of the retro-ene reaction.[30]



(10) (11)

Selective addition of the primary hydroxy group of D-glucose, D-galactose, and methyl α-D-glucopyranoside to allyl isocyanates gave the corresponding 6-O-carbamoyl-derivatives.[31] When the disaccharide glycosyl chloride (12) reacted with the amino acid derivative (13) an unexpected migration of the carbamate protecting group occurred to give the glycosyl urethane (14), Scheme 3.[32]



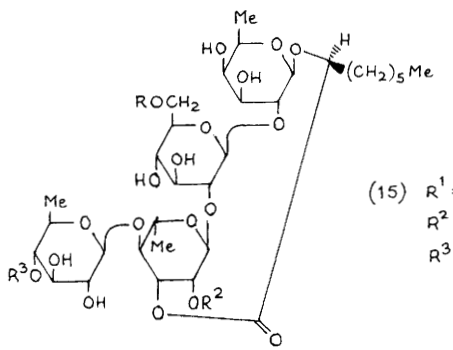
(12) (13) (14)

Scheme 3

Synthetic routes leading to glycopeptides have been reviewed; it was concluded that the easiest approach to those carrying a cluster

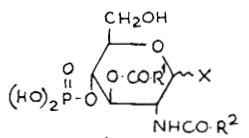
of monosaccharide units was to use the active ester method working stepwise from the C-terminus. The use of EEDQ or DCC was recommended for the more complex glycopeptides.[33] Monosaccharide-modified tuftsins and rigins have been prepared by glucosylation of the α-amino function, amidation of the carboxyl group with 2-amino-2-deoxy-β-D-glucopyranose, O-glucosylation of the threonine hydroxy group and glycosylation of the glutamine side chain amido group. A scheme for the synthesis of H-Gly-Glu(NHGlc)-Pro-Arg-OH was given.[34] The synthesis of O-(2-acetamido-2-deoxy-D-glucopyranuronos-3-yl)-D-lactoyl-L-alanyl-D-isoglutamine has been accomplished in several steps from benzyl N-acetyl-4,6-O-benzylidene-α-D-muramic acid benzyl ester.[35]

Reference to the antitumour glycoside (-)-phyllanthostatin, a C-1 ester, is made in Chapter 19. Macrocyclic esters (15) isolated from the root of *Ipomoea orizabensis*, have (11R)-hydroxypalmitic acid as both an aglyconic and an ester group on a tetrasaccharide.[36]



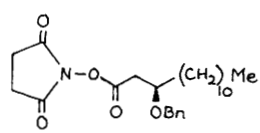
(15) R^1 = 3-hydroxy-2-methyl-butanoyl
R^2 = tigloyl
R^3 = R^1, 2-methylpropanoyl, 2-methyl-butanoyl

Japanese workers have continued their comprehensive investigations into syntheses of lipid A and related compounds. A review of the structure and total synthesis of *Salmonella* lipid A has appeared.[37] Analogues of the non-reducing subunit of bacterial lipid A have been synthesized in conventional manner to study their structure-activity profile.[38-40]



(16)

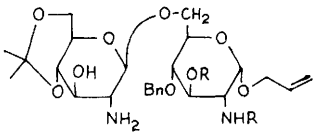
R^1, R^2 = lipid chains of C_{12}-C_{14} acids
X = OH, β-SAc, β-S·CO$(CH_2)_{12}$Me, β-SH, α-OP(O)$(OH)_2$



(17)

A related compound lipid X (16) (R^1=R^2=$CH_2CH(OH)(CH_2)_{10}Me$, X=$OP(O)(OH)_2$) has been synthesized as its tris(hydroxymethyl)amino-

methane salt by treatment of 2-amino-2-deoxy-D-glucose with the succinimide derivative (17) followed conventional manipulations.[42] Further details of the synthesis of lipid X and similar compounds previously reported (see Vol. 19, p.71 and Vol. 20, p.72) have been published.[43-45] Reference to the glycosidations of synthetic lipid X analogues to give various disaccharides related to lipid A is made in Chapter 3. The *Proteus mirabilis* lipid A has been synthesized *via* a versatile intermediate disaccharide (18) bearing two amino and six hydroxy groups each chemically differentiated.[46] Synthesis of immunomodulators which combine the structures of lipid A and 1-deoxy-muramyl dipeptide linked to a spacer arm has been accomplished, in order to exploit the discovery that lipophilic derivatives of 1-deoxy-muramyl dipeptide showed strong immunoadjuvant and antiinfective activity (see Vol. 20, p.176).[47]



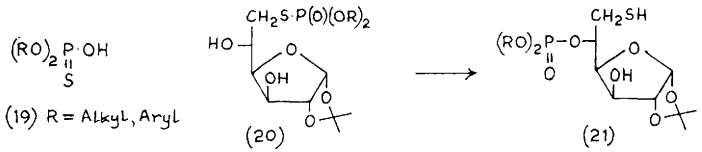
(18) R = $Cl_3C{\cdot}CMe_2O{\cdot}CO\rightarrow$

3 Phosphate and Related Esters

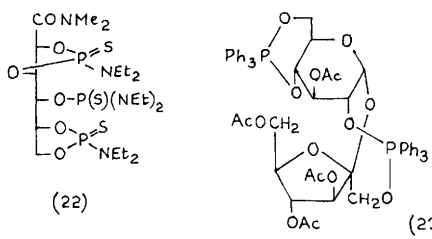
The synthesis of glycosyl phosphates *via* lithium salts of acetylated mono- and oligo-saccharides has been described. Thus 2,3,4,6-tetra-*O*-acetyl-D-galactopyranose and dibenzyldiphosphate in the presence of butyllithium gave the pyranosyl dibenzyl phosphate which was hydrogenolyzed and treated with lithium hydroxide to yield the β-galactosyl phosphate. The reaction was also successful with the oligosaccharides Rha-Gal and Man-Rha-Gal.[48] Conventional methods have been used to convert 1,2-*O*-alkylidene-α-D-glucofuranose 3,5,6-bicyclophosphites into the bicyclophosphates and their thiophosphono and selenophosphono analogues.[49] *N*-Acetylgalactosaminyl and *N*-acetylglucosaminyl phosphates, prepared *via* phosphorylation of the appropriate monosaccharide peracetates, have been treated with moraprenyl phosphoimidazolide to give the corresponding glycosyl moraprenyl diphosphates.[50] Diphosphonate treatment of α-D-glucose 1-phosphate gave α-D-glucose 1-phosphonylphosphate without concomitant phosphonylation of the remaining hydroxy groups.[51] Ketose phosphate derivatives have been prepared by aldolase mediated condensations of 3-dihydroxypropanone and L- or D-glyceraldehyde. High yields of D-fructose and

L-sorbose 1-phosphates were obtained.[52]

Careful monitoring of the reaction of monothio-acids of phosphorus (19), with 5,6-anhydro-1,2-O-isopropylidene-α-D-glucofuranose has given a deeper insight into the mechanism of the reaction. New convincing arguments have been adduced for the participation of a pentacoordinate intermediate in the transphosphorylation step leading from the thiophosphate (20) to the 5-phosphoryl-6-thioglucose (21).[53]



Authentic phosphates of KDO, 3-deoxy-D-arabino-heptulosonic acid and 3-deoxy-D-glucooctulosonic acid were converted into methylated derivatives suitable for g.c.-m.s. as an aid to the detection of such phosphates in lipopolysaccharides and related biomaterials.[54] The thiophosphonamido derivative (22) has been prepared by reaction of $P(NEt_2)_3$ with N,N-dimethyl-D-gluconamide followed by treatment with sulphur.[55] The structure was established by an X-ray crystallographic study.



A high yield synthesis of carbon-labelled intermediates of the L-pentose pathway has been reported. Enzymic synthesis was used to prepare ^{14}C-labelled octulose mono- and biphosphates and sedoheptulose 1,7-biphosphate from 1,3-dihydroxypropanone phosphates and ^{14}C-labelled aldopentose 5-phosphates and erythrose 4-phosphate respectively (see also ref. 52 above). A similar enzymic condensation of β-hydroxypyruvate with ^{14}C-labelled aldohexose 6-phosphate gave D-*glycero*-D-*ido*-octulose 8-phosphate. The paper also describes the synthesis of D-[U-^{14}C]-arabinose 5-phosphate from D-[U-^{14}C]glucosamine 6-phosphate by reaction with ninhydrin.[56]

The disaccharide α-D-Manp(1→2)α-D-Manp-OMe has been converted by standard methodology to 6- and 6'-mono- and 6,6'-di-phosphate deriv-

atives.[57] 6'-Phosphates of α-1,3- and 1,6-linked mannose disaccharide glycosides of methyl 9-hydroxynonanoate have likewise been prepared.[58] Triphenylphosphine-di-isopropyl azodicarboxylate treatment of sucrose tetraacetate gave bisphosphinate (23) whose structure was confirmed by ^{31}P and ^{13}C-n.m.r. spectroscopy.[59]

Diglycosyl phosphate derivatives linking arabinose through phosphate to sucrose or fructose, which are derivatives of agrocinopins A and B respectively, have been synthesized by reaction of the free 3-hydroxy groups of the fructose unit with the ethylammonium salt of benzyl 3,4-O-benzylidene-α-L-arabinopyranoside 2-(2-trichloroethyl)-phosphate.[60] Linkage of α-D-glucopyranosyl and α-D-mannopyranosyl phosphates to give (1→6)-linked glycosyl phosphosugars has been achieved using the p-nitrophenyl 6-unsubstituted glycoside with the glycosyl phosphate in the presence of DCC.[61] Terminal 6"-phosphates of α-D-Manp-(1→2)-α-D-Manp-(1→2)-α-D-Man, α-D-Manp-(1→2)-α-D-Manp-(1→3)-α-D-Man, and α-D-Manp-(1→2)-α-D-Manp-(1→6)-α-D-Man, present as end groups on the high mannose oligosaccharide chains of lysosomal enzymes, have been synthesized *via* glycosidation of the 6-diphenylphosphate of 2,3,4-tri-O-acetyl-α-D-mannopyranosyl bromide with the appropriate free hydroxy derivative of the mannose disaccharide.[62]

The synthesis of dolichyl phosphates from a tetrasaccharide obtained from mannosidosis-affected calves is referred to in Chapter 4, and inositol phosphates are covered in Chapter 18. Treatment of inositol 1,4,5-triphosphate with a water soluble carbodiimide gave the 1,2-cyclophosphate-4,5-diphosphate.[63]

4 Sulphonate Esters and Derivatives

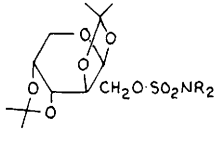
The partial tosylation of methyl α- and β-L-arabinopyranoside has been studied. The order of reactivity was found to be 2>3>4 for the β-glycoside and 3~4>2 for the α-anomer.[64]

Full ^{13}C-n.m.r. data for both pairs of anomers of the tosylates and ditosylates of methyl D-gluco- and -galactopyranosides has been collected.[65] A study of the mechanism of the photolytic deprotection of p-toluenesulphonate esters in basic methanol suggests that the p-toluenesulphonyl radical and the alkoxide of the parent alcohol are formed. Tertiary amine bases were found to be better promoters of the reaction than sodium hydroxide.[66]

Some 3-O-sulphamoyl derivatives of glucofuranose have been prepared by reduction of the corresponding 3-azidosulphates using either sodium borohydride or hydrogen-Adams catalyst.[67]

Selective tosylation of 2,3-O-isopropylidene-β-D-fructopyranose with one equivalent of reagent in pyridine yielded 55% of the 5-tosylate, while the 1,2-O-isopropylidene-analogue gave the 4,5-di-tosylate as the major product. With 2,3-O-isopropylidene-α-L-sorbo-furanose and four equivalents of tosyl chloride the major product (75%) was the 1,6-ditosylate. Similar results were found with mesyl chloride.[68] Methanesulphonate derivatives of 1,2-O-isopropylidene-α-D-glucofuranose have been used as chiral auxiliaries in enantio-selective methylation of glycine-related enolates.[69]

Sulphamate derivatives (24) and (25) of 2,3:4,5-di-O-isopropylidene β-D-fructopyranose have been described. The free sulphamate (24), which shows potent anticonvulsant activity, was found, from n.m.r. and X-ray crystal evidence, to possess a $^{O}_{4}S$ twist boat conformation.[70]



(24) R = H
(25) R = Me

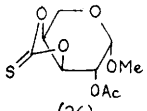
Reference to selective tosylation of methyl 4,6-di-O-benzyl-α-D-mannopyranoside is made above (ref. 25).

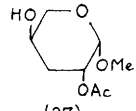
5 Other Esters

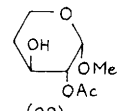
Eluants composed of aqueous borate-polyol combinations, including several mono- and di-saccharide and sugar acid borates, have been studied for use in the anion-exchange chromatography of inorganic anions.[71,72] A study has been made of the increased abilities of a number of polyhydroxycarboxylates to coordinate calcium in aqueous alkaline solution when borate was added.[73]

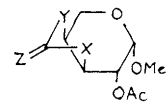
Reaction of 3,4-O-thionocarbonyl-β-L-arabinoside (26) with tri-butyltin hydride (see Vol. 20, p.80) has been investigated in detail. The major expected products (27) and (28) were accompanied by minor amounts of the isomerized products (29) and (30), the cyclic carbonate (31) and the methylidene acetal (32). Excess of the hydride gave (32) as the major product, whereas if air was bubbled into the reaction mixture, the sole product was the carbonate (31).[74] The reaction of thionocarbonates with methyl iodide and 2,3-epoxypropane has been further investigated (see Vol.20, p.80). Usually the product is the corresponding carbonate, but with the 5,6-thionocarbonate (33) the 6-iodo-5-thiomethylcarbonate (34) was obtained.[75]

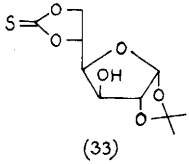
1,2-O-(1-exo-Cyanoethylidene)-β-L-arabinofuranose and 1,2-O-[α-(1-exo-cyano)benzylidene]-β-L-arabinofuranose on storage in chloroform or as syrups form the tricyclic esters (35).[76]

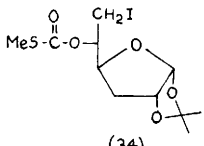

(26)

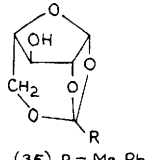

(27)


(28)


(29) X = O, Y = S, Z = O
(30) X = S, Y = Z = O
(31) X = Y = Z = O
(32) X = Y = O, Z = CH_2

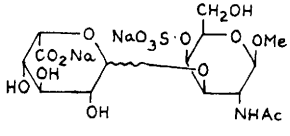

(33)

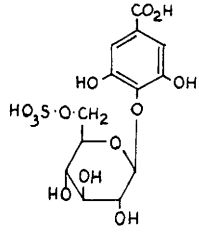

(34)

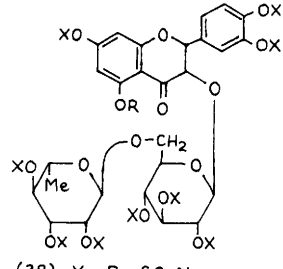

(35) R = Me, Ph

1,2-Migrations of nitrate groups under acid hydrolysis conditions in methyl 4,6-O-ethylidene-β-D-glucopyranoside nitrates has been demonstrated.[77] A kinetic study of the nitration of 1,4:3,6-dianhydro-D-sorbitol has allowed optimization of the exact proportions of 'mixed acid' (88% nitric acid - 12% sulphuric acid) to sugar.[78]

Sulphation of the appropriate blocked monohydroxy disaccharides followed by deprotection has enabled the syntheses of the sodium salts of the 4-sulphates (36).[79] The sulphate (37) has been prepared by treatment of the parent glycoside with sulphur trioxide-pyridine.[80] Sulphation of rutin has led to the deca- and nona-O-sulphates (38) and (39), both of which were shown to be potent inhibitors of the complement part of the immune system.[81]


(36) α or β-linked


(37)


(38) X = R = SO_3Na
(39) X = SO_3Na, R = H

A comprehensive review of the chemical and enzymic syntheses of xenobiotic conjugates has appeared. Emphasis is given to the preparation of sugar sulphate and mercapturic acid pathway conjugates

of S-containing amino acids.[82]

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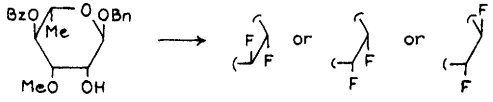
8
Halogeno-sugars

An extensive review on the preparation of biologically active organofluorine compounds has included a useful review of carbohydrate examples.[1] A review of the synthesis of a number of biologically interesting amino-sugars refers to some one-pot regioselective syntheses of chlorodeoxy- and fluorodeoxy sugars.[2]

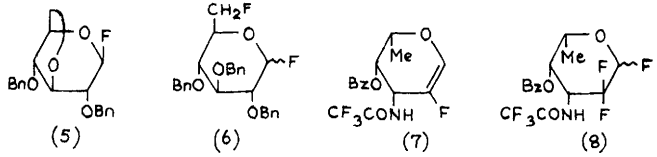
1 Fluoro-sugars

The C-2-fluoro-oleandrosyl fluorides (1) - (3) have been synthesized from the L-rhamnoside (4) by treatment of the appropriate alcohols with DAST. The formation of (2) and (3) was preceeded by an



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

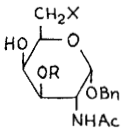
epimerization at C-2.[3] Reaction of 2,3,4-tri-O-benzyl-D-glucose with DAST gave mostly the 3,6-anhydride (5), whereas in the presence of triethylamine the difluoride (6) was the predominant product.[4] Treatment of the fluoroglycal (7) with trifluoroacetyl fluoride



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

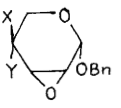
gave the 2,2-difluoroglycosyl fluoride (8) as the major product which suggests that 2,2-difluorodaunosamine should be available by this route.[5] Iodofluorination of glycals using $I^+(collidine)_2BF_4^-$ has given rise to corresponding 2-deoxy-2-iodoglycosyl fluorides.[6]

Treatment of some di- and trisaccharide diols (9) with DAST gave corresponding 6-monodeoxy-monofluoro products (10).[7] Epoxide triflates have been reacted with tetrabutyl ammonium fluoride to give products of fluoride displacement of the triflate in high yield,



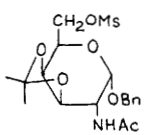
R = Protected mono- and di-saccharides

(9) X = OH
(10) X = F



(11) X = H, Y = OTf
(12) X = F, Y = H

e.g., (11) → (12).[8] Displacement of the mesylate in the galactosamine derivative (13) has been effected with caesium fluoride and the product deprotected to give N-acetyl-2-amino-2,6-dideoxy-6-fluoro-D-galactose (14). Alternatively treatment of the derivative (15) with DAST gave the 6-fluoride and hence (14).[9] DAST was also used to prepare allyl 2-acetamido-2,4-dideoxy-4-fluoro-α-D-galactopyranoside from the corresponding gluco derivative.[10] Methyl 2,3,4-



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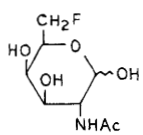

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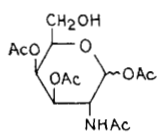

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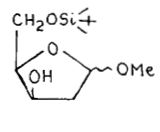

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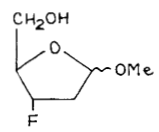
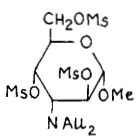


(17)

tri-O-benzyl-6-O-p-toluenesulphonyl-α-D-glucopyranoside was converted into its 6-deoxy-6-fluoro derivative by reaction with potassium fluoride in polyethylene glycol.[11] The 2,3-dideoxy-3-fluoro pentoside (17) has been synthesized by displacement of the triflate ester of alcohol (16) with tetrabutyl ammonium fluoride.[12] Further examples of the use of $Et_3N.3HF$ for the preparation of deoxyfluoro sugars have been described. The trimesylate (18) gave the rearranged fluoro-amino sugar (19) by way of an aziridinium intermediate, epoxytriflate (20) gave the product (21) of displacement of the sulphonate ester only, and 1,2:5,6-di-O-isopropylidene-3-O-trifluoromethanesulphonyl-α-D-allofuranose yielded the corresponding



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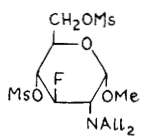

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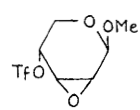

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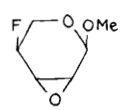
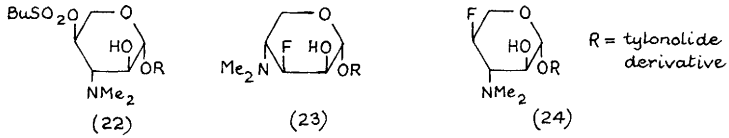


(21)

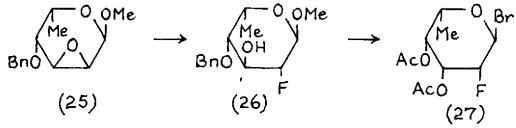
3-deoxy-3-fluoro-glucofuranose derivative.[13] Other deoxyfluoro sugar derivatives have been prepared by reaction of tris(dimethylamino)sulphonium difluorotrimethylsilicate on triflate esters with inversion of configuration.[14] Displacement of amino-sugar sulphonate ester (22) with KHF_2 gave the rearranged fluoro-amino

sugar (23) when the reaction was conducted in DMF, but the unrearranged product (24) with retained configuration in ethylene glycol - presumably via the same aziridinium intermediate.[15]



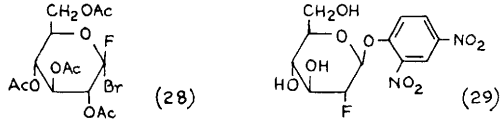
(22) (23) (24)

Epoxide (25), derived from L-fucose, was opened with KHF_2 in ethylene glycol to give the 2-fluoro sugar (26) which was converted to the talo-isomer (27) and coupled with daunomycinone to give an



(25) (26) (27)

anthracycline analogue showing anti-tumour activity.[16] The reaction of acetyl hypofluorite with a number of glycals has been investigated. Furanoid glycals underwent stereospecific reactions to give the 2-deoxy-2-fluoro-glycosyl acetate. A benzyloxy group at C-3 encouraged addition from the opposite side of the double bond, whereas the unsubstituted hydroxy group induced addition from the same side. Mixtures were obtained with pentopyranose glycals.[17] Photobromination of tetra-O-acetyl-β-D-glucopyranosyl fluoride gave mostly the 1,1-dihalide (28).[18] The 2-deoxy-2-fluoro-glucoside (29) is a powerful inhibitor of β-glucosidases. It was postulated that the glycoside (29) glycosylates the enzyme to give a glycoside which is only very slowly hydrolysed, due to the electron withdrawing fluorine substituent.[19] The synthesis and n.m.r. spectra of methyl



(28) (29)

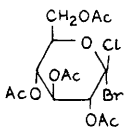
2-deoxy-2-fluoro-α and β-D-glucopyranosides and methyl 3-deoxy-3-fluoro-α- and β-D-glucopyranosides have been reported.[20] The enzymatic interconversion of 2-deoxy-2-fluoro-D-glucose or its 6-phosphate with 2-deoxy-2-fluoro-D-mannose or its 6-phosphate has been observed in vivo and in vitro.[21]

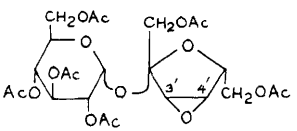
An autosynthesizer for the production of 2-deoxy-2-fluoro-18-D-glucose has been described.[22] The reaction of labelled acetyl

hypofluorite with tri-O-acetyl-D-glucal,[23,24] and with tri-O-acetyl-D-galactal[25] to give, after acid hydrolysis, the corresponding labelled 2-deoxy-2-fluoro-hexoses has been reported. The contamination of 2-deoxy-2-^{18}F-D-mannose in the corresponding D-glucose derivative prepared from the reaction of labelled acetyl hypofluorite with tri-O-acetyl-D-glucal has been investigated.[26] The nucleophilic displacement of sulphonyloxy groups with labelled fluoride ions has been used to synthesize labelled 2-deoxy-2-fluoro-D-glucose,[27,28] 3-deoxy-3-fluoro-D-glucose,[29,30] and 2-deoxy-2-fluoro-D-mannose.[31]

2 Chloro-, Bromo-, and Iodo-sugars

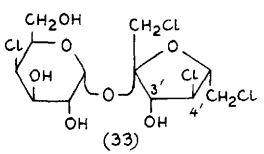
The photobromination of tetra-O-acetyl-β-D-glucopyranosyl chloride gives mainly the α-bromo product (30), with the bromine axial.[18] The sucrose epoxide derivatives (31) and (32) with chloride or bromide ions gave corresponding C-4' halo sugars.[32] An intensely

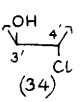

(30)


(31)

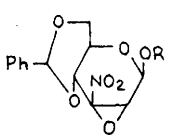

(32)

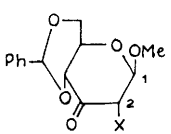
sweet tetra-chloro-tetra-deoxy sucrose derivative (33) was obtained along with its regioisomer (34) from the reaction of 6-O-acetyl-sucrose with sulphuryl chloride after conventional isolation procedures.[33] Nucleophilic opening of the α-nitroepoxide (35) gave


(33)


(34)

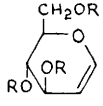
the α-halogeno ketones (36) via an epimerization at C-2 of the initially formed product. Corresponding reaction of the phenyl analogue (37) was always accompanied by elimination to give the enones (38).[34]


(35) R = Me
(37) R = Ph

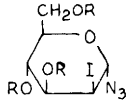

(36) X = Br, Cl, I


(38)

Addition of iodine azide to the D-glucal derivatives (39) gave mostly 2-deoxy-2-iodo-glycosyl azides (40) derived from trans-diaxial addition to the double bond. D-galactal and D-xylal derivatives

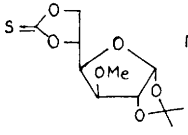


(39) R = Ac, Bn, MOM

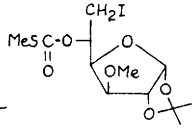


(40)

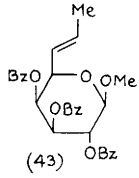
reacted similarly although the D-xylal reaction was less stereoselective.[35] Chlorination of 4,6-O-benzylidene derivatives of D-glucal gave predominantly the 2-chloro-2-deoxy mannosyl chloride, whereas previous work with acetyl or benzyl protected derivatives gave mostly compounds with D-gluco stereochemistry.[36] Treatment of cyclic thiocarbonates with methyl iodide has received further attention (see Vol.20, p.89). In the presence of propylene oxide, some thiocarbonates gave the corresponding carbonates, whereas the furanose (41) with a primary site especially prone to nucleophilic attack afforded (42).[37] The identity of the product of addition of



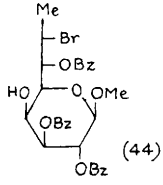
(41)



(42)

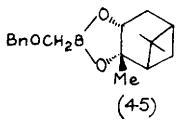


(43)

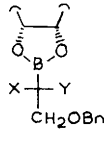


(44)

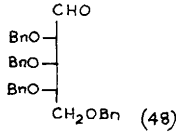
hypobromous acid (NBS, H_2O, HOAc) to alkene (43) has been revised and now shown to be (44).[38] Reaction of organoboron derivative (45) with dibromomethyl lithium gave (46) with high stereoselectivity. Displacement of the bromine with lithium benzyloxide gave (47) on which the sequence could be repeated to build up a carbohydrate of defined stereochemistry such as L-ribose derivative (48).[39]



(45)



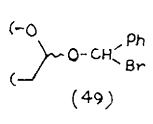
(46) X = H, Y = Br
(47) X = OBn, Y = H



(48)

The synthesis of methyl (2,3,4-tri-O-acetyl-α-D-glucopyranosyl bromide) uronate from tri-O-acetyl-1,6-anhydro-β-D-glucopyranose by standard methods has been described.[40] The conversion of benzyl glycosides into glycosyl bromides by photobromination has been achieved. The initial product (49) of photobromination rearranges

quickly in the presence of HMPA to the glycosyl bromide.[41] Use of a 3-bromo-3-deoxy-ketosyl bromide in glycoside synthesis is mentioned in chapter 3. The conversion of methyl glycosides into glycosyl chlorides using boron trichloride has been studied and benzyl ethers, acetyl groups and other glycosyl linkages are listed as compatable with the reagent.[42] A study on the formation of 6-deoxy-6-iodohexopyranosides has been done in order to find methods for the selective iodination of certain primary hydroxy groups in polysaccharides.[43] Some 6-O-tosyl glycosyl azides have been treated with LiX (X=Cl,Br,I) in HMPA to give the corresponding 6-deoxy-6-halo-glycosyl azides.[44] The 2-O-triflates (50) and (51) undergo displacement with inversion with Cl^-, Br^- or I^- in good yield.[45] The successive chain extension of D-xylopyranosyl derived bromides via free radicals



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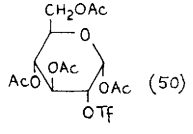

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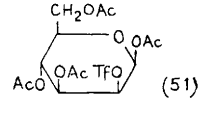

(51)

generated at C-1 and C-5 is mentioned in chapter 3. A non-hydrolytic glycoside cleavage method involving an NBS-initiated oxidative addition of the ring oxygen to a remote olefinic centre is covered in chapter 3.

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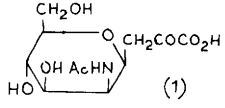
9
Amino-sugars

1 Natural Products

Galactostatin (5-amino-5-deoxy-D-galactopyranose), the galacto-isomer of nojirimycin, has been isolated as a *Streptomyces lydicus* fermentation product and shown to be a β-galactosidase inhibitor.[1] 4,8-Anhydro-*N*-acetyl-neuraminic acid (1) has been isolated from edible birds' nest and shown to exist in 2 tautomeric forms in solution.[2]



(1)

2 Synthesis

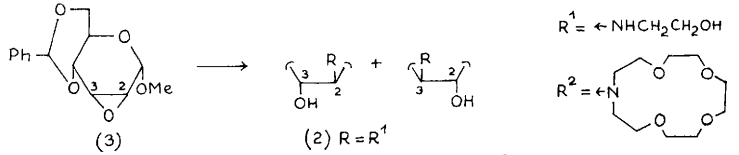
Reviews on the syntheses of a number of biologically interesting amino-sugars,[3] and on the synthesis and chemistry of monosaccharide isothiocyanates,[4] have appeared.

Syntheses covered in this section have been grouped according to the method used for introducing the amine functionality.

The aminonitrile synthesis, in which a free sugar reacts with a primary amine and hydrogen cyanide, has been used to extend the chain of D-galactose, D-glucose, and D-allose into isomeric 2-amino-2-deoxy-heptoses, and thence by reaction with aryl isothiocyanates into (glycoheptofurano)imidazolidine-2-thione derivatives.[5,6] The Maillard browning reaction between glucose and aspartame yielded *N*-(1-deoxy-D-fructos-1-yl) derivatives of aspartame, phenylalanine methyl ester, aspartic acid, and phenylalanine that were identified by FAB-m.s.[7]

The 2-amino-2-deoxy-altrose derivative (2) was the sole product, isolated in 71% yield, from diaxial ring opening of the *allo*-epoxide (3) with ethanolamine, whereas in the synthesis of chiral crown ethers the bulkier *N*-nucleophile gave a mixture of 2- and 3-amino-products (4) and (5), in 31 and 27% yield, respectively.[8] The

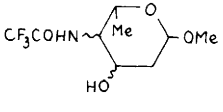
combination of N,N-dimethyl- or diethyl-trimethylsilylamine with aluminium trichloride as catalyst has been promoted for the synthesis



(3) (2) R = R^1 (4) R = R^2 (5) R = R^2

Scheme 1

of N,N-dialkylamino-sugars by trans-diaxial ring opening of epoxides. The reaction apparently gives an aminosilane salt which hydrolyses on work-up. Yields were in the 41-53% range, the remainder being mainly unreacted epoxide, although only the use of equimolar amounts of epoxide and reagent were reported.[9] The four diastereomeric 4-amino-2,4,6-trideoxy-L-hexopyranosides (6) have been synthesized from the epimeric diols (7) and (8) by conventional epoxide formation and opening, and sulphonate displacement (by azide or acetate) reactions, and used for glycosylation of daunomycinone to produce the new anthracyclinone (9) and its C-4 epimer.[10] Both epimeric sucrose epoxides (10) were opened by attack of azide ion at C-4',



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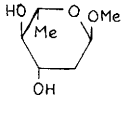

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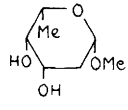

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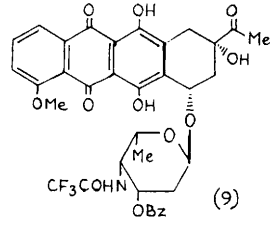
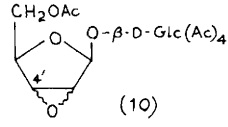


(9)

the products being converted into 4'-amino-sucrose analogues.[11]

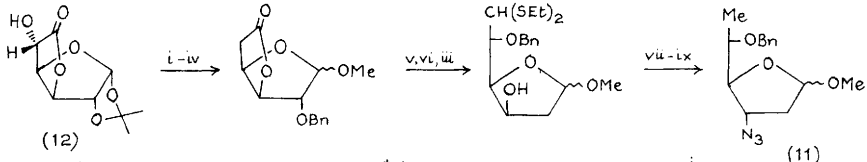


(10)

Displacement of a sulphonyloxy group with a nitrogen nucleophile has been employed in several amino-sugar syntheses. 3-Azido-furanoside (11), which can be converted to L-daunosamine by standard reduction and hydrolysis procedures, was obtained in 10 steps from the D-glucuronolactone derivative (12) as detailed in Scheme 2.[12] 1,6-Anhydro-2-azido- and -2-phthalimido-2-deoxy-β-D-galactopyranoses required for disaccharide construction (see Chapter 3), were

synthesized from 1,6-anhydro-3,4-O-isopropylidene-β-D-galactopyranose in five steps: oxidation, reduction, triflation, displacement with azide or phthalimide ion, and deacetonation.[13] Fleet and Smith have published full details on their syntheses of 2,5-dideoxy-2,5-imino-D-mannitol (Vol.19, p.169) and the piperidine precursor 2,6-imino-mannofuranoside (13) from diacetoneglucose *via* the common intermediate azide (14) (Scheme 3). While azide (14) was obtained in 75% yield from triflate (15), the β-anomer of (15) did not undergo clean displacement.[14] A 3-azido-3,6-dideoxy-D-glucoside derivative has been obtained from the corresponding 3-O-triflyl-D-alloside, and used in the synthesis of amphotericin B, which has a 3-amino-3,6-dideoxy-β-D-mannopyranoside unit.[15] Eight N-(D-galactopyranos-6-yl)amino acids were obtained by reaction of standard amino acid esters with 1,2:3,4-di-O-isopropylidene-6-O-triflyl-α-D-galactopyranose.[16]

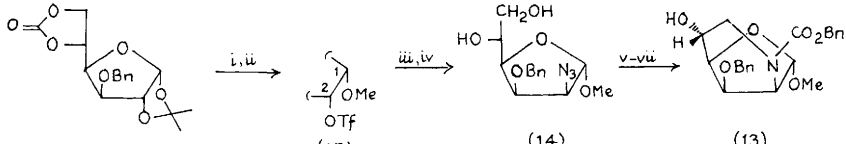
In the synthesis of N-linked dipeptide derivatives, *e.g.* (16), of 8-amino-2,6-anhydro-3,8-dideoxy-D-*glycero*-D-*talo*-octonic acid methyl ester (17), which are novel antibacterial agents which interfere with lipopolysaccharide biosynthesis, the 8-amino function was selectively introduced into the tetraol (18) using the Ph_3P-CBr_4-LiN_3 reagent system.[17]



(12) (11)

Reagents: i, SO_2Cl_2-Py; ii, Bu_3SnH; iii, MeOH-H^+; iv, BnBr-Ag_2O; v, EtSH-HCl; vi, Bu^i_2AlH; vii, Raney Ni; viii, MsCl-Py; ix, NaN_3-DMF

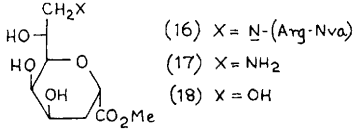
Scheme 2



(15) (14) (13)

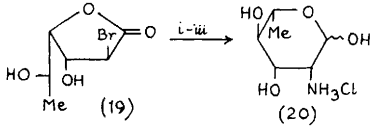
Reagents: i, MeOH-H^+; ii, Tf_2O-Py; iii, NaN_3-DMF; iv, MeONa-MeOH; v, TsCl-Py; vi, NaOAc; vii, DbzCl-$NaHCO_3$

Scheme 3



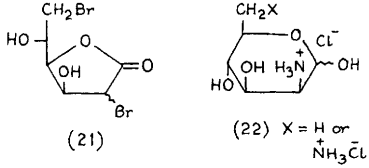
(16) X = N-(Arg-Nva)
(17) X = NH_2
(18) X = OH

In the synthesis of 3-acetamido-3,6-dideoxy-1,2-O-isopropylidene-α-D-xylo-hexofuranos-5-ulose (see Chapter 15), introduction of the 3-amino-function involved a double inversion process (OMs → I → N_3).[18] Amino-sugars have also be obtained from bromodeoxylactones. Thus 2-bromide (19) derived from L-rhamnonolactone yielded 2-amino-2,6-dideoxy-L-mannose (20), while 2,6-dibromide (21) with either the D-gluco- or the D-manno- configuration could be similarly converted into either the 2-amino-2,6-dideoxy- or 2,6-diamino-2,6-dideoxy-D-mannoses (22).[19]



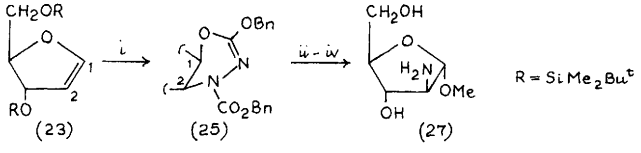
Reagents: i, NaN_3-DMF; ii, $NaBH_4$; iii, H_2-Pd/C.

Scheme 4



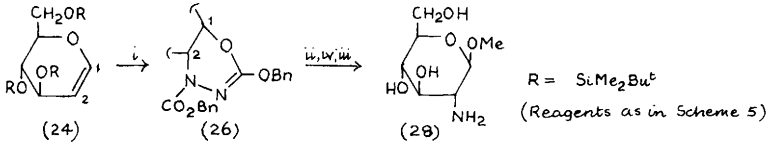
4-Amino-4-deoxy-ketopyranosides and their 4-C-methyl analogues have been obtained by condensation of the periodate cleavage products of D-fructopyranose derivatives with nitromethane or nitroethane respectively, and hydrogenation of the resulting C-nitro derivatives (see Chapter 10, section 3).[20]

A new method for the preparation of 2-amino-2-deoxy-glycosides involved the cycloaddition of dibenzyl azodicarboxylate to glycals. Furanoid and pyranoid glycals, (23) and (24), gave single cycloadducts (25) and (26) which methanolysed with inversion at C-1 to provide glycosides (27) and (28), respectively (Schemes 5 and 6).[21]



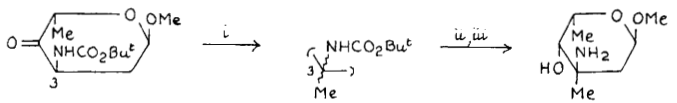
Reagents: i, $BnO_2C{\cdot}N{=}N{\cdot}CO_2Bn$ - hν (350nm); ii, MeOH-H^+; iii, Bu_4NF; iv, H_2-Raney Ni

Scheme 5



Scheme 6

Azidonitration has been used to convert 6-deoxy-L-fucal into 2-acetamido-2,6-dideoxy-L-galactose (N-acetyl-L-fucosamine),[21a] and (6S)-6-$^{2}H_{1}$-D-glucal triacetate (prepared from labelled D-glucose, c.f., Vol.20, p.59) into (6S)-(6-$^{2}H_{1}$)-2-acetamido-2-deoxy-D-glucose, the latter being used in a study of the rotamer population about the C-5/C-6 bond.[22] The methyl glycoside (29) of the antibiotic component 3-amino-2,3,6-trideoxy-3-C-methyl-L-xylo-hexose, its C-3 epimer L-vancosamine, and its C-4 epimer (an amino-precursor of the nitro-sugar L-decilanitrose), were obtained from the 4-uloside (30) by α-alkylation to yield a separable mixture of C-3 epimers (31) followed by selective reduction of the ketone, L-selectride or sodium borohydride providing products with an axial or equatorial hydroxy-group, respectively (Scheme 7). The starting ketone (30) was prepared by oxidation of a known alcohol (c.f., Vol.17, p.93).

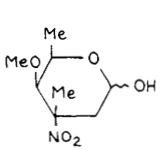


(30) (31) (29)

Reagents: i, MeI-KOBu^{t}-DMF; ii, L-Selectride; iii, MeOH-HCl

Scheme 7

Using similar methodology, D-rubranitrose (32) was synthesized from methyl 4,6-O-benzylidene-2-deoxy-α-D-ribo-hexopyranosid-3-ulose oxime.[23] Addition of ammonia to an unsaturated sulphone yielded, after acetylation, the 3-acetamido-derivative (33).[24]



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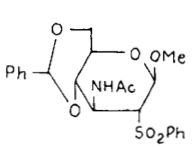

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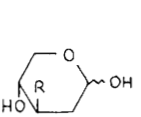
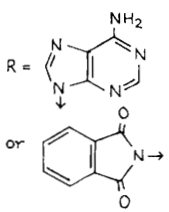
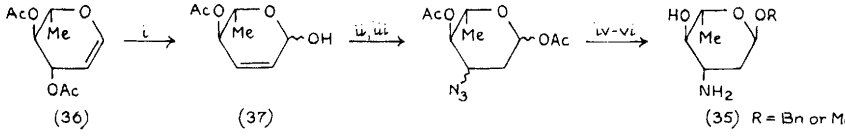


(34)



Further investigations have been reported on the synthesis and the O- and N-glycosidation of anomalously linked nucleosides of structure (34) formed by condensation of adenine derivatives or phthalimide with 2-deoxy-D-ribose presumably via an enal intermediate (c.f., Vol.20, p.95).[25-28] Benzyl and methyl acosaminide (35) has been obtained in 35% overall yield from L-rhamnal diacetate (36) by conjugate addition of hydrazoic acid to the masked enal (37) and mild glycosidation, followed by chromatographic separation from a 4 component mixture of the major α-L-arabino-isomer (Scheme 8).[29]

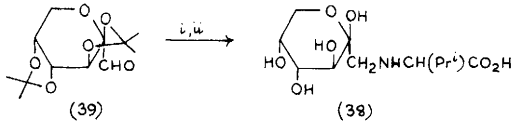


(36) (37) (35) R = Bn or Me

Reagents: i, H_2O (80°C); ii, NaN_3-HOAc-H_2O; iii, Py-Ac_2O; iv, ROH-K_{10} montmorillonite; v, NaOMe-MeOH; vi, H_2-Pd/C-Et_3N

Scheme 8

An effective synthesis of N-(1-deoxy-D-fructos-1-yl)amino acids, e.g., the product (38) that would be produced in the Maillard reaction of L-valine with D-glucose, involved reductive amination with the D-fructose derived aldehyde (39) (Scheme 9).[30] Methyl

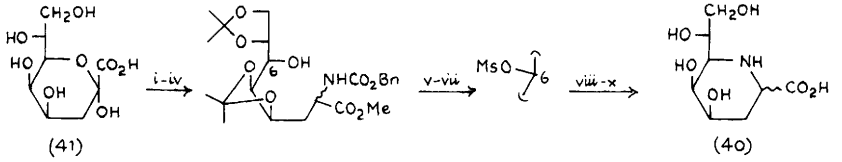


(39) (38)

Reagents: i, L-Valine-$NaBH_3CN$; ii, Resin(H^+)-H_2O

Scheme 9

O-(2-acetamido-3,4,6-tri-O-acetyl-2-dexoy-α-D-gluco- and manno-pyranosyl)-L-serinates have been obtained by reduction (H_2-Pd/C) of the sugar oxime precursors. Reaction of these 2-oxime derivatives with sodium azide served to replace their 3-acetoxy-group to generate an epimeric mixture of 3-azides.[31] Azacyclic 2-deoxy-KDO analogues (40) have been synthesized in a 2:1 β:α-ratio from KDO (3-deoxy-D-manno-octulosonic acid, 41), the nitrogen function being introduced by reductive amination (Scheme 10), but they proved to be



(41) (40)

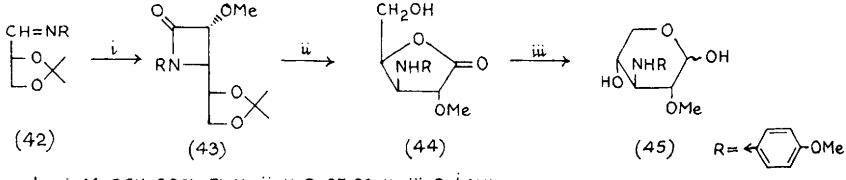
Reagents: i, Me_2CO-H^+; ii, $NaBH_3CN$-NH_4OAc-MeOH; iii, BnOCOCl; iv, CH_2N_2; v, $(COCl)_2$-DMSO-Et_3N; vi, $NaBH_4$; vii, MsCl-Et_3N; viii, Pd-⬡; ix, Pr^i_2NEt; x, H^+

Scheme 10

poor inhibitors of CMP-KDO synthetase [c.f., compounds (16) and (17) in this chapter which were potent inhibitors]. A noteworthy feature of this synthesis was the high stereoselectivity (>95% inversion at C-6) of the oxidation-reduction sequence (steps v and vi).[32] Full details on the synthesis of L-sibirosaminide from L-rhamnose

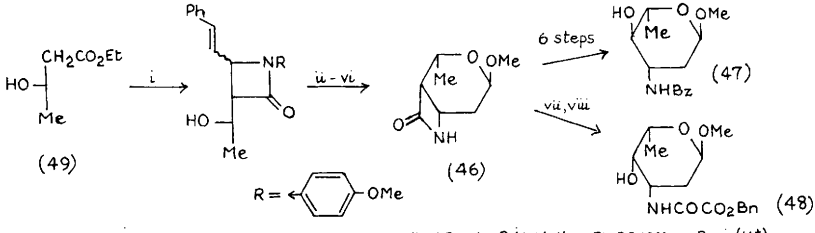
(*c.f.*, Vol.19, p.90) have been published, and a synthesis of the related *N*-acyl-kanosamine included.[33] A 6-[(2-pyridyl)amino]-6-deoxy-substituted gluco-pentasaccharide has been synthesized as an α-amylase substrate by reductive amination of an 6-aldehydo-sugar.[34]

The synthesis of amino-sugars from chiral non-carbohydrate starting materials continues to be a popular area of work. Three groups have employed β-lactam intermediates. Condensation of the D-glyceraldehyde Schiff base adduct (42) with methoxyacetyl chloride gave β-lactam (43) which isomerized in acid to the lactone (44) which yielded the 3-amino-pentose (45) on reduction (Scheme 11).[35] The synthesis of 2,3-dideoxy-2-amino-3-*C*-hydroxymethyl-α-D-manno-furanoside and related 3-*C*-branched amino sugars *via* a β-lactam is covered in Chapter 14. The fused β-lactam (46) was a common intermediate in the synthesis of L-acosamine precursor (47) and L-daunosamine derivative (48) from ethyl (S)-3-hydroxybutanoate (49) (Scheme 12), both conversions employing an oxidative decarboxylation step (reagent viii).[36]



Reagents: i, $MeOCH_2COCl$-Et_3N ; ii, H_2O-CF_3CO_2H ; iii, Bu^i_2AlH

Scheme 11

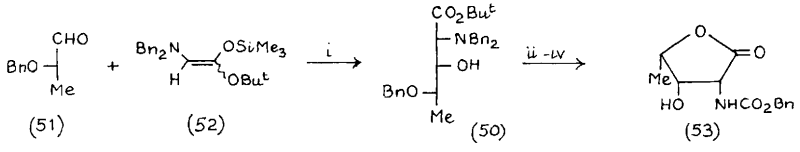


Reagents: i, Pr^i_2NLi - Ph⌒NR ; ii, O_3, then Me_2S ; iii, DBU ; iv, Pr^i_2NLi, then $Ph_3PCHOMe$; v, Resin(H^+); vi, Ceric ammonium nitrate ; vii, BnOCOCOCl ; viii, MCPBA- $Na_2H_2PO_4$ - $(HO\text{-}C_6H_4\text{-}S)_2$

Scheme 12

Ethyl (S)-lactate has been the primary source of chirality in three amino-sugar syntheses. 2-Amino-2-deoxy-L-lyxonate (50) was almost the exclusive diastereomer formed when magnesium bromide was employed as the Lewis acid catalyst for the aldol condensation of L-lactaldehyde derivative (51) with silyl ketene acetal (52)

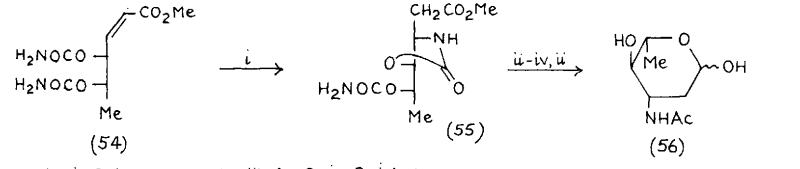
(Scheme 13) although it was only isolated in 40% yield (c.f., lower selectivity attained with similar reactions earlier; G.Guanti et al., Tetrahedron Lett., 1985, 3517). Ester (50) was converted to lactone (53), a known intermediate for the synthesis of L-daunosamine and L-vancosamine (Vol.18, p.94).[37] The cis-3,4-dihydroxy-



Reagents: i, $MgBr_2$-CH_2Cl_2, -40°C ; ii, H_2-Pd/C ; iii, BnO_2CCl-$NaHCO_3$; iv, CF_3CO_2H

Scheme 13

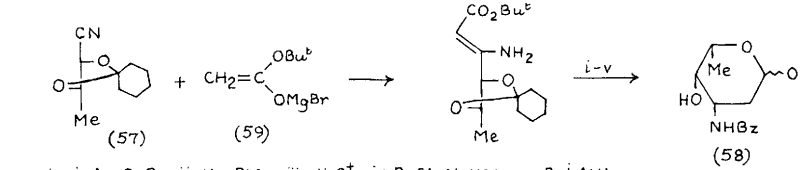
hex-2-enoate (54), derived from an L-lactaldehyde derivative in 4 steps including the non-chelation controlled addition of methyl propiolate anion (c.f., Vol.20, p.97), underwent intramolecular Michael addition of the carbamate group, the product (55) being converted to N-acetyl-L-acosamine (56) (Scheme 14). A related synthesis of the 3-epimeric N-benzoyl-L-ristosamine was also reported.[38] The (2S , 3S)-nitrile (57), available from ethyl (S)-



Reagents: i, Bu^{t}OK ; ii, NaOH ; iii, Ac_2O ; iv, Bu^i_2AlH

Scheme 14

lactate or dimethyl L-tartrate, has been elaborated to N-benzoyl-L-daunosamine (58) in 41% overall yield, the additional two carbon atoms being added via the magnesium enolate (59) (Scheme 15). The



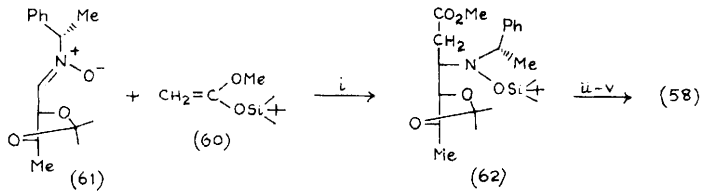
Reagents: i, Ac_2O-Py; ii, H_2-PtO_2 ; iii, H_3O^+ ; iv, BzCl-$NaHCO_3$; v, Bu^i_2AlH

Scheme 15

(2R,3S)-isomer of nitrile (57) was similarly elaborated to N-benzoyl-L-acosamine [the C-4 epimer of (58)] in 25% overall yield.[39]

Another synthesis of N-benzoyl-L-daunosamine (58) employed the

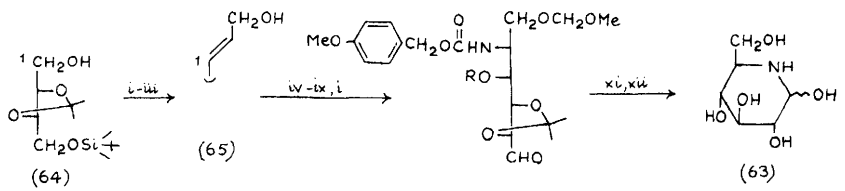
addition - rearrangement (with silyl group transfer) of ketene silyl acetal (60) with the chiral nitrone (61) derived in 8 steps from diethyl L-tartrate, the adduct (62) being obtained stereospecifically (Scheme 16).[40]



Reagents: i, ZnI_2 ; ii, H_2-Pd/C-HOAc ; iii, BzCl-Py ; iv, HOAc-H_2O ; v, Bu^i_2AlH

Scheme 16

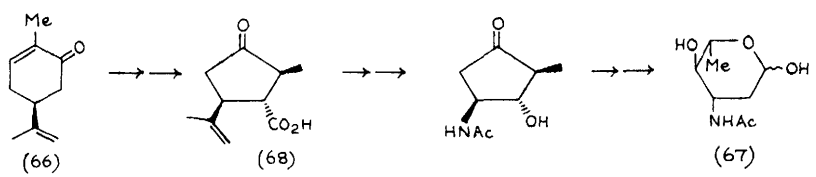
Nojirimycin (63) and 1-deoxynojirimycin have been synthesized from diethyl L-tartrate via tetritol (64). Wittig chain extension gave C_6-alkene (65), which was functionalized by Sharpless epoxidation (Scheme 17).[41]



Reagents: i, $(COCl)_2$-DMSO-NEt_3 ; ii, $Ph_3P{=}CHCO_2Et$; iii, Bu^i_2AlH ; iv, $Ti(OPr^i)_4$-Bu^tO_2H-diethyl tartrate ; v, NaN_3; vi, $MeOCH_2Cl$; vii, H_2-Pd/C ; viii, $MeOC_6H_4CH_2O_2CS$(4,6-dimethylpyrimidin-2-yl) ; ix, Bu_4NF ; x, H_2O-H_2SO_3 ; xi, Resin (OH^-)

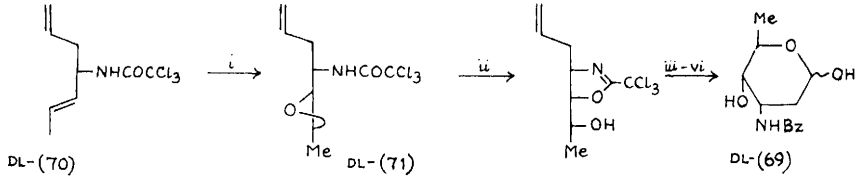
Scheme 17

(S)-Carvone (66) served as a novel source of chirality in a lengthy formal synthesis of N-acetyl-L-acosamine (67) via the cyclopentanone derivative (68) and involving a Beckmann rearrangement and two Baeyer-Villiger oxidations (Scheme 18).[42]



Scheme 18

In the preparation of racemic N-benzoyl-ristosamine (69) from the amino-diene (70), the initial epoxidation was only moderately stereoselective, providing the desired threo-epoxide (71) along with its erythro-isomer and diepoxide in 42, 12, and 10% yields

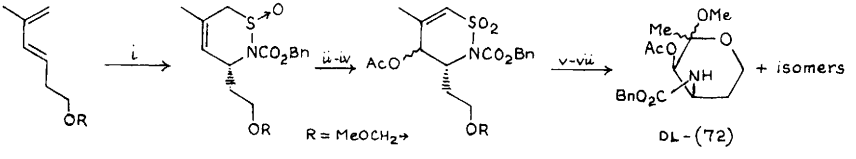


Reagents: i, MCPBA; ii, Resin(CO_3^{2-})-MeOH; iii, H_3O^+; iv, BzCl-$NaHCO_3$; v, O_3; vi, Me_2S

Scheme 19

respectively (Scheme 19).[43]

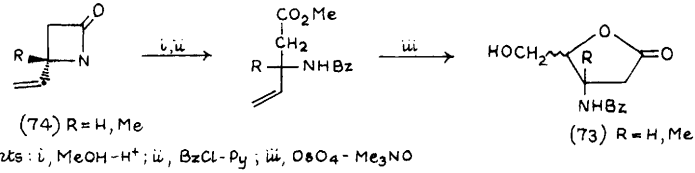
An N-sulphinyl Diels-Alder approach has been employed in the synthesis of racemic precursors for the aminohexose moieties of the Streptomyces product staurosporine and nogalorol, as exemplified for the amino-hexulose (72) (Scheme 20).[44,45]



Reagents: i, BnO_2CNSO; ii, CF_3CO_3H; iii, KH; iv, AcCl; v, O_3; vi, Me_2S; vii, H^+

Scheme 20

The epimeric mixture of racemic 3-amino-2,3-dideoxy-pentonolactones (73, R=H) and their 3-C-methyl analogues (73, R=Me) have been obtained from azetidinones (74), R=H or Me respectively, which are readily available by cycloaddition of the appropriate diene with chlorosulphonyl isocyanate (Scheme 21).[46] For a further synthesis of a racemic amino-sugar, see Scheme 27.



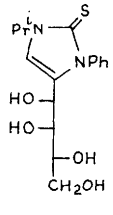
Reagents: i, MeOH-H^+; ii, BzCl-Py; iii, OsO_4-Me_3NO

Scheme 21

3 Reactions

Kinetic studies have been reported on the hydrolysis of the Schiff bases formed from 2-amino-2-deoxy-D-glucose and substituted benzaldehydes,[47] and the geometric isomerization of the Schiff bases

formed between 2-amino-2-deoxy-D-glucose, -galactose and -mannose and 4-hydroxybenzaldehyde.[48] The reaction of 1-deoxy-1-propylamino-D-lyxo-hexulose with phenyl isothiocyanate in methanol gave a complex mixture of compounds from which the heterocyclic derivatives (75) and (76) were isolated.[49]



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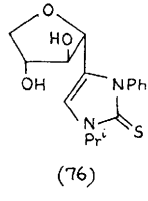
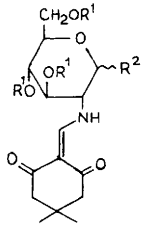


(76)



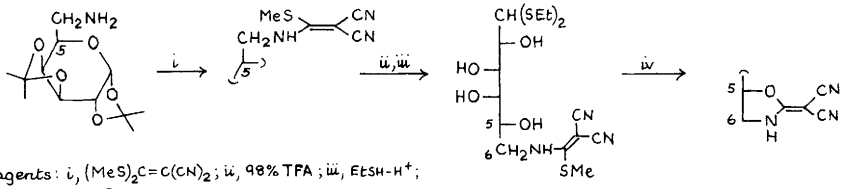
(77) $R^1 = H$, $R^2 = OH$

(78) $R^1 = Ac$, $R^2 = \alpha$-Br

The N-(2,2-diacylvinyl)-protected derivative (77) was readily obtained from 2-amino-2-deoxy-D-glucose, and yielded mixtures of the corresponding pyranosides and furanosides on Fischer glycosidation. N-Deprotection could be effected under mild conditions (Resin-OH^- in H_2O-Me_2CO).[50] The related bromide (78), a reasonably stable crystalline solid, has been used as a donor in Koenigs-Knorr glycosidation reactions to give 1,2-trans-glycosides in good yields, which could be N-deprotected with chlorine in chloroform or by basic hydrolysis.[51] 1,2-trans-Glycosides were also available using 2-N-allyloxycarbonyl derivatives of 2-amino-2-deoxy-D-glucosyl bromides or acetates, the N-protecting group being easily removed with palladium (0) complexes.[52] Results from the synthesis and binding to isolated rat hepatocytes of a variety of N-acylated 2-amino-2-deoxy-β-D-glucopyranosides and mono- and di-O-methyl ethers of allyl 2-acetamido-2-deoxy-β-D-galactopyranoside and allyl 2-acetamido-2,4-dideoxy-2-fluoro-α-D-galactopyranoside suggested that the 2-, 3- and 4- but not 6-hydroxy-group was involved in the binding.[53] A four stage synthesis of p-nitrophenyl 2-acetamido-2-deoxy-β-D-glucopyranoside from 2-amino-2-deoxy-D-glucose hydrochloride has been reported.[54] Syntheses of O- and C-glycosides of other amino-sugars are covered in Chapter 3.

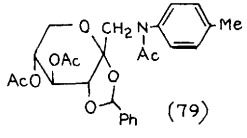
Methyl 2-amino-2,4-dideoxy-β-D- and L-threo-pentopyranosides have been resolved by chromatographic separation of diastereomeric esters, and their absolute configurations determined.[55]

Derivatives of 6-amino-6-deoxy-D-galactose have been prepared as shown in Scheme 22, and by another route.[56] Benzylidenation of 1-deoxy-1-p-toluidino-D-fructose (PhCHO in EtOH) followed by acetylation yield the 2,3-acetal (79).[57]



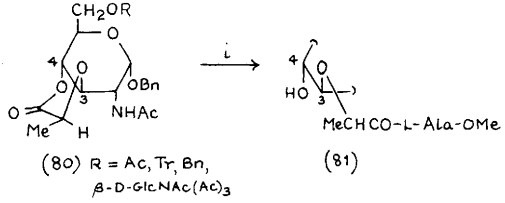
Reagents: i, $(MeS)_2C{=}C(CN)_2$; ii, 98% TFA; iii, EtSH-H^+; iv, Et_3N-PhMe

Scheme 22



(79)

The synthesis and biological activity of MDP(N-acetyl-muramoyl-L-alanyl-D-isoglutamine) and bacterial lipid A analogues continue to attract considerable attention. Aminolysis of lactones (80) has been used to prepare muramoylamides (81) (Scheme 23).[58] The



(80) R = Ac, Tr, Bn, β-D-GlcNAc(Ac)$_3$

(81)

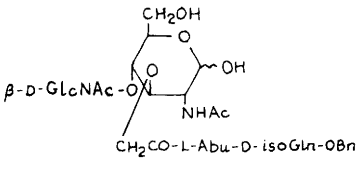
Reagents: i, H-Ala-OMe - Imidazole - $(C_6H_{13})_4\overset{+}{N}\bar{O}Bz$

Scheme 23

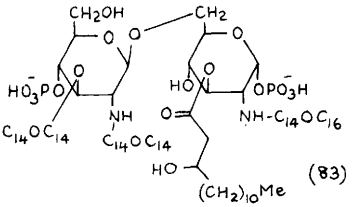
disaccharide analogue (82), with a modified 3-substituent containing an α-aminobutanoyl moiety (L-Abu) replacing the L-alanyl moiety, has been synthesized by standard means. It was 3-4 times more active as an immunoadjuvant than MDP itself and less pyrogenic.[59] The synthesis of a 2-benzamido-5,6-epithio-D-glucofuranoside analogue of MDP is covered in Chapter 11, while conformational studies on two MDP derivatives are reported in Chapter 21.

Lipid A, its relatives lipid X and Y, and their analogues are esterified 2-amino-2-deoxy-D-glucopyranose derivatives, as exemplified by the recently synthesized Proteus mirabilis lipid A (83).[60] Novel synthetic aspects generally involve protecting group manipulations and carboxylic and phosphoric ester forming procedures; further details may be found in Chapter 7. The majority of publications have come from the groups of Achiwa (mostly full disclosures of preliminary communications, see Vols 19 and 20)[60-64]

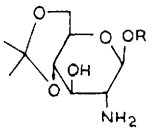
and Hasegawa,[65-69] who employed the related amines (84) and (85), respectively, as key intermediates that could be variously acylated at N-2 then O-3, and then phosphorylated at O-4. Further elaboration involved glycosylation at O-6 (as with KDO[67]), or conversion to



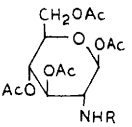
(82)



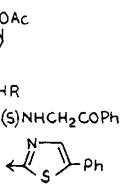
(83)



(84) R = Allyl
(85) R = Bn



(86) R = C(S)NHCH2COPh
(87) R =



(88) X = NH_2
(89) X = NCS
(90) X = $NHC(S)NEt_2$

1-thio- or 1-O-phosphono-analogues.[68] The synthesis of a 1-C-phosphonate analogue of lipid X is covered in Chapter 17.

Phenacylthiourea derivatives, e.g., (86), have been prepared from 2-amino-2-deoxy-D-glucose and cyclized to N-thiazolyl derivatives, e.g., (87).[70] Similarly the 2-amino-2-deoxy-D-glycero-α-L-gluco-heptopyranose derivative (88) has been converted (with $CSCl_2$) to isothiocyanate (89) and thence to various thiourea derivatives, e.g., (90).[71] The reaction of 2-alkylamino-2-deoxy-D-glucose with isothiocyanates is covered in Chapter 10.

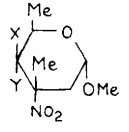
Two new reagents for reducing azides to amines have been applied to some carbohydrate examples: $[Et_3NH][Sn(SPh)_3]$ is the fastest reductant for azides yet reported, while Bu_2SnH_2 is compatible with water and carbonyl functionality.[72]

The ^1H- and ^{13}C-n.m.r. spectra of methyl 2-acetamido-2-deoxy-D-galacto- and D-gluco-pyranosides in the presence of lanthanide ions suggested preferential complexation with the N-acetyl group, the result having relevance to understanding the binding of calcium (II) ions to polysaccharides containing acetamido-sugar units.[73]

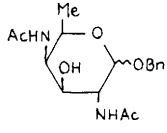
4 Di- and Tri-amino-sugars

Methyl 2,4-diacetamido-2,4,6-trideoxy-α-D-ido-, -α-D-talo-, -α-D-altro-, and -α-D-manno-pyranosides have been synthesized from methyl

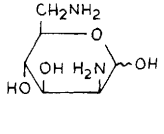
2-O-acetyl-3,4-anhydro-6-deoxy-α-D-galactopyranoside by standard procedures, particularly azide opening of epoxides and mesylate displacement reactions.[74] Methyl α-D-kijanoside (91) has been synthesized from nitro-alcohol (92) (c.f., Vol.20, p.111), the conversion involving a triflate displacement with azide and selective reduction ($NaBH_4$-$NiCl_2$) of the azido-function in the presence of a nitro-group.[75] A 15 step synthesis of benzyl 2,4-diacetamido-2,4,6-trideoxy-D-galactopyranoside (93), a model for a fragment of Streptococcus pneumoniae "complex polysaccharide", from 1,6-anhydro-β-D-mannopyranose, involved sequential displacements with inversion of triflyloxy groups from C-2 and C-4 by azide ion.[76]



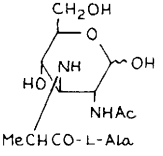
(92) X = H, Y = OH
(91) X = $NHCO_2Me$, Y = H



(93)



(94)



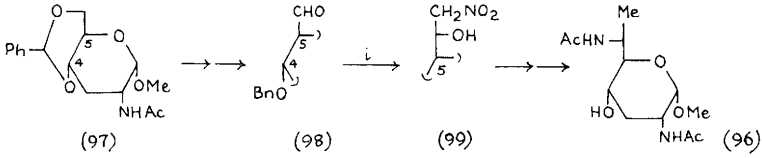
(95)

The synthesis of 2,6-diamino-2,6-dideoxy-D-mannose (22, X=$\overset{+}{N}H_3Cl$) has been covered in section 2.

Six 2,3-diamino-MDP (muramoyl dipeptide) analogues varying in the peptide moiety, e.g., (95), have been synthesized for a study of adjuvant activity, starting from a previously reported 2,3-diamino-sugar (c.f., Vol.20, p.103, ref.65).[77]

The 4-hydroxypurpurosamine B derivative (96) and its C-6 epimer have been synthesized from 2-amino-2-deoxy-D-glucose via the known 3-deoxy-derivative (97) (Scheme 24). Nitromethane addition to 6-aldehyde (98) gave the L-talo-nitro-sugar (99) as the only isomer in high yield. The nitrogen function was then relayed from C-7 to C-6 via formation and catalytic hydrogenation of a 6,7-epimine.[78]

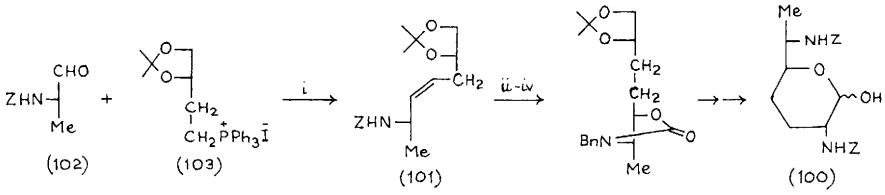
Other syntheses of diamino-sugars have employed non-carbohydrate starting materials. 6-epi-D-Purpurosamine D (100), a constituent of the antibiotic fortimycin A, has been elaborated from the adduct (101) obtained by coupling the L-alanine derived aldehyde (102) with the L-malic acid derived Wittig salt (103) (Scheme 25); the amino-group at C-2 was introduced via mesylate displacement with inversion by azide.[79] High pressure Lewis acid-catalyzed [4+2]cycloaddition of α-aminoaldehyde (104) or (105; from L-alanine) to diene (106) yielded hex-2-enosides (107) and (108), which were converted to the 2,6-diamino-sugars DL-purpurosamine C (109)[80] or 6-epi-α-D-purpuros-aminide (110),[81] respectively (Scheme 26). Regioselective hydro-



(97) (98) (99) (96)

Reagents: i, $MeNO_2$-NaOMe

Scheme 24



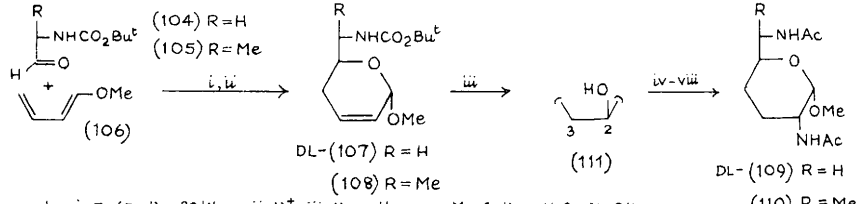
(102) (103) (101) (100)

Reagents: i, KH-THF ; ii, BnBr-NaH ; iii, I_2 ; iv, Bu_3SnH Z = $-CO_2Bn$

Scheme 25

boration of alkenes (107) or (108) yielded the alcohols (111) which were aminated via the 2-oxime.

The racemic 4,5-diamino-4,5-dideoxy-lyxopyranose and 5-deoxy-5-amino-lyxopyranosylamine derivatives, (112) and (113), have been obtained from the regioisomeric cycloadducts of acylnitroso dieno-

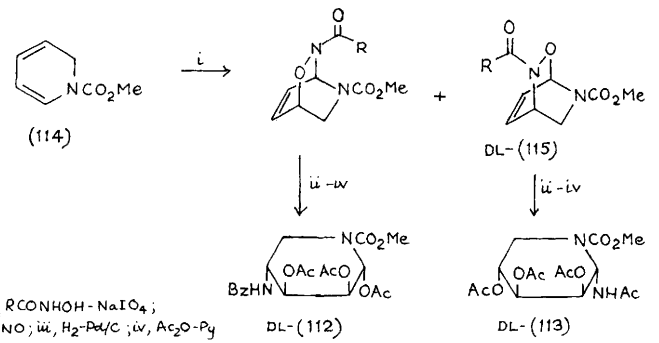


(106) DL-(107) R = H (108) R = Me (111) DL-(109) R = H (110) R = Me

Reagents: i, Eu(Fod)$_3$-20 Kbar ; ii, H^+ ; iii, thexylborane-Me_2S, then H_2O_2-NaOH ; iv, PCC-Mol. sieve ; v, NH_2OH ; vi, Ac_2O-Py ; vii, BH_3.THF ; viii, TFA

Scheme 26

philes with dihydropyridine derivative (114), the addition being regioselective for adduct (115) when R=Ph, Bn or Me (Scheme 27). Attempts to induce chirality using chiral nitroso compounds were not very successful.[82]



Scheme 27

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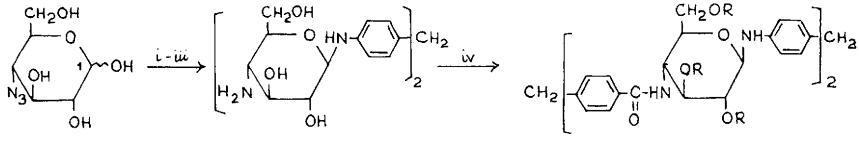
10
Miscellaneous Nitrogen Derivatives

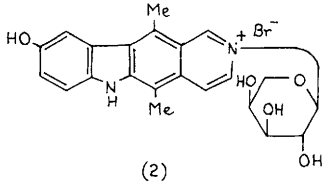
1 Glycosylamines

A review on the synthesis of glycopeptides has covered the formation of N-linked compounds by reaction between glycosylamines and aspartic acid units.[1] The synthesis of 2-acetamido-2-deoxy-β-D-glycopyranosylamines and their N-acylation with amino-acid derivatives (Vol. 20, p. 106) has been published in full.[2] The formation and stability of glycosylamines from drugs with a primary aromatic amine moiety (e.g., procaine, procainamide, and 4-amino-benzoic acid) and various reducing sugars has been examined, using an h.p.l.c. assay.[3] Reaction between base and free sugar has similarly been employed in the synthesis of N-glycopyranosides (D-glc, D-xyl, D-ara) of 5-amino-2-(ethoxycarbonyl)indole,[4] and the dextrophane prototype (1), which is a novel cavity molecule (Scheme 1).[5] The synthesis and rearrangement reactions of some diglycosylamines has been reinvestigated. Di(β-D-glucopyranosyl)amine, the main product from transglycosylation of β-D-glucopyranosylamine, yielded a mixture of tetra-O-acetylated β,β- and α,β-isomers on

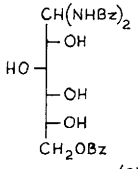


Scheme 1

acetylation, and these could be deacetylated without further anomerization. β-D-Xylopyranosylamine behaved analogously, except that the tri-O-acetylated β,β- and α,β-isomers yielded only di(β-D-xylopyranosyl)amine on deacetylation.[6] The 1,2-trans-selective condensation of acylated glycosyl halides with free bases has been employed in the synthesis of the N-β-D-glucopyranosyl derivative of 2,5-dimethyl-4-ethynyl-4-piperidinol,[7] and seven antitumor active 9-hydroxyellipticine N-glycosides, e.g., α-L-arabinosyl derivative (2), with improved water solubility.[8]



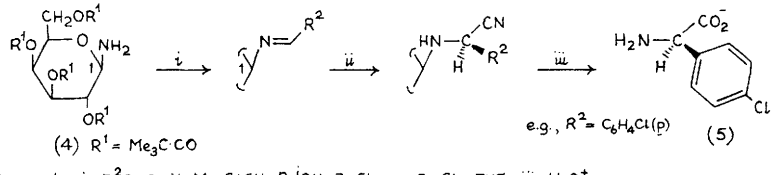
(2)



(3)

The acetylation of 5-amino-4-glycosylamino-pyrimidines, including some conditions which cause cleavage of the N-glycosidic bond, has been examined.[9] The reaction of penta-O-benzoyl-α-D-glucopyranose with liquid ammonia in organic solvent yielded 1,1-bis(benzamido)-1-deoxy-6-O-benzoyl-D-glucitol (3) (29% yield), three partially benzoylated N-benzoyl-α-D-glucofuranosylamines (24%) and four partially benzoylated derivatives of α-D-glucopyranose (10%).[10]

D-Galactosylamine (4) was used as the chiral template in a diastereoselective Strecker synthesis of α-aminonitriles which could be converted into D-amino-acids, e.g., (5) (Scheme 2).[11]

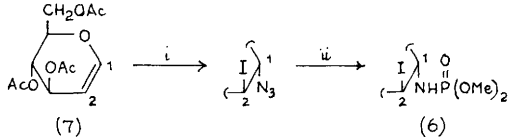


(4) $R^1 = Me_3C{\cdot}CO$ e.g., $R^2 = C_6H_4Cl(p)$ (5)

Reagents: i, R^2CHO; ii, Me_3SiCN-Pr^iOH-$ZnCl_2$ or $SnCl_4$-THF; iii, H_3O^+

Scheme 2

2-Deoxy-2-iodo-glycosyl phosphoramidates, e.g., (6), have been synthesized from glycals, e.g., using D-glucal (7) (Scheme 3).[12]



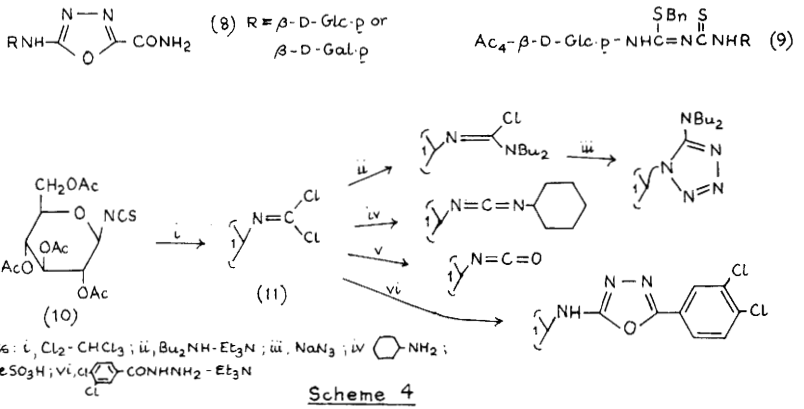
(7) (6)

Reagents: i, IN_3; ii, $P(OMe)_3$

Scheme 3

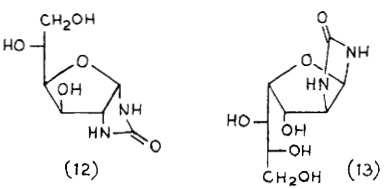
The synthesis and chemistry of glycosyl isothiocyanates has been reviewed,[13] and the phase transfer catalysed synthesis of acetylated glycosyl isothiocyanates of D-galactose and lactose from the corresponding glycosyl bromides reported.[14] The N-β-D-gluco- and -galacto-pyranosyl 2-amino-5-carbamoyl-1,3,4-oxadiazoles (8), potential antiviral agents, were obtained from the condensation of the corresponding peracetylated glycosyl isothiocyanates with oxamic

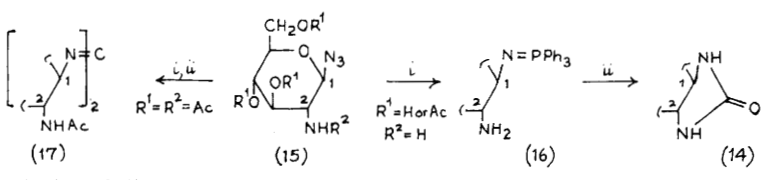
hydrazide ($H_2NNHCOCONH_2$), cyclization (HgO) and deacetylation.[15] 1- and 5-N-(Tetra-O-acetyl-β-D-glucopyranosyl)-2,4-isodithiobiurets (9) were obtained from either the glucosyl isothiocyanate or the glucosyl 2-S-benzylisothiocarbamide by addition of the requisite isothiocarbamide or isothiocyanate moiety.[16] Chlorination (Cl_2-$CHCl_3$) of tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate (10) yielded the dichloride (11) which was used to synthesize a range of derivatives as shown in Scheme 4.[17]



Scheme 4

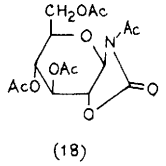
Cyclic ureas (12) and (13) have been obtained by reaction of 2-amino-2-deoxy-D-glucose and 2-amino-2-deoxy-D-glycero-L-gulo-heptose, respectively, with silver cyanate.[18] The pyranosidic cyclic ureas (14) were synthesized from the 2-amino-2-deoxy-D-glucosyl azides (15, R=H or Ac, R^1=H) via the phosphimines (16) (Scheme 5). Under the same conditions, the 2-acetamido-glucosyl





Scheme 5

azide (15, R^1=R^2=Ac) gave the symmetrical carbodiimide (17).[19] An n.m.r. study of conformationally rigid compounds such as (18) using 2D methods revealed deviations from the expected Karplus relationship between $^3J_{C,H}$ values and dihedral angles.[20] 2-Alkylamino-2-deoxy-aldoses condense with isothiocyanates to give (glycofurano)-imidazolidine-2-thiones such as the D-gluco-derivative (19) (see also Chapter 9). Isomerization and dehydration of this latter derivative yielded the C-glycoside (20).[21] Acetylation of compounds such as (21) yielded peracetates such as (22) rather than



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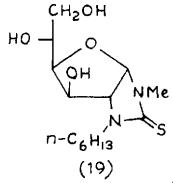
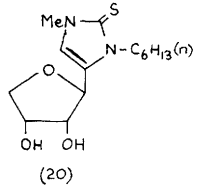


(19)



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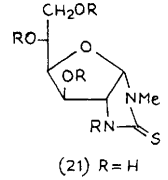
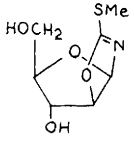


(21) R = H
(22) R = Ac



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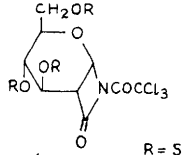
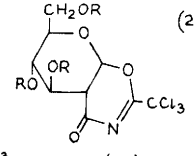


(24)
R = SiMe3



(25)

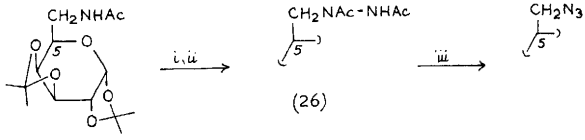
pyranosidic structures ascribed earlier.[22] ^1H-, ^{13}C- and ^{15}N-n.m.r. and e.i and f.d.m.s. studies have been reported on ^{13}C- and ^{15}N-labelled 2-methylthiooxazoline derivatives, e.g., (23), readily synthesized by sequential condensation of aldoses (6 pentoses, 6 hexoses) with thiocyanate ion then methylation; in some cases both furanoid and pyranoid derivatives were obtained.[23]

Chmielewski and co-workers have reviewed (mostly their own) work on the high-pressure [2+2]cycloaddition of active isocyanates to glycals,[24] and have reported that the addition of trichloroacetyl isocyanate to various glycals yields mixtures of [2+2]- and [4+2]-cycloadducts in which the isocyanate adds anti to the C-3 substituent, often with the latter adduct predominating. Thus tris-O-(trimethylsilyl)-D-glucal yielded the β-lactam (24) and the [4+2]cycloadduct (25) (see also Chapters 13 and 14).[25]

The Maillard reaction of D-xylose and glycine has been investigated by ^{13}C- and ^{15}N-solid state - n.m.r. and diffuse reflectance i.r. spectroscopic examination of the insoluble melanoidins prepared using ^{13}C- and ^{15}N-labelled substrates. Although no definite structure could be formulated for these melanoidins, the fate of the labelled carbon atoms was elucidated to some extent.[26]

2 Azido-sugars

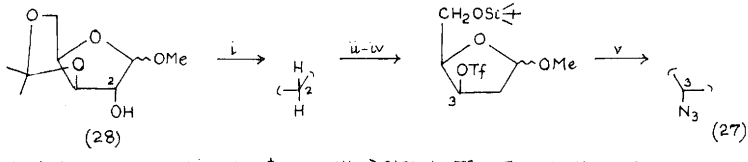
A new procedure for converting amines and amides to the corresponding azides is exemplified in Scheme 6. It involves controlled reduction of N-alkyl-N-nitrosoamides to hydrazides, e.g., (26), followed by nitrosation - fragmentation.[27]



Reagents: i, $NO^+HSO_4^-$ - Ac_2O-AcOH-NaOAc ; ii, Zn ; iii, Am^iONO

Scheme 6

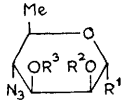
Azido-sugars can be synthesized by nucleophilic displacement of reactive chlorosulphate groups from chiral centres with potassium azide. Less reactive chlorosulphates underwent chlorine displacement to yield azidosulphates, but these groups could be replaced by azide with inversion using crown ethers at room temperature.[28] Syntheses of 2,3,4-tri-O-acetyl-6-azido-6-deoxy-α and β-D-gluco- and galacto-pyranosyl azides from the corresponding 6-O-tosylates employed lithium azide in HMPT.[29] In the synthesis of amphotericin B, which has a 3-amino-3-deoxy-β-D-mannopyranoside unit, an O-(3-azido-3,6-dideoxy-D-glucopyranosyl)trichloroacetimidate was prepared from a 3-O-triflyl-D-alloside.[30] The 3-azido-2,3-dideoxy-D-erythro-pentofuranoside (27), a potential precursor for the 3'-azido-2',3'-dideoxy-nucleoside AZT, has been synthesized from the methyl xyloside (28) (Scheme 7).[31] Methyl 4-azido-4,6-dideoxy-α-D-manno-



Reagents: i, Barton deoxygenation ; ii, H^+-MeOH ; iii, $\rightarrow$SiCl ; iv, Tf_2O-Py ; v, NaN_3-DMF

Scheme 7

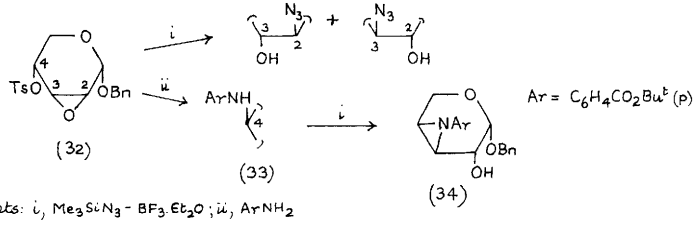
pyranoside (29), synthesized from methyl 2,3-O-isopropylidene-D-rhamnopyranoside [involving sequential C-4 epimerization by oxidation-reduction, 4-O-triflation, and azide displacement (with KN_3-18-crown-6) reactions] has been converted into the glycosyl acceptor (30) and donor (31), which were used for the synthesis of 1,2-α-linked di- and tri-saccharide units found in Brucella A and M



(29) R^1 = OMe, R^2 = R^3 = H
(30) R^1 = OMe, R^2 = H, R^3 = Bn
(31) R^1 = Cl, R^2 = Ac, R^3 = Bn

antigens.[32]

Epoxide (32), and two related epoxides containing nucleophilically displaceable groups, can be opened with the azide reagent shown (Scheme 8),[33] whereas an aromatic amine gave the 4-amino-sugar epoxide (33) which then gave the epimine (34) on reaction with the azide reagent.[34]



Reagents: i, Me_3SiN_3 - $BF_3.Et_2O$; ii, $ArNH_2$

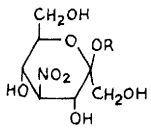
Scheme 8

Two new reagents have been developed for reducing azides to amines, and applied to some carbohydrate examples. One ($[Et_3NH][Sn(SPh)_3]$) is the fastest reducing agent for azides yet reported, while the other (Bu_2SnH_2) is compatible with water and carbonyl groups.[35]

Reactions of 2,3-anhydro-3-nitro-pyranosides with azide and other nucleophiles are covered in Chapter 15.

3 Nitro- and Nitroso-sugars and Glycosyl Nitrones

The nitro-sugar (35) was the main product isolated chromatographically (18% yield) from condensation between nitromethane and the dialdehyde (36), derived from selective lead tetraacetate cleavage of sucrose. With nitroethane this dialdehyde gave the branched nitro-sugar (37) (7.4%) in which the centre asterisked had epimerized prior to condensation. The tetraaldehyde (38) from periodate cleavage of sucrose condensed with nitromethane to yield the dinitro-sugar (39) (23%). Both compounds (35) and (39) were reduced (Raney Ni) to the corresponding amino-sugars.[36]



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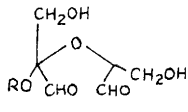

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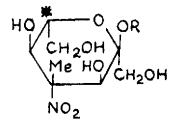
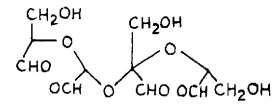


R = α-D-Glc-P (37)



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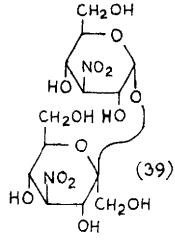
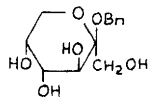


(39)



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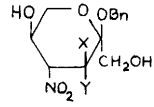
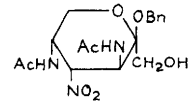


(41) X = OH, Y = H

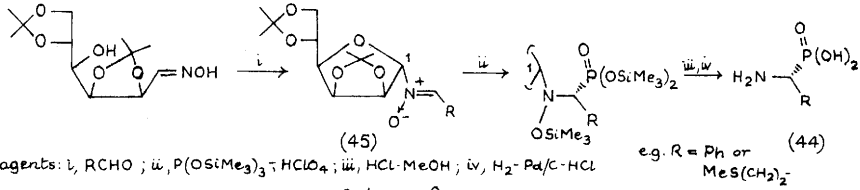
(42) X = H, Y = OH



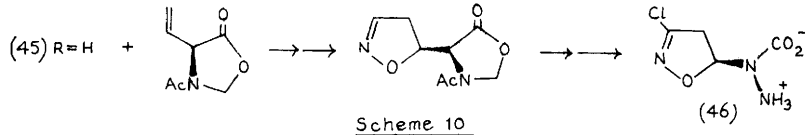
(43)

Addition of nitromethane to the dialdehyde generated from periodate cleavage of fructopyranoside (40) has been re-examined. The two nitro-sugars (41) and (42) were obtained in a 4:1 ratio, and were readily converted to the corresponding 4-amino-4-deoxy-keto-pyranosides by hydrogenation. The peracetate of (41) gave the diaminonitro-sugar (43) as the major product upon treatment with methanolic ammonia and subsequent N-acetylation. Similar products were obtained from 1,2-O-isopropylidene-α-D-fructopyranose, which also provided a route into branched-chain amino- and nitro-sugars (see Chapter 14).[37] Analogous periodate cleavage-nitromethane condensation was employed in the synthesis of 1,4,7-trioxaspiro[5.5]-undecane from 1,2-O-ethylene-β-D-fructopyranose (see Chapter 24).[38] 2,6-Anhydro-1-deoxy-1-nitroalditols have been prepared by application of known procedures involving addition of nitromethane to D-glucose, D-mannose, D-galactose, D-xylose, D-lyxose, and L-arabinose and subsequent cyclization. Only in the case of D-xylose were furanoid products obtained in addition to pyranoid products.[39] References to the synthesis of branched-chain nitro-sugars may also be found in Chapters 9 and 14, and to reactions of α-nitro-epoxides in Chapter 15.

Carbohydrate nitrones and nitroso-sugars have been employed as chiral auxiliaries. Chiral α-aminophosphonic acids, e.g., (R) - (44), have been obtained in high enantiomeric excess by nucleophilic addition to N-glycosyl nitrones, e.g., (45), as shown in Scheme 9.[40] The application of dipolar cycloaddition to related nitrones in the synthesis of chiral acivicin (46) is outlined in Scheme 10.[41] The 1-C-nitroso-D-mannofuranosyl chloride (47) has a significantly

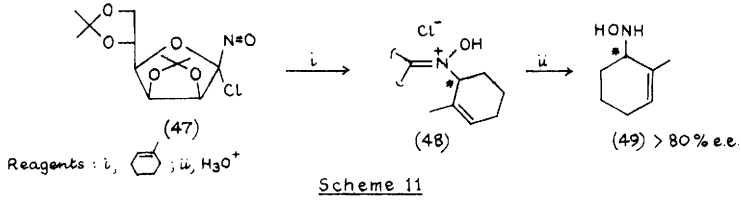


Scheme 9



Scheme 10

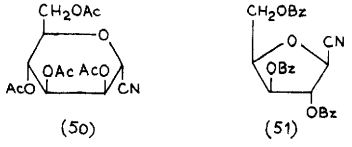
higher reactivity towards alkenes than other α-chloronitroso- compounds. It undergoes highly diastereoselective ene reactions to yield nitrone hydrochlorides, e.g., (48), from which chiral allylic hydroxylamines, e.g., (49), may be obtained on hydrolysis (Scheme 11).[42]



Scheme 11

4 Nitriles, Oximes, Hydroxylamines, and Imines

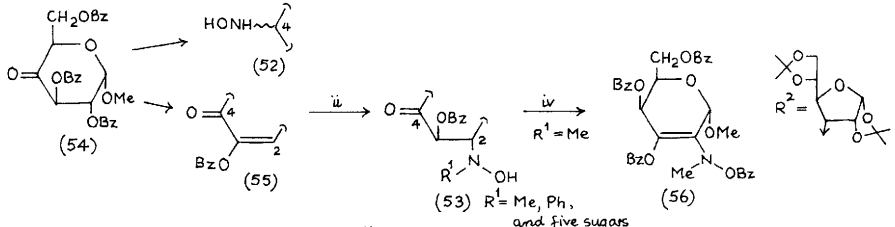
Improved syntheses of the D-mannosyl and D-xylosyl cyanides (50) and (51), respectively, from the corresponding α,β-glycosyl acetates (using Me_3SiCN-$BF_3{\cdot}OEt_2$ in $MeNO_2$) have been reported.[43] Using the same reagent system, 2,3,4,6-tetra-O-benzyl-α,β-D-galacto- and gluco-pyranosyl acetates gave separable ca. 1:1 mixtures of glycosyl cyanides.[44] ^1H- and ^{13}C-N.m.r. spectra of a number of perbenzoyl-



ated aldonitriles, their azide addition products [the 5-(polyben-

zoyloxyalkyl)tetrazoles], and related acyclic compounds have been interpreted.[45,46]

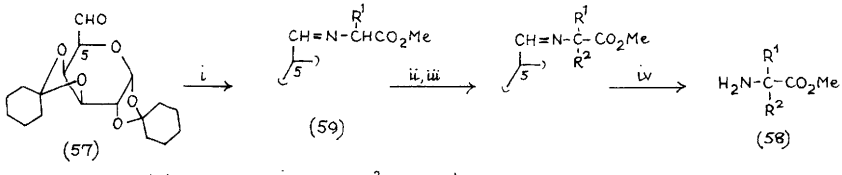
The deoxyhydroxylamino-sugars (52) and (53) have been synthesized from 4-uloside (54) either by an oximation - reduction sequence, or by Michael addition to the enolone (55) (Scheme 12) (c.f., Vol.11, p.112). The 4-ulosides (53) could be oximated, but reduction of these ketones or the derived oximes proved difficult. Benzoylation of the N-methyl derivative (53, R^1=Me) unexpectedly gave alkene (56).[47] Reduction of keto-oximes to aminodeoxyalditols is covered in Chapter 18.



Reagents: i, NH_2OH; ii, $NaBH_3CN$-HCl-MeOH; iii, RNHOH; iv, BzCl-Py

Scheme 12

The 6-aldehydo-D-galactose derivative (57) could be employed as a chiral auxiliary in the synthesis of a set of α-alkylated (S)-valine, (S)-leucine and (S)-isoleucine derivatives (58) in high enantiomeric excess, via alkylation of imine (59) (Scheme 13).[48]



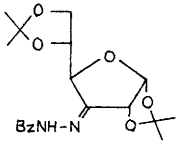
Reagents: i, $H_2NCH(R^1)CO_2Me$; ii, Pr^i_2NLi; iii, R^2Br; iv, H^+

Scheme 13

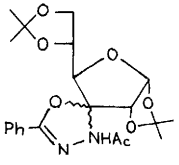
5 Hydrazones, Osazones, and Related Heterocycles

Treatment of the benzoylhydrazone (60), derived from the corresponding ketone, with boiling acetic anhydride afforded the epimeric mixture (61).[49] 3-Deoxyaldos-2-ulose bis(thiosemicarbazones) were readily obtained from D-glucose [i.e. (62)], D-arabinose, and D-glycero-D-gulo-heptose on reaction with thiosemicarbazide (in

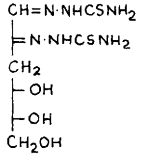
p-toluidine-HOAc-H_2O-EtOH under reflux), presumably by Amadori-type rearrangements and eliminations.[50] Heterocyclization (Ac_2O-py) of the 4-arylthiosemicarbazones of free sugars (Glc, Gal, Man, D-Ara, and lactose) yielded many compounds of type (63).[51]



(60)



(61)



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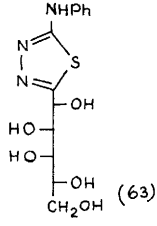
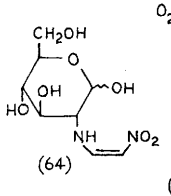


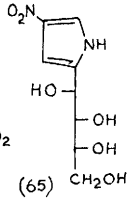
(63)

6 Other Heterocyclic Derivatives

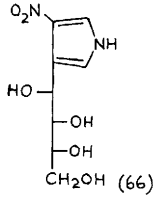
N-(2-Nitrovinyl)amino-2-deoxy-D-glucose (64), synthesized by reaction of the free amino-sugar with ethyl 2-nitrovinyl ether in methanol at 0°C, converted to the 2-(alditol-1-yl)-4-nitropyrrole (65) on being heated in methanol. N-Alkylpyrroles were similarly produced from the N-alkylated free sugar. 1-Amino-1-deoxy-D-fructose gave the 3-(alditol-1-yl)-analogue (66).[52] 3-(D-*erythro*-Trihydroxypropyl)-1-neopentylpyrrole-2-carboxaldehyde (67) was isolated as an advanced Maillard reaction product from D-glucose and neopentylamine in phosphate buffer under physiological conditions of pH and temperature.[53]



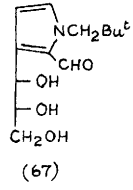
(64)



(65)



(66)

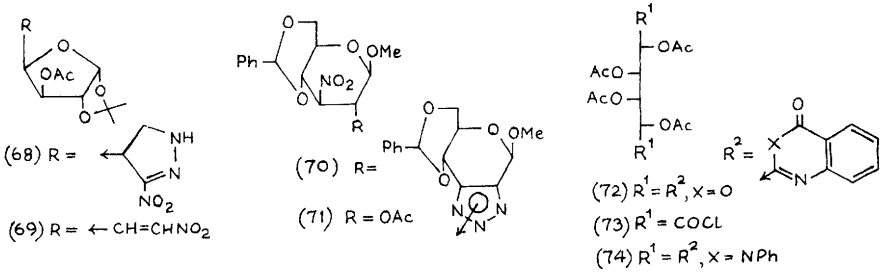


(67)

The nitroheterocycle (68), which exists in four tautomeric forms only one of which is shown, was obtained in modest yield from addition of diazomethane to nitro-olefin (69). Analogous results were obtained with two other sugar nitro-olefins.[54] The isomeric dimers (70) resulted from condensation of the 3-nitro-sugar (71) with sodium azide (in DMF), the configuration at C-2 being established through alternative syntheses of specifically C-1 and C-2 deuterated analogues.[55]

The bis-benzoxazine (72) was synthesized by acylation of

anthranilic acid with tetraacetyl-D-galactaric acid dichloride (73) and subsequent dehydrative cyclization. Further reaction ($PhNH_2$-PCl_3) yielded the bis-quinazolone (74).[56]



Full details on the synthesis of the spiro- and bicyclo-nucleosides reported last year (Vol.20, p.115, Scheme 13) have been published.[57]

The cycloadducts formed from glycals and dibenzyl azodicarboxylate, anomalously linked nucleosides from 2-deoxy-D-ribose, and certain other heterocyclic derivatives are covered in Chapter 9.

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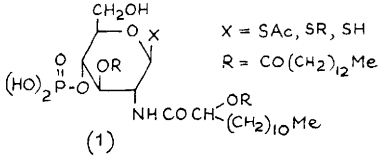
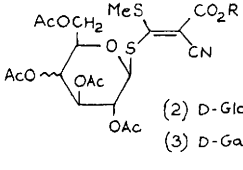
11
Thio- and Seleno-sugars

A review on monosaccharide isothiocyanates and thiocyanates has appeared.[1] The anodic deprotection of the carbonyl group has been applied to dethioacetalization of sugars; it was found that O-isopropylidene acetals were unaffected by the treatment.[2]

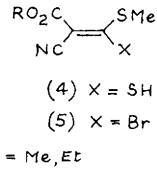
Peracetylated 1,2-trans-1-thioglycoses have been prepared in high yield from the peracetyl glycopyranoses by treatment with aluminium chloride and thioacetic acid, i.e. with the intermediacy of the 1-cis-chloro-derivative.[3] The reaction of D-glucose and D-xylose with 2-methyl-propane-2-thiol in concentrated hydrochloric acid afforded the corresponding tert-butyl 1-thio-glycopyranosides as an anomeric mixture. The acetylated aldehydo-derivatives of D-glucose, D-xylose, and D-erythrose gave di-tert-butyl dithioacetals with 2-methyl-propane-2-thiol.[4] Reference to alditol disulphides and sulphides is made in Chapter 18. 1-Thio-derivatives (1) of 2-deoxy-4-O-phosphono-3-O-tetradecanoyl-2-[(3RS)-3-tetradecanoyloxytetradecanamido]-D-glucose have been synthesized by conventional means; the products are analogues of the non-reducing sub-unit of bacterial lipid A.[5] Substituted methyl and ethyl glycopyranosylthioacryl-



(1)



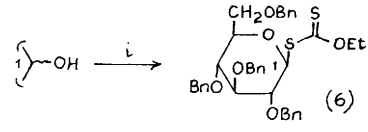
(2) D-Glc
(3) D-Gal



(4) X = SH
(5) X = Br
R = Me, Et

ates (2) and (3) have been prepared by either condensation of the thiol (4) with acetobromo-glucose or -galactose, or by condensation of the bromoalkene (5) with the appropriate 1-β-thioglycopyranoses.[6] The action of thiols on the furanose forms of the four D-pentoses is reported to give 2-(alkylthio)pentose dialkyl dithioacetals and 2,5-epithiopentose dialkyl dithioacetals with inversion at C-2.[7] Glycosyl xanthates such as (6) have been prepared from reducing sugar derivatives under phase-transfer conditions as shown in Scheme 1. Generally the products are anomeric mixtures but the case in Scheme

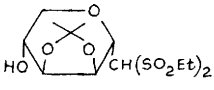
1 gave the β-anomer specifically.[8] The rearrangement of the bis-

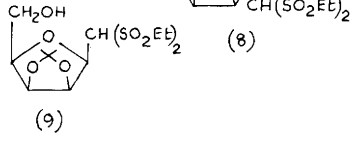


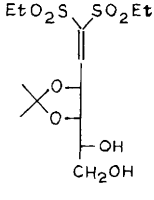
Reagents: i, TsCl - KSC(S)OEt - Bn_4NCl - C_6H_6 - H_2O - NaOH

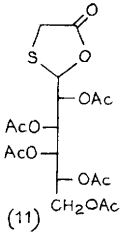
Scheme 1

sulphone (7) has been investigated. In pyridine (7) equilibrated to an equimolar mixture of the two furanoses (8) and (9) and the acyclic enedisulphone (10).[9] Treatment of 2,3,4,5,6-penta-O-acetyl-

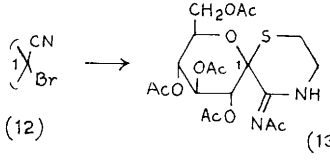


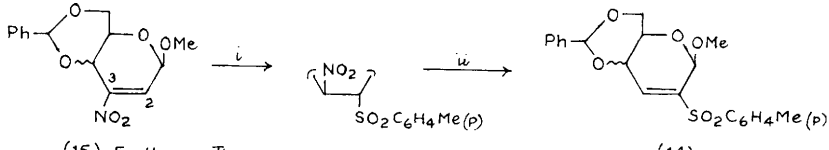






D-galactose with thioacetamide gave a product which was identified as the thialactone (11). Other aldehydo-sugars reacted analogously.[10] New spiroglycosylidene heterocycles have been prepared from 1-bromoglycosyl cyanides by treatment with sulphur nucleophiles. Thus the galacto-bromocyanide (12) on treatment with 2-aminoethane thiol gave the spirothiazane (13).[11]



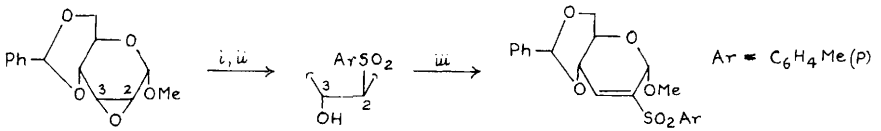


Reagents: i, (p)$MeC_6H_4SO_2Na$ - $R_4P^+Br^-$ - HOAc - H_2O - C_6H_6; ii, NEt_3

Scheme 2

4,6-O-Benzylidene -2-C-tosyl-hex-2-enopyranoses (14) have been

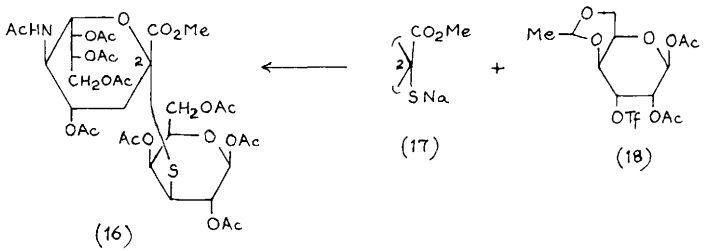
prepared from the corresponding nitroalkenes (15) as shown in Scheme 2. The 3-O-tosyl enols could be made analogously from the 2-nitro sugar. An alternative approach for obtaining the 2-O-tosyl compounds was via the epoxide shown in Scheme 3.[12,13]



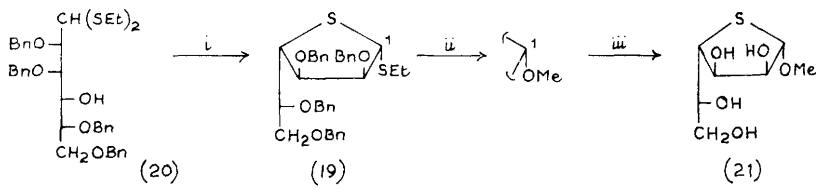
Reagents: i, ArS^-; ii, MCPBA; iii, MsCl-NEt_3

Scheme 3

The derivative (16) of 3-S-(N-acetyl-α-D-neuraminyl)-3-thio-D-galactopyranose has been synthesized by a sulphonate displacement using the neuraminylthiol sodium salt (17) with the β-D-gulose 3-triflate (18) as the key step.[14]



The ethyl 1,4-dithio-α-D-talofuranoside (19) has been obtained in 86% yield from the 4-unprotected D-mannose dithioacetal (20), and was then converted to the methyl glycoside (21) (Scheme 4).[15] A new radical-catalyzed O,S-rearrangement of cyclic thionocarbonates

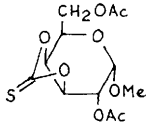


Reagents: i, Ph_3P-tri-iodoimidazole; ii, Br_2-MeOH; iii, H_2-Pd/C

Scheme 4

to yield thiosugars has been described; thus methyl 2,6-di-O-acetyl-D-galactopyranoside 3,4-cyclothionocarbonate (22), on treatment with tributyltin hydride-aluminium boronitride, yielded a 1:1 mixture of the 3-thiocarbonate (23) and the 4-thiocarbonate (24), while the

5,6-thionocarbonate (25) gave a 5:3 mixture of 5-thiogluco-(26) and 5-thioido-(27) cyclic carbonates.[16,17] The mechanism proposed is shown in Scheme 5.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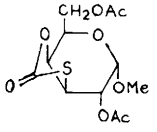
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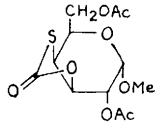
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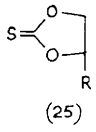
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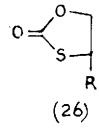
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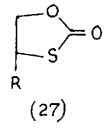
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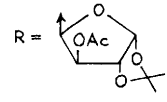
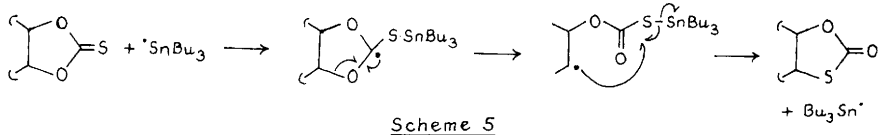
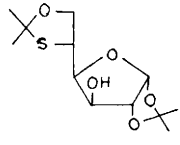




Scheme 5

The first example of a naturally-occurring 5-thiosugar has been reported when 5-thio-D-mannose was isolated from the marine sponge Clathria pyramida.[18] In an effort to understand the origins of the greater sweetness of the thiopyranoid-ring analogues 5-thio-α-D-glucopyranose and 6-thio-β-D-fructopyranose over α-D-glucopyranose and β-D-fructopyranose, ab initio quantum mechanical calculations (LCAO-MO at the STO-3G level) have been performed on these four compounds, and discussed in terms of the calculated net atomic charges.[19] Acetonation of 5-thio-D-glucopyranose and -D-altropyranose gave the di-isopropylidene-5-thio-furanose derivatives (28) and (29) respectively, as the thermodynamic products, while 5-thio-D-allopyranose gave the 2,3:5,6-diisopropylidene compound (30). The pyranose 2,3:4,6-diacetals were the kinetic products.[20] Both sulphonate groups of methyl 2,3-anhydro-4,6-di-O-mesyl-5-thio-α-D-allopyranoside (31) readily undergo displacement reactions with nucleophiles; the 4-O-mesyl group is more reactive and is displaced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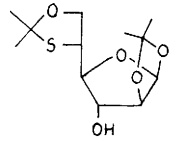
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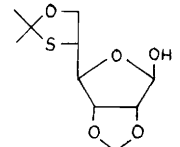
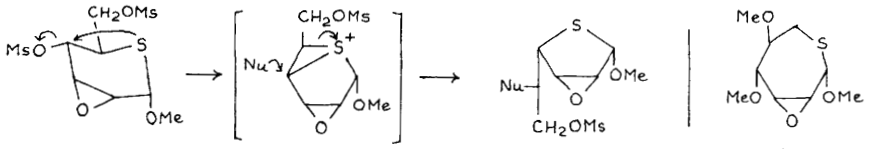

(30)

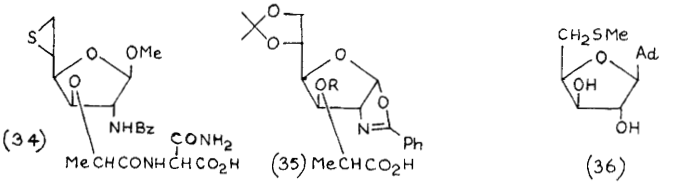
with retention of configuration, suggesting that participation of the ring sulphur is taking place (Scheme 6). In support of this the thio-

furanosides (32) were isolated and evidence of the ring expanded product (33) from treatment of (31) with methanol-barium carbonate wa presented.[21]

A 5,6-epithio analogue (34) of N-acetylmuramyl dipeptide has been synthesized from the 1,2-oxazolidino-D-glucofuranose (35) in several steps.[22] The first naturally occurring analogue (36) of methylthio-

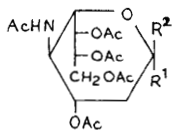


Scheme 6

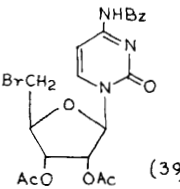


adenosine has been isolated from the digestive glands and mantles of the marine nudibranch Doris verucosa.[23] 5'-S-(5-Acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonic acid)-5'-thiocytidine and its β-anomer have been synthesized by coupling the sodium salts (37) and (38) with 5'-bromo-5'-deoxy-cytidine derivatives (39).[24]

Standard reactions have been used to convert D-glucitol to bis(6-deoxy-D-glucitol) 6,6'-disulphide and the corresponding 6,6'-sulphide.[25] Methyl 2-n-octanoylamido- and n-dodecanoylamido-2-deoxy-6-thio-α-D-glucopyraosides have been prepared by standard reactions from N-acylamidoglucose analogues. The paper also describes the preparation of the 6,6'-disulphide (40).[26] The two epimeric acetamido-6-thiosialic acids (41) and (42) have been synthesized.[27]

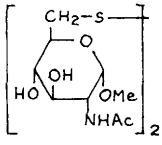


(37) R^1 = SNa, R^2 = CO_2Me
(38) R^1 = CO_2Me, R^2 = SMe

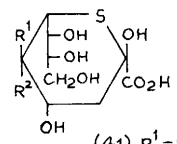


(39)

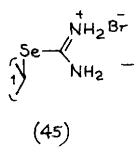
Selenoglucosinolates (43) and (44) have been synthesized from the corresponding selenourea derivative (45).[28]



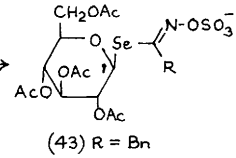
(40)



(41) R^1=H, R^2=NHAc
(42) R^1=NHAc, R^2=H



(45)



(43) R = Bn
(44) R = Me

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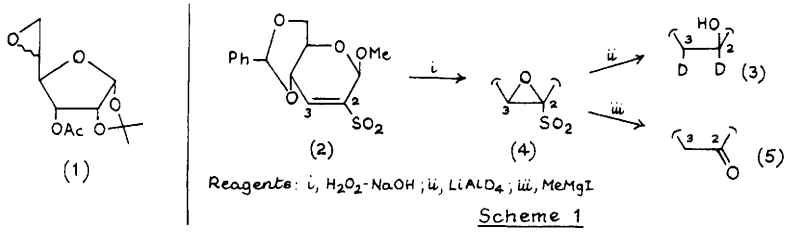
12
Deoxy-sugars

The conformation of digitoxose (2,6-dideoxy-D-ribo-hexose) groups in solutions of digitoxin has been determined to be $^4C_1$, and the implications for receptor binding discussed.[1] The ^{13}C-n.m.r. spectra of the ring forms of digitoxose in DMSO-d_6 solution have been fully assigned.[2]

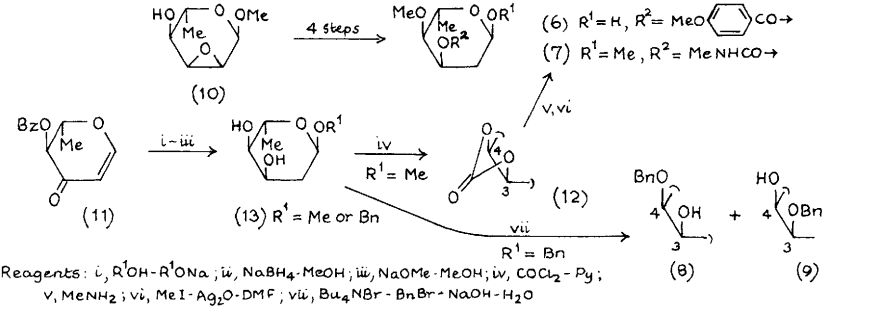
The eight possible monodeoxy-analogues of methyl β-maltoside, and also the 6,6'- and 1,2-dideoxy-analogues, have been synthesized using a range of conventional deoxygenation methodologies. Their conformations were determined by n.m.r. spectroscopy, and they were tested as substrates for amyloglucosidase; hydroxy groups at 3, 4' and 6' were found essential for substrate activity.[3]

6-Deoxy-D-allo- and -L-talofuranose were obtained by reduction ($LiAlH_4$) of the C-5 epimeric epoxides (1) available from 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose.[4] An epoxidation and reduction sequence applied to the unsaturated sulphone (2) (see Chapter 11) yielded the 3-deoxy-2,3-dideutero-D-arabinoside (3), whereas reaction of the epoxide (4) with methylmagnesium iodide led to the 3-deoxy-2-uloside (5) (Scheme 1).[5] Selectively alkylated and



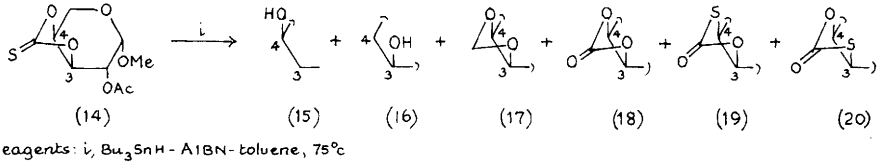
Scheme 1

acylated derivatives (6) - (9) of L-digitoxoside have been synthesized either from the epoxide (10) via methylation and reduction ($LiAlH_4$), or from the enone (11) via Michael addition - reduction (Scheme 2). While the cyclic carbonate (12) yielded a mixture of 3- and 4-carbamoyl derivatives on reaction with methylamine, only one product, (7), was obtained when this mixture was methylated. Phase transfer catalyzed alkylation of diol (13, R^1=Bn) gave a mixture of 4- and 3-benzyl ethers, (8) and (9), in the ratio 3:1.[6]



Scheme 2

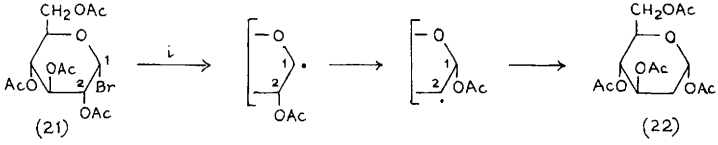
Radical chemistry continues to be widely applied in the synthesis of deoxy-sugars. Reviews entitled "Radical reactions in organic chemistry",[7] and "Tri-n-butyltin hydride as a reagent in organic synthesis"[8] have included numerous examples of the synthesis of deoxy-sugars by deoxygenation (thiocarbonyl derivatives), deamination, dehalogenation and denitration. Details on the synthesis of deoxy-sugars by regioselective thioacylation (Bu_2SnO then PhOCSCl), acetylation, and radical deoxygenation (Bu_3SnH) (see Vol.20, p.123) have been published in full,[9] while the behaviour of methyl 3,4-O-thionocarbonyl-β-L-arabinoside (14) with tributyltin hydride has been investigated in detail (Scheme 3). The major 3- and 4-deoxy-products, (15) and (16), are accompanied by minor products (17) - (20). In the presence of excess hydride, the 3,4-O-methylidene derivative (17) predominates (75% yield). If air is bubbled into the reaction mixture, the carbonate (18) becomes



Scheme 3

the almost exclusive product.[10] Deoxygenation *via* thiocarbonyl ester derivatives has been central to syntheses of benzyl 2,4-diacetamido-2,4,6-trideoxy-α,β-D-galactopyranoside (Chapter 9), 2',3'-dideoxycytidine analogues (Chapter 20), and 3-deoxy-D- and L-erythro-pentofuranose derivatives used as intermediates in the total synthesis of amphoteronolide B (Chapter 24).

A novel radical rearrangement has been postulated to account for the conversion of 2-O-acyl-glucosyl halides, e.g., (21), to the corresponding 2-deoxy-sugars (22) (Scheme 4). To minimize direct reduction of halide (21), high dilution conditions were employed, with addition of hydride over a 12h period.[11] Reductive radical

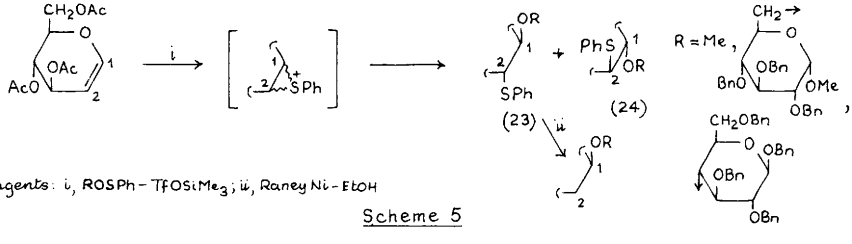


Reagents: i, Bu_3SnH-AIBN

Scheme 4

debromination has been employed in the construction of 2-deoxypyranosides and disaccharides using the N-iodosuccinimide - alcohol glycosylation procedure (Chapter 3), and in the construction of trisaccharide units of the aureolic acids (Chapter 4).

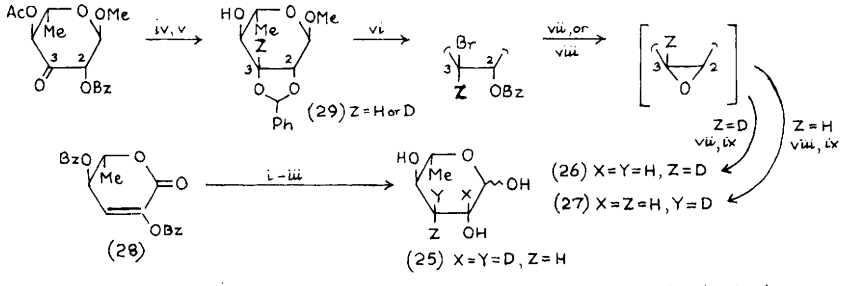
A new approach to 2-deoxyglycosides, including disaccharides, involves the addition of sulphenate esters (ROSPh) to glycals, and subsequently desulphurizing the adducts (Scheme 5). Ratios of β:α-anomers, (23) and (24), ranged from 1.5 - 4:1.[12]



Reagents: i, ROSPh - $TfOSiMe_3$; ii, Raney Ni - EtOH

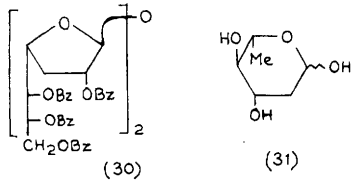
Scheme 5

Specifically deuterated ascaryloses (3,6-dideoxy-L-arabino-hexoses) (25) - (27) have been synthesized from L-rhamnose, via either the α,β-unsaturated lactone (28) or the benzylidene acetals (29) (Scheme 6).[13] 3-Deoxy-D-gluco-heptono-1,4-lactone tetrabenzoate has been prepared from D-glycero-D-gluco-heptono-1,4-lactone pentabenzoate using the hydrogenolysis procedure of Bock et al. (H_2-Pd/C-Et_3N-EtOAc ; Vol.15, p.153), and reduced (Bu^i_2AlH) to provide some of its furanose derivatives [e.g., (30)] including the free sugar, 3-deoxy-D-gluco-heptose.[14] 2,6-Dideoxy-L-arabino-hexose (31) and some derivatives have been synthesized from 6-deoxy-L-glucal utilising methoxymercuration, or via 1,2-dibromo-1,2,6-trideoxy-L-glucose obtained from a hexonic acid precursor.[15]



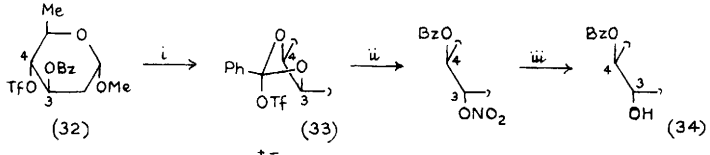
Reagents: i, D_2-Pd/C; ii, Bu^i_2BH; iii, NaOMe-MeOH; iv, $NaBD_3CN$ or $NaBH_3CN$; v, $PhCH(OMe)_2$-H^+; vi, NBS-$BaCO_3$; vii, $LiAlH_4$; viii, $LiAlD_4$; ix, H_3O^+

Scheme 6



The four possible [1-^{13}C]-enriched 5-deoxy-L-pentoses have been obtained by addition of [^{13}C]-cyanide to tetroses prepared by lead tetraacetate cleavage of appropriate 6-deoxyhexoses, separable mixtures of C-2 epimers being produced. The four unenriched 5-deoxy-D-pentoses were prepared from selectively protected pentoses, e.g., 5-deoxy-D-ribose was obtained by 5-deoxygenation of methyl 2,3-O-isopropylidene-β-D-ribofuranoside, and equilibrated with 5-deoxy-D-arabinose in the presence of a molybdate catalyst.[16]

Further interconversions of 2,6-dideoxy-sugars (Vol.20, p.79) have been reported. The triflate (32) rearranged at room temperature to the orthoester (33) which hydrolysed to give the expected mixture of D-lyxo-monobenzoates, or underwent nucleophilic displacement at C-3 to provide the D-xylo-monobenzoate (34) (Scheme 7).[17]



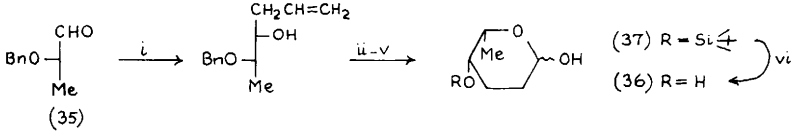
Reagents: i, Room temp; ii, $Bu_4^+N\bar{N}O_3$; iii, hν

Scheme 7

Many reports have appeared on the synthesis of chiral deoxy-

sugars from non-carbohydrate starting materials. Five groups have elaborated 3- or 4-carbon chiral synthons.

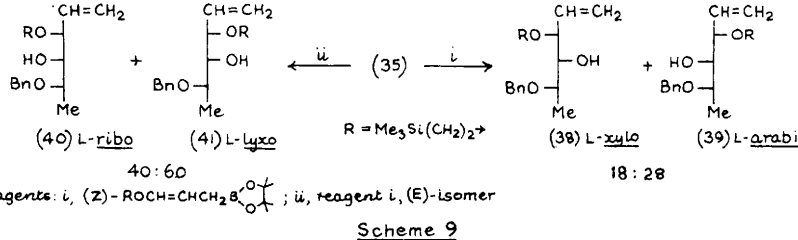
The synthesis of methyl 4-deoxy-heptoside stereoisomers by cis-hydroxylation of the dihydro-2H-pyran type [4+2]-cycloadducts from 2,3-O-isopropylidene-D-glyceraldehyde with 1-methoxy-1,3-butadiene (c.f., Vol.19, p.124), has been further detailed.[18] Chelation - controlled allylation of L-lactaldehyde derivative (35) provided access to L-rhodinose (36) and a 4-protected derivative (37) required for a synthesis of streptolydigin (Scheme 8).[19] Alternat-



Reagents: i, $CH_2=CHCH_2SnBu_3$-$MgBr_2$; ii, Et_3SiOTf-2,6-lutidine; iii, 9-BBN; iv PCC; v, H_2-Pd/C; vi, Bu_4NF

Scheme 8

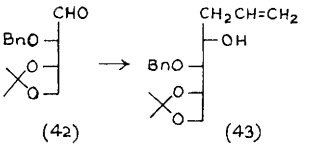
ive addition to this aldehyde (35) of oxygenated (E)- or (Z)-allyl boron reagents provided the isomeric alkenes (38) - (41) in the ratios shown (Scheme 9). After chromatographic separation three of the products were transformed into the corresponding methyl 2,6-



Scheme 9

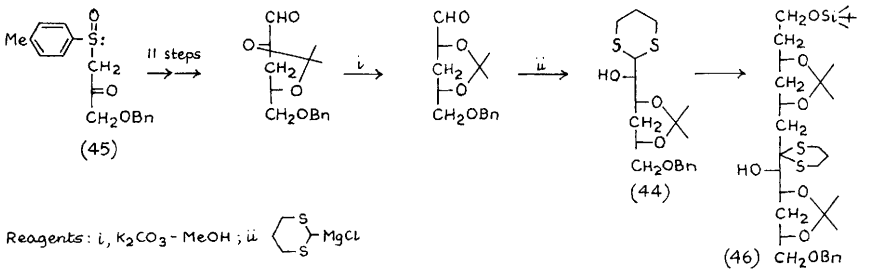
dideoxy-L-arabino-, L-ribo-, and L-lyxo-hexopyranosides by a benzylation - hydroboration (9-BBN)-oxidation (PCC)-deprotection-methanolysis sequence.[20]

In the addition of allyltrimethylsilane to the aldehydo-L-erythrose derivative (42), available from D-glucose via 1,3-O-ethylidene-L-erythritol, chelation of the catalyst ($MgBr_2$) involving the α-benzyloxy-group ensured high selectivity (>98%) in favour of the L-arabino-product (43). Ozonolysis then provided 2-deoxy-L-arabino-hexose. 2-Deoxy-L-xylo-hexose was similarly synthesized with high selectivity (98%) from the analogous aldehydo-L-threose derivative, available in 4 steps from diethyl L-tartrate.[21] The 4-deoxy-D-arabino-hexose derivative (44) has been synthesized from



(42) (43)

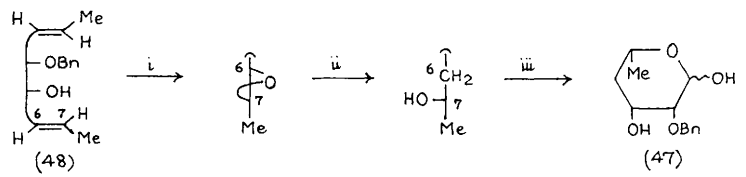
the (R)-β-ketosulphoxide (45), available in 4 steps from α-bromo-acetic acid. The synthesis (Scheme 10) featured a diastereospecific one carbon homologation (step ii). The product was further converted into the C-1 to C-12 unit (46) of amphotericin B.[22]



Reagents: i, K_2CO_3-MeOH; ii

Scheme 10

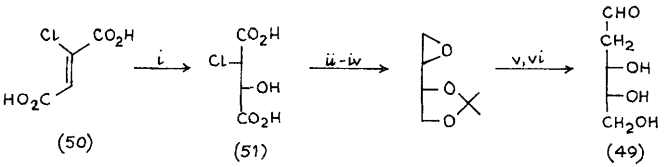
Details on the synthesis of L-chalcose and its D-enantiomer *via* Sharpless epoxidation of a racemic divinyl glycol derivative (Vol.20, p.127) have been published in full, and the methodology has been extended to provide the 4,6-dideoxy-L-*lyxo*-hexose derivative (47) from the racemic monobenzyl ether (48) (Scheme 11).[23]



Reagents: i, $Ti(OPr^i)_4$-diethyl L-tartrate-Bu^tO_2H; ii, Red-Al; iii, O_3-Me_2S

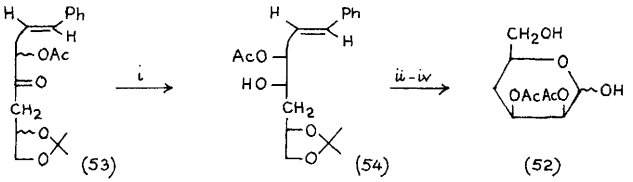
Scheme 11

Two deoxy-sugar syntheses have employed enzymatic procedures to convert racemic starting materials into chiral intermediates. 2-Deoxy-D-*erythro*-pentose (49) was synthesized from chlorofumaric acid (50), employing immobilized fumarase enzyme to produce the diacid (51) in ≥ 99.5% ee on a 50g scale (Scheme 12).[24] The 4-deoxy-D-*lyxo*-hexose (52) was obtained *via* diastereospecific yeast reduction of the mixture of four diastereoisomers (53), which gave the pure isomer (54) in 20% yield (Scheme 13).[25] Details on the



Reagents: i, fumarase ; ii, BH_3.THF ; iii, Me_2CO-H^+ ; iv, KOH ; v, $(\rightleftharpoons)_2Cu(CN)Li_2$; vi, O_3, then Me_2S

Scheme 12



Reagents: i, Yeast reduction ; ii, Ac_2O-Py ; iii, H_3O^+ ; iv, O_3, then Ph_3P

Scheme 13

synthesis of enantiomeric boivinose (2,6-dideoxy-xylo-hexose) derivatives utilizing an enantioselective enzymatic hydrolysis of a racemic pair of epoxides (Vol.20, p.128) have been published in full.[26]

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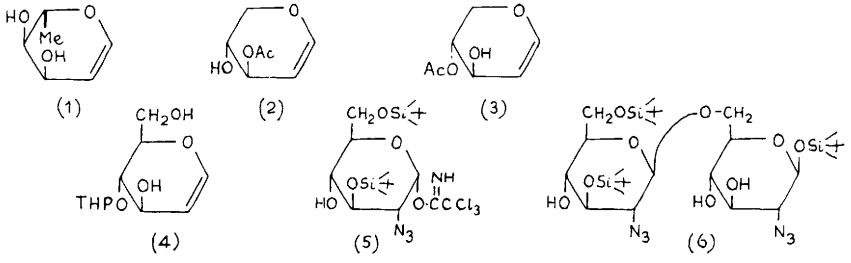
13
Unsaturated Derivatives

1 Glycals

Reaction of otherwise protected furanose and pyranose 1,2-diols with methanesulphonyl chloride and triethylamine, followed by treatment of the resulting 2-O-mesylaldosyl chlorides with excess of active zinc dust and iodide ion, gave the corresponding substituted glycals in high yields.[1]

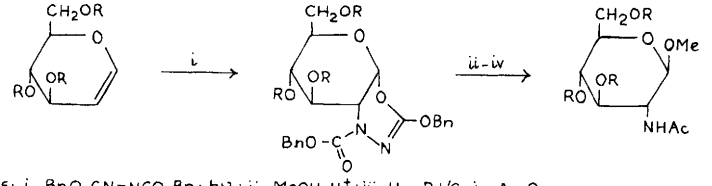
Specifically, "L-digitoxal" (1) has been made by selective reduction of the corresponding 3-one and, more efficiently, from the corresponding 2,6-dideoxy free sugar via its benzoylated glycosyl chloride. Various 3-O- and 4-O-substituted derivatives



(e.g., benzyl, allyl ethers) were prepared by selective substitution using phase transfer and stannylidene-dependent methods.[2] Selective deacetylation of 3,4-di-O-acetyl-D-xylal can be effected with hydrazine acetate in DMF to give 62% of the 3-acetate (2), whereas selective acetylation of D-xylal to give the 4-isomer (3) in 45% yield can be carried out with acetyl chloride in dichloromethane and pyridine.[3]

D-Glucal and D-galactal, on reaction with t-butyldimethylsilyl chloride, selectively give the 3,6-disubstituted ethers and hence a route to 4-substituted derivatives, e.g., (4). Compound (5), derived from the D-glucal diether, was used as a glycosylating reagent to obtain the disaccharide derivative (6).[4]

A new method for preparing 2-amino-2-deoxy glycosides is illustrated in Scheme 1 and can be applied with furanoid derivatives

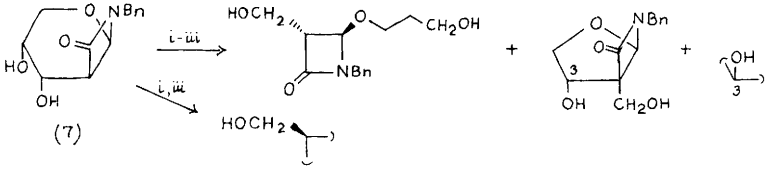


Reagents: i, $BnO_2CN{=}NCO_2Bn$; hν; ii, MeOH-H^+; iii, H_2-Pd/C; iv, Ac_2O

Scheme 1

to give analogous 2,3-trans-related products.[5]

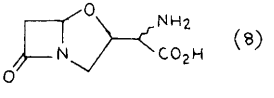
Work on the [2+2] cycloaddition of active isocyanates to glycals to give β-lactams has been reviewed,[6] and the authors have also described the preparation of adduct (7) and its conversion into



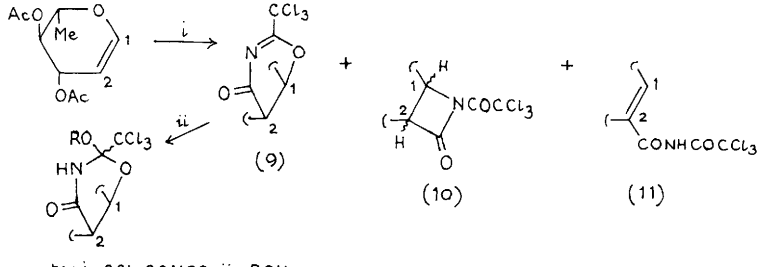
Reagents: i, IO_4^-; ii, $NaHCO_3$; iii, $NaBH_4$

Scheme 2

enantiomerically pure monocyclic compounds as indicated in Scheme 2. They also identified routes to 1-oxapenams and 1-oxacephems, e.g., (8).[7]



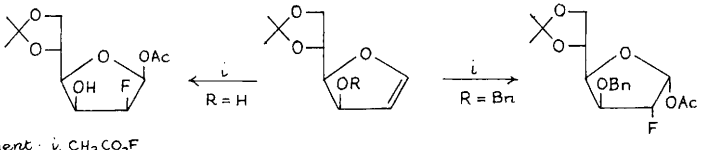
Cycloaddition of trichloroacetyl isocyanate to L-rhamnal diacetate gave the products (9)-(11), and (9) reacted with alcohols (including carbohydrate alcohols) as shown in Scheme 3.[8]



Reagents: i, CCl_3CONCO; ii, ROH

Scheme 3

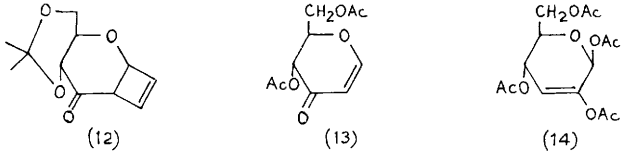
2-Deoxy-2-[^{18}F]fluoro-D-galactose has been made by treating tri-O-acetyl-D-galactal with labelled acetyl hypofluorite followed by acid hydrolysis of the product.[9] The unlabelled reagent gave mixtures of 1,2-cis-related-2-deoxy-2-fluoropentopyranosyl acetates with acylated pentopyranose glycals, but in the furanoid series the direction of addition was controlled by the orientation and nature of the C-3 substituent as illustrated in Scheme 4.[10]



Reagent: i, CH_3CO_2F

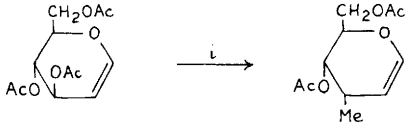
Scheme 4

Photochemical cycloaddition of acetylene to the appropriate enone gave in excellent yield the cyclobutene (12) which was characterized by x-ray analysis - but no data were given.[11] (c.f. M.Fetizon et al., Tetrahedron Lett., 1986, 27, 1777). The enone (13) and the 2-ene (14) were amongst the products of treatment



of 1,3,4,6-tetra-O-acetyl-β-D-mannose 2-triflate with tetrabutylammonium fluoride in benzene. With this reagent the ene (14) reacted further to give the enone (13).[12]

An extensive study of the reactions of unsaturated hexopyranosyl derivatives with lithium dimethylcuprate revealed that S_N2 and anti-S_N2' products were obtained (see Chapter 14). Tri-O-acetyl-D-glucal gave mainly the S_N2 product as indicated in Scheme 5.[13] On

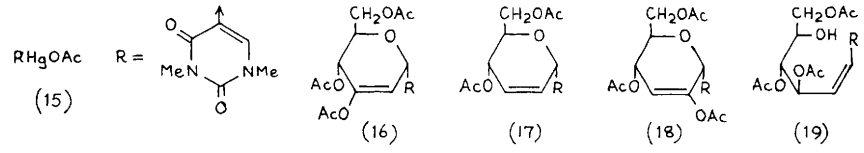


Reagent: i, $LiCuMe_2$

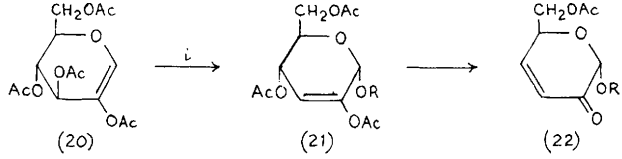
Scheme 5

the other hand, this glycal, converted into a palladium-complex intermediate and treated with the organomercurial (15), gives a range of products, e.g., (16)-(19). The rationale for these

products is given in a lengthy paper.[14]



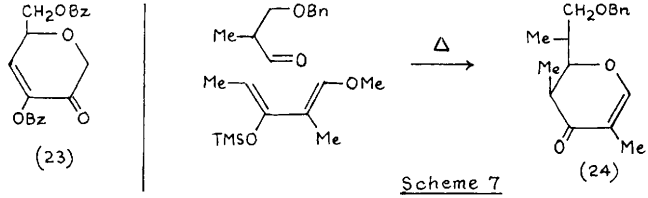
In the area of 2-hydroxyglycal chemistry the D-glucose derived (20) can be converted with equimolar amounts of alcohols and catalytic N-iodosuccinimide (probably HI in effect) into (21). With larger proportions of alcohols enones (22) are produced (Scheme 6). Other hydroxyglycal esters behaved similarly (c.f. Vol. 17, p.87, 127).[15] A related hydroxyglycal ⟶ hex-2-enopyranoside ⟶ enone sequence occurs with lithium cyanomethylcuprate, the enone undergoing a Michael addition step (See Chapter 14). A further reaction of this type occurred when



Reagents: i, NIS-ROH (1 equiv); ii, NIS-ROH (excess)

Scheme 6

the isopropyl compound (21) was treated with lithium aluminium hydride; the enone product (22) ($R=Pr^i$) underwent carbonyl reduction to afford the 3,4-dideoxy-D-erythro-hex-3-enopyranoside.[15A] The previously known enone (23) has now been made by an improved process (65% yield) from D-glucose (via the 2-oximo-intermediate)[16] and has been used in the synthesis of (S,S)-bissetone (Chapter 24).

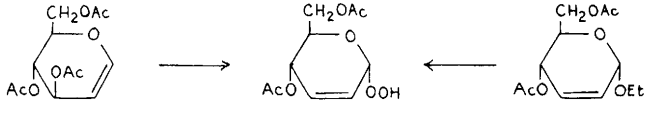


Scheme 7

The racemic enone (24) has been made as indicated in Scheme 7[17] and used in the synthesis of the polypropionate chain of Rifamycin S (Chapter 24).

2 Other Unsaturated Derivatives

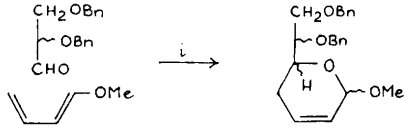
The unusual cystalline hydroperoxide (26) can be made either by treatment of tri-O-acetyl-D-glucal (25) with acidic hydrogen peroxide[18] or from the ethyl glycoside (27) using hydrogen peroxide and catalytic molybdenum trioxide (Scheme 8).[19] In the latter case



(25) (26) (27)

Scheme 8

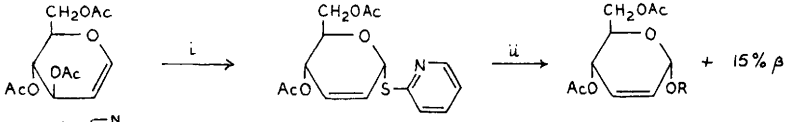
the 2,3-dideoxy-β-hexopyranosyl hydroperoxide was formed as a by-product. Several other 2,3-unsaturated glycosyl hydroperoxides were described in these papers; they are readily reducible to the corresponding 2,5-unsaturated lactones.[19] Diels Alder chemistry has been used to obtain the glycosides (28) (Scheme 9).[20]



Reagents: i, Pressure, Eu(fod)$_3$ (cat.) (28)

Scheme 9

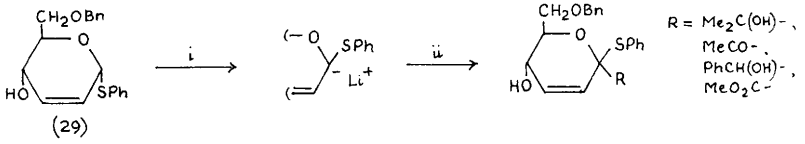
A novel synthesis of hex-2-enopyranosyl glycosides, including dissacharide derivatives, involves standard rearrangement of tri-O-acetyl-D-glucal to give a 1-thiopyridyl compound and subsequent alcoholysis (Scheme 10).[21] In a related paper the phenylthio-



Reagents: i, =N-SH - BF_3.OEt_2 ; ii, ROH-NBS

Scheme 10

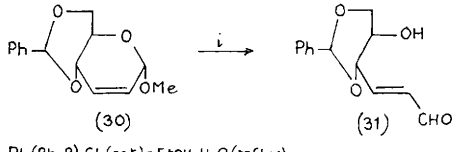
glycoside (29) was also made from tri-O-acetyl-D-glucal and used, by way of a stable C-1 carbanion, to obtain α-C-1 alkylated and acylated derivatives (Scheme 11).[22] Several references are made to other 2,3-unsaturated C-glycosides in Chapter 3.



Reagents: i, BuLi ; ii, Me_2CO, EtOAc, PhCHO, or $(MeO)_2CO$

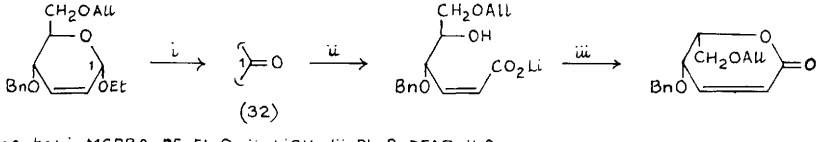
Scheme 11

Reactions of 2,3-unsaturated glycosides to have been reported are the high yielding conversion of the glycoside (30) to the trans-enal (31) (Scheme 12),[23] and the C-5 epimerization of the lactone (32) by application of the Mitsunobu procedure (Scheme 13).[24]



Reagents: i, $Rh(Ph_3P)_3Cl$ (cat) - EtOH - H_2O (reflux)

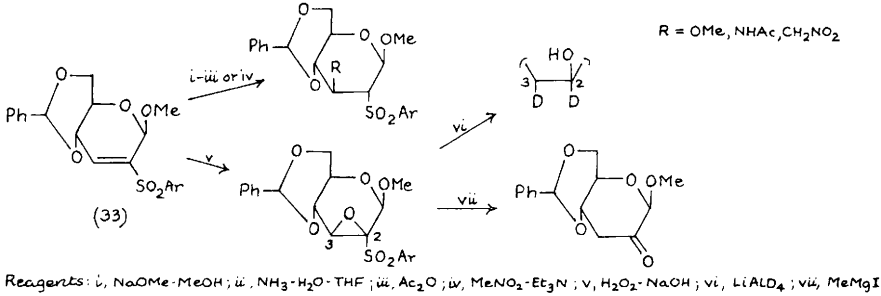
Scheme 12



Reagents: i, MCPBA - $BF_3.Et_2O$; ii, LiOH ; iii, Ph_3P - DEAD - H_2O

Scheme 13

The sulphones (33) were obtained from the corresponding 3-nitro-alkenes by addition of arylsulphinic acids followed by the elimination of nitrous acid.[25,26] Various reactions of (33) are illustrated in Scheme 14.[25] Its α-anomers can be made from methyl

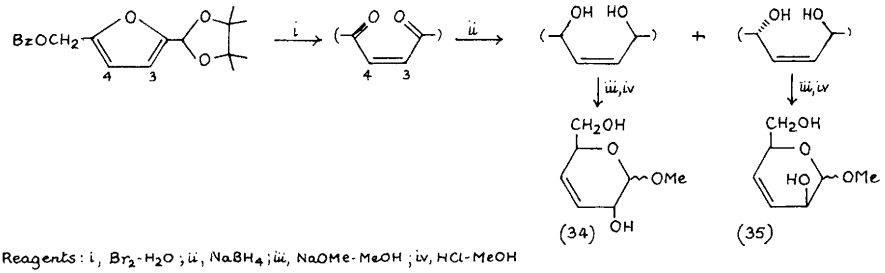


Reagents: i, NaOMe-MeOH ; ii, NH_3-H_2O-THF ; iii, Ac_2O ; iv, $MeNO_2$-Et_3N ; v, H_2O_2-NaOH ; vi, $LiALD_4$; vii, MeMgI

Scheme 14

2,3-anhydro-4,6-O-benzylidene-α-D-glucopyranoside by ring opening with the thiophenates followed by oxidation to the D-altro-sulphones and mesylation of the C-3 hydroxy group.[26]

In the area of 3,4-unsaturated compounds, the racemic epimers (34) and (35) have been made as shown in Scheme 15.[27] The 3,4-

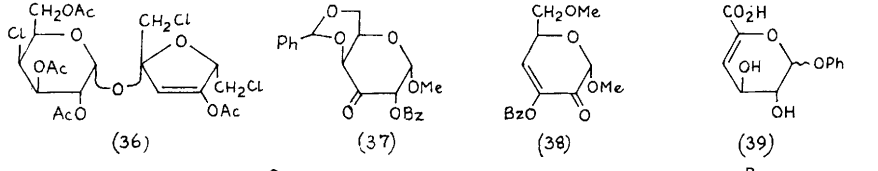


Reagents: i, Br_2-H_2O; ii, $NaBH_4$; iii, NaOMe-MeOH; iv, HCl-MeOH

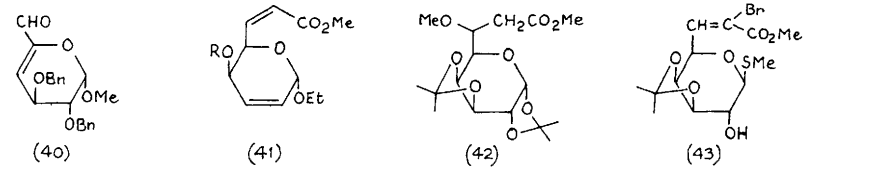
Scheme 15

unsaturated derivative (36) of the fructosyl component of sucrose was obtained following treatment of an epoxide with lithium dimethylcuprate.[28]

Reference is made to a Diels Alder adduct of the 3-en-2-one levoglucosenone in Chapter 24, and to the addition with rearrangement of the elements of isobutane to an enolone in Chapter 14. Treatment of the uloside (37) with potassium tert-butoxide followed by methyl iodide affords the rearranged enolone (38). Other 3-enes are also reported in this paper.[29]



(36) (37) (38) (39)



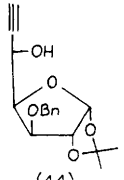
(40) (41) (42) (43)

The α- and β-glycosides (39) have been individually prepared as substrates for a glycosiduronase.[30] Hydrogenation of the enal (40) gave mainly the L-arabino-aldehyde which could be epimerized in alkali to the D-xylo-analogue. Reduction of (40) with Bu^i_2AlH was surprisingly poor yielding and the hydroxymethyl product afforded

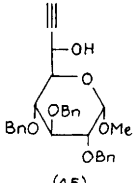
the xylo-adduct on hydrogenation - against expectations.[31]

A method has been reported for the synthesis of z-alkenes of the series (41), and related compounds were obtained from 1,2:3,4-di-O-isopropylidene-α-D-galacto-dialdose, but extended reaction of this compound with Wittig reagent in methanol afforded single adduct diastereomers (42) (unknown configuration at C-6).[32] Use of compounds related to (41) in the synthesis of antileukemic olguine analogues is referred to in Chapter 5. Compound (43) has been reported,[33] and another 6-ene, used in the synthesis of asperlin, is noted in Chapter 24.

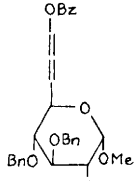
Inversion of configuration at the propargylic centres of the alcohols (44) and (45) has been effected by the Mitsunobu procedure, but attempts to displace corresponding sulphonate esters of the alcohols with sodium benzoate in DMF led to some of the unusual allenic esters (46).[34]



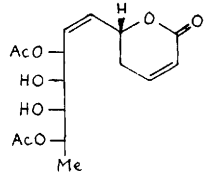
(44)



(45)



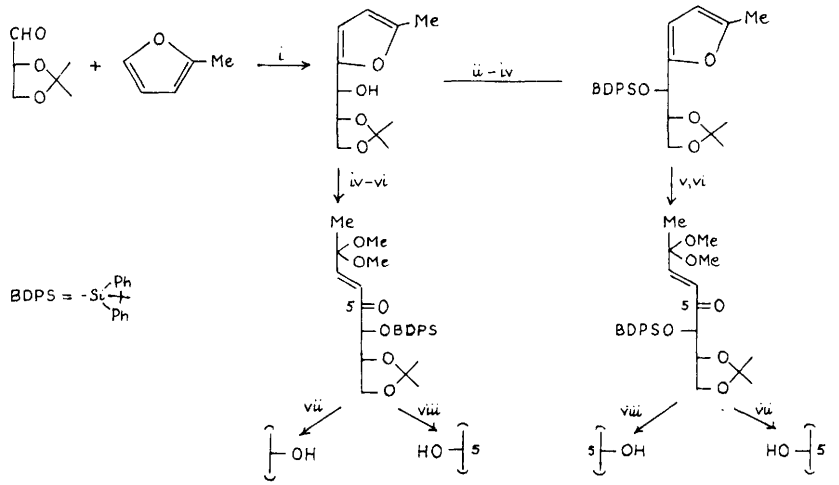
(46)



(47)

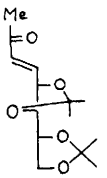
The acyclic alkene derivative (47) (also a dodec-6-enopyranose derivative) has been isolated from a South African plant and characterized by X-ray cystallography. (For a relevant synthetic study see Chapter 24).[35] Further studies have been carried out on polysaccharide structures using reductions of carboxylic acid groups to hydroxymethyl and hence iodomethyl followed by zinc treatment and reduction to afford glycosyl-substituted 1,2-dideoxyhex-1-enitols.[36] 2,3-O-Isopropylidene-D-glyceraldehyde has been used to produce a set of branched-chain 1,2-dideoxyhex-1-enitols (Chapter 18) and also some 3,4-unsaturated 1-deoxyketone derivatives as illustrated in Scheme 16.[37]

Knoevenagel reactions have been carried out on 2,3:4,5-di-O-isopropylidene-aldehydo-D-xylose with methyl acetoacetate and pentane-2,4-dione and products such as (48) have been obtained.[38] Reactions of Wittig reagents with carbohydrate aldehydes have been used to obtain access to cyclopentanes (Chapter 18) and an isomer of Compound (47) (Chapter 24).



Reagents: i, BuLi-$ZnBr_2$; ii, MnO_2; iii, L-Selectride; iv, Bu^tPh_2SiCl; v, Br_2-Py; vi, $MeC(OMe)_3$-H^+-MeOH; vii, $Zn(BH_4)_2$ [$BnOCH_2$ for BDPS]; viii, Bu^i_2AlH

Scheme 16



(48)

References to unsaturated compounds containing exocyclic double bonds are made in Chapter 14.

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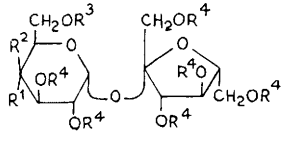
14
Branched-chain Sugars

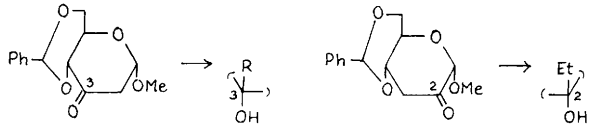
1 Compounds with an R-C-O Branch

The reaction of Grignard reagents with the sucrose derivatives (1) and (2) has been investigated. Treatment of (1) with methyl magnesium iodide at -78°C afforded only (3), whereas at room temperature both (3) and (4) were obtained, and with ulose (2) both (5) and (6) were formed. Allyl magnesium iodide reacted with (2) to give only (7).[1] Similarly, the addition of organometallic reagents to the

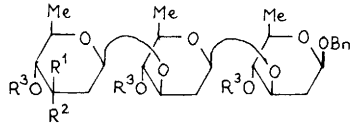


(1) $R^1, R^2 = O$, $R^3 = Tr$, $R^4 = Bn$
(2) $R^1, R^2 = O$, $R^3, R^4 = COBu^t$
(3) $R^1 = Me$, $R^2 = OH$, $R^3 = Tr$, $R^4 = Bn$
(4) $R^1 = OH$, $R^2 = Me$, $R^3 = Tr$, $R^4 = Bn$
(5) $R^1 = Me$, $R^2 = OH$, $R^3, R^4 = COBu^t$
(6) $R^1 = OH$, $R^2 = Me$, $R^3, R^4 = COBu^t$
(7) $R^1 = All$, $R^2 = OH$, $R^3, R^4 = COBu^t$

ketone (8) afforded predominantly the products (9) with ribo stereochemistry, whereas the 2-ulose (10) gave exclusively (11).[2] Methyl lithium added stereospecifically to the ketone (12) to give

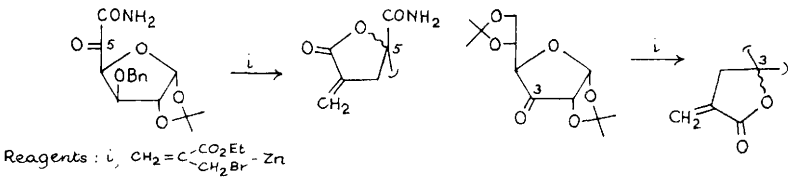


(8) (9) R = Me, Et, C≡CH (10) (11)



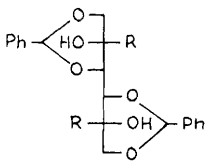
(12) $R^1, R^2 = O$, $R^3 = Bz$
(13) $R^1 = OH$, $R^2 = Me$, $R^3 = H$

a trisaccharide unit (13) of the aureolic acids.[3] α-Methylene-γ-lactones spiro-fused to sugar moieties have been synthesized by a Reformatsky reaction with the corresponding ketones (Scheme 1). Both epimers of each product were isolated.[4]



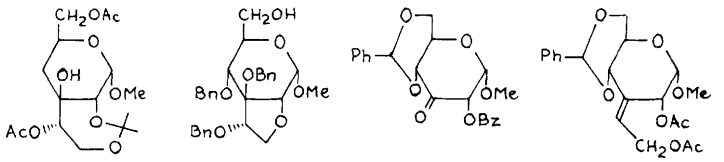
Scheme 1

The branched compounds (14), (15) and (16) have been obtained from a corresponding bis-spiro epoxide intermediate; attempts to use these tertiary diols in tandem with lithium aluminium hydride for the asymmetric reduction of a number of ketones gave only low optical yields.[5]



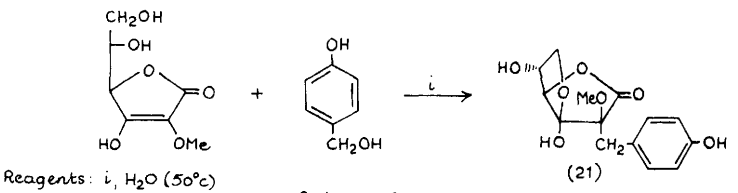
(14) R = Me
(15) R = Et
(16) R = Bn

The conversion of D-glucose into the branched-chain derivatives (17) and (18) via the ulose (19) and the Wittig adduct (20) has been reported in an approach to the synthesis of the antibiotics amipurimycin and miharimycin.[6] A facile synthesis of dellesserine



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

(21), a marine algal metabolite thought to have anticoagulant properties, has been achieved by the simple treatment of 2-O-methyl-L-ascorbic acid with p-hydroxybenzyl alcohol (Scheme 2). Similarly,



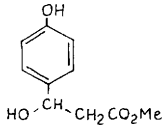
Reagents: i, H_2O (50°C)

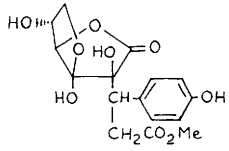
(21)

Scheme 2

treatment of L-ascorbic acid with the benzyl alcohol derivative (22)

afforded a 4:1 mixture of (23) and (24), the latter on reduction with diborane giving leucodrin (25), a phenolic constituent of


(22)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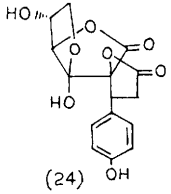
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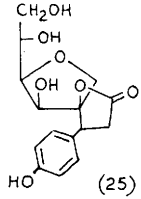
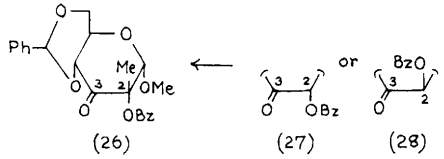
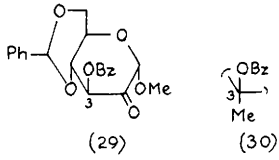
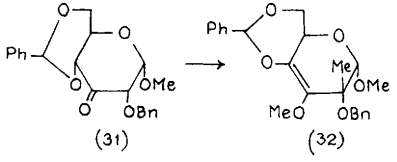
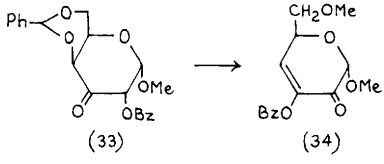

(25)

species of proteaceae.[7] Further work on the alkylation of sugar enolates has afforded the axial alkylation product (26) from either 3-ulose epimer (27) or (28). Similarly the 2-ulose (29) gave (30), whereas (31) gave (32), and (33) was not alkylated but afforded (34).[8]

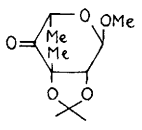

(26) (27) (28)

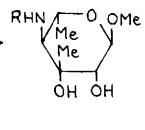

(29) (30)

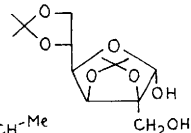

(31) (32)

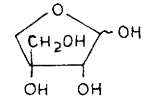

(33) (34)

The known L-rhamnose derivative (35), which is obtained by methylation of the parent ketone, has been converted into methyl L-sibirosaminide (36) and N-acyl kansosamine (37) by standard methodology.[9] The synthesis of 2-C-methyl-D-ribose derivatives (and related nucleosides) has been reported, utilizing periodate cleavage of 3-C-methyl-D-glucose compounds.[10] The known 2-C-(hydroxymethyl)-D-mannose derivative (38) has been converted into 6-deoxy-2-C-methyl-D-mannitol and 2-C-(hydroxymethyl)-D-mannitol, which were made as potentially sweet compounds.[11] A new method for the synthesis of D,L-apiose (39) enables the selective preparation of (1-^{13}C), and/or (2-^{13}C), and/or (1-^{2}H), and/or (2-^{2}H) enriched derivatives.[12]


(35)

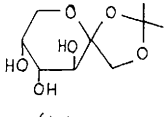

(36) R = Me
(37) R = COCH(Me)(OMe)

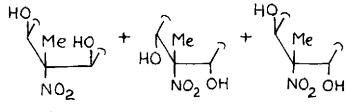

(38)

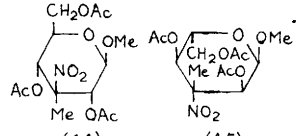

±(39)

2 Compounds with an R-C-N Branch

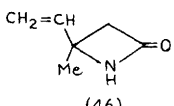
The product of periodate cleavage of the fructose derivative (40) has been treated with nitroethane to give (41), (42) and (43) in the ratio of 6:3:1, which on reduction afforded the respective 4-amino-4-C-methyl hexulose derivatives.[13] Similarly, methyl β-D-glucopyranoside after treatment with periodate and basic nitroethane


(40)


(41) (42) (43)


(44) (45)

gave (44) and (45) in 12% and 9% yields, the latter presumably arising from epimerization of the intermediate aldehyde.[14] The azetidinone (46) (readily available from the cycloaddition of isoprene to chlorosulphonyl isocyanate) has been used for the preparation of the 3-C-methyl-3-aminopentoses (47) and (48) in racemic form.[15]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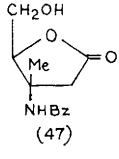
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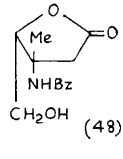
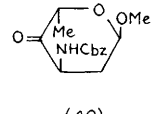

(48)


(49)

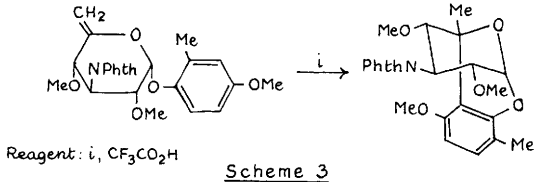
Alkylation of the enolate of ketone (49) with methyl iodide afforded both epimers of the C-3 methyl compound, and these products gave access to L-vancosamine, L-decilanitrose and D-rubranitrose.[16]

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

A new branched-chain sugar, 3,6-dideoxy-4-C-(1-hydroxyethyl)-D-xylo-hexose (yersiniose), has been isolated from Yersinia enterocolitica O:4.32 lipopolysaccharide,[17] and a new apiose-containing coumarin glycoside has been extracted from root bark of Adina Cordifolia.[18] The c.i. mass spectra of some branched-chain hexopyranosides with Ac, CO_2Me, $CONH_2$ or CN branch at C-3 as well as some geminal disubstituted compounds have been reported.[19]

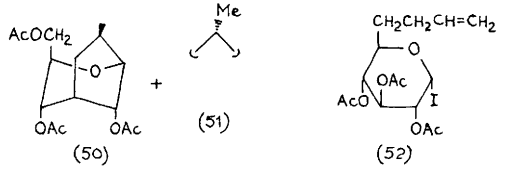
In an extensive review of radical reactions in organic synthesis a number of examples of branched-chain sugar synthesis are covered.[20] A review of tri-n-butyltin hydride includes some examples of branched-chain sugar synthesis.[21]

A novel attempt to prepare the western section of nogalamycin involved the cyclization shown in Scheme 3. The yields were low and erratic but suggested the possible success of this approach

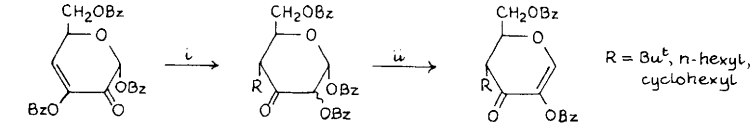


Scheme 3

under optimal conditions.[22] Treatment of tetra-O-acetyl-3-deoxy-3-iodo-β-D-glucopyranose with allyltributyltin gave the C-3-allyl gluco compound (60%) and its C-3 epimer (11%). The major product was converted to the corresponding glycosyl iodide, which, in the presence of tributyltin hydride, afforded the bicyclic compounds (50) and (51) in a 9:1 ratio, whereas the iodide (52) did not

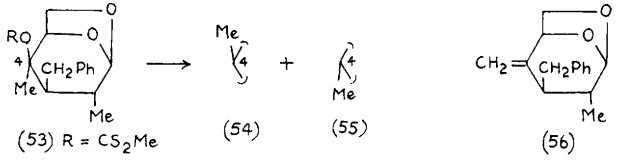


cyclize on formation of the glycosyl radical.[23] The conjugate addition of a number of radicals to a carbohydrate enolone proceeded with good to excellent diastereoselectivity with concomitant migration of a benzoyl group (Scheme 4).[24]



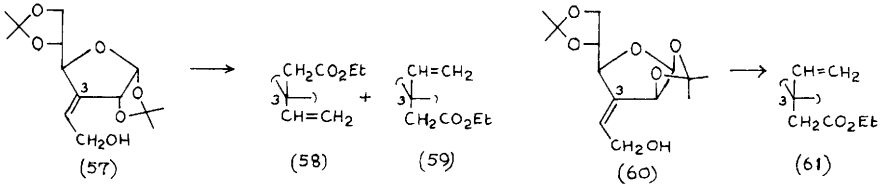
Scheme 4

Deoxygenation of the xanthate (53) by tributyltin hydride gave a 12:1 mixture of (54) and (55). The same mixture was obtained by hydrozirconation of exo-methylene derivative (56) using $(Cp)_2ZrHCl$.[25] The nitro-compounds (44) and (45) on treatment with

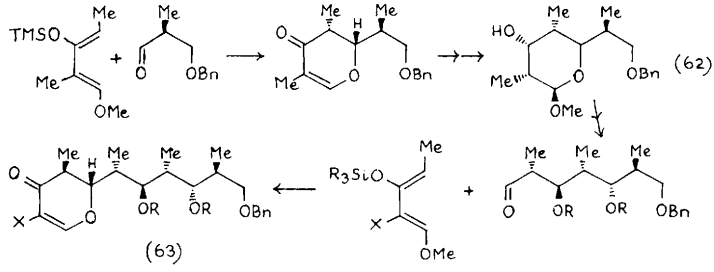


tributyltin hydride gave mixtures of the corresponding 3-deoxy-3-C-methyl compounds.[14]

In a study of the Claisen reaction applied to a number of carbohydrate derivatives, the allylic alcohol (57) was heated in triethylorthoacetate in the presence of propionic acid catalyst to afford the doubly-branched compound (58) with high selectivity - the Z isomer of (57) proved much less reactive, giving under the same conditions a mixture of (58) and (59) with unchanged starting material. Alkene (60) and its Z isomer under these conditions

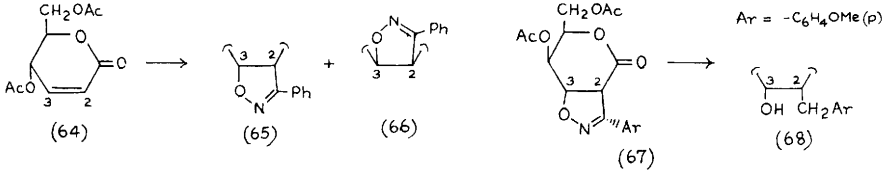


generated only (61). A large number of compounds with a double branch were made and characterized in this study.[26] Danishefsky has used his hetero-Diels-Alder reaction for the preparation of the branched-chain octo-pyranoside derivative (62) and hence the undecose (63) (Scheme 5), which are intermediates in the synthesis of the polypropionate chain of Rifamycin S.[27] A review on the high pressure [4+2] cycloaddition of 1-methoxy-buta-1,3-diene to carbonyl compounds, as well as the [2+2] cycloaddition of active

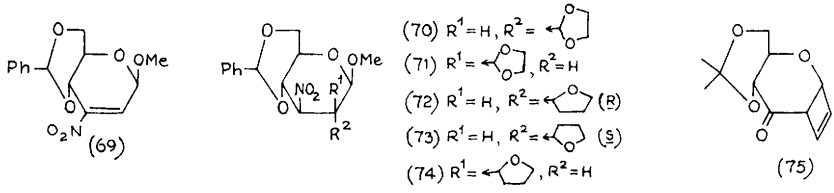


Scheme 5

isocyanates to glycals covers mostly the authors' own work.[28] These same authors have published further work on the [2+2] cycloaddition of trichloroacetyl isocyanate to various glycals.[29,30] A 1,3-dipolar cycloaddition of benzonitrile oxide to hex-2-enono-1,5-lactone (64) gave (65) and (66), isolated in 58 and 7% yields respectively.[31] The major 1,3-dipolar cycloadduct (67) derived



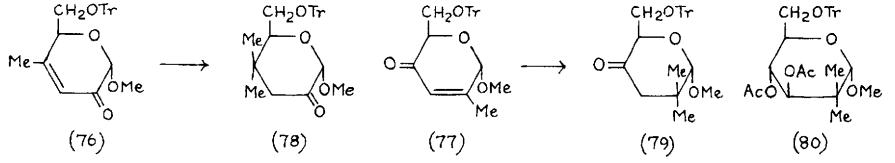
from the C-4-epimer of lactone (64) was converted by hydrogenation to the branched deoxy derivative (68).[32] Photolysis of (69) in 1,3-dioxan afforded (70) and (71), while in tetrahydrofuran low yields of (72), (73) and (74) were obtained.[33] Adduct (75) was



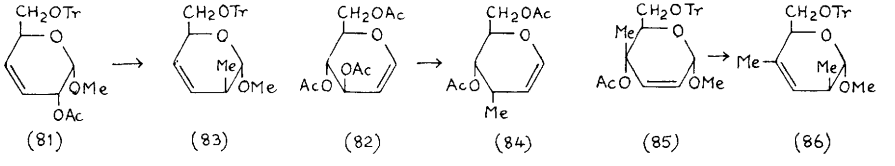
obtained by photochemical addition of acetylene to the corresponding enone.[34]

Conjugate addition by higher order cuprate $Me_2Cu(CN)Li_2$ to enones (76) and (77) gave the 4,4 and 2,2-di-C-methyl-hexopyranosides (78) and (79) respectively. Trapping of the intermediate enol in the formation of (79) as the enol silyl ether and subsequent

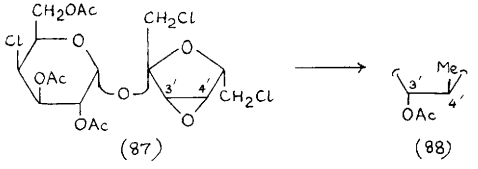
hydroboration afforded, after acetylation, the 2,2-di-C-methyl-α-D-glucopyranoside (80).[35] An extensive study of unsaturated hexo-



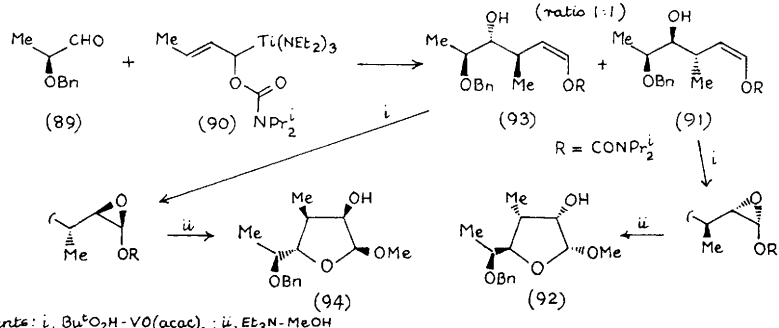
pyranoside derivatives treated with lithium dimethylcuprate has been reported. Products derived from S_N2 and anti-S_N2' reactions were obtained depending on the substrate, e.g., allylic acetates (81) and (82) afforded (83) and (84) respectively, whereas (85) gave (86).[36] Lithium dimethylcuprate opening of the sucrose epoxide



derivative (87) and subsequent acetylation afforded (88).[37]

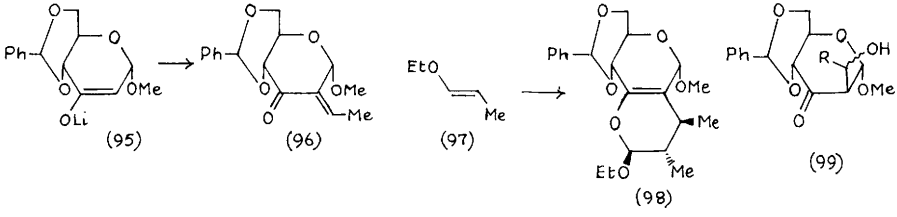


Condensation of S-2-benzyloxypropanal (89) with the titanium alkene (90) provided a route to methyl furanosides of unnatural 3,6-dideoxy-3-methyl-aldohexoses (Scheme 6). Thus (91) afforded

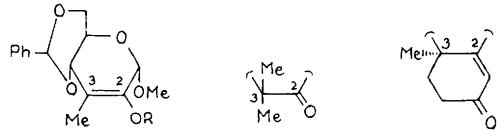


Scheme 6

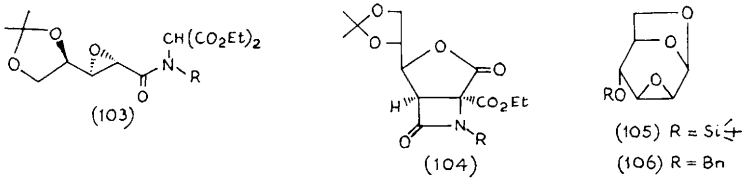
the α-L-allofuranoside derivative (92), and (93) gave the β-L-talofuranoside compound (94).[38] The enolate (95), obtained by treating methyl 2,3: 4,6-di-O-benzylidene-α-D-mannopyranoside with butyl lithium, was alkylated with acetaldehyde and the adduct dehydrated to give enone (96). This enone undergoes Lewis acid-catalysed hetero-Diels-Alder reaction with enol ethers, *e.g.*, (97), (4 examples given) with the formation of single isomers, *e.g.*, (98).[39] Replacing lithium in (95) with zinc gives a better nucleophile at carbon. Thus aldol condensations were effected



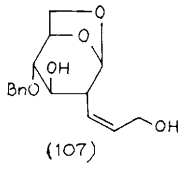
between the zinc enolate and a number of aldehydes, giving adducts (99). Epimerization at C-2 could be effected by base.[40] The enolate of methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-*arabino*-hexopyranosid-2-ulose has been trapped on oxygen [giving (100)], on carbon [giving (101)] and submitted to Robinson annelation [giving tricycle (102)].[41]



The amide (103), derived from 2,3-O-isopropylidene-D-glyceraldehyde, was converted by base treatment into β-lactam (104) which served as a precursor to 2,3-dideoxy-2-amino-3-hydroxymethyl-α-D-mannofuranoside derivatives.[42] 2-Deoxy-2-C-methyl-D-glucose has been prepared from 1,6-anhydro-β-D-glucopyranose *via* treatment of the known epoxide (105) with methyl lithium and subsequent hydrolysis.[43]



Further work on "pyranoside homologation" has illustrated its use in producing compounds with multiple chiral centres. Epoxide (106) was transformed via (107) into the dipyranosides (108) and then (109).[44] Further elaboration gave tripyranoside (110) which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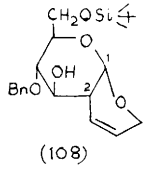
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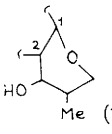
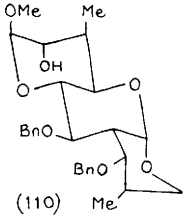

(109)

contains 7 of the 8 chiral centres of the ansa chain of Rifamycin S.[45] Similarly the epimers (111) were synthesized by way of a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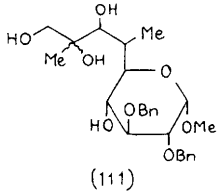
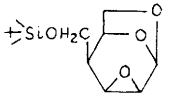

(111)

dipyranoside intermediate as a model study of the synthesis of the ansa chain of streptovaricin A.[46] The branched-chain dianhydride (112) has been prepared by hydroboration of alkene (113). The product (114), on treatment with sodium hydride undergoes a silyl migration and generates (112) directly.[47] During attempts to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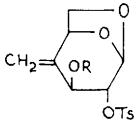
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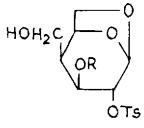
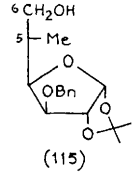

(114)

R = Si

synthesize the C-5 branched compound (115) stereoselectively it was found that hydrogenation of alkene (116) gave a 1:1 mixture of (115) and its C-5 epimer, whereas hydroboration of (117) gave exclusively (115). Compound (115) was subsequently transformed into 1,3,5-trideoxy-3,5-di-C-methyl-L-talitol.[48]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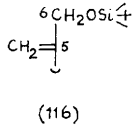
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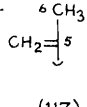
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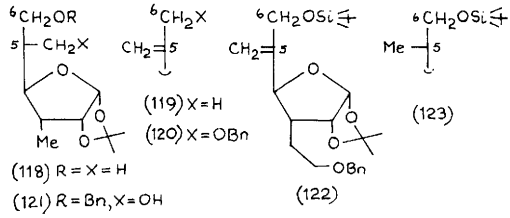
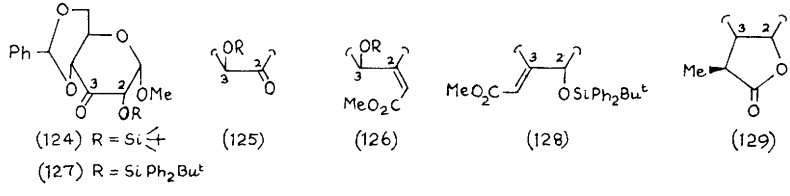
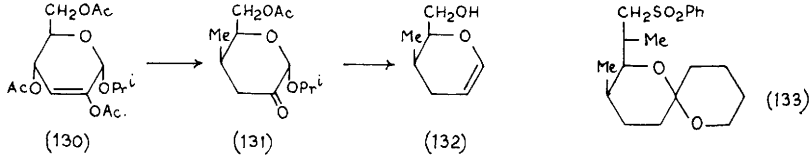


Similarly, during a stereocontrolled synthesis of (118) it was found that hydroboration of (119) gave mainly the undesired isomer and hydrogenation of (120) was not selective. However, hydroboration of (120) gave a 96:4 ratio of epimers in favour of (121) - which was then transformed into (118).[49] Hydroboration of (122) was reported to give (123) selectively.[50] During studies on some C-4 exocyclic methylene hexopyranoside derivatives, it was found that the stereochemical outcome of hydroboration could be affected by the protecting group on O-6. Additionally hydrogenation could be controlled to favour either C-4 methyl epimer by choice of catalyst and solvent.[51]

Wittig reaction of uloses (124) and (125) gave only (126) from both starting materials as they equilibrate under the reaction conditions. However, olefination of (127) gave (128) which served



as precursor to the fused butyrolactone (129).[52] The known conversion of (130) to (131) (using Me(CN)CuLi) has allowed the synthesis of branched-chain glycal (132) which was converted to synthon (133), required for a synthesis of okadaic acid.[53] Some



branched-chain nucleosides have been mentioned in chapter 20.

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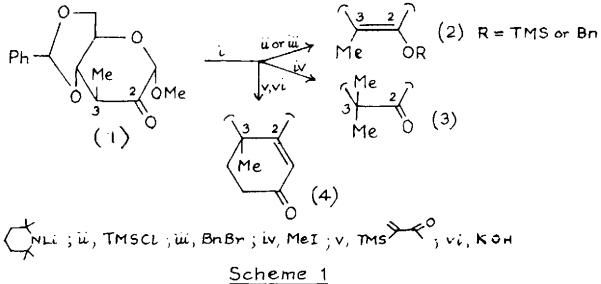
15
Aldosuloses, Dialdoses, and Diuloses

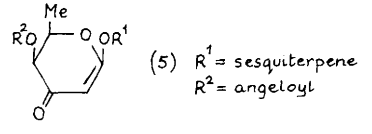
1 Aldosuloses

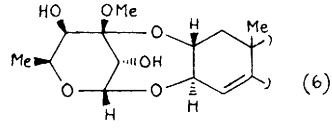
The enolate of methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-arabino-hexopyranosid-2-ulose (1) has been trapped by reaction at oxygen to give (2) and at carbon to give (3) and submitted to Robinson annulation to give (4) (Scheme 1).[1]



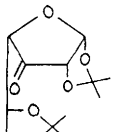
Scheme 1

Two reports have appeared of the occurrence of β-D-ribo-hexopyranosid-3-ulose residues in plants: in cardenolide glycosides of air dried (but not fresh) leaves of two Cerbera species,[2] and in iridoid glycosides from Penstemon confertus leaves.[3] Modified members of the series (5)[4] and a compound containing the unit (6)[5] which are, likewise, plant products have also been described.

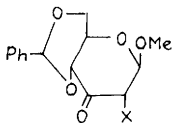




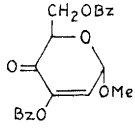
Also in the hexos-3-ulose series the ketone (7) has been made easily from the D-galacto-alcohol by use of PCC on alumina under reflux in benzene,[6] the D-ribo-compounds (8) were obtained by treatment of the corresponding 3-nitro-D-allo-2,3-epoxide with nucleophiles (epimerization occurring at C-2),[7] and reduction with zinc borohydride of the enolone (9) gave the 3-ulose derivative (10). The isomer (11) was made in parallel fashion.[8]



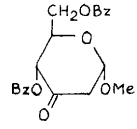
(7)



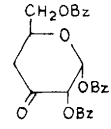
(8) X = N_3, Br, Cl, I, H



(9)



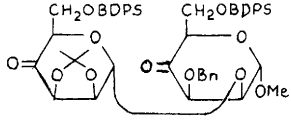
(10)



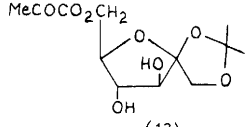
(11)

Diketones, e.g., (12), obtained from D-mannose-containing compounds, on reduction have given access to both 1,2-[9] and 1,3-[10] linked D-mannosyl-D-talose and D-talosyl-D-talose disaccharides.

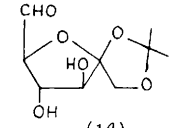
Photolysis of the D-fructose 6-pyruvate (13) gave the unusual D-lyxo-hexos-5-ulose derivative (14),[11] and the tricarbonyl compound (15) was made by anodic oxidation of 1,2-O-isopropylidene-α-D-glucofuranose in high yield.[12] The 3-acetamido-D-xylo-hex-5-ulose derivative (16) has been synthesized from 1,2:5,6-di-O-isopropylidene-α-D-glucose by way of a 5-alkene.[13]



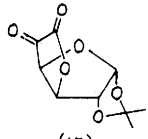
(12) BDPS = $SiBu^tPh_2$



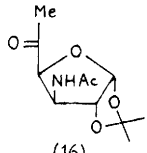
(13)



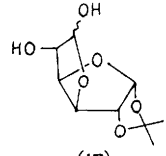
(14)



(15)



(16)



(17)

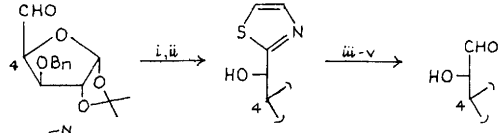
2 Dialdoses

A review has been published on the irradiation of hexoses in methanol in the presence of titanium tetrachloride which results in pentodialdoses by C-5, C-6 cleavage.[14] More specifically, 1,2-O-isopropylidene-α-D-glucose 6-pyruvate on photolysis in benzene gives the dialdose (17).[11]

Specifically C-6 deuterated D-galactopyranose derivatives have been shown by n.m.r. to have the gt preferred rotamer state about

C-5 - C-6, and the methyl β-D-pyranosides were used to show that a D-galactose oxidase gives the dialdose glycoside mainly by pro-S hydrogen specific oxidation.[15]

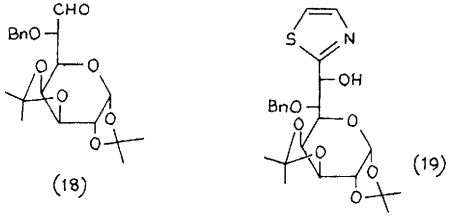
Homologation by highly stereoselective addition of 2-trimethylsilylthiazole (a formyl anion equivalent) has been effected by a highly stereoselective process as indicated in Scheme 2. 1,2:3,4-



Reagents: i,  ; ii, Bu_4NF; iii, MeI; iv, $NaBH_4$; v, $HgCl_2$-H_2O

Scheme 2

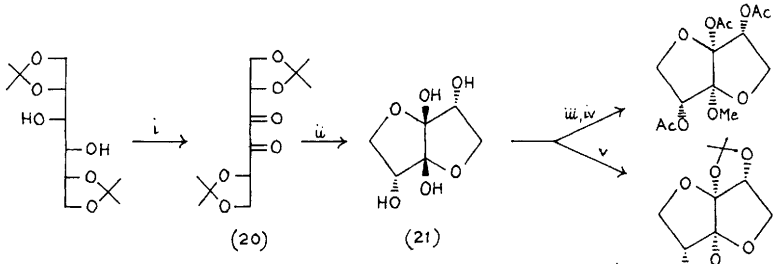
Di-O-isopropylidene-D-galactose was treated similarly and the product (18) was again treated to give (19), but with reduced diastereoselectivity.[16]



(18) (19)

3 Diuloses

Oxidation of 1,2:5,6-di-O-isopropylidene-D-mannitol gave the diulose (20), which on hydrolysis gave the crystalline (21), and this afforded derivatives as shown in Scheme 3.[17]



(20) (21)

Reagents: i, DMSO-Ac_2O; ii, H_2SO_4-MeOH; iii, H^+-MeOH; iv, Ac_2O-Py; v, Me_2CO-H^+

Scheme 3

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16
Sugar Acids and Lactones

1 General

A review has appeared on the analysis, structures, nomenclatures and reactions of acids derived from monosaccharides and polysaccharides.[1]

2 Aldonic Acids

6-Deoxy-D-mannono-1,4-lactone has been found for the first time as a plant product.[2]

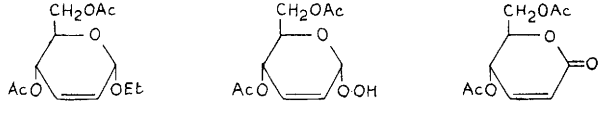
Configurational and conformational conclusions have been drawn from the ^{1}H n.m.r. spectra of aldonates and aldarates,[3] and the solution conformations of aldono-1,4-lactones enriched with ^{13}C at C-1 have been determined using ^{1}H-^{1}H, ^{13}C-^{1}H and ^{13}C-^{13}C coupling constants.[4] More specifically, the conformational solution equilibrium of 2,4,6-tri-O-benzoyl-3-deoxy-D-arabino-hexono-1,5-lactone has been described following ^{1}H n.m.r. analysis.[5]

The non-enzymic oxidation of D-glucose (to D-gluconic acid) and of related polyhydroxyaldehydes by pyrroloquinoline quinone, the coenzyme PQQ of several oxidoreductases, e.g., glucose dehydrogenases, has been shown to involve the 1,2-enediolate, and the differences in substrate reactivity correlate mainly with the equilibrium concentrations of the acyclic modifications from which the enediolate is produced.[6]

2-Deoxyaldonic acids result in good yield from the treatment of aldose 2-sulphonates with aqueous lead (II) hydroxide under nitrogen.[7] Related conversion in excellent yield of 1,6-di-O-tosyl-D-fructose into 2-deoxy-D-arabino-hexonic acid on reaction with this lead derivative in chloroform is much more remarkable.[8]

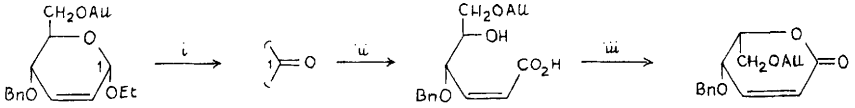
Studies carried out on aldonic acids relate to the C-2 epimerization of the pentonic acids in aqueous alkali,[9] the increased abilities of aldonates to coordinate calcium ion in alkaline solution when in the presence of borate ions,[10] and the thermal behaviour of 2-benzylamino-2-deoxyheptonic acids in air and in nitrogen.[11]

Several studies have concerned 2,3-unsaturated aldonolactones. Oxidation of glycoside (1) with hydrogen peroxide and catalytic molybdenum trioxide gave mainly the unstable α-hydroperoxide (2) which readily affords the lactone (3).[12]



(1) (2) (3)

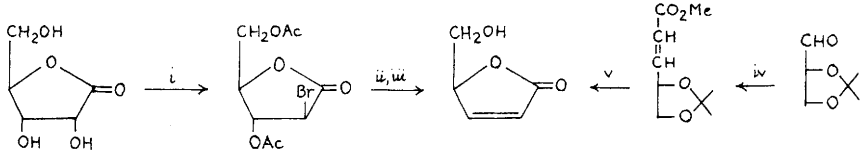
More specifically, an L-threo-hexonolactone derivative was made by a specific C-5 inversion procedure as indicated in Scheme 1.[13] Two



Reagents: i, MCPBA-BF_3. Et_2O; ii, LiOH-H_2O; iii, Ph_3P-DEAD

Scheme 1

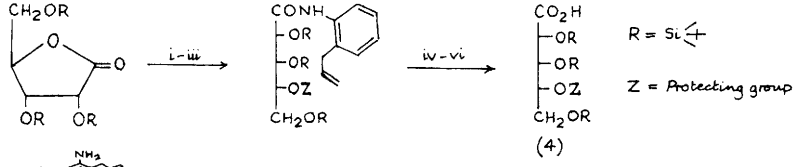
approaches, one from D-ribono-1,4-lactone[14] and one by way of a Wittig procedure,[15] to the crystalline synthon (S)-5-hydroxymethyl-2(5H)-furanone are illustrated in Scheme 2.[16]



Reagents: i, HBr-HOAc; ii, $NaHSO_3$(aq); iii, HCl-H_2O-MeOH; iv, $Ph_3P{=}CHCO_2Me$; v, H^+

Scheme 2

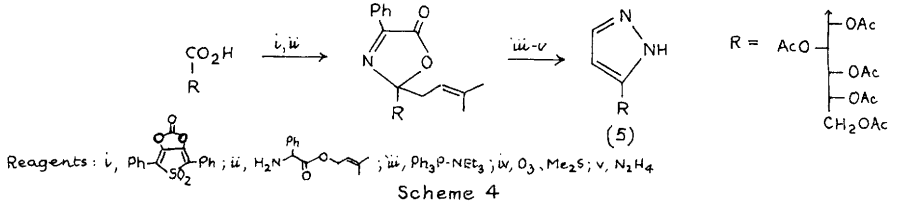
A considerable number of aldonic acid derivatives have been reported. Acyclic derivatives are the substituted free acids (4) (Scheme 3)[17] and the pyrazoles (5) (Scheme 4).[18] The spiro-



(4)

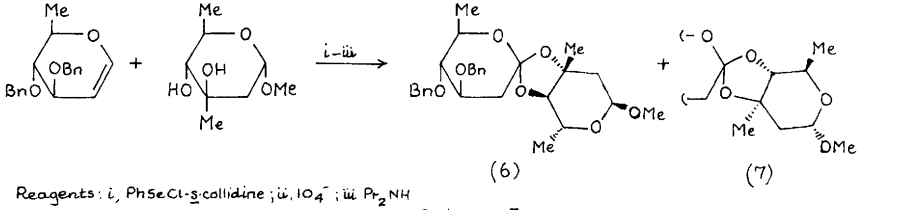
Reagents: i,  ; ii, Me_2AlCl; iii, Protecting reagent; iv, O_3; v, Me_2S; vi, OH^-

Scheme 3



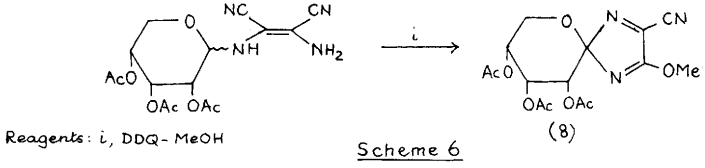
Scheme 4

compounds (6) and (7) have been prepared as indicated in Scheme 5, the latter having the stereochemistry at the spiro-centre of a



Scheme 5

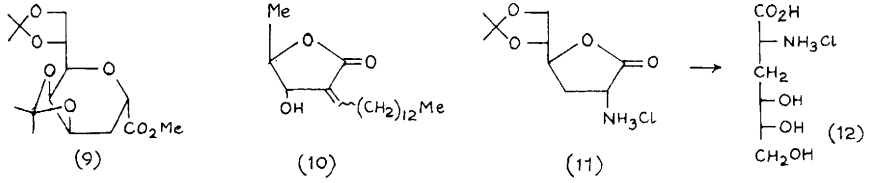
unit of the orthosomycins.[19] The diaza-spiro compound (8), which is related to the nucleosides, was made as shown in Scheme 6.[20]



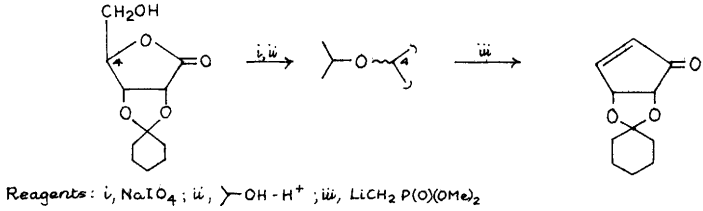
Scheme 6

The anhydro-octonic acid derivative (9) and several derivatives made by modification of the ester group have been synthesized as CMP-KDO synthetase inhibitors.[21]

In the 1,4-lactone series compounds (10), the plant products (-) litsenolides, were made by Wittig procedures from a 2-uloside derivative,[22] and the aminolactone (11) was derived from 5,6-O-isopropylidene-D-mannono-1,4-lactone as a precursor of trihydroxy-



norleucine (12).[23] The chemistry outlined in Scheme 7 illustrates a novel and useful entry into the optically pure cyclopentanes.[24]



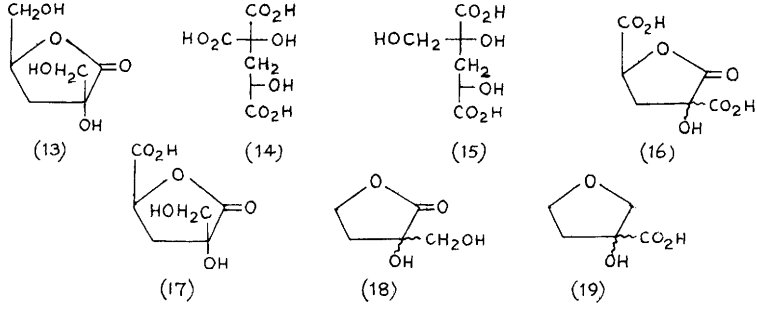
Reagents: i, $NaIO_4$; ii, $\rangle$—OH - H^+; iii, $LiCH_2P(O)(OMe)_2$

Scheme 7

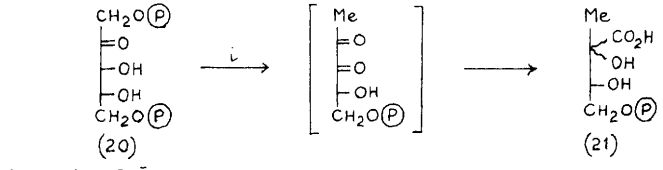
3 Saccharinic Acids

A ^{13}C n.m.r. study has been carried out on the alkaline degradation products of monosaccharides; the acidic products with up to six carbon atoms were readily identified. [1-^{13}C]-D-Glucose was used during the work.[25]

The main products of nitric acid oxidation of glucoisosaccharinic acid lactone (13) were found by g.l.c.-m.s. after trimethylsilylation to be the acids (14) and (15) and their respective lactones (16) and (17).[26] The same author has found that D,L-xyloisosaccharinic acid lactone (18) rearranges in aqueous acid mainly to the tetrahydrofurancarboxylic acid (19).[27]



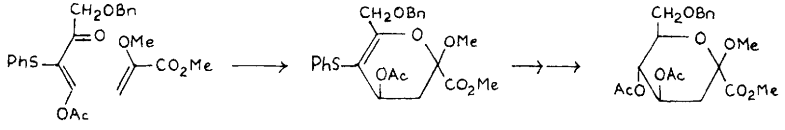
D-Erythro-pentulose 1,5-diphosphate (20) with alkali gives the saccharinic acid monophosphate (21), a process suggested to parallel that occurring during the incorporation of pentose chains into the base unit of riboflavin. It was proposed that decarboxylation of a compound such as (21) provides the four carbon atoms required.[28]



Scheme 8

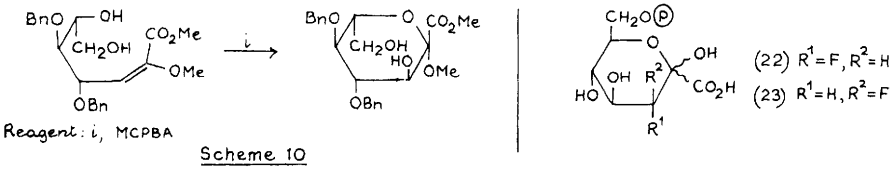
4 Ulosonic Acids

A synthesis of a racemic 3-deoxy-arabino-hept-2-ulosonate derivative is outlined in Scheme 9,[29] and that of a β-L-gluco-hept-2-ulosonic



Scheme 9

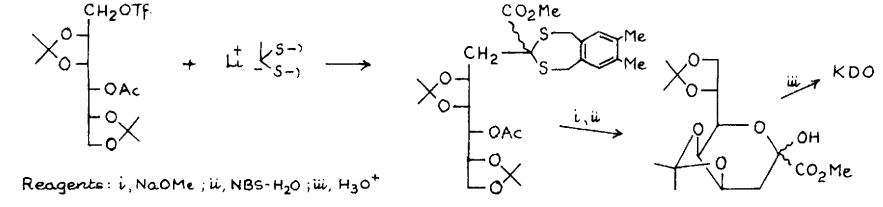
acid ester in Scheme 10, the starting material having been obtained by a Wittig procedure.[30] Treatment of a 2-deoxy-2-fluoro-D-glucose and -D-mannose 6-phosphates with 3-dehydroquinate synthetase from



Scheme 10

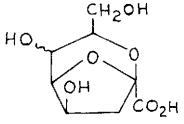
E. coli (an enzyme of the shikimic acid pathway) gave the hept-2-ulosonic acids (22) and (23), respectively, and these were tested as biosynthetic precursors of 6-fluoroshikimic acid derivatives.[31]

A new synthesis of 3-deoxy-D-manno-oct-2-ulosonic acid (KDO) has been described (Scheme 11).[32] Treatment of the product with dilute

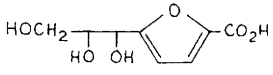


Scheme 11

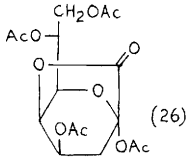
acid gives mixed compounds from which the furanoid 2,7-anhydride (24) and the furan (25) have been isolated.[33] Acetylation of the



(24)

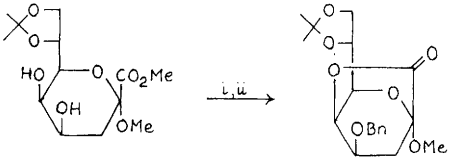


(25)



(26)

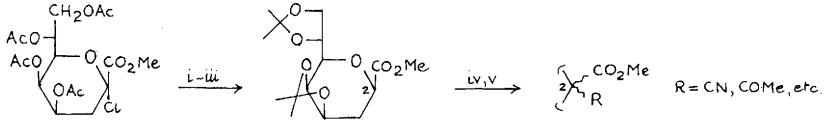
ammonium salt of KDO with acetic anhydride in the presence of sodium acetate gave mainly the α-penta-acetate, but some amounts of the lactone tetraester (26) were also formed. The small lactone system was formally obtained by the process indicated in Scheme 12.[34]



Reagents: i, Bu_2SnO; ii, BnBr

Scheme 12

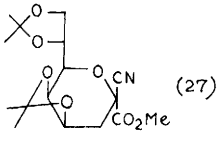
Some C-glycoside derivatives of KDO have been prepared as indicated in Scheme 13. Compound (27) was characterized by x-ray



Reagents: i, H_2-Pd/C; ii, MeO^-; iii, Me_2CO-H^+; iv, LDA; v, RX

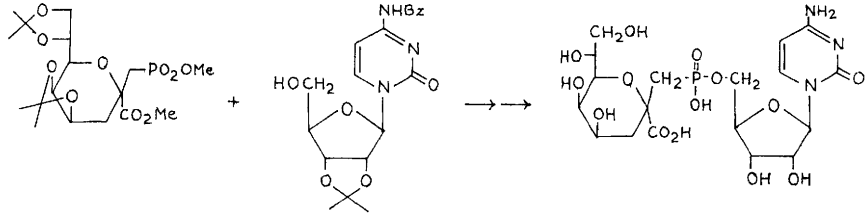
Scheme 13

diffraction as a reference for determining anomeric configuration.[35]

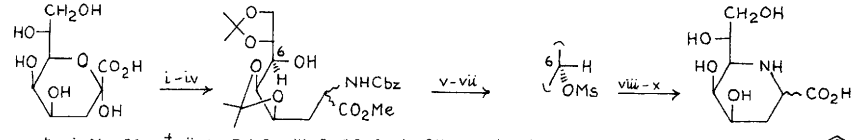


(27)

The phosphonate analogue of cytidine 5′-monophospho-3-deoxy-D-manno-oct-2-ulosonic acid has been synthesized as illustrated in Scheme 14,[36] and "azacyclic-2-deoxy-KDO" was produced from KDO as shown in Scheme 15; both anomers were poor inhibitors of CMP-KDO synthetase.[37]



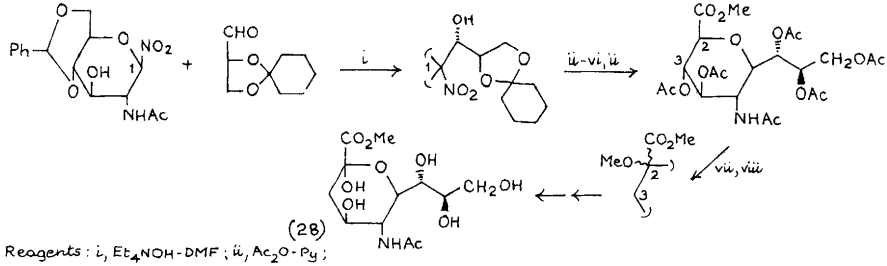
Scheme 14



Reagents: i, Me_2CO-H^+; ii, $NaBH_3CN$; iii, BnOCOCl; iv, CH_2N_2; v, $(COCl)_2$-DMSO; vi, $NaBH_4$; vii, MsCl; viii, Pd-⬡; ix, Pr^i_2NEt; x, H^+

Scheme 15

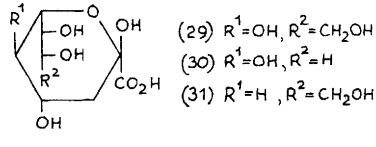
In the area of nonulosonic acids, three acetylated 2,3-unsaturated neuraminic acid derivatives have been isolated from urine or from submandibular glands of mammals.[38] A synthesis of N-acetylneuraminic acid (28) from N-acetyl-D-glucosamine is illustrated in Scheme 16,[39] and 3-deoxy-D-glycero-D-galacto-nonulosonic acid (29),



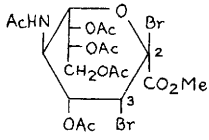
Reagents: i, Et_4NOH-DMF; ii, Ac_2O-Py; iii, Bu_3SnH; iv, H_2-Pd/C; v, PtO_2; vi, CH_2N_2; vii, DBU; viii, NBS-MeOH

Scheme 16

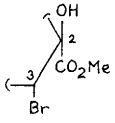
which occurs naturally in a trout glycoprotein, has been made by condensation of D-mannose with pyruvic acid in the presence of immobilized acylneuraminate pyruvate lyase. D-Lyxose and 2-deoxy-



D-arabino-hexose similarly gave (30) and (31).[40] From the relevant 2,3-ene the glycosyl donors (32), (33) and (34) have been prepared,[41] and the last of these gives β-glycosides, including disaccharides linked via primary and secondary positions, in the presence of trimethylsilyl triflate.[42] On the other hand, α-glycosides were formed from 3-hydroxy β-glycosyl halide analogues, the hydroxy group



(32)



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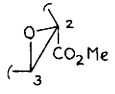

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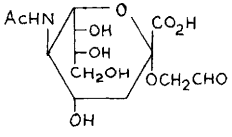
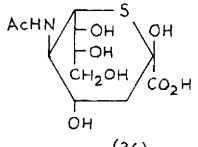


(35)

being removable after glycoside formation.[43] The α-glycoside (35), produced from the allyl analogue, was made for coupling to proteins as immunogenic neoglycoproteins, and the allyl glycoside copolymerized with acrylamide gave a water soluble polymer with useful serological properties.[44] Various 7- and 8-oxo-derivatives of N-acetylneuraminic acid have been synthesized by specific methods,[45] and 7- and 8-epimers of the 2,3-unsaturated analogue have been reported.[46] The 6-thio compound (36) has been prepared from (37) by use of oxalylacetic acid,[47] and N-acetylneuraminic acid gave (38) in 70% yield on treatment with benzyl, allyl or methyl halides in the



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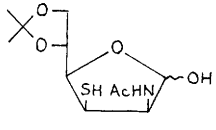

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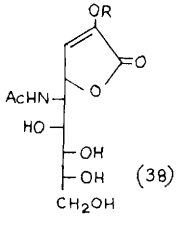


(38)

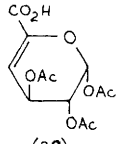
presence of cesium carbonate in DMF.[48]

5 Uronic Acids

Sitosterol 3-O-α-D-xyluronofuranoside, the first natural product recognized as containing this carbohydrate unit, has been isolated from a plant source.[49]

Treatment of α-D-galactopyranuronic acid with acetic anhydride and (diethylamino) pyridine gave the alkene (39) in high yield; heating in acetic anhydride together with acetic acid led to the pyranone (40).[50] Elimination reactions were also used to obtain the

phenyl glycoside (41) and its β-anomer which were required for the examination of a glycosiduronase.[51]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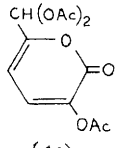
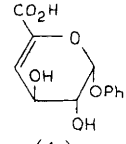
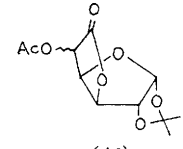

(40)


(41)


(42)

Two conformational investigations - one a force-field study[52] and the other a high field n.m.r. study[53] - have been carried out on the α-idopyranuronic acid ring in connection with polysaccharide research. In the latter work disaccharide derivatives having the acid linked to D-mannose were prepared, and sulphation was found to influence the adopted conformations appreciably. In both studies the $^{4}C_{1}$, $^{1}C_{4}$ and $^{2}S_{o}$ conformations were found to be significant.

The deacylation of compounds such as the epimers (42) is difficult chemically, but can be achieved by selective enzymes; the D-gluco-compound was hydrolysed with an Aspergillus enzyme, and the L-ido-isomer by porcine pancreatic lipase.[54]

Several derivatives, including the ethyl ester and the 3-O-dichlorophosphoryl acid chloride, of 1,2-O-cyclohexylidene-α-D-xylofuranuronic acid have been reported.[55] 3,5-Anhydrides of 1,2-O-isopropylidene-α-D-glucuronic and -β-L-iduronic acid derivatives are described in Chapter 5.

D-Glucuronolactone has been used in the preparation of several aminoacids related to D-glucuronic acid having nitrogen as the ring hetero-atom (Chapter 24), and some octuronic acid derivatives are noted in Chapter 20.

6 Ascorbic Acids

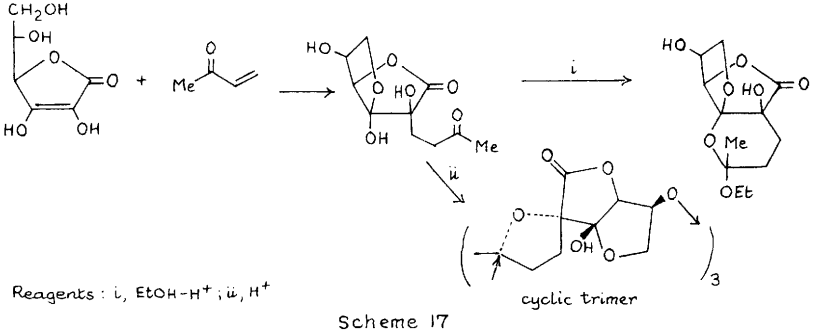
A theoretical ab initio MO study of the oxidation of L-ascorbic acid to dehydroascorbic acid has been reported,[56] and several further practical investigations have been described as follows: the Cu^{2+} catalysed reaction over a range of pH values,[57] the related reaction using polyamine chelates of the metal ion,[58] the Ru^{3+} - EDTA catalysed oxidation with hydrogen peroxide[59] and the related oxygen oxidation.[60] An essay has appeared on the existence of an equilibrium between ascorbic and dehydroascorbic acids.[60A]

Alkaline degradation of L-ascorbic acid affords over 50 products of which 32 have been identified as carboxylic acids which bear a

relationship to human urinary organic acids.[61]

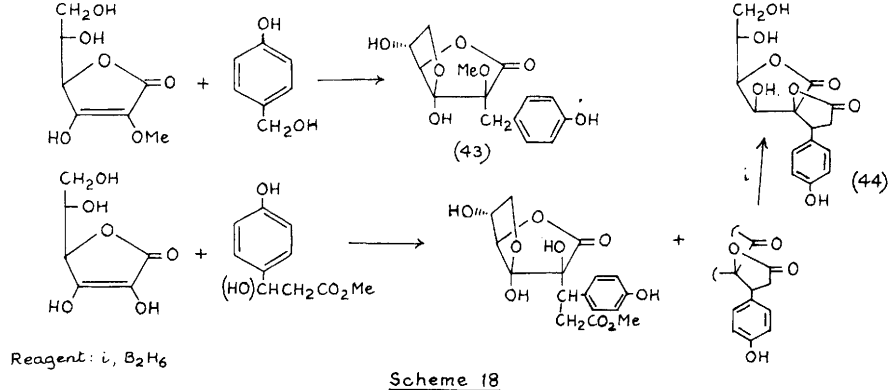
Evidence from the study of the complexing between vitamin C and cobalt-ammine cations suggests the acid binds monodentally through O-3 in $[Co(NH_3)_5$ ascorbate$]^{2+}$ and bidentally via O-1 and O-4 in $[Co(NH_3)_4$ ascorbate$]^{2+}$.[62]

The product of treatment of L-ascorbic acid with butenone is shown in Scheme 17; it reacts with ethanol and trimerizes as



Scheme 17

indicated. The trimeric product was characterized by x-ray diffraction analysis.[63] Related work led to syntheses of the marine algal metabolite delesserine (43) and leucodrin (44) a phenolic constituent of proteaceae (Scheme 18).[64]



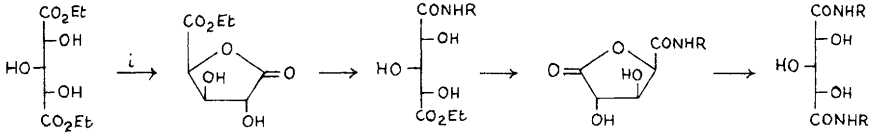
Scheme 18

The positive and negative ion laser-desorption Fourier transform mass spectra of ascorbic and isoascorbic acid have been reported.[65] See Chapter 15 for the electrochemical synthesis of 1,2-O-isopropylidene-D-xylo-5-hexulofuranurono-6,3-lactone.

7 Aldaric Acids

The electrocatalytic oxidation of D-gluconic acid at a ubiquinone-mixed carbon paste electrode with an immobilized layer of D-gluconate dehydrogenase has been described.[66]

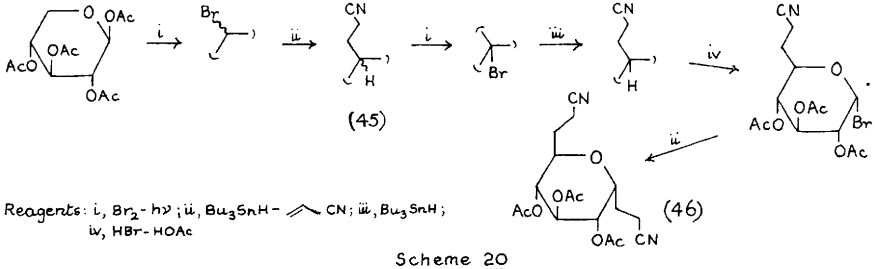
The aminolysis of diethyl xylarate proceeds as shown in Scheme (19).[67]



Reagent: i, RNH_2

Scheme 19

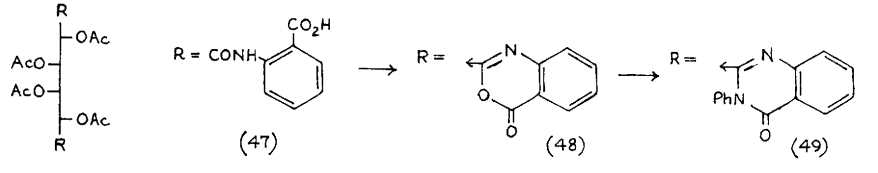
The 4,8-anhydroundecaldaric acid derivative (46) has been prepared as indicated in Scheme 20. The epimeric mononitriles (45)



Scheme 20

were converted into the D-gluco-compound by a second photobromination procedure which can be rationalized in terms of the conformation of the intermediate C-5 radical.[68]

Condensation between tetra-O-acetyl-D-galactaric acid dichloride and anthranilic acid gave the diamide (47) and thence with acetic



anhydride compound (48) and further with aniline and phosphorus trichloride the quinazolone (49).[69]

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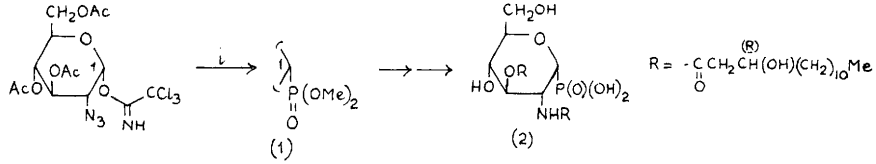
17
Inorganic Derivatives

1 Carbon-bonded Phosphorus Derivatives

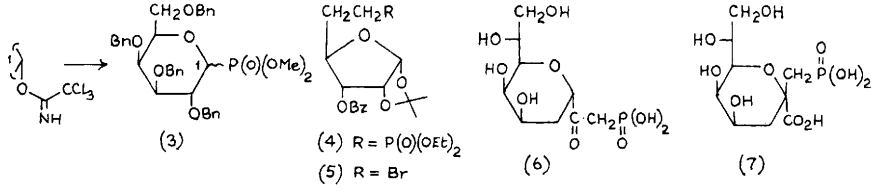
The first sugar analogues with a phosphinothioyl group in the ring have been described with the synthesis of 5-deoxy-3-O-methyl-5-C-[phenylphosphinothioyl]-α- and β-D-xylopyranoses.[1] A glycosyl phosphonate (1) has been prepared as outlined in Scheme 1, during the synthesis of a lipid analogue (2). The same strategy in the D-galacto series gave a 1:1 mixture of the phosphonate anomers (3).[2]



Reagents: i, $P(OMe)_3$ - TMSOTf - CH_2Cl_2

Scheme 1

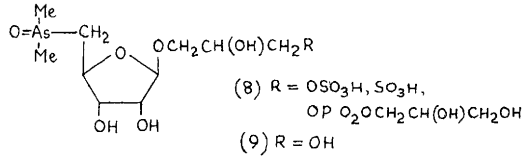
The phosphonate (4) has been synthesized by employing an Arbusov reaction on the 6-bromo derivative (5), leading to nucleoside derivatives of (4).[3] Synthesis of the 2-deoxy-β-KDO analogue (6) has been reported,[4] as well as a 5'-cytosine derivative of the

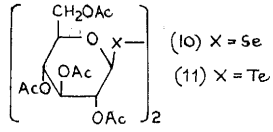


phosphonic acid (7).[5]

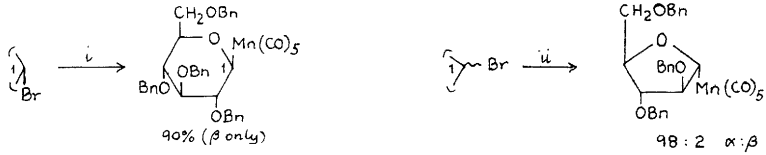
2 Other Carbon-bonded Derivatives

A number of arsenic - containing ribofuranosides (8) have been isolated from edible brown seaweed,[6,7] and the synthesis of the glyceride (9) has been reported.[8] The circular dichroism of some diselenides, e.g., (10), and the ditelluride (11) has been studied.[9]





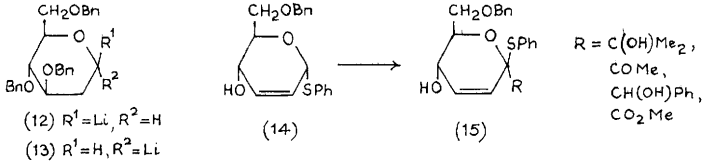
Further studies on the formation of glycosyl manganese complexes (Vol.19, p.29-30, 161) has shown that both the yield and stereoselectivity of the reaction is affected by adding bromide ion to the reaction mixture (Scheme 2).[10]



Reagents: i, $NaMn(CO)_5$ - KBr (3 eq.) ; ii, $NaMn(CO)_5$ - Bu_4NBr (3 eq.)

Scheme 2

The use of glycosyl lithium reagents for the synthesis of higher sugars by reaction with aldehydes has been reviewed.[11] The configurationally stable glycosyl lithium species (12) and (13) (derived from the corresponding stannanes) were used to synthesize 2-deoxy-C-glycosides by effecting a conjugate addition on cyclic or acyclic enones.[12] Proton abstraction from the thioglycoside (14)

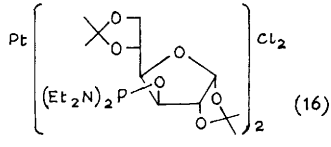


gave the corresponding glycosyl lithium species which trapped electrophilic reagents from the α-face to give C-1 alkylated or acylated derivatives (15). It was postulated that the α-lithium species was formed due to intramolecular bonding of Li with O-4.[13]

3 Oxygen-bonded Derivatives

A chelate of phenyl 4,6-O-(R)-benzylidene-2,3-O-bis(diphenylphosphino)-β-D-glucopyranoside with rhodium (I) gives a stable highly active catalyst for the hydrogenation of N-acyl-dehydro-α-amino acids yielding, in high enantiomeric excess, N-acyl-(S)-α-amino

acids.[14] The reaction of diethyldithioacetals of some pentoses with tris(diethylamino)phosphite afforded 2,3:4,5-di-O-cyclic amidophosphites, which on treatment with sulphur gave the corresponding amidothiophosphates.[15] Treating phosphorus derivatives of monosaccharides with the platinum compound Pt(1,5-cyclooctadiene)Cl_2 yielded platinum complexes, e.g., (16).[16]



(16)

The structures of borate esters of some polyhydroxy carboxylates in water has been studied using ^{13}C and ^{1}H n.m.r.[17] Sucrose has been selectively acetylated using its per-diethylboryl ester and derived boronate esters.[18] The introduction and removal of tert-butyldimethylsilyloxy groups using boron derivatives has been carried out. The diethylboronate ester of an alcohol was converted to a tert-butyldimethylsilyl ether under Lewis acid catalysed conditions. Desilylation back to the diethylboronate derivative was achieved using bis(diethylboronyl)oxide and trimethylsilyl-triflate.[19] Treatment of 2,3:5,6-di-O-ethylboranedi-yl-α-D-manno-furanosyl bromide with C_{7-16} n-alkanols and sodium triethylborate gave corresponding β-mannofuranosyl alkyl glycosides.[20]

A review on organotin derivatives of sugars has appeared covering trialkyltin alkoxides, dialkyltin alkoxides and derivatives containing other types of tin-sugar links.[21] Cross-linked metal-containing networks have been shown to be formed through the condensation of organostannanes with sucrose.[22] The C-2 epimerization of aldoses by various metal complexes has been the object of a number of studies outlined in chapter 2. The Cotton effects of bidentate complexes between [Mo_2 $(OAc)_4$] and some sugar diols has been studied. It is proposed that the absolute configurations of open chain vicinal diols of the threo - configuration and of vicinal primary - secondary diols can be determined in this way.[23]

In a study of the interaction between calcium ions and fructose, the I.R. spectra of free β-D-fructose and its various calcium complexes were examined, and a correlation between the spectral changes and the co-ordination sites involved was established.[24] The standard enthalpies of transfer of ribose and arabinose from water to aqueous solutions of various metal salts has allowed the equilibrium constants and free energies and entropies of the associations

to be determined.[25] L-Arabinose interacts with Sr^{++} and Ba^{++} salts in aqueous solution to give complexes of the type $M(L\text{-}Ara)X_2.4H_2O$ which have been isolated and characterized spectroscopically.[26] Similarly uranium - arabinose solid complexes of the type $UO_2(L\text{-}Ara)X_2.2H_2O$ have been characterized.[27] β-D-Glucurono-γ-lactone forms solid complexes with silver (I) salts which have been characterized by F.T.I.R. and X-ray powder diffraction.[28] Freshly precipitated aluminium hydroxide has been complexed with a number of sugars in hot water to give non-ionic colloidal chelates, where stability, percentage aluminium content and isoelectric points were determined.[29]

The increased abilities of a number of polyhydroxycarboxylates to co-ordinate calcium in aqueous alkaline solution in the presence of borate ions has been studied.[30] An e.p.r. and potentiometric study of the complexation of copper ions by galacturonic acid and galacturonans has indicated the stepwise formation of Cu(II)-galacturonate complexes. Weaker bonds were formed with polymers than with monomers, so the greater affinity of Cu(II) for the polymers in due mainly to entropic effects.[31] Magnetic susceptibility and Mossbauer emission measurements have been used to study the local modifications appearing around the cobalt cation after the dehydration reaction of the Co-5'-inosine phosphate $7H_2O$ complex.[32] A study of the ^1H and ^{13}C - n.m.r. spectra of methyl 2-acetamido-2-deoxy-hexopyranosides in the presence of lanthanide ions is mentioned in chapter 9.

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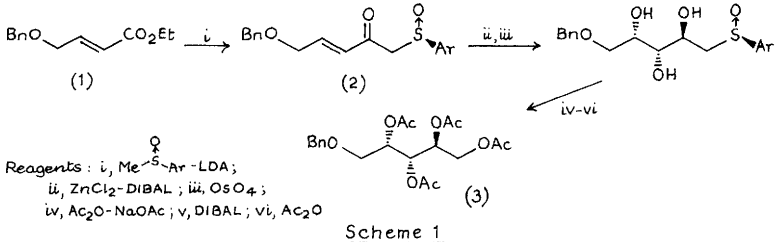
18
Alditols and Cyclitols

1 Alditols

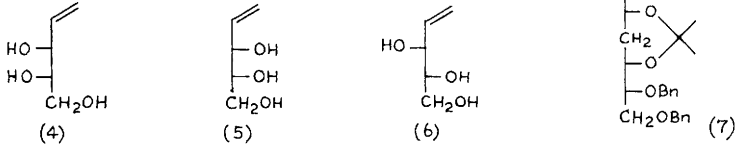
1.1 Acyclic Alditols.- A new approach to the synthesis of optically pure polyhydroxylated compounds by i) the stereospecific reduction of chiral β-ketosulphoxides and ii) the stereospecific hydroxylation of chiral allylic β-hydroxysulphoxides has been described. Thus the unsaturated ester (1) gave the chiral sulphoxide (2), which was sequentially reduced, hydroxylated, and further reduced as outlined in Scheme 1 to give the L-arabinitol derivative (3) and hence penta-O-acetyl-L-arabinitol in high yield; enantiomers are available by appropriate choice of the sulphoxide reagent.[1]



Scheme 1

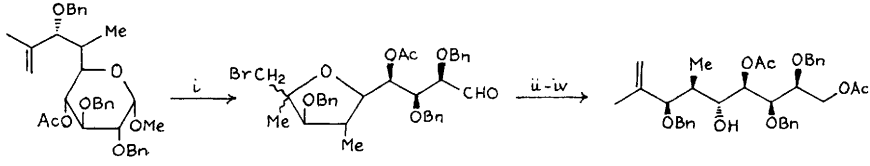
Further studies have been reported by Brimacombe's group on the synthesis of decitol derivatives; previously-described procedures have been used to prepare D-altro-D-galacto-decitol together with the L-altro- and D- and L-gluco- isomers derived from 1,2;3,4-di-O-isopropylidene-D-galactopyranose.[2]

A comparison of routes to 4-pentenetriols using chiral-phase g.c. showed that whereas D-ribonolactone gave the optically pure L-erythro isomer (4), Grignard reaction of 2,3-O-isopropylidene-D-glyceraldehyde gave a 62:38 mixture of the D-erythro and D-threo isomers (5) and (6) respectively, and Sharpless asymmetric epoxidation of divinylcarbinol gave either of the threo enantiomers with



96% diastereoselectivity and 91-96% enantioselectivity.[3] The derivative (7) of 3-deoxy-D-ribo-hexitol has been prepared from the 3-deoxy-hexose to confirm the configuration of an enantiomer obtained by routes from L-glutamic acid, D-ribonolactone or D-mannitol during syntheses of the C(1)-C(13) segment of amphotericin B.[4]

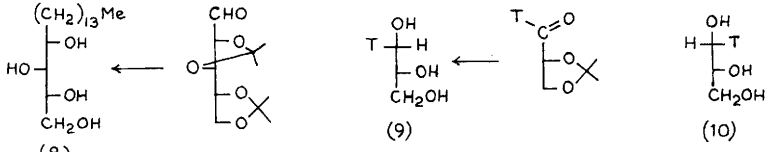
A novel method for converting glycosides to acyclic derivatives involves the oxidative addition of the ring oxygen to a remote olefinic centre, with subsequent reductive cleavage, as illustrated in Scheme 2.[5]



Reagents: i, NBS-MeCN-$NaHCO_3$; ii, $NaBH_4$; iii, Ac_2O-DMAP; iv, Zn-EtOH-NH_4Cl

Scheme 2

Standard reactions have been used to convert aldehydo derivatives of D-ribose, D-xylose, and D-arabinose to the L-ribo-, L-xylo-, and D-lyxo- stereoisomers of octadecane-1,2,3,4-tetrols; the natural product guggultetrol-18 was shown to be the enantiomer of the L-xylo compound (8).[6]

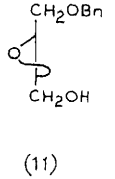


D-Mannitol has been used to prepare chiral glycerol derivatives. Mannitol 1,2;5,6-bis-acetonide 3-monobenzoate was labelled at C-4 with tritium by an oxidation-sodium borotritiide reduction procedure and then conventional 3-4 cleavage yielded the 1-tritiated glyceraldehyde, which was enzymatically reduced to the labelled glycerol (9); reduction of the unlabelled aldehyde with the enzyme (horse-liver alcohol dehydrogenase) in presence of tritium-labelled cyclohexanol yielded the epimeric labelled glycerol (10).[7] Another paper describes the conversion of 1,3;4,6-di-O-acetalated D-mannitol to (R) and (S)-1-substituted-2-O-benzyl-glycerol derivatives using conventional procedures.[8] Fluorine-containing long-chain alkyl ethers of glycerol have been prepared from D-threitol, which were then converted to phosphorylcholine derivatives (see also Chapter 24).[9]

A study of the optimum parameters for the hydrogenation of D-glucose to D-sorbitol has been reported.[10] Physico-chemical properties of D-sorbitol have also been recorded.[11]

1.2 Anhydro-Inositols.- A dianhydro-nonitol, a novel antitumour antibiotic, is mentioned in Chapter 19.

Sharpless oxidation of (Z)-2-butendiol 1-benzyl ether gave the D-threo oxiran (11) in 85% e.e..[12] D-Mannitol has been used to



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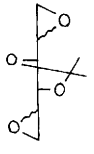

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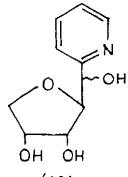
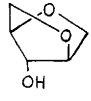


(13)



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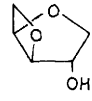
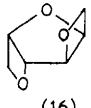


(15)

prepare 1,2;5,6-dianhydro derivatives (12) of mannitol and iditol, together with corresponding diaziridines, and hence enantiomerically pure α-hydroxy and α-amino-aldehydes and -acids.[13] 1,2;3,4;5,6-Tri-oxiran derivatives of hexitols have also been reported from dianhydro-hex-3-enitol and hexatriene precursors using standard epoxidation procedures.[14]

2,5-Anhydro derivatives (13) of 2-(D-allo and D-altro-pentitol-1-yl)-pyridines have been synthesized from 2,4;3,5-di-O-benzylidene-D-ribose and 2-silylated pyridine via the corresponding acyclic pentitols.[15]

Di-anhydro-pentitols (14) and (15) have been prepared from 1,4-anhydro-5-chloro-5-deoxy-D-arabinitol and -D-xylitol respectively,[16] and another paper has described a similar synthesis of the L-enantiomer of (15) together with oxetans of 2,5-anhydro-hexitols and the dioxetans (16) and (17),[17]



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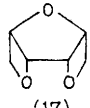

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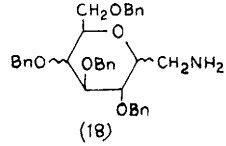


(18)

Reaction of D-gluco- or D-galactosyl 1-acetates with trimethylsilylcyanide - boron trifluoride etherate yielded α- and β-glycosyl cyanides which were reduced to 1-amino-2,6-anhydro-heptitols (18) using lithium aluminium hydride.[18]

Procedures have been described for synthesizing 1,4;3,6-dianhydro-hexitols from D-glucitol[19,20] and D-mannitol,[19] and for 1,4-anhydro-DL-xylitol from D-xylitol,[21] under acid-catalysed

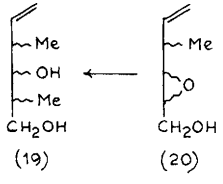
conditions.

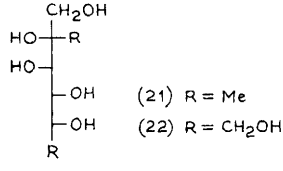
Acylation of 1,4;3,6-dianhydro-D-glucitol with acid anhydride in presence of lead oxide at room temperature gave mainly endo O-5 ester, whereas using the anhydride alone at 120-140°C gave a mixture which, on distillation in presence of basic catalysts, yielded the more volatile exo O-2 ester.[22]

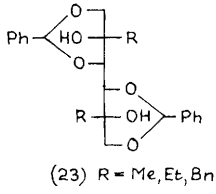
A new synthesis of 1,4-anhydro-2-deoxy-D-erythro-pentitol has been described, and phosphotriester and phosphoramidite derivatives were prepared and incorporated into synthetic DNA fragments.[23] Synthetic immunomodulators combining lipid A and 1-deoxy-muramyl dipeptides have also been reported.[24] Full details on the synthesis of a macrocyclic polyether incorporating 1,5-anhydro-D-glucitol have been published.[25] (see Vol. 19, p.171).

The contribution to the c.d. of pair interaction between acetyl groups in acetyl derivatives of 1,5-anhydro-alditols accounts for the observed signal, and allows their stereochemistry to be deduced.[26]

1.3 Branched-Chain Alditols.- Doubly branched alditols (19) have been prepared (as sections of erythronolide B) by cuprous cyanide catalysed cleavage of oxiran precursors (20) using methyl-lithium, the precursors being readily available from D-glyceraldehyde.[27]

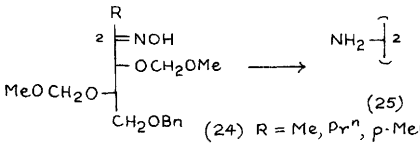






2-C-Hydroxymethyl-2,3;5,6-di-O-isopropylidene-D-mannofuranose has been converted conventionally to 6-deoxy-2-C-methyl-D-mannitol (21) and 2-C-hydroxymethyl-D-mannitol (22) as potentially sweet compounds but neither were sweeter than sucrose.[28] The related branched-chain mannitols (23) have also been prepared as potential asymmetric ligands for lithium aluminium hydride reagents, but these only showed low enantioselectivity in ketone reductions.[29] 1,3,5-Trideoxy-3,5-di-C-methyl-L-talitol, a chiron for the C(33)-C(37) segment of amphotericin B, has been prepared by standard reactions from glucose (see also Chapters 14 and 24).[30]

1.4 Amino-Alditols.- Anti-selective reduction of acyclic α-alkoxy and α,β-dialkoxy ketone oximes occurs with aluminium hydride reagents, L-threo-ketotetrose derivatives (24) giving L-xylitol analogues (25) preferentially (4:1 ratio); chelation control was postulated.[31]

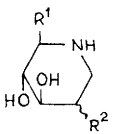


(24) R = Me, Pr^n, p-$MeOC_6H_4$

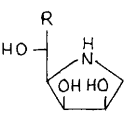
1-Amino-1-deoxy-alditol derivatives have been prepared conventionally from glucose and reducing oligosaccharides to provide linkage units to proteins[32] and resins[33] (see also Chapter 23); mixtures of reducing oligosaccharides can be easily separated on h.p.l.c. of their 1-amino-alditol derivatives.[32]

The stereochemistry of N-transacylation of 1,1-bis(acylamido)-1-deoxy-alditols using carboxylic anhydrides has been studied.[34]

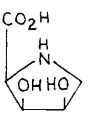
The biological activity of some cyclic imino-alditol derivatives has provoked extensive interest in their chemistry. Fleet's group has published full details of syntheses of 1,4-dideoxy-1,4-imino-D-mannitol (see Vol. 18, p.168), 1,4-dideoxy-1,4-imino-D-lyxitol (Vol. 19, p.170) and swainsonine (Vol. 18,p.253) from D-mannose,[35] syntheses of 2,5-dideoxy-2,5-D-mannitol and 2,6-dideoxy-2,6-imino-D-mannofuranoside (Vol. 19,p.169) from D-glucose,[36] and the conversion of the latter imino-mannoside into a range of 1,5-dideoxy-1,5-imino-alditols (26).[37](Vol.20,p.276, ref.65). They have also synthesized 1,4-dideoxy-1,4-imino-L-gulitol (27) and -D-lyxitol (28), together with the dihydroxy-proline (29) and 8-episwainsonine (30), from D-glucose via 3,6-dideoxy-3,6-imino-D-glucose (31),[35] and have used



(26) $R^1 = CH_2OH$ or CO_2H; R^2 = H, OH, or NHAc



(27) R = CH_2OH; (28) R = H



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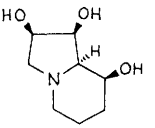

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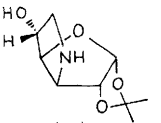
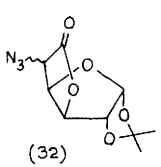


(31)

D-glucuronolactone to synthesize the epimeric 5-azido-sugars (32) and hence hydroxy-amino-acids which are proline or pipecolic acid derivatives, e.g., (33)-(35).[39,40](See also Chapter 24).



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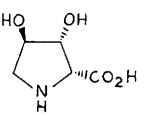

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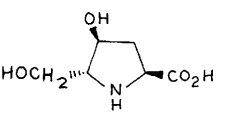

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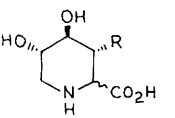
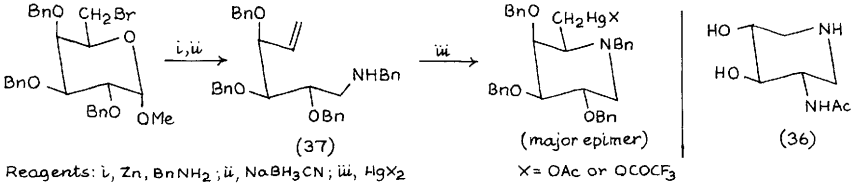


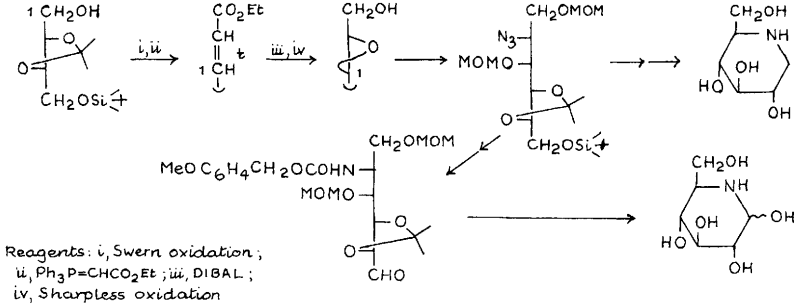
(35) R = H or OH

Other workers have reported syntheses of 1,5-dideoxy-1,5-imino-D-

galactitol from D-galactose, with the key steps illustrated in Scheme 3,[41] synthesis of the xylosaminitol derivative (36) from D-glucosamine in which the analogue of (37) was first ozonolysed and then reductively cyclized to form the ring,[42] a multistep conversion of 1-deoxy-nojirimycin to 2-acetamido-1,2-dideoxy-nojirimycin,[43] and a conversion of L-threitol to nojirimycin and 1-deoxy-nojirimycin as outlined in Scheme 4.[44]

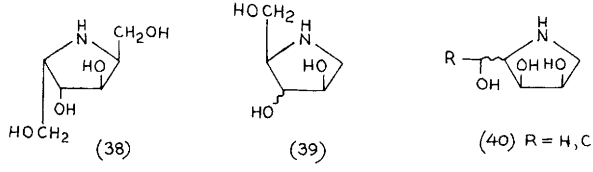


Scheme 3



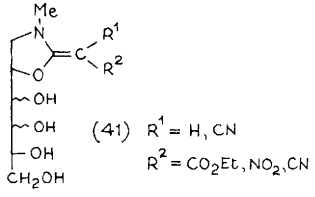
Scheme 4

Syntheses of 5-membered ring compounds have included an efficient four-step conversion of 1,3:4,6-di-O-benzylidene-D-mannitol to 2,5-dideoxy-2,5-L-iditol (38),[45] the preparation of 1,4-dideoxy-1,4-imino-D-arabinitol and -D-lyxitol (39) from non-carbohydrate precursors[46] (see also Chapter 24) and syntheses of 1,4-dideoxy-1,4-imino-pentitols and hexitols (40) from a 1-amino-1-deoxy-D-mannitol precursor.[46a]

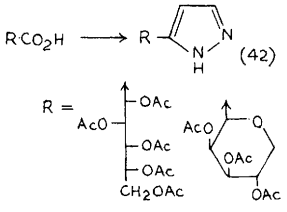


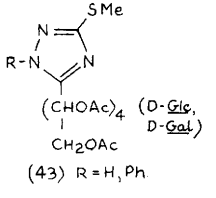
1.5 Heterocyclic Derivatives.- Alditol-1-yl heterocycles are of interest as analogues or precursors of C-nucleosides. 1-Deoxy-1-methylamino-D-hexitols treated with ketene dithioacetals produced

corresponding heterocycles (41).[47] 3,4,5,6,7-Penta-O-acetyl-1-bromo-1-deoxy-D-galacto-heptulose has been used to construct a number of D-galacto-pentitol-1-yl heterocycles, including thiazole derivatives.[48] Sugar acid derivatives have been converted to 3-substituted pyrazoles (42) in a five-stage reaction sequence.[49]



(41) R^1 = H, CN
R^2 = CO_2Et, NO_2, CN

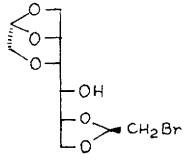




(43) R = H, Ph

1,2,4-Triazole derivatives (43) have been constructed from penta-O-acetyl-N-[bis(methylthio)methylene] hexanamides using hydrazine and hydrazino derivatives.[50] D-Gluco- and D-galacto-pentitol-1-yl derivatives of a number of heterocycles based on the 3-substituted indole skeleton have been prepared.[51]

1.6 Miscellaneous Compounds.- 1,2-O-Isopropylidene-5-O-tosyl-α-D-xylofuranose has been used to prepare 1- and 5-deoxy-xylitol disulphide and sulphide derivatives in standard steps.[52] Base treatment of cis,trans-1,2:5,6-di-O-(2-bromoethylidene)-D-mannitol and the corresponding cis,cis isomer gave the polycyclic derivatives (44) and (45) respectively, the products being unusually resistant to acid hydrolysis.[53] Standard reactions have been used to convert



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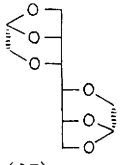


(45)

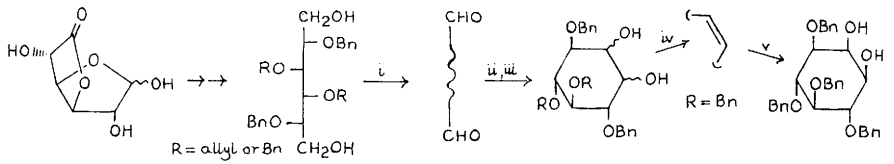
3,4-di-O-benzyl-D-mannitol to 2,3-O-protected D-glyceraldehyde derivatives using acetyl, silyl, or diisopropylmethylene acetal protecting groups.[54]

2 Cyclitols

2.1 Inositols.- Four new polyacylated derivatives of d- or l-inositol have been isolated from aerial parts of Mashallia tenuifolia, in which up to four hydroxy groups carry acetyl or angeloyl groups.[55] A new inositol glycoside, 2-O-β-L-arabinopyranosyl-myo-inositol, has been isolated as a major tea component.[56]

A new synthesis of (±)-pinitol utilizes enzymatic hydroxylation of benzene by Pseudomonas to give a cis-cyclohexadiene-1,2-diol which was then chemically oxidized in conventional steps to the required inositol mono-methyl ether.[57]

A new monosaccharide to inositol conversion has been developed in which D-glucuronolactone was transformed into a 2,3,4,5-tetrasubstituted hexitol intermediate and then cyclized as illustrated for myo-inositol in Scheme 5.[58]



Reagents: i, DMSO-$(COCl)_2$; ii, $TiCl_4$; iii, Zn/Cu-THF; iv, Ph_3P-Tri-iodo-imidazole; v, OsO_4-NMMO

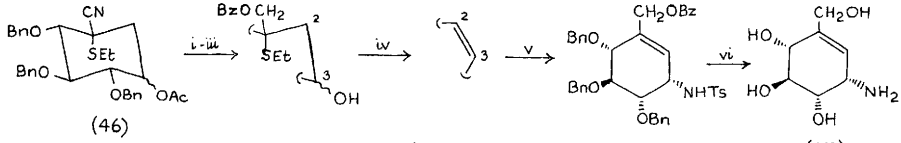
Scheme 5

Deuterium exchange on myo-inositol using deuterated Raney nickel in deuterium oxide yielded six other inositol isomers besides labelled myo-inositol; six of these labelled inositols could be separated by a combination of recrystallization and anion-exchange chromatography.[59] Gigg's group have recorded the conversion of myo-inositol to its 1,2,4- and 2,4,5-tri-O-benzyl ethers and its 1,2,3,4-tetra-O-benzyl ether,[60] its 1-L-1-O-methyl ether and its 1-D-1,2,4,5,6-penta-O-benzyl ether,[61] and its 1,2:5,6- and 1,2:3,4-di-O-isopropylidene derivatives.[62]

Potassium superoxide in presence of crown-ether has been used as an oxygen nucleophile to invert myo- to scyllo-inositol.[63] Standard procedures have been used to convert myo-inositol to 1-, 4-, and 5-deoxy-fluoro and 5-bromodeoxy and 5-chlorodeoxy analogues together with their epimers.[64]

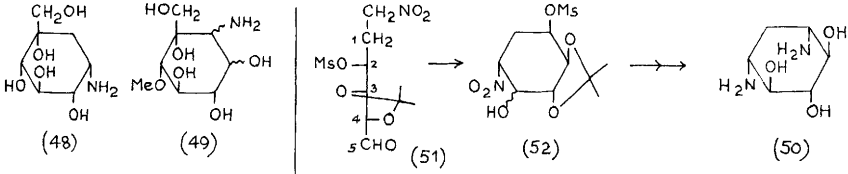
2.2 Amino-Inositols.- An enantioselective synthesis of (-)-fortamine in a multistep procedure from a chiral half-ester of cyclohex-4-ene-cis-1,2-dicarboxylic acid has been described,[65] as has a conversion of D-glucose to valienamine, using the Ferrier rearrangement to form an inosose ring, which was then reacted with cyanotrimethylsilane to introduce the branch carbon as a nitrile function; the intermediate (46) was then converted to valienamine (47) as outlined in Scheme 6.[66] Valiolamine (48) together with the analogues (49) have been prepared from a chiral cyclenose precursor.[67]

A new synthesis of 2-deoxystreptamine (50) has been described, in which D-mannose was converted to the nitro-aldose (51)(mannose numbering), cyclized to the corresponding epimeric nitro-cyclitols



Reagents: i, DIBAL; ii, LAH; iii, BzCN-MeCN-NEt_3; iv, PPh_3-DEAD; v, Chloramine T; vi, Na-NH_3(l)

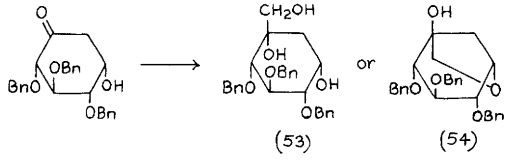
Scheme 6



Scheme 7

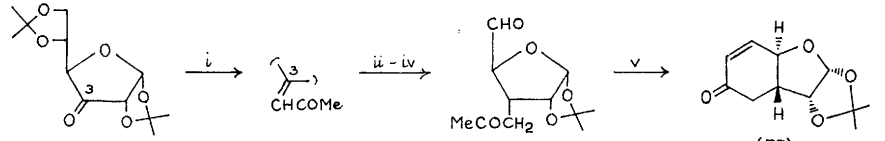
(52), the appropriate epimer then giving 2-deoxystreptamine (Scheme 7).[68] Discogenic (liquid crystal) amido- and azido-derivatives of deoxy-scyllo-inositol have been described, in which a hexanoyl group is attached directly to the ring or through an amino nitrogen substituent.[69] The acetalation of tetra-N-acylated neamine has been studied; acetone and cyclohexanone preferentially block the trans-5,6-diol in the deoxystreptamine ring rather than the trans-3,4-diol in the neosamine ring; lead tetra-acetate oxidation then allows the isolation of 2-deoxy-5,6-O-isopropylidene-streptamine.[70]

2.3 Branched-Chain Inositols.- A variety of strategies has been used to synthesize pseudo-sugars. The inosose made from D-glucose mentioned above (ref.66) has also been used to make ψ-glucose and hydroxy-analogues (53) and (54) using known reactions.[71] Ferrier's



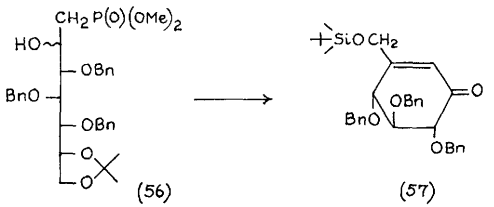
group has used the same approach to convert D-glucose to ψ-α-D-glucose.[72] The key intermediate (55), synthesized from D-glucose as outlined in Scheme 8, has been used to prepare ψ-α-L-altropyranose, ψ-β-D-glucopyranose, ψ-2-amino-2-deoxy-β-L-altropyranose, ψ-2-amino-2-deoxy-α-D-glucopyranose,[73] and ψ-β-L-allopyranose and ψ-α-D-mannopyranose,[74] by addition to the enose function followed by cleavage of the C-1 - C-2 bond to generate the required hydroxymethyl group on the cyclohexane ring. D-Glucose has also been used to make the phosphonate ester (56), which after oxidation at C-2 and

C-6, underwent intramolecular Wittig condensation to the cyclenose (57), which could then be converted to α and β analogues of ψ-D-glucose and ψ-L-idose.[75] Full details of the synthesis of pseudo sugars using Knoevenagel condensation of aldehydo-sugars have been published (see Vol.20,p.180).[76] A very similar method used a

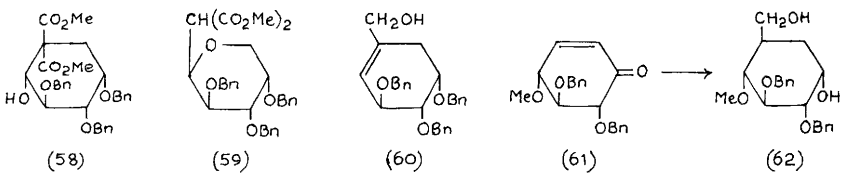


Reagents: i, Ph_3P=CHCOMe; ii, H_2-Ni; iii, H^+; iv, IO_4^-; v, DBU

Scheme 8

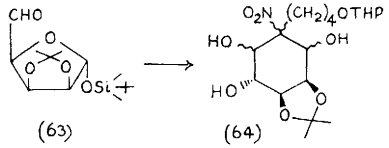


5-deoxy-5-iodo-aldehydo-L-arabinose derivative to generate the cyclic dicarboxylate (58)(together with the anhydro compound (59)), leading to ψ-α-D-glucopyranose and ψ-β-L-altropyranose via the cyclohexene derivative (60), borane reduction in this case being non-stereoselective.[77] Quebrachitol served as a source of the cyclenose (61) leading to the ψ-α-D-glucose derivative (62); many



related compounds are described in this paper.[78] The pseudo-sugars were subsequently linked conventionally to methyl glucopyranoside derivatives to give α-1$\rightarrow$4 and α-1$\rightarrow$6 linked ψ-disaccharides.[79] ψ-β-D- and -L-fructopyranose have been synthesized from optically active endo-adducts of furan and acrylic acid using methodology already applied in the racemic series (see Vol.20,p.181).[80]

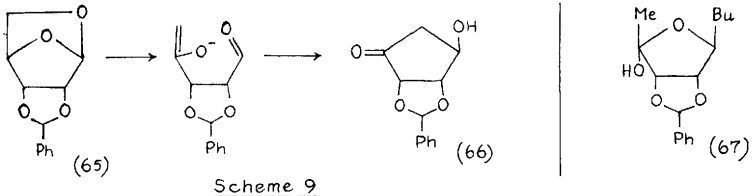
A synthesis of the ring skeleton of the alkaloid histrionicotoxin involves condensation of the lyxodialdose (63) with a 5-nitropentanol derivative followed by cyclization to the branched-chain nitrocyclitol (64)(see also Chapter 24).[81] Di-O-isopropylidene derivatives of (±)-ψ-α-D-galactopyranose have been synthesized, the 1,2:3,4



(63) (64)

di-O-isopropylidene derivative then being used to prepare further 6-substituted derivatives including 1-6 linked ψ-disaccharides with β-D-glucose, obtained as separable diastereoisomers.[82]

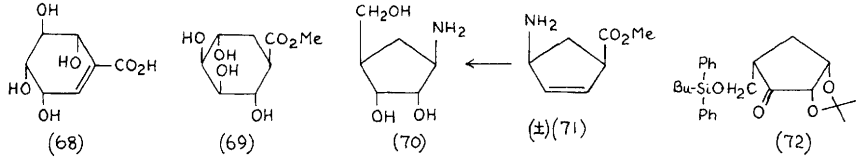
Treatment of 1,5- or 1,6-anhydro-sugars with LDA yields isomeric cyclopentanone or cyclohexanone derivatives, e.g., (65)→(66); with butyllithium, alkylation leading to ketose sugars also occurred, e.g., (67)(Scheme 9).[83]



(65) (66) (67)

Scheme 9

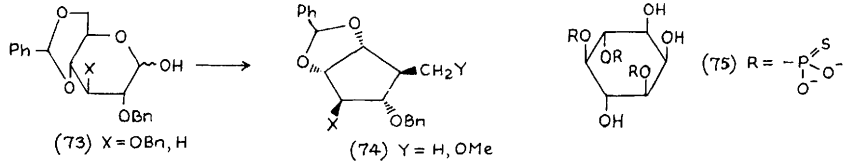
A new plant-growth regulator, streptol, isolated from an unidentified Streptomyces strain, is the shikimic acid analogue (68).[84] A synthesis of DL-shikimic acid from a Diels-Alder adduct of furan and acrylic acid has been described, utilizing the intermediate (69).[85]



(68) (69) (70) (±)(71) (72)

Another paper has reported a multistep conversion of D-lyxose to methyl (-)-shikimate.[86]

Interest in carbocyclic analogues of nucleosides has led to syntheses of ψ-β-D-arabinofuranose from an aldehydo-D-xylose derivative via a Knoevenagel condensation with methyl malonate (see also ref.76 above),[87] the carbocyclic ribosylamine (70) from the racemic amino-acid (71) using an esterase to achieve asymmetric saponification and hence resolution,[88] and another synthesis of this same analogue (70) from ψ-α-L-arabinofuranose using the cyclopentanone (72) to epimerize the hydroxymethyl group.[89] A novel carbocyclization generating

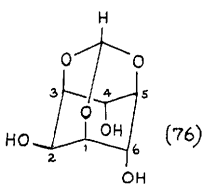


(73) X = OBn, H (74) Y = H, OMe (75) R = $-P(=S)(O^-)-O^-$

cyclopentanes from pyranose derivatives has been reported; Wittig olefination of the derivative (73) gave an alkene which on radical deoxygenation at C-5 gave the single product (74); by contrast, the 4,6-di-O-benzyl analogue of (73) gave a mixture of stereoisomers.[90] References to carbocyclic nucleosides are given in Chapter 20.

2.4 Inositol Phosphates.- There has been a surge of interest in these biologically interesting compounds. Gigg's group has published papers on the synthesis of myo-inositol phosphates and thiophosphates using phosphite intermediates,[91] the synthesis of (±)-myo-inositol 4,5-bisphosphate,[92] (±)-myo-inositol 1,4,5-trisphosphate,[93,94] and myo-inositol 1,4,5-trisphosphorothioate (75), a novel analogue of the biologically active 'second messenger'.[95] Other groups have also reported syntheses of D- and L-myo-inositol 1,4,5-trisphosphate,[96] DL- and D-myo-inositol 1,4,5-trisphosphate,[97] and DL-myo-inositol 1,3,4-trisphosphate, 2,4,5-trisphosphate, and 1,3,4,5-tetrakisphosphate,[98] D-myo-inositol 1,3,4,5-tetrakisphosphate,[99] and DL-myo-inositol 2,4,5-trisphosphate.[100]

The myo-inositol orthoformate (76) underwent highly regio-selective mono-phosphorylation to give the 4-phosphate derivative, and



(76)

conventional steps were used to prepare the 1,3-bisphosphate and 1,3,4,5-tetrakisphosphate;[101] the same group has also reported synthesis of racemic and resolved myo-inositol 1- and 4-phosphates from benzyl ether or cyclohexylidene myo-inositol precursors.[102]

The identities of inositol 1,3,4-trisphosphate and 1,3,4,5-tetrakisphosphate have been confirmed using 1D and 2D multinuclear n.m.r. data, which showed that all phosphates occupy equatorial positions on the cyclohexane ring.[103]

2.5 Miscellaneous Cyclitols.- Racemic tetra- and penta-O-acetyl-sn-myo-inositols have been resolved using diastereoisomeric orthoesters with mannose.[104]

The effect of pH on calcium binding to phytic acid has been studied.[105]

A semi-empirical theory of optical activity incorporating high energy states of relevance to vacuum u.v. has been applied to cyclohexane polyols, giving moderately good correlation with experimental results.[106]

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19
Antibiotics

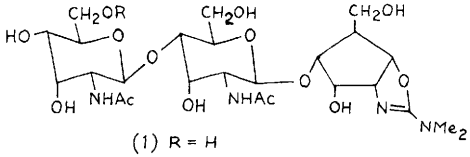
1 Amino-Glycoside Antibiotics

Amino-glycoside antibiotics have been reviewed.[1]

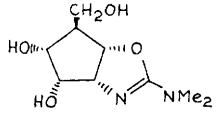
Novel insect chitinase inhibitors, allosamidin (1) and methyl allosamidin (2), have been characterized as pseudo-trisaccharides composed of 2-acetamido-2-deoxy-D-allose attached to a new amino-cyclitol derivative allosamizoline (3).[2] 2''-N-formamidoyl-sporaricin A has been isolated from a Saccharopolyspora Hirsuta sub-species,[3]

A total synthesis of neomycin B has been reported, coupling together neobiosamine and neamine derivatives.[4]

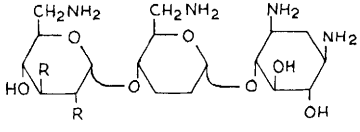
A multi (>40) stage synthesis of dibekacin (3',4'-dideoxykanamycin B) has been described, using D-glucose or D-glucosamine precursors.[5] A synthesis of 2',3'-dideoxy-kanamycin A has utilized a 2',3'-unsaturated intermediate from kanamycin A.[6]



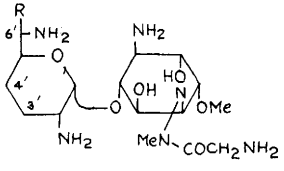
(1) R = H
(2) R = Me



(3)



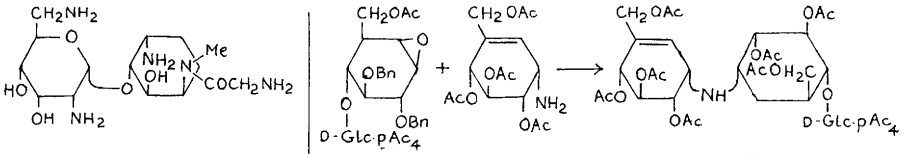
(4) R = OH
(5) R = H



(6) Fortimicin D, R = H
" A, R = Me

Other syntheses reported have included the apramycin analogues (4)[7] and (5),[8] and analogues of fortimicins (6) modified in the sugar ring, a 4'-hydroxy analogue of fortimicin D,[9] 7'-C-propyl-fortimicin A,[10] 7'-(3-hydroxypropyl)fortimicin A and its 6'-epimer,[11] 7'-phenyl-fortimicin A and its 6'-epimer,[12] 3'-enofortimicin D,[13] all involving coupling modified amino-sugars to fortamine derivatives. Another report describes the conversion of maltose to the

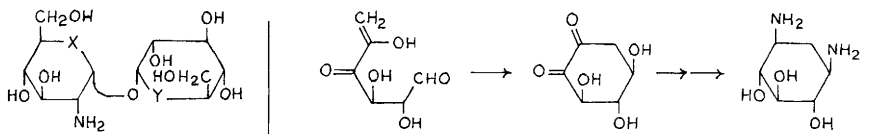
fortimicin analogue (7), which shows moderate antimicrobial activity.[14] (+)-Validamycin B dodeca-O-acetate has been synthesized from



(7) (8) (9) (10)

Scheme 1

a resolved furan-acrylic acid Diels-Alder adduct, coupling the epoxide (8) with valienamine derivative (9), the required regioisomer (10) being the major product (3:2 ratio)(Scheme 1)(see also Vol.18,p.172).[15] Analogous procedures were used to make the trehalosamine analogues (11) and (12), racemic pseudo-monosaccharides giving rise to diastereoisomeric mixtures.[16]



(11) X = CH_2, Y = O
(12) X = O, Y = CH_2

(13)

Scheme 2

A series of palmitoyl derivatives of aminoglycoside antibiotics have been prepared, extending previous work on kanamycin A derivatives; all those tested exhibited excellent *in vitro* antiviral activity.[17] Some acetalation studies on neamine are mentioned in Chapter 18, and a synthesis of the aminoglycoside dehydroxymethylbulgecin A is referred to in Chapter 3.

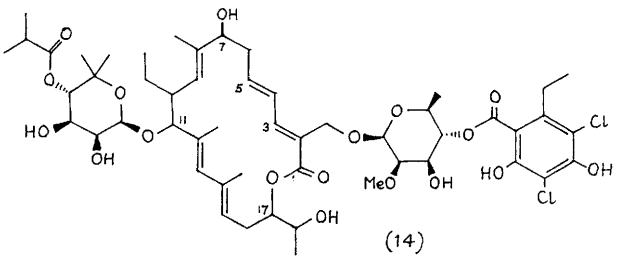
The loss of the C-4 hydrogen atom of D-glucose in the biosynthesis of the deoxy streptamine ring of neomycin has been taken to support the intermediacy of a 4-keto-intermediate (13)(Scheme 2).[18]

^{1}H and ^{13}C n.m.r. assignments for validamycin A have been reported.[19] Assignments for tobramycin are mentioned in Chapter 21.

Fluorescence measurements on Fluram derivatives of some aminoglycoside antibiotics have been recorded; no simple correlation exists between the intensity of fluorescence and the number of free primary amino groups.[20] The activity of aminoglycoside antibiotics against *E. Coli* have been compared, including *N*-acyl and *N*-aminoacyl derivatives of apramycin and nebramine.[21]

2 Macrolide Antibiotics

Tiacumicins, a complex of 18-membered macrolides produced by a species of Dactylosporangium, has been separated into six components and identified by spectroscopic methods. The major component, tiacumicin B, was assigned structure (14), with the minor components A-F showing minor structural variations in the macrolide ring and the number and esterification pattern of the sugars, which were considered to be rhamnose derivatives.[22]

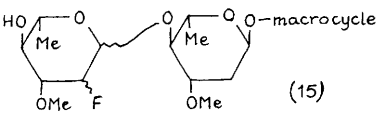


(14)

A genetically-engineered strain of Saccharopolyspora erythraea has been used to produce 2-nor-erythromycins.[23] A mutant strain of S. fradiae generates tylosin analogues in which the mycinose sugar unit is converted to 2-demethoxy, 2-demethoxy-4-epi, and 2-O-demethyl derivatives.[24] 4"-O-(4-methoxyphenyl)-acetyl-tylosin has been synthesized, in which the terminal mycarose sugar is acylated, the product showing improved resistance to hepatic esterase.[25]

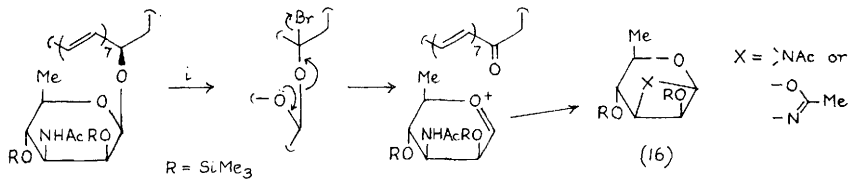
A new macrolide antibiotic, swalpamycin, elaborated by a strain of S. anandii, has been characterized as a 16-macrolide with separately attached D-mycinose and D-algarose sugar units.[26]

C-2-Fluoro-oleandrosyl fluorides have been synthesized from L-rhamnose (see Chapter 8), and then used to glycosylate avermectin B_{1a} monosaccharide to give derivatives with a disaccharide sidechain of generalized formula (15).[27]



(15)

The mycosamine unit of amphotericin B has been cleaved by a novel oxidation procedure; allylic bromination in the aglycone led presumably to a bromide which cleaved to give an enone and a glycosyl oxonium ion, leading to products considered to have structure (16) (Scheme 3).[28]

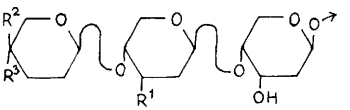


Scheme 3

3 Anthracycline and Related Polycyclic Antibiotics

New anthracycline antibiotics, A 447 C and A 447 D, have been isolated from S. cyaneus, which contain two trisaccharide chains attached to β-rhodomycinone, the trisaccharide being combinations of rhodinose, rhodosamine, 2-deoxy-fucose, and cinerulose A. Other components of the complex, A 447 A and A 447 B, proved to be identical with cosmomycins D and C respectively.[29] A further paper on the structure of arugamycin has been published (see Vol.17, p.176, ref.60).[30]

Further components of the ciclamycin complex elaborated by S. capoamus have been identified as desamino anthracyclines; ciclamycins O and 4 have the trisaccharide units (17) and (18) respectively.[31]



(17) R^1 = OH; R^2,R^3 = O
(18) R^1 = R^2 = H; R^3 = OH

A new class of biosynthetic anthracyclines have been produced by mutant strains of S. peucetius, which have glucuronic acid attached at O-4 on the anthracyclinone nucleus.[32]

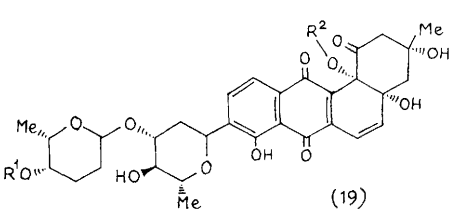
Adriamycin and daunorubicin analogues have been reported in which daunosamine is replaced by 2,6-dideoxy-2-fluoro-α-L-talopyranose[33] and diastereoisomeric 4-acylamino-2,4,6-trideoxy-L-hexopyranoses.[34] Anthracyclinones have been synthesized and converted to glycosides using daunosamine (giving 1-deoxy-N,N-demethylpyrromycin),[35] 4-deoxy-daunosamine,[36] 2-deoxy-L-fucose,[36,37] and amino-tri- and tetra-deoxy-hexopyranoses.[36] N-Alkyldaunorubicin derivatives have been synthesized by Michael addition of the amino-group to substituted maleimides,[38] and by reaction of daunorubicin with dimethylformamide dimethyl acetal and various 1,3-dicarbonyl compounds.[39] 3'-Deamino-3'-morpholino derivatives of carminomycins have been

reported.[40] The synthesis of a D-ring indolino analogue of daunomycin is mentioned in Chapter 3, which also includes a reference to the synthesis of anthracycline oligosaccharides.

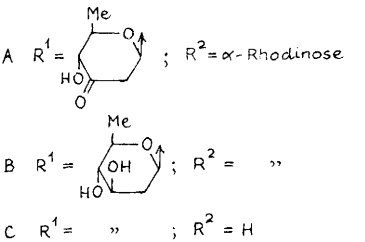
A new technique of field desorption tandem mass spectrometry has been applied to underivatized cosmomycins, giving spectra which yield sugar sequence information.[41]

Further studies on the structure of the angucycline antibiotics urdamycins B-F have been reported; they show minor differences in the aglycone compared with urdamycin A (see Vol.20,p.191).[42]

New isotetracenone antibiotics, kerriamycins A,B, and C, have been isolated from S. violaceolatus; these contain the aromatic chromophore of aquayamycin (a C-glycoside) with two or three O-attached hexose units (19); a novel keto-sugar, kerriose (2,6-dideoxy-D-erythro-hexopyranos-3-ulose), is postulated as a component of kerriamycin A.[43]



(19)



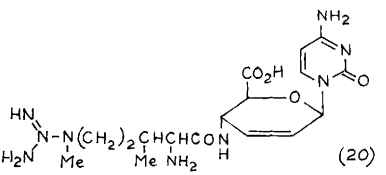
A R^1 = ; R^2 = α-Rhodinose

B R^1 = ; R^2 = "

C R^1 = " ; R^2 = H

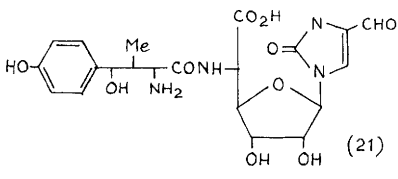
4 Nucleoside Antibiotics

A new nucleoside antibiotic arginomycin (20), isolated from S. arginensis, is structurally related to blasticidin S.[44]

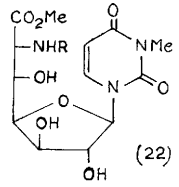


(20)

Nikkomycin B_x (21) and some side-chain analogues have been synthesized by DCC-mediated coupling of the amine and carboxylic acid sub-units.[45] The oxygen analogue (22) of δ_1-albomycin has been prepared, building the sugar unit from a xylodialdose derivative using an aldol condensation approach.[46] Mono- to tri-acylated derivatives of griseolic acid (23) have been synthesized either by

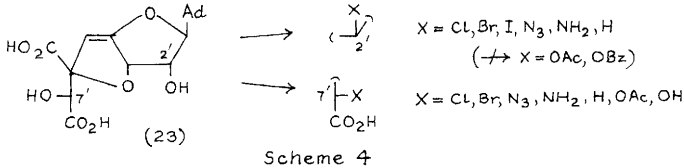


(21)



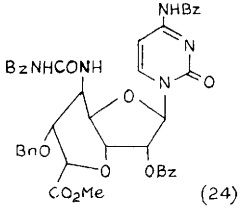
(22) R = peptide unit

selective acylation or selective alkaline hydrolysis of poly-acylated compounds.[47] Analogues of griseolic acid have been made in which triflate esters at C-2' or C-7' were displaced by standard nucleophiles (with inversion)(Scheme 4).[48] The octose moiety of ezomycins A_1 and A_2 has been synthesized as the substituted derivative (24).[49] Uridine 5'-aldehyde has been used to prepare modified polyoxin derivatives, e.g., (25), by condensation with amines or amino-acid derivatives using trimethylsilylcyanide in presence of boron trifluoride etherate.[50] Oxetanocin (26) has been synthesized, constructing the oxetan ring as outlined in Scheme 5.[51,52] Adenine-modified oxetanocins have also been reported.[53]

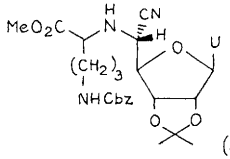


(23)

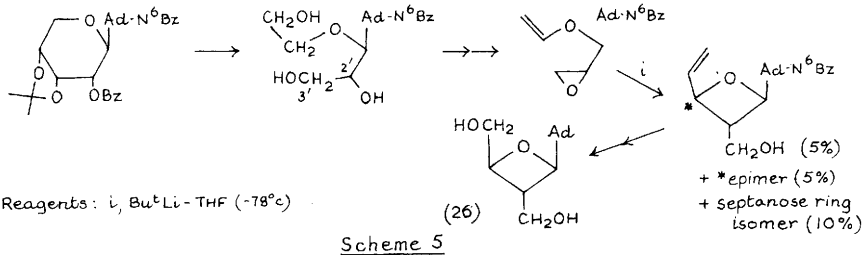
Scheme 4



(24)



(25)

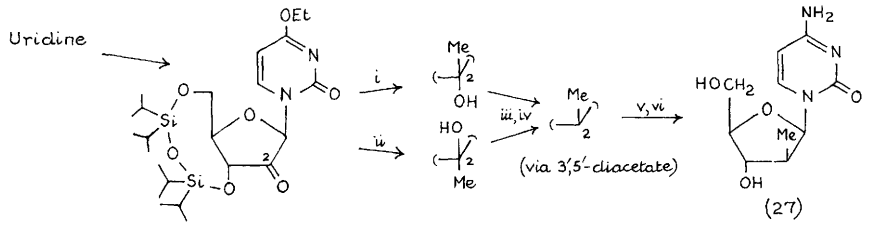


Reagents: i, Bu^tLi-THF (-78°C)

(26)

Scheme 5

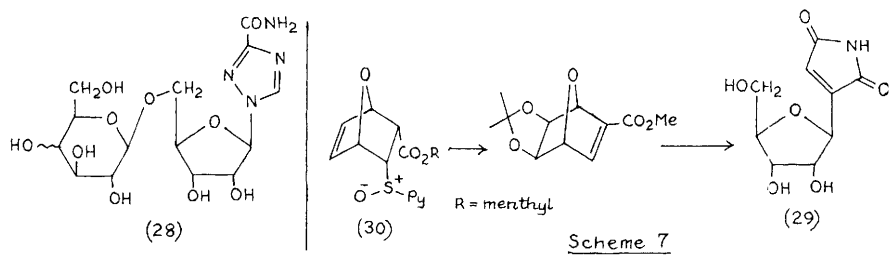
2'-Deoxy-2'-C-methyl-ara-cytidine (27) has been synthesized from a keto-nucleoside precursor as shown in Scheme 6.[54]



Reagents: i, MeMgBr-Et_2O, -50°; ii, Me_3Al or MeLi; iii, MeO_2C-COCl-DMAP; iv, Bu_3SnH; v, F^-; vi, NH_3-MeOH

Scheme 6

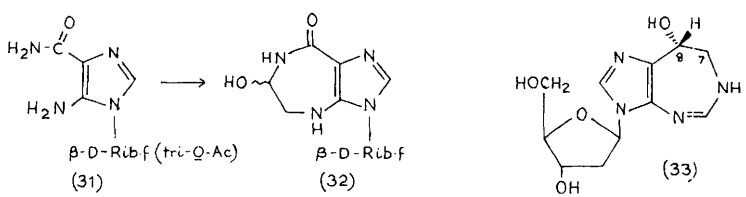
Analogues of tubercidin, toyocamycin, sangivamycin, and formycin have been prepared (2'- and 3'-deoxy derivatives, and arabino- and xylo- stereoisomers), and tested for antiviral activity; xylo-tubercidin retained potent activity with reduced cytotoxicity.[55] The glycosylated ribavirin derivatives (28) have been made from 5-O-trityl-ribavirin using a modified Koenigs-Knorr procedure with appropriate glycosyl bromides.[56]



Scheme 7

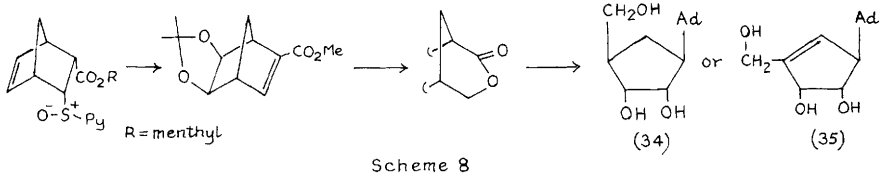
Showdomycin (29) has been prepared in high enantiomeric purity from the chiral Diels-Alder adduct (30) as indicated in Scheme 7,[57] the latter stage having been previously reported for the racemic compound (see Vol. 14, p.162).

The imidazole nucleoside derivative (31) has been used to prepare the β-D-ribofuranoside of azepinomycin (32).[58] Facile syntheses have also been reported for tubercidin (7-deazaadenosine) and related 7-deazaguanosine nucleosides by sodium salt glycosylation



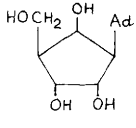
procedures.[59] A study of the biosynthesis of 2'-deoxycoformycin (33) indicates that C-7 is derived from C-1 of D-ribose, and not from C-3 of serine, using ^{13}C labelling experiments; an enzyme was also isolated which reduces the intermediate 8-ketocoformycin.[60]

The cyclopentadiene analogue of the chiral Diels-Alder adduct (30) has been used to make aristeromycin (34) and neplanocin (35) as outlined in Scheme 8.[61] 7-t-Butoxynorbornadiene has been converted to racemic 6'-β-hydroxy-aristeromycin (36) by conventional methods.[62]



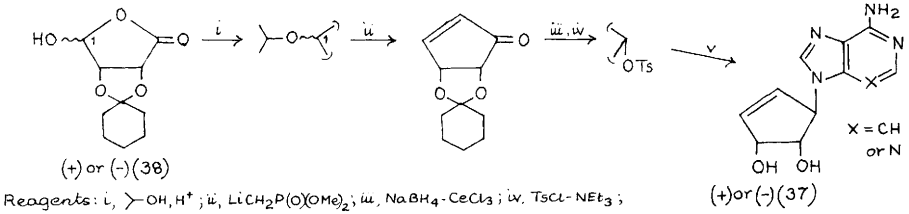
(34) (35)

Scheme 8



(36)

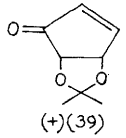
Analogues (37) of neplanocin A have been synthesized from either D-ribonolactone or D-mannose which were used to make enantiomeric uronic acid lactones (38), leading to the analogues as shown in Scheme 9.[63] Another group has used the isopropylidenated cyclopentenone (39) to make (−)-neplanocin A by a similar procedure.[64]



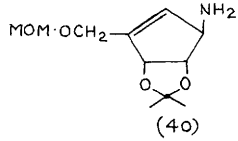
(+) or (−)(38) (+)or(−)(37)

Reagents: i, >-OH, H+ ; ii, $LiCH_2P(O)(OMe)_2$; iii, $NaBH_4$-$CeCl_3$; iv, TsCl-NEt_3 ; v, Adenine-NaH-DMF

Scheme 9



(+)(39)



(40)

Standard procedures have also been used to prepare a number of

neplanocin A analogues from the amino-cyclopentene (40), including imidazole and uracil analogues as well as 2'-deoxy, 2,2'-anhydro, and ara-compounds.[65]

A study of the biosynthesis of sinefungin using a cell-free extract of S. incarnatus suggests the immediate precursor to be L-arginine, and a biosynthetic scheme is proposed.[66]

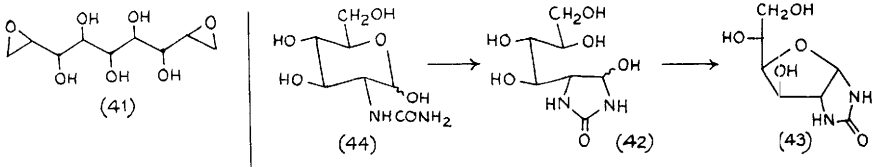
5 Glycopeptide Antibiotics

The chemistry of the vancomycin group of antibiotics has been reviewed.[67]

New compounds reported include the chloropolysporins A-C, produced by a strain of Faenia interjecta, which possess a cyclic polypeptide core with attached D-glucose, D-mannose, and L-ristosamine, and additionally L-rhamnose in A and B, and D-galactose in A,[68] and parvodicins, obtained from a new strain of Actinomadura parvosata, which also have a cyclic polypeptide core with attached -D-manno-pyranose and 2-acylamido-2-deoxy-α-D-glucopyranosyluronic acid residues, the components differing in the nature of the C_9-C_{11} fatty acid units attached to the amino group and whether or not the C-6 hydroxy group of mannose is acetylated.[69] Actinoidin A_2 differs from actinoidin A in having rhamnose in place of acosamine, otherwise similarly containing D-glucose, D-mannose and L-actinosamine attached to a peptide core;[70] a 2D n.m.r. study on these two antibiotics has been reported.[71]

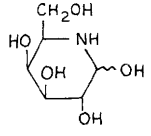
6 Miscellaneous Antibiotics

A novel antitumour antibiotic, WF-3405, isolated from a culture of Amauroascus aureus F-3405, has been characterized as the 1,2:8,9-dianhydro-nonitol (41), with unspecified stereochemistry.[72] CV-1, a new antibiotic produced by a strain of Streptomyces, is thought to possess a unique open chain hemi-acetal structure (42), which slowly changes to the stable cyclic form (43) in water; (42) could be synthesized from 2-amino-2-deoxy-D-glucose and potassium isocyanate via 2-deoxy-2-ureido-D-glucose (44)(Scheme 10).[73]

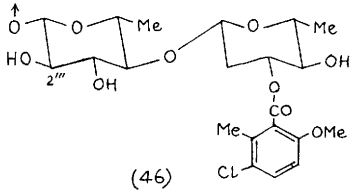


Scheme 10

Galactostatin (45), a new β-galactosidase inhibitor obtained from S. lydicus, is the latest member of the 5-amino-5-deoxy-hexose series of enzyme inhibitors.[74]



(45)



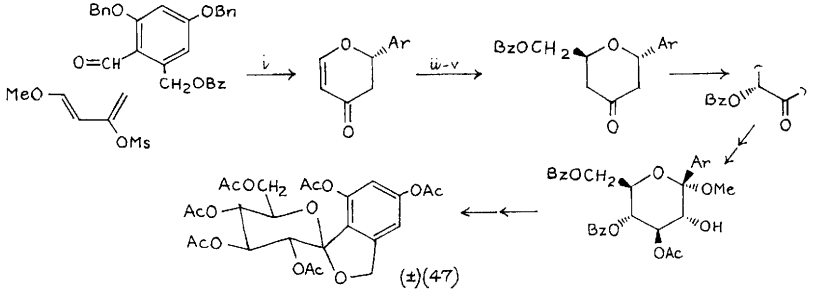
(46)

A chlorothricin relative, 2'''-hydroxychlorothricin (46, part structure) has been isolated from a culture of S. sp.K818; it contains 6-deoxyglucose in place of 2,6-dideoxy-D-glucose in the disaccharide unit.[75]

Paldimycins A and B, and also antibiotic 273a_2, have been obtained from fermentations of S. paulus which also produces paulomycins A and B (see Vol.20, p.30); the paldimycins contain one (B) or two (A) units of N-acetyl-L-cysteine attached to the non-carbohydrate portion of the paulomycins,[76] and they can be prepared from the latter by reaction with this amino-acid.[77]

New streptothricin antibiotics, AN-201 I-III, elaborated by S. nojirienis, have been characterized as N^{β}-acylated derivatives of streptothricins D-F, carrying acetyl groups in the β-lysine peptide side-chain in these compounds.[78] (For streptothricin F, see Vol.16, p.199).

A total synthesis of the spiro-C-glycoside core (47) of the papulacandins has been described, summarized in Scheme 11; unusually, a non-carbohydrate Diels-Alder adduct is systematically hydroxylated to build up the D-glucose ring.[79] Derivatives of papulacandin B

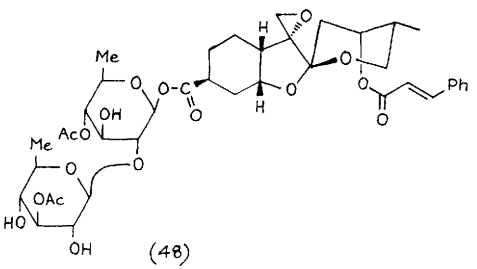


Reagents: i, $Yb(fod)_3$; ii, $\swarrow$MgBr-CuI; iii, OsO_4-$NaIO_4$; iv, $LiAlH(OCEt_3)_3$; v, BzCl

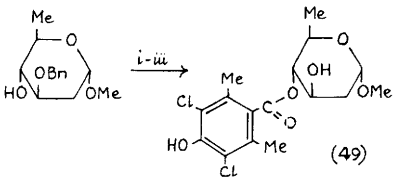
Scheme 11

have been prepared; some O-10 alkyl ether and C-11 acylamino derivatives (substituents in the aromatic ring) show improved antibiotic activity.[80]

The anti-tumour glycoside (−)-phyllanthostatin (48) has been synthesized by preparing the 6-deoxy-D-glucose β- 1→2 linked disaccharide conventionally and coupling the free sugar to the aglyconic carboxylic acid using triphenylphosphine-diisopropyl azodicarboxylate; chloroacetyl protecting groups were selectively removed in presence of the acetyl groups without acetyl migration using hydrazine dithiocarbonate.[81]



(48)



Scheme 12

Stepwise degradation of the oligosaccharide chain in moenomycin A has been accomplished in connection with structure-activity studies; standard periodate cleavage of diol structures was combined with Barry degradation or β-elimination chemistry.[82]

Ellagitannins possessing a dimeric structure with several galloyl groups on the glucose core display marked antitumour activity, apparently by potentiation of the host's immunity.[83]

The methyl glycoside of curacin (49)(the chromophoric terminus of several orthosomycin antibiotics) has been prepared as shown in Scheme 12; the 3-O-substituted isomer was obtained similarly.[84]

FAB-m.s. has been applied to the sugar sequence analysis of octasaccharide everninomicin antibiotics.[85]

9-Hydroxyellipticene N-glycosides, which can show high antitumour activity, are mentioned in Chapter 10.

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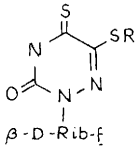
20
Nucleosides

1 Synthesis

Standard condensation procedures have been used to prepare β-D-ribofuranosyl derivatives of 5-fluoro-6-methyluracil,[1] fluorine-substituted 4-amino -2(1H)-pyridones,[2] various pyridazinones,[3] as-triazene derivatives of type (1),[4] 4-substituted-3-hydroxypyrazoles such as (2),[5] and some diazepinones including the homocytidine (3).[6] Some quinolinium nucleosides have been reported,[7] N^6 aryl-2-methyl adenosines have been prepared by the fusion method,[8] and improved



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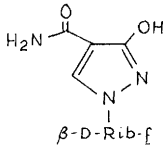

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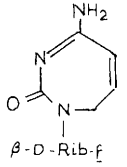


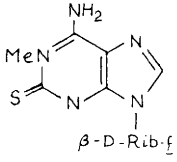
(3)

routes have been developed for the synthesis of 7-methyl-8-oxoguanosine[9] and 1-deazaadenosine.[10]

The use of 2-N-acetyl-6-O-diphenylcarbamoylguanine in Vorbrüggen - type couplings ensures the formation of 9-glycosyl guanine nucleosides in the β-D-ribo-, α-D-arabino- and β-D-xylofuranosyl series.[11] Both ribofuranosylpurines and -pyrimidines can be formed from 1-fluorofuranoses and silylated bases in the presence of SiF_4, O-acyl protection ensuring β-D-isomers.[12]

Various isoguanosine nucleosides related to doridosine, such as (4), were prepared via glycosylation of 6-amino-2-mercaptopurine,[13] and a further report has appeared on the synthesis of glycosides of pyrazino[2,3-c]-1,2,6-thiadiazine-2,2-dioxides (see Vol 20, p202);[14] the riboside (5) of the related imidazo[4,5-c]-1,2,6-thiadiazine-2,2-dioxide system has been synthesized.[15]

The stereospecific sodium salt glycosylation procedure was used to prepare the ribofuranosylpyrrole (6) via the reaction between 2,3-O-isopropylidene-5-O-t-butyldimethylsilyl-α-D-ribofuranosyl chloride and the salt of 2-cyanopyrrole.[16]



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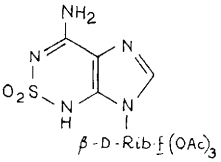

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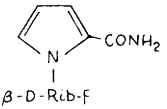
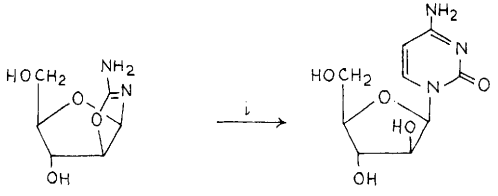


(6)

1-β-D-Arabinofuranosides of 4-substituted pyrazolo[3,4-d]pyrimidines have been prepared either by direct glycosylation or by inversion of the 2'-configuration in a β-D-ribofuranoside,[17] and β-D-arabinofuranosylcytosine has been made by the novel method outlined in Scheme 1.[18]



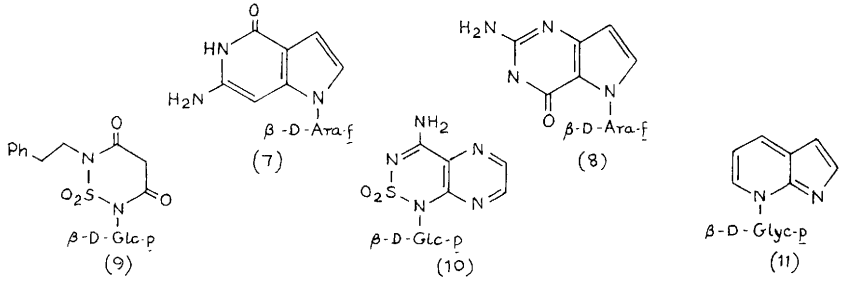
Reagent : i, $H_2C=C(Cl)CN$

Scheme 1

Use of the sodium salt glycosylation method gave rise to β-D-arabinofuranosylpyrroles and analogous 2'-deoxy systems,[16,19] (see also Vol 20, p.203), and such a 2-cyanomethyl-3-ethoxycarbonyl pyrrole was further converted to the pyrrolopyridine (3,7-dideazaguanine) nucleoside (7).[20] A similar reaction between the 2,4-dichloroheterocycle and 2,3,5-tri-O-benzyl-α-D-arabinofuranosyl chloride led to some pyrrolo[3,2-d]pyrimidines such as (8).[21]

A transglycosylation procedure has been used to convert guanosine into 9-β-D-xylofuranosylguanine,[22] whilst the systematic synthesis of α- and β-D-lyxofuranosyl nucleosides of the five common nucleobases has been reported; α-anomers were obtained by direct glycosylation using tetra-O-acetyl-α-D-lyxofuranose, and the β-anomers by oxidation-reduction of 3', 5'-O-TIPDS-β-D-xylofuranosyl systems.[23] An account of a plenary lecture reviews the work of this group on both lyxo- and xylofuranosyl systems (see Vol 20, p.203-4),[24] and a paper on analytical aspects of these compounds is mentioned in Chapter 23.

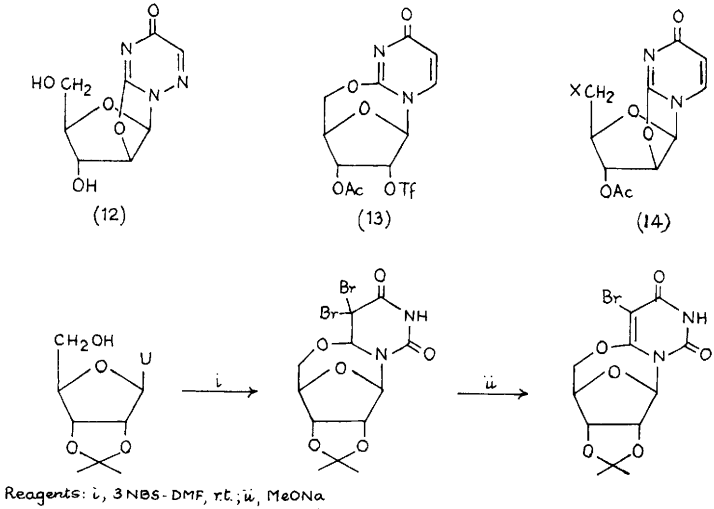
A standard condensation was used to prepare the β-D-glucopyrano-



syl-1,2,6-thiadiazine (9), the peracetyl derivative of which exists as rotationally-restricted syn - anti conformers at room temperature;[25] a similar study was carried out on the related bicyclic compound (10).[26] Glycopyranosyl 7-azaindoles (11) have been reported, via standard glycosylations.[27]

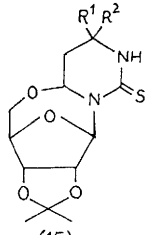
2 Anhydro- and Cyclonucleosides

2,2'-Anhydro-6-azauridine (12), and its 5'-deoxy analogue, were formed when the appropriate 2',3'-cyclic carbonate was treated with imidazole in DMF; alkaline hydrolysis gave the arabinofuranosyl nucleosides.[28] When the 2'-triflate (13) was treated with various nucleophiles, the products obtained were those of interconversion into 2,2'-anhydro nucleosides of type (14, X = OAc, Cl, Br, N_3).[29]



Scheme 2

Scheme 2 illustrates a good route to 5'-O, 6-cyclo -5,5-dihalogeno-5,6-dihydropyrimidine nucleosides; in the uridine case shown, elimination of HBr occurred readily with base as indicated.[30]



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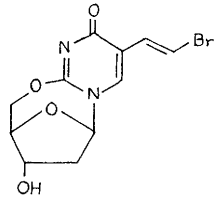

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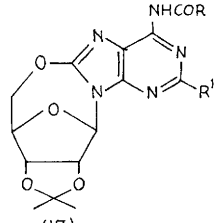
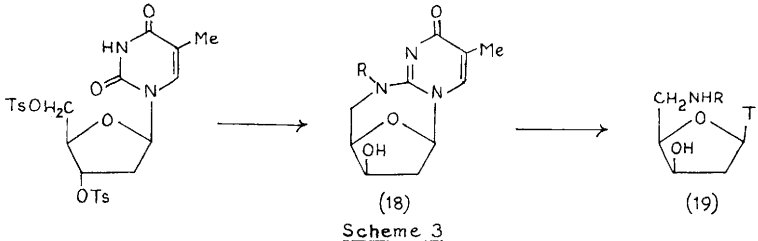


(17)

Cyclonucleosides of type (15, R', R^2 = H, Me) were prepared by reaction between 2,3-O-isopropylidene β-D-ribofuranosylamine tosylate and $R^1R^2C(NCS)CH_2CHO$.[31] The O^2, 5'-anhydride of BVDU (16) has been reported and shown to have good antiviral activity.[32] It has been demonstrated that N^6-acyl derivatives of 5'-O, 8-cyclo-adenosines (17) can be cleaved reductively to the corresponding adenosines by sodium cyanoborohydride.[33]

When 3', 5'-di-O-tosylthymidine was treated with methylamine or ammonia at 35°, the 2,5'-imino compounds (18, R=H,Me) were formed in high yield (Scheme 3). The 2,3'-anhydronucleoside was presumed to be an intermediate, and (18) underwent hydrolysis to the amino-nucleosides (19).[34]

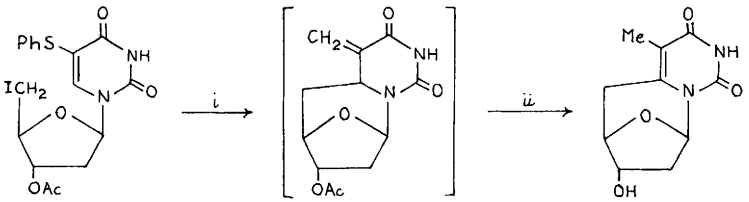


(18) (19)

Scheme 3

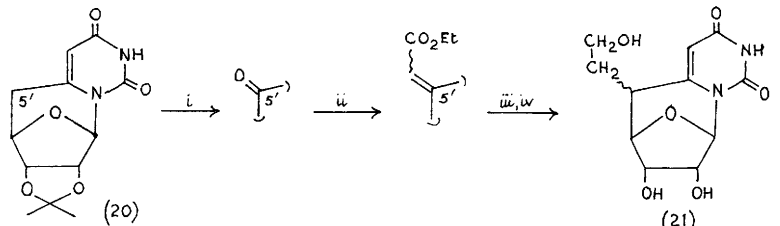
A further account has been given of the formation of 3',5'-epithio-3',5'-dideoxy-1-β-xylofuranosyluracils mentioned last year (Vol 20, p.204).[35]

Free radical methodology has been used to prepare some 6,5'-cyclo-5'-deoxypyrimidine nucleosides, as illustrated by the sequence in Scheme 4,[36] whilst cyclonucleoside (20), previously made by such an approach (see Vol 16, p.207-8) has been converted into the higher-sugar analogue (21) (Scheme 5).[37]



Reagents: i, Bu_3SnH–AIBN ; ii, NaOMe

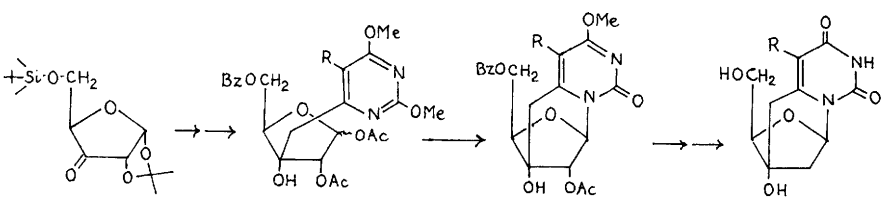
Scheme 4



Reagents : i, SeO_2–Py ; ii, $Ph_3P{=}CHCO_2Et$; iii, $NaBH_4$–$NiCl_2$; iv, H_3O^+

Scheme 5

An intramolecular glycosidation was used as a key step in the route to some 2'-deoxy-6,3'-methano-cyclopyrimidine nucleosides (Scheme 6); the 2'-oxygen was removed by free radical reduction.[38]



Scheme 6

A paper on the hydrolysis of purine 5'-cyclonucleosides is mentioned in Section 14.

3 Deoxynucleosides

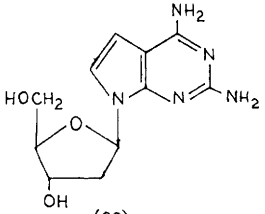
5'-Deoxyinosine has been isolated from the urine of patients with chronic myelogenous leukaemia.[39]

It has been shown that the stereoselectivity in the reaction between a 2,4-bis(trimethylsilyloxy)pyrimidine and 3,5-di-O-p-chlorobenzoyl 2-deoxy-α-D-ribofuranosyl chloride depends on the reaction conditions; in the presence of p-nitrophenol, 2'-deoxy-β-

uridines are produced with high stereoselectivity, whilst with p-nitrophenol and pyridine present, α-isomers are favoured.[40,41]

Standard procedures have been used to prepare 2'-deoxy-α-and β-D-ribofuranosides of 5-(2,2-difluorovinyl)uracil[42] and 5-(2-haloalkyl)uracils,[43] and 1-(2'-deoxy-β-D-ribofuranosyl)-1H-benzimidazole has been obtained by deoxygenation of the 3',5'-TIPDS derivative of the ribonucleoside.[44] The use of the Fmoc group to protect the sugar hydroxyls gave an improved overall yield of 2'-deoxy-5-azacytidine, as a result of the mild basic conditions required for deprotection.[45]

The use of phase-transfer glycosylation with 2-deoxy-3,5-di-O-toluoyl-α-D-ribofuranosyl chloride has led to the synthesis of 2-amino-2'-deoxytubercidin (22),[46] 5-aza-7-deaza-2'-deoxyguanosine (23),[47] and 2'-deoxyribofuranosides of some pyrrolo[3,2-c]pyridines



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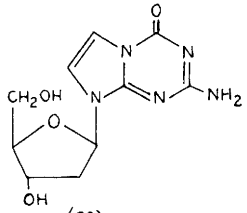

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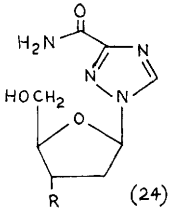
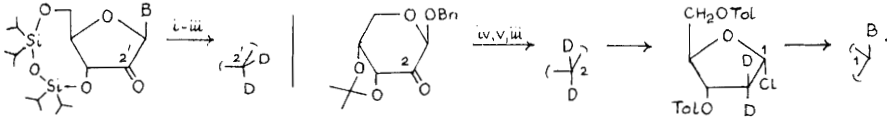


(24) R = OH
(25) R = H

(3,7-dideazapurines).[48] In a plenary lecture, Seela has reviewed some of his work in this area.[49] The related homogeneous sodium salt glycosylation procedure was used to prepare 2,4-dibromo- and -dichloro-9-(2'-deoxy β-D-ribofuranosyl)purine,[50] and 2'-deoxyribavirin (24), which was further reduced in a Barton-type reaction to the 2',3'-dideoxyanalogue (25).[51] Tributylstannane was similarly used for stepwise deoxygenation to give 2',3'-dideoxy derivatives of various 5-substituted uridines and cytidines, and also of 5-azacytidine.[52] A range of other 2',3'-dideoxynucleosides and 3'-substituted -2',3'-dideoxynucleosides have been reported as potential anti-HIV agents.[53]

2'-Deoxy-2',2'-dideuterionucleosides, required for studies of DNA conformation by n.m.r. methods, have been synthesized by the two routes outlined in Scheme 7 (see Vol. 20, p.208 for an enzymic route to such compounds),[54] whilst 2',2',3',4'-tetradeuterio-2'-deoxynucleosides can be made by treating methyl β-D-arabinopyranoside with Raney nickel in D_2O to give the 2,3,4-trideuterio compound and then further manipulations similar to those in Scheme 7.[55] Deuteriation or tritiation of 2'-deoxynucleosides at the 5'-



Reagents: i, $NaBD_4$; ii, PhOCSCl - DMAP; iii, $Bu_3Sn.D$ - AIBN; iv, $LiAlD_4$; v, $NaH-CS_2-MeI$

Scheme 7

position has been carried out by borodeuteride/tritiide reduction of a 5'-aldehyde, and epimerization of such an aldehyde in D_2O/tritiated water serves to label the 4'-position.[56]

Some 2'-deoxy-β-D-ribo-hexopyranosyl nucleosides have been prepared from silylated bases and the peracylated sugar, this method giving the β-anomers in good yield,[57] and a range of 6'-deoxyhexopyranosyl nucleosides of adenine have been reported.[58]

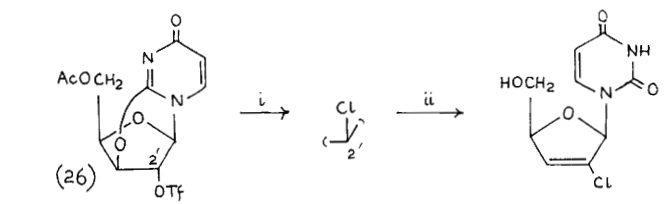
Some deoxyanalogues of tubercidin are referred to in Chapter 19.

4 Halonucleosides

An improved synthesis of the antiherpes agent 2'-deoxy-2'-fluoro-β-D-arabinofuranosyl derivatives of some 5-(2-haloalkyl)uracils have been synthesized,[43] as have various 2'- and 3'-fluorinated 2',3'-dideoxypentofuranosyladenines.[60] Standard routes were used to prepare various 5'-modified analogues of 2'-deoxy-2'-fluoroarabinofuranosylpyrimidines,[61] and the synthesis of 5-halo-1-(2'-fluoro-2'-deoxy-β-D-ribofuranosyl)[2-^{14}C]uracils was carried out by ring opening of 2,2'-anhydroarabinofuranosyl systems.[62]

An account of a plenary lecture describes routes to 2',2'- and 3',3'-difluoronucleosides.[63]

Whilst direct displacement of the 2'-O-triflyl group in (26) could be effected, attempts to hydrolyse the anhydro-linkage resulted in formation of an unsaturated chloronucleoside (Scheme 8).[64]



Reagents: i, LiCl - HMPA; ii, OH^-

Scheme 8

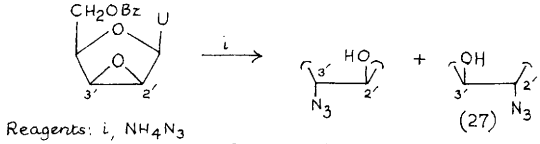
A range of unprotected nucleosides, such as uridine or adenosine, have been brominated or iodinated at the 5'-position in high yield by the use of the carbon tetrahalide and triphenylphosphine in dimethylacetamide or HMPA.[65]

5 Amino- and Azidonucleosides

The synthesis of the aminonucleosides (19) was described earlier.[34]

A general method for the synthesis of 3'-azido -2',3'-dideoxyribofuranosyl nucleosides involves the reaction of methyl 3-azido-2,3-dideoxy-5-O-toluoyl-D-ribose with the nucleoside base in the presence of TMSOTf.[66] A range of 3'-azido- and 3'-amino-2',3'-dideoxypyrimidine ribonucleosides have been prepared and evaluated as antiviral agents.[67]

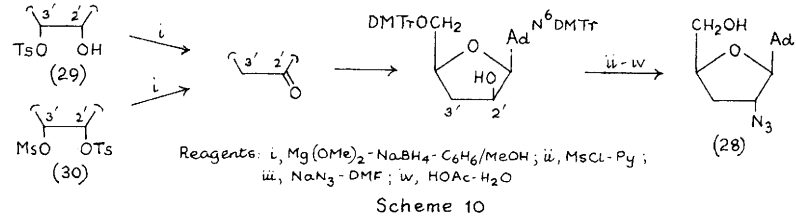
A study has been carried out on the reaction shown in Scheme 9, and the reasons for the variation in isomer ratio was discussed (see



Scheme 9

also Vol.18, p.198). The minor isomer (27) was isolated and deprotected to give 1-(2-azido-2-deoxy-β-D-xylofuranosyl)uracil.[68]

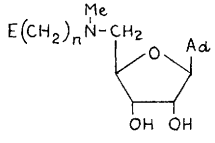
2'-Azido-2',3'-dideoxyadenosine (28) has been made for the first time via the chemistry of Scheme 10; the 2'-keto intermediate is postulated to arise from (29) by a 1,2-hydride shift, and from (30) by β-elimination and detosylation.[69]



Scheme 10

Secrist, in a plenary lecture, has described the synthesis of new substrate analogues as inhibitors of S-adenosylmethionine decarboxylase. The compounds made were of type (31), where E is a nucleophilic end group designed to react with the pyruvoyl group at the active site.[70]

Various bromoacetylamido nucleosides (32) have been reported as potential inhibitors of nucleoside biosynthesis.[71]



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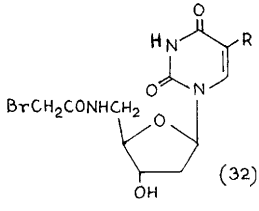

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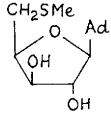


(33)

6 Thionucleosides

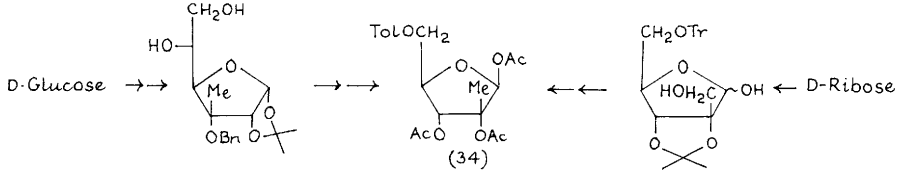
The xylofuranosyl analogue of methylthioadenosine (33) has been isolated from the marine nudibranch Doris verucosa, thus providing evidence for the existence in nature of analogues of S-adenosylmethionine.[72]

S-Formycinyl-L-homocysteine has been prepared via 5'-chloro-5'-deoxyformycin (Vol 20, p.212), and the 3'-deoxy analogue was also reported.[72]

A thioglycoside of cytidine is mentioned in Chapter 11.

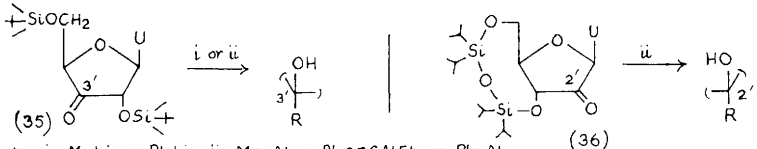
7 Branched-chain nucleosides

The 2-C-methyl ribose derivative (34) has been prepared in two ways, as outlined in Scheme 11; this intermediate underwent Vorbrüggen-type coupling to give, after deprotection, 2'-C-methylnucleosides, but the rate of reaction was very slow.[74,75]

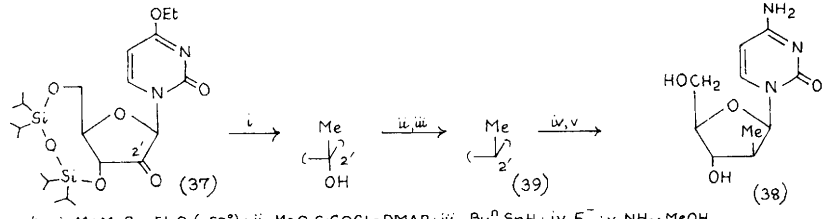


Scheme 11

Branched-chain nucleosides have been synthesized by reaction of organometallic reagents with ketonucleosides. The 3'-keto compound (35) reacted satisfactorily with organolithium or organoaluminium reagents whilst the 2'-ketouridine (36) reacted well only with the latter (Scheme 12).[76] However, other workers have found that the 2'-ketonucleosides (37) reacted with a Grignard reagent to give



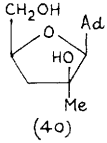
Scheme 12



Scheme 13

ultimately 2'-deoxy-2'-(S)-methylcytidine (38) (Scheme 13); when (37) reacted with methyl lithium or trimethylaluminium, the 2'-epimer was formed. The free radical deoxygenation to give (39) was stereospecific, and the 2'-epimer also gave (39) as the major isomer (3:1).[77]

The 2'-C-methyl analogue (40) of cordycepin was similarly prepared by Grignard addition to a 2'-ketone,[78] whilst the 3'-methyl analogue (41) was made by copper-catalysed Grignard opening of an epoxide.[79] Epoxide opening was also used to prepare a range of branched-chain uracil nucleosides of type (42).[80]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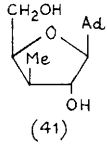
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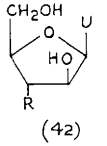
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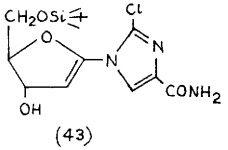

(43)

8 Nucleosides of Unsaturated Sugars, Ketosugars and Uronic Acids

The unsaturated nucleoside (43) was formed during ortho-lithiation of the corresponding 2',3'-O-isopropylidene ribonucleoside.[81] 1',2'-Unsaturated nucleosides and 3'-deoxy-2'-ketonucleosides were amongst

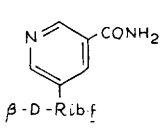
the products of reaction of 2'-O- and 3'-O-tosylated adenosines with Grignard reagents; this paper describes a convenient route to 3'-deoxy-2'-ketoadenosine.[82]

The glycosidation of xanthine and guanine with 1,2,5-tri-O-acetyl-β-D glucofuranurono-6,3-lactone gives N-9 and N-7 glycosides mainly; 6'-amides were accessible by ammonolysis of the lactones.[83]

9 C-Nucleosides

A review in Japanese has appeared on the chemistry of C-nucleosides, with the methodologies employed in synthesis categorized into four groups.[84]

The pyridine C-nucleoside (44), an isosteric and isoelectronic analogue of nicotinamide riboside, was prepared via the addition of a lithiated pyridine to 2,4 : 3,5-di-O-benzylidene-D-aldehydo-ribose, and subsequent cyclization.[85] Syntheses of 3-chloro-4-(β-D-ribofuranosyl)pyridine and of 3-(β-D-ribofuranosyl)-2-pyridone have also been reported.[86] A paper on the analysis of pyridine



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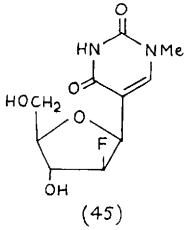

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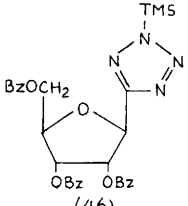

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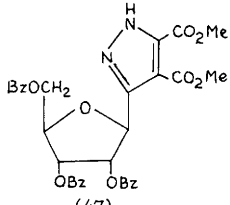


(47)

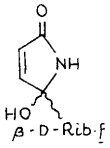
C-nucleosides is discussed in Chapter 22.

The fluorinated C-nucleoside (45) is an isostere of the potent antiviral agent FMAU, and has been made from pseudouridine by standard methods.[87]

When the tetrazole (46), prepared via cycloaddition of azide to the nitrile, was thermolysed in the presence of a dipolarophile, the nitrile imine produced *in situ* was trapped to give new heterocycles, *e.g.*, the pyrazole (47) using dimethylacetylene dicarboxylate.[88]

The C-nucleoside (48) has been prepared from 2-(β-D-ribofuranosyl)furan (Vol. 17, p.195), the key step involving the photooxygenation of a protected 2-amino-5-(β-D-ribofuranosyl)furan.[89] Some peptide derivatives of the antitumour C-nucleoside tiazofurin have been reported, along with similar derivatives of ribavirin.[90]

The D-lyxopyranosylpyrroles (49) have been made by cyclization



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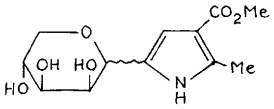


(49)

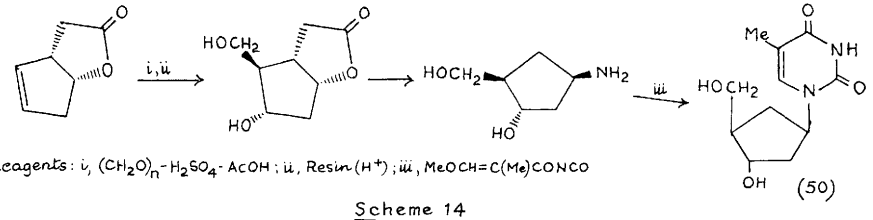
of the acyclic polyol, which in turn was synthesized by condensation of a 2-amino-2-deoxyheptose with methyl acetoacetate.[91]

The synthesis of S-formycinyl-L-homocysteine was mentioned above.[73]

10 Carbocyclic Nucleoside Analogues

Racemic carbocyclic analogues of purine nucleosides can be resolved using adenosine deaminase; thus, the 'D'-isomers of inosine and 2'-deoxyguanosine were obtained, together with the 'L'- forms of the aminated substrates.[92] Further examples of carbocyclic analogues of xylofuranosyl nucleosides have been reported (see Vol. 18, p.202), involving 2-amino-6- substituted purines and 8-azapurines as aglycones; some of the analogues showed antiviral activity.[93]

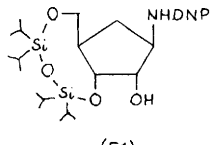
The (+)-carbocyclic analogue of thymidine (50) has been prepared stereospecifically for the first time, as outlined in Scheme 14.[94]



Reagents: i, $(CH_2O)_n$-H_2SO_4-AcOH; ii, Resin(H^+); iii, MeOCH=C(Me)CONCO

(50)

Scheme 14



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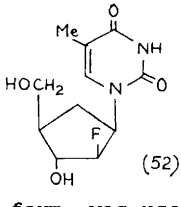
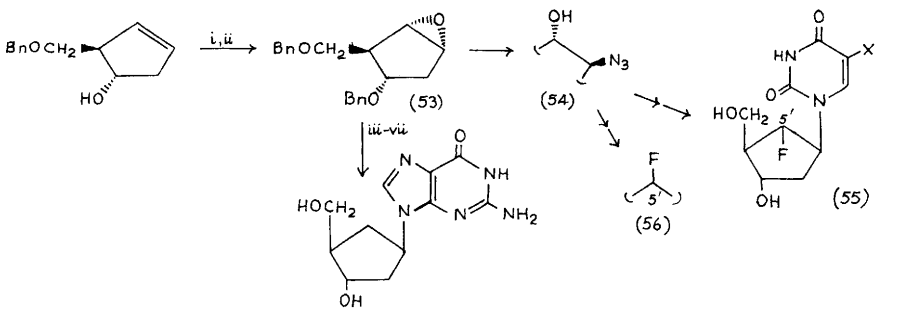


(52)

The intermediate (51), in racemic form, was used for the synthesis of various 2'-fluoro-carbocyclic nucleosides; the analogue (52) of the important antiviral FMAU was prepared by introducing fluoride with inversion of configuration, whilst the compound of

ribo configuration was made by a double inversion sequence. Oxidation of (51) to a 2-ketone and then fluorination with DAST gave the 2',2'-difluoroanalogue of (52).[95] The optically-pure epoxide (53) prepared as indicated in Scheme 15, underwent regioselective ring opening to azidoalcohol (54), which was then used to prepare the fluoro-analogues (55) and (56)(X=H,I); the iodinated compounds are analogues of the antiviral IDU with the isosteric replacement of CHF for O, and the 6'-α-fluorocompound (55, X=I) displayed good antiviral activity.[96] Opening of epoxide (53) with the anions of uracil, thymine, or 2-amino-6-methoxyethoxypurine gave ultimately carbocyclic analogues of 2'-deoxynucleosides; the deoxyguanosine case is outlined in Scheme 15. The use of 2-amino-6-methoxyethoxypurine in epoxide openings was further illustrated by a synthesis of carbocyclic guanosine, using a different epoxide.[97]

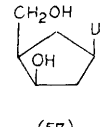


Reagents: i, Bu^tO_2H-VO(acac)$_2$; ii, BnBr-NaH-Bu_4NI; iii, 2-amino-6-methoxypurine-LiH-DMF; iv, PhOCSCl; v, Bu_3SnH; vi, H_2-Pd/C; vii, 3M HCl

Scheme 15

The use of (+)-endo-5-norbornen-2-yl acetate, obtained by enzymic resolution, has led to the synthesis of optically-pure (57),[98] and similar chemistry, but involving an azide displacement, gave access to 3'-azido-2',3'-dideoxythymidine (58) in optically-pure form.[99] The unsaturated carbocyclic compounds (59, B=Ad and Cyt), related to known anti-AIDS agents, were prepared by two consecutive deoxygenations of known compounds, but proved to be inactive.[100] A range of carbocyclic analogues of 3'-deoxypurine and -azapurine nucleosides of type (60) have been prepared and evaluated as antivirals.[101]

A further report has appeared about the approach to carbocyclic C-nucleosides mentioned last year (Vol 20, p.214),[102] and this chemistry has been adapted to the synthesis of the carbocycle corresponding to oxazinomycin (61) (Scheme 16).[103]



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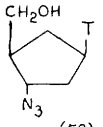

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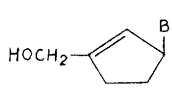

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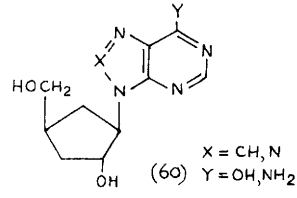

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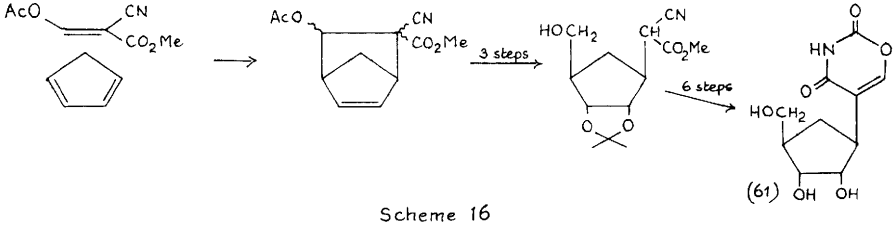


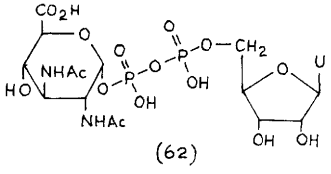
(61)

Scheme 16

11 Nucleoside phosphates and phosphonates

A new nucleoside diphosphosugar isolated from P.aeruginosa P1-III (Hals serotype 5) has been shown to have structure (62).[104]

Bis [2-(p-nitrophenyl)ethyl]phosphorochloridate has been further advocated as a new versatile phosphorylating agent,[105] and it has been shown that the phosphorylation of nucleosides by phosphochloridates, pyrophosphates and triazolides is catalysed by sodium iodide, and, in the case of phosphorochloridates, by iodine.[106] A



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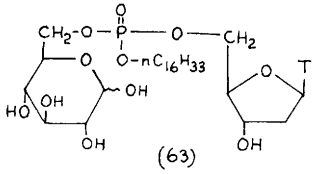


(63)

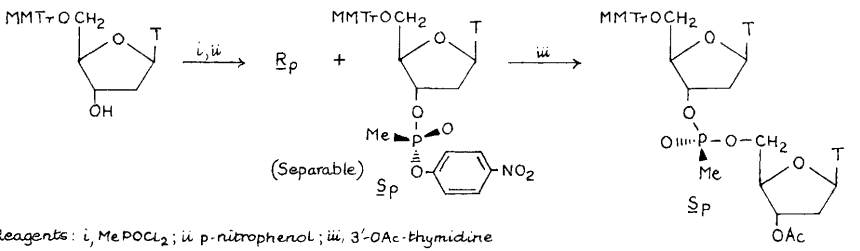
new general approach to nucleoside 3'- and 5'-phosphates involves formation of nucleoside diallyl phosphates, either by reaction with diallyl phosphorochloridate promoted by a Grignard reagent, or via oxidation of the phosphite; deprotection is then carried out with Pd^0 catalysis.[107]

5'-O-Phosphatidyl nucleosides and deoxynucleosides have been made by enzymic transfer of the phosphatidyl unit from phosphatidyl choline,[108] and the glucosyl phospholipid (63) of thymidine has been synthesized from glucose-6-phosphate, as a model for transmembrane

transport; it was anticipated that hydrolysis of such compounds would give TMP.[109]

Two routes have been reported to the 2-5A core structure, i.e., A2'p5'A2'p5'A,[110,111] and the analogous 3'-deoxycompound, derived from cordycepin, has also been synthesized,[112] as have phosphorothioate analogues.[113,114]

Stec has reviewed, in a plenary lecture, the work of his group on the synthesis and absolute configuration at P-stereogenic centres in oligonucleotide triesters andd phosphorothioates.[115] The same group have reported a synthesis of (R_p)-thymidine-3'-[^{16}O, ^{17}O, ^{18}O] phosphate of diastereomeric purity ≥92%,[116] and have prepared the (R_p)-and (S_p)-diastereomers of thymidylyl (3'-5')-thymidylyl methane phosphonate as outlined in Scheme 17;[117] other workers have applied a similar approach to synthesize the corresponding methylphosphonothioates.[118]



Reagents: i, $MePOCl_2$; ii p-nitrophenol; iii, 3'-OAc-thymidine

Scheme 17

A review has appeared dealing with phosphonate analogues of biological phosphates, including analogues of nucleoside mono- and higher phosphates.[119] Some nucleoside methylene diphosphonate sugars, potential inhibitors of glycosyl transferases, have been reported,[120] and an isosteric phosphonate analogue of CMP-KDO, the nucleoside phosphosugar involved in the incorporation of KDO into lipopolysaccharide, has been prepared and shown to be a modest inhibitor of CMP-KDO synthetase.[121]

Holy, in a plenary lecture, has discussed O-phosphonomethyl analogues of nucleotides and their derivatives.[122]

Two lariat trinucleotides, $A^{2'p5'G}_{3'p5'U}$ and $A^{2'p5'G}_{3'p5'C}$, have been chemically synthesized.[123]

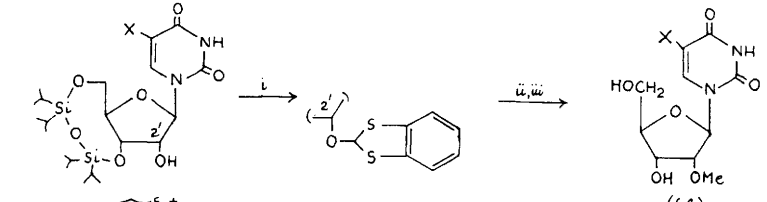
Cyclic AMP analogues have been prepared from pyrazolo[3,4-d] pyrimidine nucleosides by DCC cyclization of the 5'-phosphates,[124] and a ^{31}P-n.m.r. study of the reaction of cyclic AMP with triisopropylbenzene sulphonyl chloride has shown the rapid formation of the three possible diastereomers (at phosphorus) of cyclic AMP

symmetrical anhydride.[125] A mechanistic study of the formation of hydrogenphosphonate diesters during oligonucleotide synthesis, using acyl chlorides as coupling agents, has indicated the formation of mixed carboxylic-hydrogenphosphonic anhydrides as the main intermediates involved.[126]

Some further references to nucleoside derivatives of relevance to nucleotide synthesis are mentioned in the next two sections.

12 Ethers of nucleosides

Four 2'-O-methylated nucleosides have been isolated as components of the transfer RNA of extremely thermophilic archaebacteria; the structures, 5,2'-O-dimethylcytidine, N^4-acetyl-2'-O-methylcytidine, 2-thio-2'-O-methyluridine and N^2,N^2-2'-O-trimethylguanosine, were confirmed by synthesis.[127] A new method for the 2'-O-methylation of uridine derivatives, which does not require the protection of N^3 of the uracil unit, is outlined in Scheme 18; this approach was used



Scheme 18

for a new synthesis of the methylated t-RNA constituent (64, X=$CH_2NHCH_2CO_2H$).[128]

A method has been developed for the introduction of a dimethoxytrityl group at O-5' of a nucleoside or nucleotide bound to a solid support via O-3'.[129] A series of 5'-O-alkyl derivatives of 5-fluorouridine were prepared by standard coupling of the base to a 5-O-alkyl ribose derivative, but none of the products showed useful biological activity.[130]

During a synthesis of N^3-benzoylthymidine, the 3',5'-bis-O-trimethylsilyl ether of this compound was isolated as a solid precipitate after an aqueous work-up indicating that the trimethylsilyl derivative is more stable than was previously thought.[131]

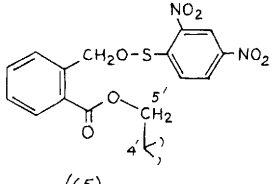
13 Esters and acetals of nucleosides

Various O-acyl derivatives of 2'-deoxy-5-trifluoromethyluridine and

-cytidine have been synthesized and their antitumour activity examined to determine their potential as pro-drugs.[132] Similarly, a range of 5'-O- and 3-N-acylated derivatives of 5-(2-chloroethyl)-2'-deoxyuridine have been prepared.[133]

In a study of the partial protection of nucleosides, it was shown that acylation of a ribonucleoside with 1.2-1.5 equivalents of an acyl chloride in pyridine gave mostly the 2'-O-acyl isomer. Use of 2.2-3.0 equivalents of acyl chloride gave mostly the 2',5'-di-O-acyl derivative, which rearranged over silica to the 3',5'-diacyl nucleoside. The 2',5'- and 3',5'-di-O-acyl derivatives could be used to gain access to the 3'- and 2'-O-THP derivatives, respectively.[134] Solid-liquid phase transfer conditions, involving formation of an intermediate dibutylstannylene derivative, have been developed for selective 2'-O-tosylation of ribonucleosides; 2'-O-tosyladenosine was obtained in 90% yield.[135]

A new protecting group for O-5' of nucleosides has been developed, particularly for use in solid phase oligonucleotide synthesis. This is the 2-(2,4-dinitrobenzenesulphenyloxymethyl)benzoyl (DNBSB) group (65), which is put on using the benzoic acid and pivaloyl chloride, and removed by a process of intramolecular catalysis using 50 mM toluenethiol and 200 mM diisopropylethylamine.[136]



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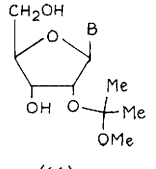

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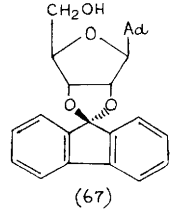


(67)

A new approach, with an appropriate choice of protecting groups, has been developed for the synthesis of 2'(3')-O-aminoacyl oligoribonucleotides related to the 3'-terminus of aminoacyl t-RNA's,[137] and 5'-O-aminoacyl derivatives of ribo- and arabinofuranosylnucleosides have been prepared.[138]

A review of protection at the 2' position in oligoribonucleotide synthesis includes discussion of a number of acetal-type protecting groups, the lability of which has been carefully tailored to the other requirements of the overall syntheses.[139] 2'-O-(2-Methoxy-2-propyl)acetals of type (66) have been prepared via the 3',5'-O-dialkylsilandiyl derivatives, and also used in oligonucleotide syntheses.[140]

Some new adenosine 2',3'-O-acetals have been prepared, and their

stereochemistry and rates of hydrolysis determined. The compounds reported included those derived from hindered aldehydes, which gave predominantly endo -isomers, and the exo-isomer of the 2',3'-O-methoxymethylidene orthoester was reported for the first time. The rates of hydrolysis were approximately as predicted, and were faster than depurination, except in the case of the exceptionally stable fluorenyl acetal (67), where the normal mechanism of hydrolysis would involve an antiaromatic cation.[141]

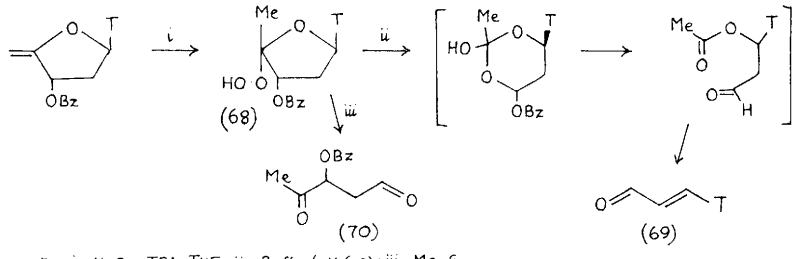
Various 3'- and 5'-mono-, and 3',5'-di-O-alkoxyalkyl derivatives of 2'-deoxy-5-trifluoromethyluridine were prepared by acetal exchange. Some showed improved antitumour activity due to suppression of metabolic degradation.[142]

14 Reactions

By studying the effects of substitution at the 6-position of purine deoxynucleosides, further evidence has been obtained that the rate-limiting step in acid-catalysed hydrolysis is the departure of the protonated base moiety with concomitant formation of an oxocarbonium ion.[143] The rate constants for acid hydrolysis of several N^6-substituted 2'-deoxyadenosines were measured in order to assess the role of various N^6- and sugar-protecting groups in depurination reactions observed in oligonucleotide synthesis; the exceptional lability of N^6-acyl derivatives can be accounted for by N^7 protonation, as determined by ^{15}N n.m.r.[144] Kinetic parameters have also been determined for the multistage reactions of 6-substituted purine nucleosides with alkali to give ultimately D-ribose and a 4,5-diaminopyrimidine.[145] The acidic hydrolysis of several carbon-bridged purine 5'-cyclonucleosides has been studied; a 5',8-bridged system hydrolyses less than 10 times more slowly than analogous nucleoside models, but 3',5'-bridges lead to very substantial rate retardations. The results were rationalized in terms of electrostatic and stereoelectronic effects.[146]

In connection with the postulated mechanism for DNA strand scission by activated bleomycin, the hydroperoxide (68) was produced as the major isomer as shown in Scheme 19. In aqueous buffer, this underwent a Criegee-type rearrangement to give ultimately the unsaturated aldehyde (69). On reduction with dimethylsulphide, (68) gave the ketoaldehyde (70), of relevance to the base-release also observed in the reaction with activated bleomycin.[147]

It has been shown that in a 1:1 mixture of GMP and the cis-



Reagents: i, H_2O_2-TFA-THF; ii, Buffer (pH 6·0); iii, Me_2S

Scheme 19

platin- like complex cis-$[Pt(NH_3)_2(H_2O)_2]$ $(CF_3SO_3)_2$, a cyclic complex is formed involving coordination of Pt^{II} to N^7 of the base and to the phosphate group;[148] a similar cyclic complex has also been demonstrated, by ^1H n.m.r., in the interaction between AMP and bis-cyclopentadienyl molybdenum dichloride in D_2O at pD 7.6-7.8.[149] Various macrocyclic polyammonium salts form stoichiometric complexes with ATP and ADP.[150] Protonation constants and stability constants of Cu^{2+}, Hg^{2+} and Pt^{2+} complexes of thymidine have been measured.[151]

The antitumour agent N^2-methyl-9-hydroxyellipticinium acetate interacts with ribonucleoside diphosphates in a manner analogous to that previously determined for the nucleosides themselves (see Vols. 18-20, particularly Vol. 19, p.209).[152]

15 Spectroscopic and Conformational Studies

Theoretical calculations of conformational energies of adenosine have shown that N^3-protonation is more favourable in the anti-configuration than in the syn-arrangement by 32.2 kcal mol^{-1} and that N^3 protonation may cause a change in conformation in adenosine derivatives.[153] Additionally, pH-dependent laser Raman spectroscopic studies of 8-bromo-AMP have indicated that a syn-conformation inhibits protonation at N^3.[154]

X-ray crystal structures of nucleosides are discussed in Chapter 22.

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21
N.M.R. Spectroscopy and Conformational Features

1 Theoretical and General Considerations

A description of ^{13}C-n.m.r. simulation methodology for the structural elucidation of carbohydrates has appeared.[1] Some long-range ^{13}C-^{1}H coupling constants have been determined in carbohydrate derivatives by 2D-n.m.r. techniques on the natural abundance compounds. The values obtained were found to compare well with values from the selectively isotopically enriched (^{13}C or ^{2}H) carbohydrates previously reported.[2] A simple procedure to simplify the 2D ^{1}H-^{1}H (2D COSY) spectra of molecules in which significant T_1 variations occur has been described and used to distinguish between methine and methylene protons of L-idose.[3]

An interesting new observation is that axial anomers induce an O(5)-C(1)-O angle greater than tetrahedral, whereas for the equatorial anomers the reverse is true. The observation was rationalized on the basis of MO analysis.[4] The effects of solvent polarity and hydrogen bond formation on the magnitude of the anomeric effect has been studied using a ^{13}C-n.m.r. method, and the results interpreted in terms of solvent interactions causing changes in the endo- and exo-anomeric effects. Water strengthens the exo-anomeric effect and the conformational rigidity of glycosides because of its H-bonding to the ring oxygen atom. The tendency of free sugars to favour an equatorial hydroxy group, it is suggested, is in part due to the ability to form stronger hydrogen bonds as proton donors.[5]

Unsaturated sugar derivatives have been studied by ^{13}C- and ^{1}H-n.m.r. spectroscopy to examine the generalized anomeric effect, particularly with regard to the allylic effect.[6] The importance of antiperiplanar n-σ^* stabilization as a contributor to the ano-

meric effect has been confirmed by variable temperature ^{1}H- and ^{13}C-n.m.r. studies on 2-substituted- and 2-substituted-4-methyl-tetrahydropyrans of the types shown in formula (1).[7] By means of ^{1}H n.m.r. studies of 2,6-disubstituted-6-carbamoyl-5,6-dihydro-2*H*-pyrans the conformational preference and hence the reverse anomeric effect of the carbamoyl group has been determined.[8]

The detection of the six tautomers of D-glucose in aqueous solution by ^{13}C-n.m.r. is referred to in Chapter 2. The complete assignment of the ^{13}C-n.m.r. spectrum of the ring forms of digitoxose (2,6-dideoxy-D-*ribo*-hexose) by DEPT editing and 2D C-H - correlation spectroscopy has been reported. The anomeric pairs of the furanose and pyranose forms were quantitatively analyzed in DMSO-d_6 solution by ^{13}C-n.m.r. and the results compared with those from ^{1}H-n.m.r. spectroscopy.[9] Examination of the ring forms of D-fructose and the effects of H-bonding on the position of equilibrium is referred to in Chapter 2, and the ^{13}C-n.m.r. spectroscopic determination of the ring sizes of isopropylidene acetals is mentioned in Chapter 6.

2 Acyclic Systems

The ^{1}H-n.m.r. spectroscopy of a range of benzoylated polyols (C_2-C_6) have been described and their probable conformations in solution discussed.[10] Similar studies of some benzoylated aldononitriles and polybenzoyl alditol derivatives of tetrazoles have been carried out by the same group.[11,12]

The conformation of 1,1-bis(acetamido)-1-deoxy-D-glucitol has been determined in aqueous solution from 500 MHz ^{1}H-n.m.r. data. No difference from that determined previously in organic solutions was found.[13]

3 Furanose Systems

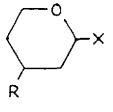
Ab initio molecular orbital calculations have been applied to erythrofuranose and threofuranose. The preferred solution conformations ascertained previously by n.m.r. spectroscopy are in good agreement with those predicted by calculation and, in contrast to th findings in reference 5 above, it was inferred that solvation by water does not appear to be a major conformational determinant.[14] The conformations in solution of both anomers of *N*-benzoyl-D-glucofuranosylamine have been determined by ^{1}H-n.m.r. spectroscopy.[15]

A 500 MHz variable temperature ^{1}H-n.m.r. study of 9-(2'-deoxy-β-D-threo-pentofuranosyl)adenine and its 3'-deoxy isomer has been carried out.[16]

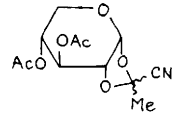
The conformations in solution of a number of aldono-1,4-lactones with ^{13}C-enrichment at C-1 have been evaluated using ^{1}H-^{1}H, ^{13}C-^{1}H, and ^{13}C-^{13}C-couplings in their n.m.r. spectra.[17]

4 Pyranose Systems

The anticipated half-chair conformations of the four benzyl 2,3-anhydro-4-azido-4-deoxy-pentopyranosides have been confirmed by ^{3}J values in their ^{1}H-n.m.r. spectra.[18] The conformational analysis of the two diastereoisomers of the pentose ortho-ester (2) has been achieved by detailed n.m.r. studies.[19]



(1) R = H, Me
X = OH, OMe, NHMe, Cl



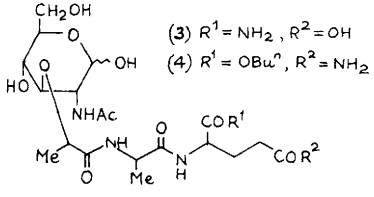
(2)

^{1}H-N.m.r. studies of glucose, maltose and some derivatives in DMSO confirm the presence of 2'-OH - 3-OH hydrogen bonding in maltose, and reveal weaker intramolecular hydrogen bonding between vicinal hydroxy groups. Cooperative intramolecular hydrogen bonding in glucose was also established.[20] The solid state ^{13}C-n.m.r. spectrum of a single crystal of methyl α-D-glucopyranoside has been studied and used to assign the c.p.-m.a.s. spectrum of a polycrystalline sample.[21] A comparative study of the ^{1}H- and ^{13}C- n.m.r. spectra of all monoacetates of methyl α- and β-D-glucopyranoside and of D-glucose and D-galactose with those of their unacetylated derivatives has shown a strong dependence of the signals on the presence of axial substituents, as well as providing data for determining the orientation of the ester groups.[22] A comprehensive analysis of the ^{1}H- and ^{13}C-n.m.r. data for the anomeric pairs of allo, manno, and talo isomers of methyl 2,3-anhydro-4,6-O-benzylidene-D-aldohexopyranosides using 2D homo- and hetero-correlation techniques has been reported.[23] Chirally deuterated galactose derivatives have been studied by ^{1}H-n.m.r. spectroscopy and the preferred rotameric state about the C-5 - C-6 bond shown to be gt. Methyl β-D-galactopyranosides specifically deuterated at C-6 were used to show that a D-galactose oxidase acted mainly at the pro-(S) hydrogen.[24] A comparison of ^{13}C spin-lattice relaxation times between sugars of

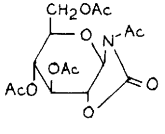
the D-gluco- and -galacto-series has been reported. The C-6 methylene protons were hardly discernable for D-galactoses, but were clearly distinguished for the D-glucoses. The different rotational patterns were attributed to avoidance of the diaxial O-4 - O-6 interactions which occur in galactose but not in glucose.[25] Water-soluble spin labelled glucose derivatives as potential n.m.r. contrast enhancing agents have been prepared, the compounds, which contain various nitroxyl radical substituents attached via O-1, O-2, O-3, or O-6, produced marked enhancements of T_1 and T_2 proton relaxation times.[26]

Solution conformations of 3,4,6-tri-O-acetyl-1,2-O-isopropylidene-α-D-galactopyranose have been compared with those of the solid obtained by X-ray crystallography and shown to be very similar, with the conformation of the pyranose ring being the expected $^4C_1$, and the dioxalan ^{C-1}E.[27]

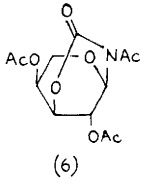
A series of specifically deuterated α- and β-C-glucopyranosides, studied by ^{1}H-n.m.r. spectroscopy, were shown to adopt analogous conformations to the corresponding O-glycosides.[28] Detailed ^{1}H-, ^{13}C-, and ^{19}F-n.m.r. spectroscopic data for methyl α- and β-glycosides of 2-fluoro and 3-fluoro-glucose, whose synthesis is described in Chapter 8, has been reported, together with those for their synthetic intermediates.[29] The conformational equilibrium of 2,4,6-tri-O-benzoyl-3-deoxy-D-arabino-hexono-1,5-lactone has been examined by means of coupling constants obtained from the ^{1}H n.m.r. spectrum.[30] A complete set of interproton-coupling data on α-L-idopyranosyluronic acid has been obtained in a high field n.m.r. study. The data indicate that α-L-iduronic acid may display considerable conformational freedom including $^1C_4$, $^4C_1$, and ^2S_o conformers.[31] Rotamer populations around C-5 - C-6 bonds of methyl 2,3,6-tri-O-methyl-α- and -β-D-galactopyranoside 6-(dimethylphosphate) in different solvents have been determined by ^{1}H-n.m.r. spectroscopy; some were shown to be solvent dependent while others were not. MNDO calculations on model systems correlated well with the n.m.r. measurements in carbon tetrachloride.[32] The conformation of



(3) $R^1 = NH_2$, $R^2 = OH$
(4) $R^1 = OBu^n$, $R^2 = NH_2$



(5)



(6)

2,3,4,6-tetra-O-acetyl-N-acetyl-α-D-galactopyranosylamine has been determined by 500 MHz ^{1}H-n.m.r. spectroscopy and found to be similar to that in organic solvents.[13] Glycopeptides (3) and (4), which have immunomodulatory and other biological activity, have been studied by 2D ^{1}H n.m.r. spectroscopy at 500 MHz and some conformational conclusions drawn.[33] 2D Methods have been used to determine $^{3}J_{C,H}$ values for conformationally rigid compounds such as (5) and (6) and the validity of the Karplus relationships examined. It was concluded that ring substituents can cause deviations.[34]

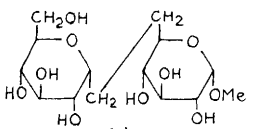
Methyl glycosides of ammonium 3-deoxy-D-manno-2-octulosonate (KDO) have been shown to adopt the $^{5}C_{2}$ conformation from ^{1}H n.m.r. data by two different groups of workers.[35,36] Conformations of the side chain of N-acetylneuraminic acid and some of its epimers have been studied by ^{1}H-, ^{13}C-n.m.r. and n.O.e techniques.[37]

5 Oligosaccharides and Related Compounds

An n.m.r. technique, based on coherence transfer in the rotating frame, which allows for the rapid determination of proton resonance assignments in oligosaccharides has been described.[38] Improved one-dimensional analysis of complicated ^{1}H-n.m.r. spectra of oligosaccharides has been achieved by a new technique which uses multiple relay magnetization transfers. The analysis allows the visualization of each sugar unit on its own by multiple relay transfer from the anomeric protons.[39] The carbonyl resonances in peracetylated D-gluco- and D-manno-pyranosides and in oligosaccharides containing D-glucopyranose residues have been assigned using 2D n.m.r. techniques. It was proposed that the carbonyl carbon resonances are useful probes of oligosaccharide structure.[40] A study of virtual and solution conformations of oligosaccharides has led to a quantitative evaluation of the possibility that n.O.e. and bulk longitudinal relaxation times, used to determine solution conformation of oligosaccharides, may be the result of averaging over many conformational states.[41] Model trimethylsilylated xylo-oligosaccharides have been examined by ^{13}C m.a.s. n.m.r., and ^{1}H-^{29}Si and ^{1}H-^{13}C heteronuclear correlation using 2D δ techniques to assign the peaks. It was concluded that the silicon δ values can be used to determine the sites of glycosidation.[42-44]

Conformational analysis of methyl 4-O-(α- and β-D-glucopyranosyl)-β-D-xylopyranoside in aqueous solutions has been carried out using

n.O.e. effects for hydrogen and carbon atoms adjacent to the glycosidic bond together with optical rotation measurements.[45] The per-O-acetyl derivatives of all (1→3)- and (1→4)-linked galactose disaccharides, as well as methyl tetra-O-acetyl-α- and -β-D-galactopyranoside and 1,2,4,6-tetra-O-acetyl-3-O-methyl- and 1,2,3,6-tetra-O-acetyl-4-O-methyl-α-D-galactopyranose have been examined by 2D n.m.r. heteronuclear correlation shift experiments, and a complete analysis achieved.[46] The conformations adopted by the C-glycosidic disaccharides (7) and (8), the C-analogues of methyl α-isomaltoside and methyl α-gentiobioside respectively, have been determined by ^{1}H-n.m.r. studies of their specifically deuterated methylene analogues. The same laboratory has described similar studies on eight 1,4-C-linked disaccharides.[48] ^{13}C-N.m.r. investigation of cellobiose using T_1 methods in the presence and absence of β-glucosidase shows



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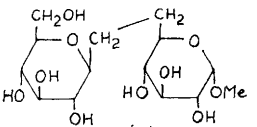
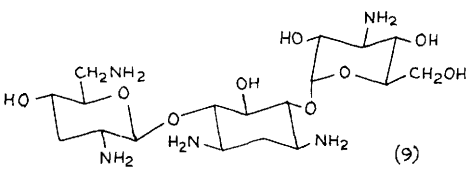


(8)

a fast interaction between cellobiose and the enzyme with the C-1 form of the disaccharide. The T_1 data justify a nearly spherical shape for cellobiose in solution.[149] Multiple-relayed coherence transfer chemical shift-correlated ^{1}H-n.m.r. spectroscopy has been applied to cello-oligosaccharides.[50] Assignments of the ^{1}H- and ^{13}C-n.m.r. spectra of tobramycin (9) at low and high pH has been achieved by use of 2D methods. The results were consistent with a $^{4}C_{1}$ conformation for each ring, independent of the state of protonation.[51]



(9)

Modern n.m.r. techniques, including HMQC, HM C, and HOHAHA pulse sequences, have been applied to the analysis of the ^{1}H- and ^{13}C-n.m.r. spectra of α-neu 5Ac-(2→3)-β-Gal-(1→4)-Glc.[52]

A combination of n.m.r. techniques and HSEA calculations has been applied to the conformational analysis of the following tetrasaccharides: α-D-Manp-(1→3)-[α-D-Manp-(1→6)]-4-deoxy-β-D-lyx-hexp-(1→4)-

D-GlcNAc, α-D-Manp-(1→3)-[α-D-Manp-(1→6)]-β-D-Talp-(1→4)-D-GlcNAc and the corresponding 1,6-anhydro-β-D-GlcNAc derivative, α-D-Manp-(1→3)-[α-D-Manp-(1→6)]-β-D-Manp-(1→4)-1,6-anhydro-β-D-GlcNAc, and α-D-Manp-(1→3)-[α-D-Manp-(1→6)]-4-deoxy-β-D-lyx-hexp-(1→4)-1,6-anhydro-β-D-GlcNAc.[53] The n.m.r. spectrum of 6-O-α-D-glucopyranosylcyclomaltohexaose has been analyzed employing phase sensitive double quantum filtered COSY techniques.[54] The hydrated and anhydrous cyclomaltohexaose, -heptaose, and -octaose cyclodextrins have been investigated by solid state cross polarization - dipolar decoupling magic-angle spinning ^{13}C-n.m.r. spectroscopy.[55]

The influence of non-aqueous solvents on the conformations of blood group oligosaccharides has been studied by application of n.m.r. and c.d.; they were found to be essentially identical in DMSO and D_2O, and very similar in pyridine for the Blood group A tetrasaccharide, consistent with the proposal that non-bonded interactions dominate the conformations.[56] The sugar residues in a number of peracetylated glycosphingolipids have been identified using 2D phase-sensitive correlated ^{1}H n.m.r. spectroscopy.[57] A review of the use of n.m.r. methods, along with energy calculations, for the study of solution conformations and dynamics of asparagine-linked oligosaccharides of glycoproteins has appeared.[58]

6 N.m.r. of Nuclei other than ^{1}H or ^{13}C

Reference to the use of ^{29}Si resonances in heteronuclear correlations for the study of oligosaccharides has been made above. The results demonstrated the usefulness of the resonances for the analysis of oligosaccharides, the number of lines equalling the number of initial hydroxy groups.[42-44]

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22
Other Physical Methods

1 I.r. Spectroscopy

A review on the vibrational spectra of carbohydrates has appeared.[1] The i.r. and Raman spectra of D-glucose and five selectively deuterated derivatives in the solid state have been further detailed (c.f. Vol.20, p.236).[2] I.r. spectra of trehalose, its O-deuterated analogue, and maltose have been recorded at 18 and 300 K, the characteristic region of torsional vibration frequencies of hydroxy groups determined, and the hydrogen bonding analysed.[3] Time dependent F.t.i.r. spectra of α-D-galactose, α-D-glucose-1-d, -2-d, -5,6,6-d_3 and α-D-fucose in aqueous solution were recorded and interpreted in terms of gradual mutarotation.[4] F.t.i.r. spectroscopy was used to determine that the conformation of guanosine 5'-monophosphate changes from C2'-endo, anti to C3'-endo, anti on interaction with magnesium (II) ions.[5]

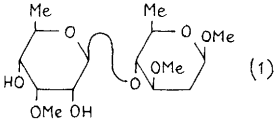
2 Mass Spectrometry

The principles and use of direct/desorption c.i.-m.s. for the structural analysis of carbohydrates and oligosaccharides have been reviewed (54 refs.).[6]

Fast-atom bombardment (FAB) m.s. has been used in the analysis of oligosaccharides, e.g., malto-oligosaccharides up to DP 17, as their N-glycosyl-2-aminopyridine derivatives,[7] of oligosaccharides containing N-substituted mono- and di-amino-sugar units in connection with the characterization of Pseudomonas aeruginosa lipopolysaccharide fragments,[8] of oligosaccharide antibiotics such as the octasaccharide antibiotic everninomycin in which the sequence of sugar residues was determined,[9] and of acetylated and acetolysed high-mannose core oligosaccharides from glycoproteins, produced from just a few micrograms of isolated oligosaccharide.[10] The fragmentations of oxyanions $[M-H]^-$ generated from alkyl glycosides under FAB-m.s. conditions have been studied using mass-analysed ion kinetic energy spectrometry; the main pathway for methyl glycosides involved loss of methanol.[11]

The positive and negative ion laser-desorption F.t.m.s. of ascorbic and isoascorbic acids and their Na^+ and K^+ salts were recorded, and a number of differences between these results and those obtained with a related technique (Vol.18, p.155) were discussed.[12]

E.i.-m.s. can be recorded on oligosaccharides composed of O-methyldeoxyhexoses and dideoxyhexoses, because they are not as involatile as normal oligosaccharides. The high-resolution e.i.-m.s. fragmentation patterns of methyl β-pahybioside (1) and the oleandrotetrose orthenthose were interpreted.[13] The differing mass spectra of several diastereomeric pyrimidine nucleosides have been described.[14]



(1)

The capillary g.c.-e.i.- and c.i.(NH_3)-m.s. of partially methylated and acetylated derivatives of 3-deoxy-2-keto-aldonic acids and 3-deoxyalditols has been reported in preparation for the methylation analysis of KDO units in bacterial lipopolysaccharides.[15] In the c.i.(i-C_4H_{10})-m.s. of some branched-chain hexopyranoside derivatives (with one or two Ac, CO_2Me, $CONH_2$ or CN groups at C-3), the $[M+C_4H_9]^+$ and several primary fragment ion intensities were found to be dependent upon the nature and stereochemistry of the C-3 substituent.[16]

A number of reports have appeared on the coupling of h.p.l.c. and m.s. systems for the analysis of sugars. Thermospray h.p.l.c.-m.s. has been applied to the analysis of mono- and di-galactosyl diglycerides which are major components of plant cell membranes,[17] desulpho-glucosinolates as models for natural glucosinolates, and the cytokinins zeatin, its riboside, and their dihydro-analogues,[18] and 2',3'-dideoxyinosine as a degradation product of 2',3'-dideoxy-adenosine in biological fluids.[19] A dual beam thermospray interface, which permits introduction of the ammonium acetate solution, necessary for this mode of ionization, independently from the h.p.l.c. eluant, has been demonstrated for sucrose and adenosine among other compounds.[20] The eluant from capillary h.p.l.c. columns of 0.22 or 0.26 mm i.d. silica tubing can be directly introduced into m.s. systems. Systems with such direct liquid introduction have been successfully used for the analysis of

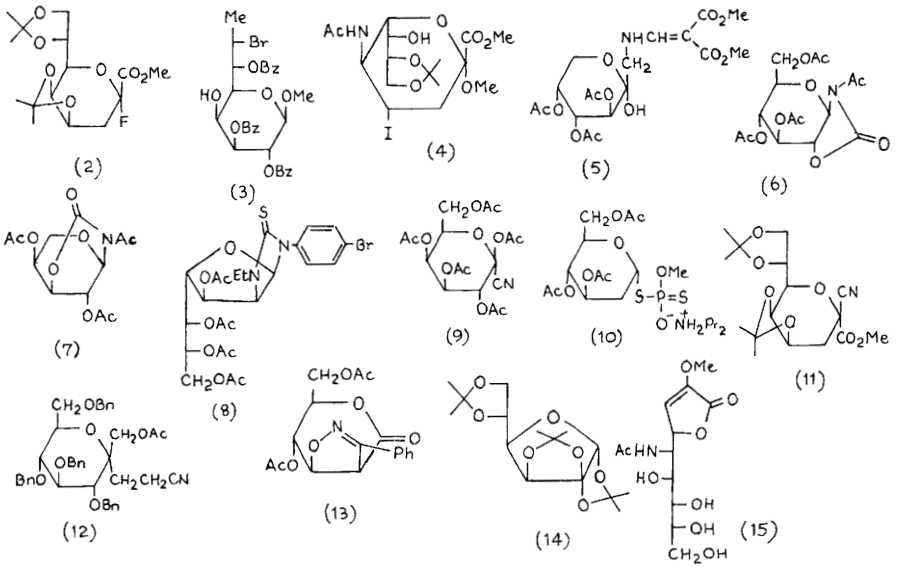
anomeric pyridine C-nucleosides,[21] raffinose and cardenolides,[22] and some oligosaccharides where FAB ionization was induced through inclusion of glycerol in the eluant.[23] A moving polyimide belt h.p.l.c.-m.s. interface using FAB desorption in the absence of added matrix, has been demonstrated for model oligosaccharides and high mannose oligosaccharides from animal urine.[24]

3 X-ray Crystallography

In an attempt to understand the effect of raffinose on sucrose morphology, a detailed crystallographic study on the theoretical surfaces of sucrose was undertaken, and face by face kinetics were determined for single and twin sucrose crystals as affected by raffinose.[25] The occurrence of propeller twisting in single crystals of nucleosides was demonstrated by analysis of material from the Cambridge database.[26]

Specific crystal structures have been reported as follows:
Free Sugars and Simple Derivatives Thereof.- β-D-Xylopyranose (a refinement, correcting an angle),[27] 2,3:4,5-di-O-isopropylidene-β-D-fructopyranose,[28] 3,4,6-tri-O-acetyl-1,2-O-isopropylidene-α-D-galactopyranose,[29] 3,4-di-O-acetyl-1,2-O-(R) and (S)-(1-cyanoethylidene)-α-D-xylopyranose,[30] and 1,2,3,4-tetra-O-acetyl-β-D-glucopyranos-6-yl 1,2:5,6-di-O-isopropylidene-α-D-glucopyranos-3-yl methyl phosphate.[31]
Glycosides and Derivatives Thereof.- n-Octyl α-D-glucopyranoside mono- and hemi-hydrate,[32] a triterpenoid glycoside containing 2-deoxy-D-glucose,[33] a diterpene β-D-xylopyranoside,[34] methyl 2-deoxy-3,5-di-O-(4-nitrobenzoyl)-β-D-erythro-pentofuranoside,[35] methyl 2,4,6-tri-O-pivaloyl-α-D-glucopyranoside and methyl 4,6-O-benzylidene-2-O- and 2,3-di-O-pivaloyl-α-D-glucopyranoside,[36] and the C-glycosides diazomethyl β-D-galactopyranosyl ketone,[37] and 3-(2-deoxy-α-D-erythro-pentofuranosyl)pyridine.[38]
Tri- and Tetra-saccharides.- A triterpene trisaccharide [with an α-L-Rhap-(1→4)-β-D-Glcp-(1→6)-β-D-Glcp→residue],[39] and stachyose [α-D-Galp-(1→6)-α-D-Galp-(1→6)-α-D-Glcp-(1→2)-α-D-Fruf].[40]
Anhydro-sugars.- Methyl 6,6-[$^2H_2$]-2,6-di-O-acetyl-3,4-anhydro-α-DL-galactopyranoside,[41] 3-O-(2,3-anhydro-4-deoxy-α-L-lyxo-hexopyranosyl)-1,2:5,6-di-O-isopropylidene-α-D-glucopyranose,[42] and methyl 3,6-anhydro-β-L-gulofuranoside.[43]
Halogen-, Nitrogen-, and Sulphur-containing compounds.- The 2,3,4,6-tetra-O-acetyl derivatives of 1-C-chloro-α-D-glucopyranosyl

bromide[44] and 1-C-bromo-α-D-galactopyranosyl cyanide,[45] the pyranosyl fluoride (2) of KDO,[46] 3,5-O-(R)-benzylidene-6-deoxy-6-iodo-1,2-O-isopropylidene-α-D-glucofuranose,[47] the 7-bromo-octoside (3),[48] the 4-iodo-neuraminic acid analogue (4),[49] 2-deoxy-2-[(4,4-dimethyl-2,6-dioxocyclohexylidenemethyl)amino]-α,β-D-glucopyranose,[50] the 1-amino-1-deoxy-D-fructose derivative (5),[51] 2-azido-3,4-O-benzylidene-2-deoxy-D-ribono-1,5-lactone, 2-azido-2-deoxy-D-ribono-1,4-lactone, and 1,4-dideoxy-1,4-imino-L-ribitol,[52] 1,5-dideoxy-4-O-(α-D-glucopyranosyl)-1,5-imino-N-methyl-D-glucitol,[53] 2-deoxy-N-(4-carboxyphenyl)-β-D-ribopyranosylamine,[54] 4-(N-acetyl-2,3,4-tri-O-acetyl-β-L-arabinopyranosylamino)azobenzene,[55] the β-D-gluco-1,2-cyclic urethane (6), its D-xylo-analogue, and the α-L-arabino-1,3-cyclic urethane (7),[56] the imidazole-2-thione derivative (8),[57] the oxime of 1,5-anhydro-D-fructose,[58] the four tetraacetylated glycopyranosyl cyanides with the β-D-gluco-, β-D-manno-, α-D-ribo-, and α-D-ido- configurations,[59] the β-D-galacto-2-heptulopyranosonitrile (9),[45] 2,4:3,5-di-O-benzylidene-D-arabinose diethyl dithioacetal,[60] and the glycosyl dithiophosphate (10).[61]



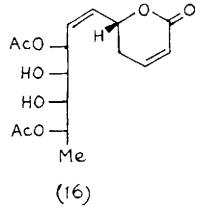
Branched-Chain Sugars.- The cyano-sugars (11)[62] and (12),[63] and the dipolar cycloadduct (13).[64]

Aldoloses, Sugar Acids, and their Derivatives.- The tri-O-isopropylidene derivative (14) of D-glucosone hydrate,[65] ammonium 3-deoxy-

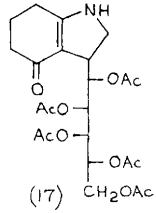
D-manno-2-octulosonate (KDO),[66] and its 2-deoxy-analogue, i.e., 2,6-anhydro-3-deoxy-D-glycero-D-talo-octonate,[67] and the 2-noneno-1,4-lactone (15).[68]

Inorganic Derivatives.- 5,6-Dideoxy-1,2-O-isopropylidene-3-O-methyl-6-C-nitro-5-C-(dimethoxyphosphinyl)-β-L-idofuranose (note: the diagram in the paper appears to be the C-5 epimer with the D-gluco configuration),[69] and the nickel (II) dichloride complex with N,N-di[N-(β-D-mannopyranosyl)-2-aminoethyl]ethylenediamine.[70]

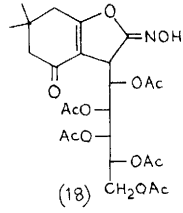
Alditols, Cyclitols and Derivatives Thereof.- 1,2:3,4:5,6-Trianhydro-D-iditol,[71] the α-pyrone plant natural product synrotolide (16),[72] the D-galacto-pentitol-1-ylated heterocycles (17)[73] and (18),[74] L-chiro-inositol,[75] the (R)-camphanate ester (19) of myo-inositol,[76] and the 1:1-complex of caffeine with potassium chlorogenate (the salt of an O-caffeoyl-quinic acid).[77]



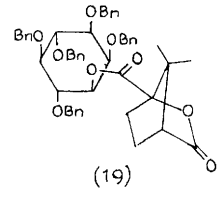
(16)



(17)



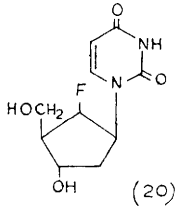
(18)



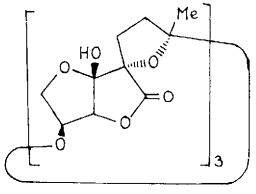
(19)

Nucleosides and their Analogues and Derivatives.- 1-Methyladenosine,[78] 3-methylcytidinium nitrate,[79] 2',3',5'-tri-O-acetyl-8-bromo-adenosine,[80] 2',5'-anhydro-arabinosylcytosine,[81] 5'-azido-5'-deoxy-1-β-D-arabinofuranosylcytosine,[82] 2'-C-methyl-uridine,[83] ethyl-1-β-D-arabinofuranosyl-2-cyanomethyl-1H-pyrrole-3-carboxylate,[84] 3-benzoyloxy-1-β-D-ribofuranosyl-pyrazole-4-carboxylic acid,[85] 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl) derivatives of tetrahydro-2H-1,3-diazepine-2,4(3H)-dione and 6,7-dihydro-2H-1,3-diazepine-2(3H)-one,[86] cis-(5R,6R)-5,6-dihydroxy-5,6-dihydrothymidine (a radiation product of thymidine),[87] 3'-azido-3'-deoxy-thymidine,[88] 2'-deoxy-N^6-(4-nitrobenzyl)-adenosine,[89] 3',5'-di-O-acetyl-2'-deoxy-adenosine,[90] 3'-O-acetyl-2'-deoxy-adenosine,[91] 2'-deoxytubercidin,[92] 3'-deoxytubercidin and 3-deaza-3'-deoxy-adenosine,[93] N-benzoyl-5'-O-tert-butyldimethylsilyl-2'-deoxy-adenosine,[94] the C-nucleosides 1,3-dimethyl-8-β-D-ribofuranosyl-xanthine monohydrate[95] and 5-C-(2-amino-2-deoxy-β-D-glucopyranosyl)barbituric acid,[96] and the carbocyclic 2'-deoxyuridine analogue (20).[97]

Others.- The trimer (21) from L-ascorbic acid and methyl vinyl ketone.[98]



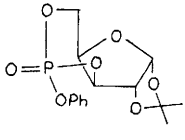
(20)



(21)

4 E.s.r. Spectroscopy

Two articles have reviewed conformations, deduced from e.s.r. hyperfine coupling constants, of radicals generated by abstraction of Br, I or SePh from C-1, -2, -3, or -4 of alkylated and acylated pyranoses with photolytically generated stannyl radicals. The preferred conformations of π-type C-1 1-deoxypyranosyl radicals were discussed in terms of stabilization by adjacent β-C-O bonds,[99] a novel 1→2-acetoxy-group migration in a tetraacetyl-galactosyl radical was reported, and the mechanism of interaction of nitro-sugars with stannyl radicals was discussed.[100] Four phosphorus-centred radicals were identified in an e.s.r. study of a single crystal of the phenoxyphosphoryl xylofuranose derivative (22) X-irradiated at low temperature (∿77K).[101] An e.s.r. analysis of



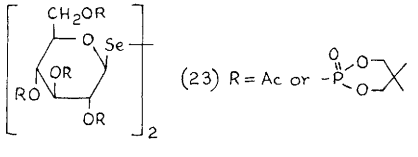
(22)

the degradation products from γ-irradiation of α-D-glucose at 77 to 415 K confirmed the decomposition of the initial radicals at 150-170 K to give sugar acids, and the formation of secondary radicals through dehydration of the initial radicals.[102]

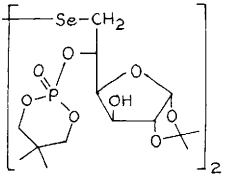
5 Polarimetry, Circular Dichroism and Related Studies

A semiempirical theory of optical activity, which incorporates high energy excited states so as to be relevant in the vacuum u.v. and which can be applied to complex molecules, has been applied to cyclohexane-polyols. A moderately good correlation with experimental data was attained.[103] O.r.d., c.d., and u.v. spectroscopy have been used to investigate the optical contributions of the nitrate

group in eight derivatives of gluco- and manno-pyranoses having one or two nitrate groups at C-1, -2, or -3,[104] and of the aglycones in eighteen aryl β-D-glucopyranosides.[105] Pairwise interactions of acetyl groups accounted for the observed relationship between the c.d. spectra and stereochemistry in eight peracetylated 1,5-anhydro-pentoses, -hexoses and certain deoxy-analogues.[106] A c.d. study of four diselenides, e.g., (23) and (24), and one ditelluride permitted the assignment of Cotton effects.[107] The Cotton effects



(23) R = Ac or



(24)

of bidentate complexes between $Mo_2(OAc)_4$ and some sugar diols have been studied, and it was proposed that the absolute configuration of acyclic vicinal threo and primary-secondary diols can be determined in this way.[108]

The exciton chirality method has been discussed. It is a powerful tool for determining the stereochemistry of organic molecules containing hydroxy-groups at stereocentres, and has been applied to oligosaccharides on a microscale using exciton chromophores in derivatives, e.g., benzoate esters, benzyl ethers.[109]

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23
Separatory and Analytical Methods

1 Chromatographic Methods

General.- A review has appeared on the purity assessment of biologically active carbohydrates, especially by h.p.l.c.[1]

Gas-Liquid Chromatography.- Unless otherwise stated, all analyses were performed on capillary g.c. columns.

The preparation and characterization by g.c.-m.s. of partially methylated and acetylated 3-deoxy-octitols (c.f. Vol.20, p.247), 3-deoxy-heptitols, and the corresponding 3-deoxy-2-ketoaldonic acids has been reported in connection with the methylation analysis of 3-deoxy-2-ketoaldonic acid units in bacterial lipopolysaccharides.[2] Permethylated derivatives of 3-deoxy-2-ketoaldonic acid 5-phosphates, suitable for g.c.-m.s., have also been prepared.[3] Glucosamine and galactosamine released from glycosaminoglycans in blood and plasma by hydrolysis have been quantitatively determined by analysis of the derived acetylated aminoalditols on a packed column.[4]

Aldoses and alduronic acids have been simultaneously analysed by g.c. as their peracetylated alditol and N-propylaldonamide derivatives, respectively. Derivatization involved reduction of sodium alduronates with sodium borohydride, lactonization of the resulting aldonates, and reaction with n-propylamine to form the N-propylaldonamides. D-Glucuronic acid is thus converted to N-propyl-L-gulonamide.[5] Alternatively, the mixture of alditols and aldonic acids obtained from the borohydride reduction can be separated on an ion-exchange resin in the acetate form, and the isolated aldonic acids lactonized and trimethylsilylated prior to g.c. analysis.[6]

A procedure recommended for the quantitative determination of carbohydrates in solution involved reduction ($NaBD_4$), permethylation (DMSO-NaOH powder - MeI), and analysis by g.c. or g.c.-m.s. The derivatization could be conducted in the same vial, and improved accuracy over other methods was claimed. The method was applied to

the analysis of reversion products and anhydroglucoses formed on high temperature dilute acid hydrolysis of cellulose.[7]

The OV-17 phase has been found to give improved separation of the diastereoisomeric pertrimethylsilylated methyl 2-(polyhydroxyalkyl)thiazolidine-(4R)-carboxylates formed from enantiomeric pairs of nine aldoses after reaction with L-cysteine methyl ester (c.f. Vol.20, p.248). Although each pair of sugar enantiomers gave separate peaks, those from different sugars, e.g., D-xylose and L-arabinose, sometimes co-eluted.[8]

An attempt has been made to relate structure to retention in the g.c. of the per-O-trimethylsilyl ethers of the four forms of the four aldopentoses on a variety of packed and capillary columns.[9] Over fifty products, mostly carboxylic acids, from the oxidative and non-oxidative alkaline degradation of L-ascorbic acid have been identified by g.c.-m.s. after conversion to their ammonium salts and pertrimethylsilylation.[10]

Mono- to tri-saccharides in honey have been identified and assayed by separate analysis of their pertrimethylsilyl ethers before and after formation of oxime derivatives. The dual system was employed to account for overlapping peaks, and sixteen components including two trisaccharides were identified.[11] A good separation of the neutral monosaccharides commonly present in glycoproteins was achieved using their acetylated O-(pentafluorobenzyl)oxime derivatives, which give peaks for syn- and anti-oxime isomers. The e.i.-m.s. of these derivatives was reported.[12]

Neutral aldoses from hydrolysis of corn bran residues were analysed as their aldononitrile acetate derivatives.[13]

Thin-Layer Chromatography.- The high performance t.l.c. of monosaccharides and related derivatives, released by hydrolysis of natural and synthetically modified polysaccharide gums, on "low specific area" or "low-activity" silica plates has been reported.[14] Unsaturated sulphated disaccharides derived from chondroitin sulphate or proteoglycan by enzymic digestion have been separated on silica gel and quantified by densitometry.[15] Anomers of the purine nucleosides adenosine and deoxyadenosine have been separated on commercial "chiral plates", constituted of C_{18}-modified silica treated with copper acetate and (2S, 4R, 2'RS)-4-hydroxy-1-(2-hydroxydodecyl)proline.[16] Other t.l.c. results can be found in the next section, reference 28.

High-Pressure Liquid Chromatography.- A review (34 refs.) on the h.p.l.c. of sugars has included a discussion on the mechanism of separation on various stationary phases.[17] The general principles of preparative h.p.l.c. of monosaccharides, sugar acids and lactones, and N-acetylated amino-sugars have been discussed, and many practical details given for the isolation of mg to g quantitates on either aminopropyl silica gel or cation exchange resins in the H^+- or Ca^{2+}-form.[18] The characteristics of H^+- and Ag^+-form cation exchange resin, aminopropylsilica gel, and C_{18}-reversed phase packings for the preparative h.p.l.c. separations of malto-oligosaccharides have also been compared.[19]

A subnanolitre, laser-based, low cost refractive index detector has been described and used in the detection of nanogram amounts of sugars separated by microbore reversed-phase h.p.l.c. (0.25 mm i.d.).[20] A new evaporative light scattering detector has been demonstrated in the h.p.l.c. analysis of mono- and oligo-saccharides on a variety of columns (amino-bonded and reversed-phase silica, and Ca^{2+}-form resins).[21] Selective detection of reducing sugars eluted from cation-exchange resins in the Pb^{2+}-, H^+- or Ca^{2+}-form has been achieved using a post-column reactor containing immobilized glucose dehydrogenase. The enzymatic oxidation of the carbohydrates is accompanied by conversion of NAD to NADH which is detected electrochemically. Glucose (down to 2 ng), xylose, 2-deoxy-glucose, glucosamine, and mannose gave good responses, and the method was applied to the determination of glucose and lactose in a fermentation broth.[22] Improved sensitivity (low ng range) and simplicity of sample preparation was attained in the analysis of sugars, e.g., in food products, by employing post-column catalytic hydrolysis (to cleave non-reducing sugars such as sucrose) and 4-aminobenzoic acid hydrazide derivatization. This detection procedure was applied to sugars separated on Pb^{2+}- and Ca^{2+}-form cation exchange resins (e.g., lactose and sucrose), and reversed-phase columns (e.g., oligosaccharides in high fructose corn syrup).[23]

Monosaccharides (Rha, Xyl, Ara, Glc, Gal) released on hydrolysis of saponins have been assayed by h.p.l.c. on primary amine bonded silica with post-column reaction with alkaline tetrazolium blue.[24] Monosaccharides (All, Glc, Gal, Man) in plant glycoside hydrolyzates have been differentiated by h.p.l.c. on a Pb^{2+}-form cation exchange resin at 85°C.[25] As part of the chromatographic analysis of products from the hydrothermolysis of poplar wood, sugars and their

decomposition products have been analyzed on a Na^+-form cation exchange resin.[26] Semi-preparative h.p.l.c. separations of such components, including gluco-oligosaccharides, present in biomass hydrothermolysis solutions have been achieved on polystyrene-based Ag^+- and H^+-form cation exchange resins, ^{14}C-labelled samples being isolated from ^{14}C-labelled biomass.[27]

Microgram amounts of neutral sugars could be detected by reductive amination [$NaBH_3CN$-$(NH_4)_2SO_4$] to produce 1-amino-1-deoxy-alditols, followed by derivatization with the fluorescent labelling reagent NBD-F (7-fluoro-4-nitrobenz-2-oxa-1,3-diazole), and reversed phase h.p.l.c. analysis. These derivatives were also suitable for t.l.c. analysis on boric acid impregnated silica plates.[28] The glycosylamines formed quantitatively from reducing mono- and oligo-saccharides with 2-aminopyridine have been shown to be suitable derivatives for h.p.l.c. analysis on amino-bonded silica with fluorescence detection. They are stable to storage and chromatography, and can be hydrolysed by mild acid to regenerate the original sugar. The procedure avoided the problems encountered in reductive amination with the same amine, and the derivatives had better chromatographic properties. Malto-oligosaccharides up to DP 17 were separated. Glucose gave minor and major peaks for α- and β-pyranosylamine derivatives.[29] In the h.p.l.c. of neutral monosaccharides as their 2,4-dinitrophenylhydrazone derivatives on silica, each sugar gave a major (often with a shoulder) and a minor peak.[30] Dansylated derivatives of glycosyl galactosyl hydroxy-lysines have been fractionated by reversed-phase h.p.l.c. with fluorescence detection.[31] H.p.l.c. analysis of perbenzoylated monohexosyl glycolipids (standards and biological samples) on silica permitted classification according to their hydrophobic structures.[32]

H.p.l.c. of a variety of natural di- and tri-terpene glycosides on a newly developed hard spherical hydroxyapatite has been reported. The hydroxyapatite proved more satisfactory than silica gel for the normal phase chromatography of water-soluble glycosides due to its greater hydrophilicity.[33]

A variety of on-line h.p.l.c.-m.s. studies have been reported, many using narrow bore (0.22 or 0.26 mm i.d.) columns. Amongst the samples examined were raffinose and cardenolides,[34] sucrose and adenosine,[35] desulphoglucosinolates and the cytokinins zeatin, its riboside and dihydro-analogues,[36] mono- and di-galactosyl diglycerides,[37] and various oligosaccharides including high mannose oligosaccharides from animal urine.[38,39]

The h.p.l.c. analyses of malto-oligosaccharides on two new silica-based packings containing bonded polyamine polymer resin or carbamoyl residues have been compared to those achieved on two conventional amine-bonded silica columns over which they display improved stability.[40] Milligram quantities of the oligosaccharides neokestose, 1-kestose, 6-kestose and nystose have been isolated by sequential chromatographic fractionation on amine-modified silica and reversed phase packings, for use as standards in the analysis of sugar cane.[41]

A sensitive method for analysis of the constituent monosaccharide components of glycoproteins involved sequential acid hydrolysis, borotritide reduction, re-*N*-acetylation, and radioactivity detection after separation of neutral alditols and aminoalditols on a cation-exchange resin in the Pb^{2+}-form at 80°C.[42]

A review on the chromatography of glycosaminoglycans and proteoglycans has included a section on the h.p.l.c. analysis of unsaturated disaccharides produced by enzymic hydrolysis.[43] Improved separations of unsaturated, mostly sulphated, di- to hexasaccharides from enzymic digestion of various hyaluronic acid, chondroitin sulphate and dermatan sulphate samples have been reported on aminopropyl-bonded silica,[44,45] and cation-exchange resin packings.[46]

1-*N*-(β-D-Glucopyranosyl)phenobarbital in plasma and bile has been quantified by reversed-phase h.p.l.c.[47]

Improved analysis of organic acids in sugar cane process juice, including 2-, 5-, and 2,5-di-ketogluconic acids, hexonic acids, and glucuronolactone, has been achieved using two cation exchange resins columns in series equilibrated at different temperatures.[48] 2-Hydroxyoestrone 2-glucuronide and 4-hydroxyoestrone 4-glucuronide in the urine of pregnant women have been separated and characterized by reversed-phase h.p.l.c.[49] Derivatization of glucuronic acid conjugates of phenol, menthol, borneol, testosterone, and estrone with 4-bromomethyl-7-methoxycoumarin (K_2CO_3-18-crown-6 in acetone) permitted analysis on either normal or reversed-phase columns; derivatives isolated by semi-preparative h.p.l.c. were characterized by direct probe c.i.(NH_3)-m.s.[50] The following reversed-phase assays for ascorbic acid have been reported: in human tears, in connection with an approach to evaluating vitamin C deficiency,[51] as one amongst other goat's milk vitamins using a photodiode array U.V. detector,[52] in beer using fatty amines as ion-pair reagents in the eluant and with electro-

chemical detection,[53] and in rose hip samples with post column reduction of dehydroascorbic acid with dithiothreitol.[54] Ascorbic and related acids in human urine have been assayed on a polyvinyl-alcohol gel using post-column reaction with a fluorescence reagent as described earlier (see Vol.19, p.245, ref.63).[55] Ascorbic acid 2-phosphate in red blood cells and plasma has been determined on a silica based anion-exchange column.[56]

Sugar phosphates and nucleotides, photosynthetic intermediates extracted from leaves, have been determined by h.p.l.c. on a strong base anion-exchange resin eluted with a borate-phosphate buffer and colourimetric detection after post-column reaction with orcinol-sulphuric acid with U.V.-irradiation. An excellent separation of an 18 component standards mixture was reported.[57]

The separation of myo-inositol and its 2-phosphate ester as their fluorescent anthranilate esters on reversed-phase or primary amine-bonded silica packings has been reported, but the methodology seems less than satisfactory since in the derivatization with isatoic anhydride not all hydroxy groups are esterified, and the chromatogram reveals mixtures of products.[58]

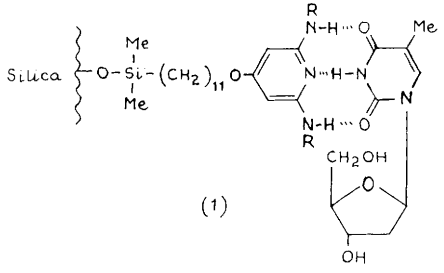
Ion-pair reversed-phase h.p.l.c. analysis of a variety of aminoglycoside antibiotics using volatile perfluorinated carboxylic acids as the pairing ions has been further studied.[59,60] Specific ion-pair reversed-phase analyses of the gentamicin components in raw material and pharmaceutical preparations,[61] and of pirlmycin, a lincosamine-based antibiotic,[62] have also appeared. An improved procedure for the fluorescence derivatization of the gentamicins with o-phthalaldehyde prior to reversed-phase analysis involved absorption of the aminoglycosides onto silica gel, onto which was eluted o-phthalaldehyde. After a suitable reaction time excess reagent could be washed off and the derivatized samples eluted with methanol.[63]

A number of papers on the reversed-phase h.p.l.c. analysis of nucleosides and related compounds have appeared. Correlations between structure and retention time have been drawn for a series of anomeric D-xylo-, D-lyxo-, D-ribo- and D-arabino- furanosyl nucleosides.[64,65] Absorption isotherms that reveal the absorption behaviour of peptide and nucleic acid constituents, including four nucleosides, have been measured by frontal chromatography on a miniaturized h.p.l.c. system requiring only mgs of sample.[66] The features associated with fast (5-10 cm column length), microbore (1 or 2.1 mm i.d. column), and fast-microbore h.p.l.c. for the

separation of nucleic acid constituents inosine, its 5'-monophosphate, and hypoxanthine, as well as a mixture of nucleosides and bases, have been studied,[67] and the modification of an existing h.p.l.c. system for microbore analysis of nucleosides and bases described.[68] The separation of nucleosides and related compounds in 15 min with isocratic elution employed an improved column (Select B), and the method was applied to the analysis of animal heart perfusates.[69] Assays have been reported for the nucleoside drugs 5-azacytidine,[70] 2',3'-dideoxyadenosine,[71] 5-fluoro-2'-deoxyuridine,[72] and ribavirin (1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide)[73,74] in biological fluids and tissues; in the latter case a preliminary class separation on gel-immobilized phenylboronate was used. The analysis of DNA nucleosides released by enzymic hydrolysis has been optimized for determining the extent of thymidine substitution by 5-iodo-2'-deoxy-uridine.[75] Nucleosides, nucleotides and bases in human and rabbit blood cells were assayed by reversed-phase h.p.l.c., and those in mouse tumor cells by using an ion-pair reagent in the eluant.[76] An ion-pair reversed-phase method was detailed for the rapid analysis of ^{14}C- and ^{3}H-labelled *S*-adenosylmethionine in enzymic reaction mixtures.[77] Pyridine C-nucleosides have been analysed by microbore, direct liquid introduction h.p.l.c.-m.s., and semi-preparative h.p.l.c. methods developed for obtaining pure materials.[78]

Other column packings have been used in the analysis of nucleosides. For the separation of minor amounts of nucleosides with base units modified by carcinogenic reagents, from non-modified ones, an h.p.l.c. column was employed that had a reagent bonded to the silica packing which specifically hydrogen-bonded to normal nucleosides [as shown for (1)] but not to the modified ones.[79] The retention of nucleosides and bases on a polyvinylalcohol column using a micellar eluant (containing sodium dodecylsulphate) has been studied, as a function of temperature, pH and concentration of detergent. A retention mechanism was proposed, and the methodology was exemplified by analysis of human serum.[80] Uracil, uridine and formic acid in egg products were assayed on an H^+-form cation-exchange resin using an acidic eluant; uracil is an indicator of deterioration, and uridine appears to be one of its precursors.[81] Improvements have been reported for the analysis of adenosine and its nucleotides in biological media using precolumn derivatization with bromoacetaldehyde (to give 1,N^6-ethenoadenosine derivatives) and a macroreticular anion-exchange resin column.[82] 5-Fluoro-2'-

deoxyuridine has been assayed in human plasma using precolumn fluorescence derivatization with 4-bromomethyl-7-methylcoumarin followed by h.p.l.c. on silica.[83]



(1)

Column Chromatography.- A methacrylate-resin column with sugar ligands has been prepared by reaction of an epoxy-activated resin with D-glucamine (i.e., 1-amino-1-deoxy-D-glucitol), maltamine, or lactamine. Stereochemical interaction between immobilized sugar ligands and applied sugar samples was detected in the partition chromatography mode, but not sufficient to separate anomers. On the D-glucamine-resin, a group separation of hexoses from pentoses plus 6-deoxy-hexoses was achieved.[84]

An automated analysis of mono-, oligo- and poly-saccharides by anion-exchange chromatography using a borate eluant has employed two post-column reactions, the first hydrolysis with p-toluene-sulphonic acid, and the second a reaction with ethanolamine to generate fluorescent products. The method was applied to determine the sugars in Picea needles, and it was shown that trees damaged by air pollution accumulated free glucose and fructose.[85] α,β-Trehalose, produced as a minor product along with β,β-trehalose by a Koenigs-Knorr glycosylation, has been isolated by anion-exchange chromatography (HO^--form resin, H_2O as eluant).[86] The preparative separation of six epimeric C-deuterated inositols (scyllo, chiro, neo, allo, muco and epi) was also achieved by anion-exchange chromatography (boric acid gradient elution) after partial purification by recrystallization.[87]

Ion-exclusion chromatography of non-ionic alcohols and sugars has been described, using an H^+-form cation-exchange resin, with an acidic eluant and conductivity detection. With dilute sulphuric acid as eluant, sugars gave negative peaks due to a lowering of the solution conductivity by low concentrations of the non-ionic solutes,

but with 0.1 M boric acid as eluant, sugars formed complexes which yielded positive responses.[88]

Ion chromatography with oxidative amperometric detection has been used to separate aldehyde-bisulphite adducts including that of mannose.[89]

The gel-permeation chromatography (Bio-Gel P2) of gluco-oligomers from hydrothermolysis of poplar wood has been detailed.[26]

Methyl 2-amino-2,4-dideoxy-β-D- and L-threo-pentopyranosides have been resolved by separation of diastereomeric (+)-mandelate esters on silica.[90]

2 Electrophoresis

A mixture of 14 normal and modified deoxyribonucleosides and related nucleic acid constituents have been separated in less than 40 min by micellar electrokinetic capillary chromatography (MECC) with u.v. detection. MECC is a new type of liquid chromatography which employs electroosmotically pumped micelle mobile phases (incorporating sodium dodecylsulphate), and offers the advantage of both electrophoresis and partitioning.[91]

3 Other Analytical Methods

Aldoses can be selectively removed from aqueous solutions containing ketoses and non-reducing sugars by reaction with aniline in the presence of acetic acid as catalyst, and extraction of the products by treatment in sequence with ether, ethyl acetate, activated charcoal, and acidic ion-exchange resin.[92]

Certain flavonoids, e.g., catechin, have been shown to interfere in the phenol-sulphuric acid colourimetric analysis of carbohydrates.[93]

A combined periodate oxidation - ^{1}H-n.m.r. spectroscopic technique has been used to determine the structure of a variety of sugar derivatives, especially those containing terminal diols, and 1-substituted pentopyranoses and tetrafuranoses.[94]

A procedure for the determination of sulphate and phosphate in sugar sulphate and phosphate esters, and in more complex glycoprotein samples, used hydrolysis and ion-chromatography.[95]

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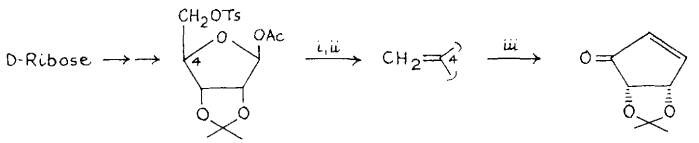
24

Synthesis of Enantiomerically Pure Non-carbohydrate Compounds

A review has appeared on the use of pyranoid building blocks for natural product synthesis,[1] and the use of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose for the synthesis of enantiomerically-pure compounds has been surveyed, in German.[2]

1 Carbocyclic Compounds

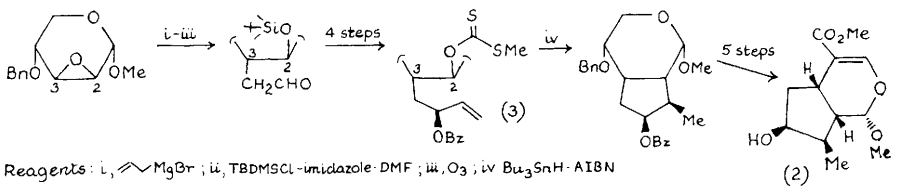
The cyclopentenone (1), considered to be a versatile chiral intermediate for the synthesis of a variety of natural products, has been prepared from D-ribose as outlined in Scheme 1.[3]



Reagents: i, NaI-MEK ; ii, DBU ; iii, MeO^--MeOH

Scheme 1

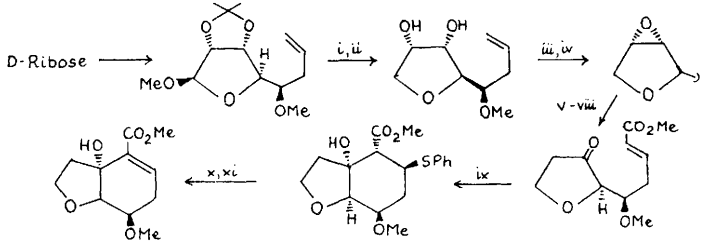
Annulation of a cyclopentane ring onto a pyranoid template was carried out by free-radical cyclization during a synthesis of 1-α-O-methylloganin (2) (Scheme 2); the intermediate (3) was obtained as a 1:1 mixture with its diastereomer, which could be separately cyclized.[4] The annulation of a cyclohexene ring on to a furanoid system shown in Scheme 3 produces a model for the oxahydrindene system of the avermectins;[5] the use of this methodology during the



Reagents: i, ⌇MgBr ; ii, TBDMSCl-imidazole-DMF ; iii, O_3 ; iv Bu_3SnH-AIBN

Scheme 2

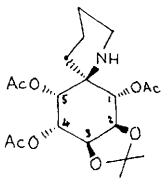
construction of the complete system is discussed in Section 4.



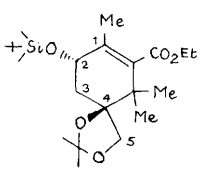
Reagents: i, HCl-MeOH; ii, BF_3-Et_3SiH; iii, α-acetoxyisobutyryl bromide; iv, IRA-400-MeOH; v, $LiBHEt_3$; vi, O_3-Zn-HOAc; vii, Wittig; viii, PCC; ix, $Me_3AlSPh\ Li^+$; x, MCPBA; xi, Δ

Scheme 3

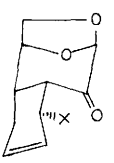
The functionalized cyclohexane (4) was prepared non-stereospecifically by a route involving two nitroaldol condensations, the carbons of mannose being indicated; this compound has the ring skeleton of histrionicotoxin.[6] Compound (5), which constitutes part of the structure of the diterpenoid Taxol-A, has been synthesized in a multistep sequence from L-arabinose (numbering



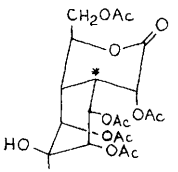
(4)



(5)



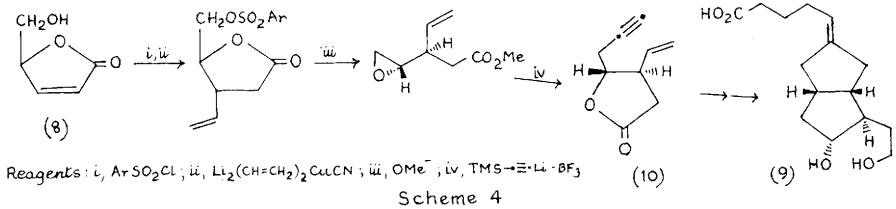
(6)



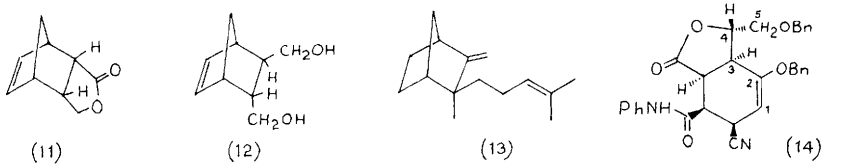
(7)

indicated).[7] A number of compounds of type (6) have been made by cycloadditions of laevoglucosenone,[8] and in the case of (6,X=OAc), further elaboration led to (7); this is of potential in the synthesis of tetrodotoxin, but the introduction of an amino-function at the asterisked carbon would be required.[9]

(S)-5-Hydroxymethyl-2(5H)-furanone (8), derived from D-ribonolactone, was used as an intermediate in a synthesis of the 6a-carbocycline analogue (9), with a Pauson-Khand reaction being used to build up the ring system from enyne (10) (Scheme 4).[10] When alcohol (8) underwent Diels-Alder reaction with cyclopentadiene, either the (2S, 3R)-isomer (11) or its enantiomer could be produced by appropriate manipulation of the initial adduct; face-selective Lewis-acid-catalysed Diels-Alder reactions of α,β-unsaturated esters derived from D-mannitol could be used to produce the (R,R)-isomer (12) or its enantiomer.[11] This chemistry was extended to give syntheses of (+)-β-santalene (13) and its enantiomer from (8);[12] the starting material was prepared as described in Vol. 20 p.260, but a number of other papers dealing with routes to this intermediate are mentioned in the next section.



Scheme 4

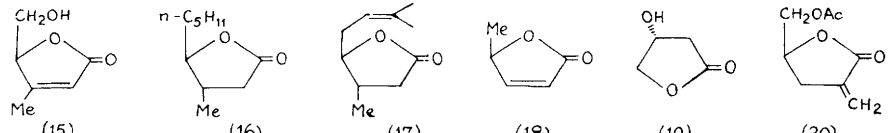


The functionalized cyclohexane (14) was produced as the major isomer by [4+2] cycloaddition of a diene derived from D-arabinose (numbering shown) and N-phenylmaleimide.[13]

2 γ-and δ-lactones

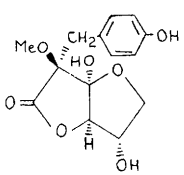
The useful synthon (S)-5-hydroxymethyl-2(5H)-furanone (8) can be obtained crystalline in 40% overall yield from isopropylidene-D-glyceraldehyde,[14] and in 48% yield from D-ribonolactone by a new, convenient route.[15] The 5-O-t-butyldiphenylsilyl ether of (8) is accessible from D-ribonolactone or L-glutamic acid by improved routes (see Vol. 19, p.265).[16] Lactone (8) was used as an intermediate in the preparation of (-)-umbelactone (15)[17] and (+)-trans-cognac lactone (16) from ribonolactone, this latter paper also describing a route from D-ribonolactone to (+)-eldanolide (17).[18] The dihydro-derivative of (8) was used as an intermediate in a route to (S)-β-angelica lactone (18), again from ribonolactone.[19]

Degradation of L-ascorbic acid was used to produce (R)-4-hydroxytetrahydrofuran-2-one (19); the enantiomer was made from D-isoascorbic acid, the chiral centres corresponding with C-5 of the

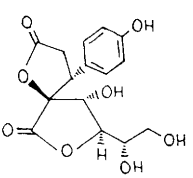


precursor.[20] The simple α-methylene lactone (20) has been synthesized from isosaccharinic acid,[21] and a full account has been given of the synthesis of the litsenolides referred to last year (Vol. 20, p.261).[22]

Some ingenious syntheses have been achieved directly from L-ascorbic acid; the marine algal metabolite delesserine (21) was prepared in 80% yield by the interaction of 2-O-methyl ascorbic acid with p-hydroxybenzyl alcohol in aqueous solution, and leucodrin (22) was similarly prepared from ascorbic acid and methyl 3-hydroxy-3-(p-hydroxyphenyl)propionate, followed by diborane reduction.[23] Piptosidin (23) was produced, together with its diastereomer at the methylated carbon atoms, from ascorbic acid and tigloyl cyanide in aqueous solution.[24]



(21)



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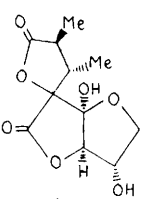
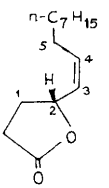


(23)

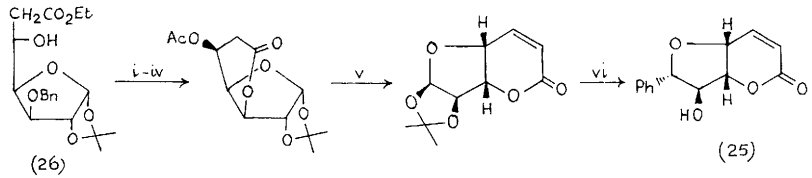


(24)

The marine metabolite leptosphaerin (Vol. 20, p.260-61) has been prepared directly by oxidation of the corresponding hemiacetal first prepared from N-acetylglucosamine some years ago (see Vol. 11, p.78).[25] A number of chiral γ-lactones have been prepared from D- or L-arabinose, including the Japanese beetle sex pheromone (24) (carbons of D-arabinose indicated),[26] and (4R, 5R)-5-hydroxy-4-decanolide, the enantiomer of the proposed autoregulator L-factor, has been synthesized from D-glucose.[27]

(-)-Altholactone (25) has been prepared in a ten-step synthesis from D-glucose, involving an interesting Friedel-Crafts-type introduction of the phenyl group (Scheme 5); the initial compound illustrated, (26), is the product of a chelation-controlled Reformatsky reaction on the 5-aldehyde.[28] Finding that (25) was the enantiomer of the natural antitumour agent, the same workers also prepared the (+)- form of altholactone (27), as outlined in Scheme 6; again, a chelation-controlled reaction established the required stereochemistry at C-5 of the first intermediate shown.[29]

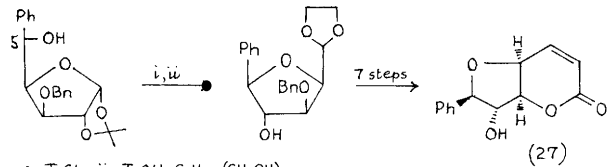
The pyrone anamarine has been prepared in its natural (+)-form (28) by the chemistry indicated in Scheme 7; the thioacetal (29) was prepared by a known procedure from D-gulonolactone, whilst the phosphonium salt (30) was derived from (R,R) tartaric acid.[30] Prior to this, two groups had reported syntheses of the unnatural (-)-anamarine, both proceeding via the enantiomer of (31), and the enantiomeric O-ethyl analogue of (30), both derived from glucose.[31,32] Somewhat similar chemistry was used to generate the pyrone



(26) (25)

Reagents: i, OH^-; ii, H_2-Pd; iii, DCC; iv, Ac_2O; v, DBU; vi, C_6H_6-HF-0°, 10 min.

Scheme 5



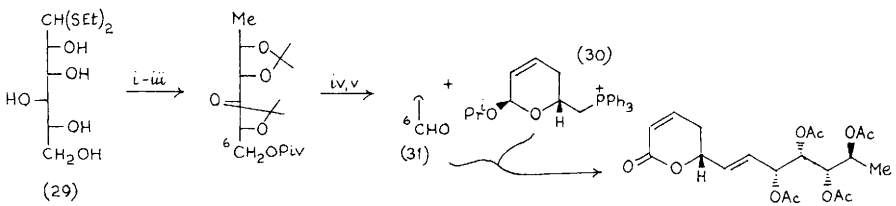
(27)

Reagents: i, TsCl; ii, TsOH-C_6H_6-$(CH_2OH)_2$

Scheme 6

system of asperlin (32), with the epoxide being formed by Sharpless epoxidation of an allylic alcohol.[33]

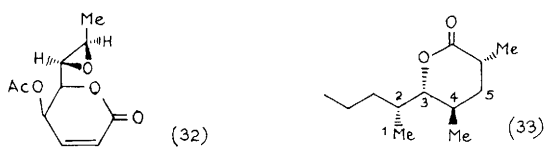
(-)-Invictolide (33) has been synthesized in a multistep procedure from laevoglucosan (carbon numbers indicated).[34]



(29) (30) (31) (28)

Reagents: i, PvCl-Py; ii, P_2O_5-Me_2CO; iii, Raney Ni; iv, t-BuOK-H_2O-Et_2O; v, PCC-Al_2O_3

Scheme 7

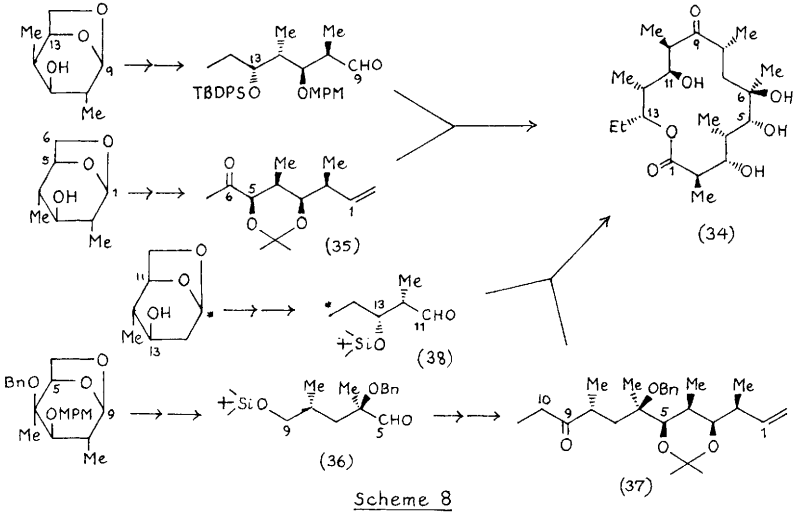


(32) (33)

3 Macrolides and their constituent segments

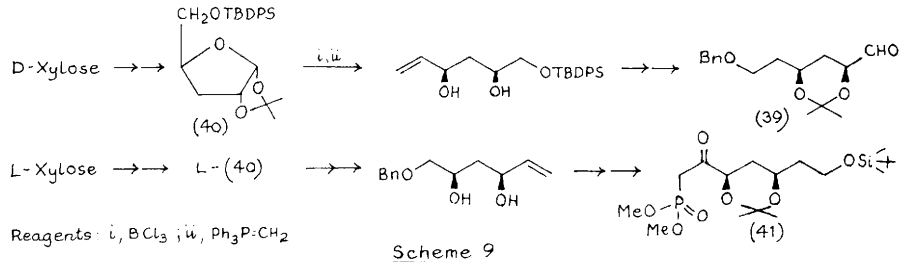
Yonemitsu's group has given full accounts of their syntheses of methynolide,[35-37] tylonolide,[38-39] and pikronolide,[40] referred to

last year (see Vol. 20, p.261-62); all proceeded ultimately from D-glucose and the routes to the different aglycones involved a number of common intermediates and similar chemistry. The same group has also completed a synthesis of (9S)-9-dihydroerythronolide A by linking together glucose-derived fragments previously reported (see Vol. 19 p.263-4).[41] Meanwhile, Kochetkov's group has carried out two syntheses of erythronolide B(34). In one route, fragments representing C(1) - C(6) and C(9) - C(13) were prepared from laevoglucosan and then linked together (Scheme 8); in making (35), an epimerization at C(5) was carried out by base treatment of a precursor of opposite configuration.[42] Alternatively C(5) - C(9) and C(11) - C(13) units were prepared, again from laevoglucosan; the C(5) - C(9) unit (36) was extended to (37) using crotyl stannane chemistry, and linked with the other building block (38) via a chelation-controlled aldol reaction (Scheme 8).[43] The same group have also reported the syntheses of the C(9) - C(13) fragments of methynolide and epineomethynolide,[44] and of neomethynolide.[45]

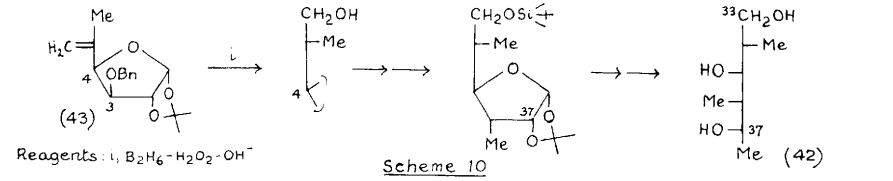


Scheme 8

The building-block (39) suitable for the synthesis of amphoteronolide B, the aglycone of the polyene macrolide amphotericin B, was prepared from D-xylose as outlined in Scheme 9, whilst the enantiomer of (40), made from L-xylose, was used to prepare synthon (41), appropriate for another segment of the same target, by very similar chemistry.[46] The chiron (42) which corresponds to the C(33) - C(37) segment of amphoteronolide, was synthesized from



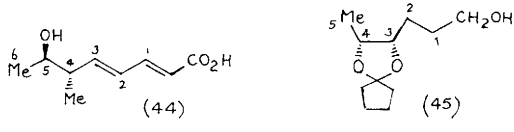
Scheme 9



Scheme 10

the glucose-derived alkene (43) as outlined in Scheme 10;[47] the stereospecificity of the hydroboration is assumed to depend on the presence of a bulky group at C-3, and contrasts interestingly with Yonemitsu's findings in cases with opposite stereochemistry at C-3.[35]

Laevoglucosan was used to prepare the hydroxyacid (44) (glucose numbers shown), which was converted into the dimeric macrodiolide, a model for elaiophylin,[48] and 2-deoxy-D-ribose (numbers indicated) was used to prepare the chiral building-block (45) for one segment of boromycin.[49]

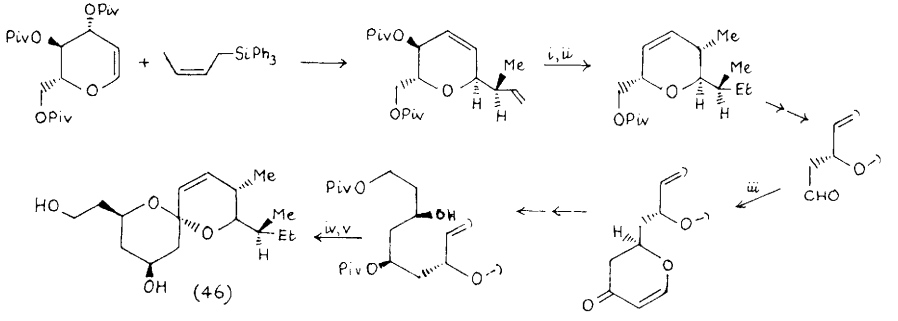


4 Spiroacetal systems

A series of full papers have detailed the synthesis of fragments of the marine toxin okadaic acid,[50-52] and the linkage of the parts to achieve the total enantiospecific and stereoselective synthesis of this complex natural product containing three spiroacetal units and 17 chiral centres.[53]

In a total synthesis of avermectin $A_{1\alpha}$, the spiroketal unit (46) was prepared as outlined in Scheme 11, involving an interesting stereospecific 'carba-Ferrier' reaction, and a chelation-controlled hetero-Diels-Alder cycloaddition as key steps.[54] Inter-

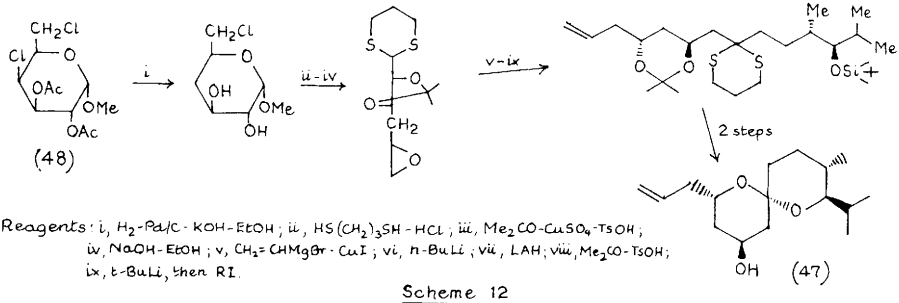
mediate (46) was extended at the primary alcohol function, and then linked with the 'southern zone', the synthesis of which[54] paralleled that indicated earlier in Scheme 3, followed by macrolactonization. The methodology for spiroacetal formation had been previously evaluated in a simpler model system.[55] The completion of the synthesis by attachment of the disaccharide unit to the aglycone is mentioned in Chapter 3.



Reagents: i, H_2-Pd/C; ii, $LiCuMe_2$; iii, Danishefsky's diene-$MgBr_2$; iv, HgO-I_2-CCl_4; v, LiOH-MeOH/THF

Scheme 11

The spiroacetal portion of milbemycin E (47) has been synthesized in 13 steps from methyl α-D-glucopyranoside, via the known dichloride (48), as indicated in Scheme 12.[56]

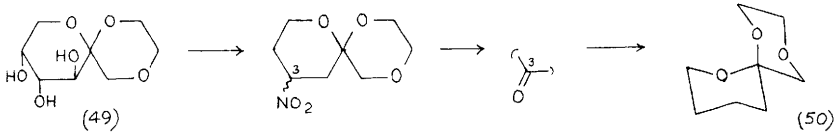


Reagents: i, H_2-Pd/C-KOH-EtOH; ii, $HS(CH_2)_3SH$-HCl; iii, Me_2CO-$CuSO_4$-TsOH; iv, NaOH-EtOH; v, CH_2=CHMgBr-CuI; vi, n-BuLi; vii, LAH; viii, Me_2CO-TsOH; ix, t-BuLi, then RI.

Scheme 12

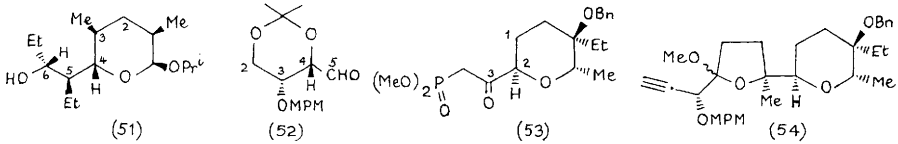
The fructose derivative (49) has been used to prepare the chiral trioxaspiroundecane (50), an oxa-analogue of the olive fruit fly pheromone, as outlined briefly in Scheme 13.[57] During a total synthesis of the spiro-acetalpolyether antibiotic salinomycin, the chiron (51), representing the middle section of the target, was prepared from D-glucose (numbers indicated), whilst (52) and (53) were synthesized from glucose and isopropylidene D-glyceraldehyde respectively, and linked to form (54) representing the right-hand end; the route to (53) involved an inversion of configuration at C-2

of D-glyceraldehyde, the other chiral centres being derived from malic acid.[58]



(49) (50)

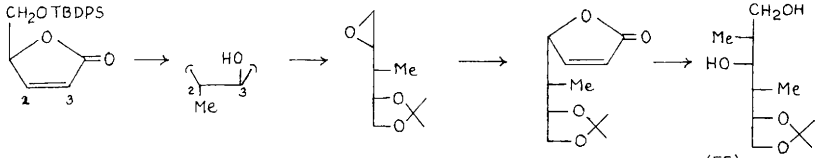
Scheme 13



(51) (52) (53) (54)

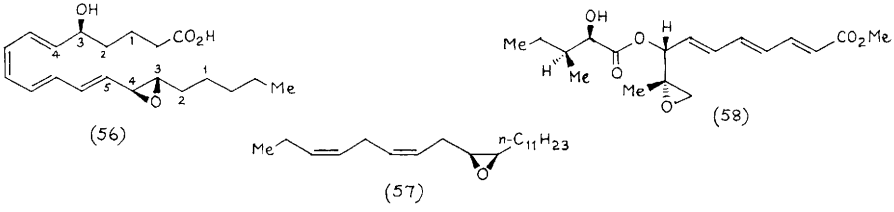
5 Other Oxygen Heterocycles

A review on synthetic routes to polyether antibiotics covers a number of procedures involving carbohydrate synthons.[59] Hanessian's group have used the concept of the 'replicating butenolide template' to prepare a chiral fragment (55) of the polyether antibiotic ionomycin as outlined in Scheme 14.[16]



(55)

Scheme 14



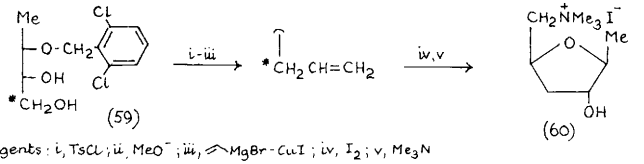
(56) (58)

(57)

2-Deoxyribose was used as precursor for both chiral segments of (5S)-5-hydroxy-14,15-LTA$_4$ (56), the biogenetic precursor of the lipoxins (sugar numbers indicated),[60] and the carbons of D-xylose were incorporated as indicated into the salt marsh caterpillar moth pheromone (57).[61] The fungal toxins AK-II and AF-IIC (58) have been synthesized from L-ascorbic acid.[62]

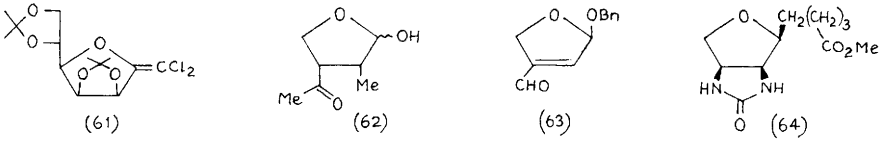
When the chiral unit (59), produced via the diastereoselective addition of methyl magnesium bromide to isopropylidene D-glyceraldehyde, was manipulated as indicated in Scheme 15, (+)-muscarine

(60) was obtained; use of the enantiomer of (59), obtained from D-glucose (the methyl group corresponding with C-6 of glucose) gave (-)-muscarine.[63] Another route to (+)-muscarine (60) and (+)-epimuscarine (epimer at the secondary alcohol) involves the manipulation of (61) (c.f. Vol. 18, p.34; see also Chapter 3).[64] The mycotoxin (-)-botryodiplodin (62) was obtained via conjugate addition of a complex cuprate to the unit (63) reported last year (Vol. 20, p.266) and the same chemistry was also carried out in the enantiomeric series.[65] A new route to (+)-oxybiotin (64) has been



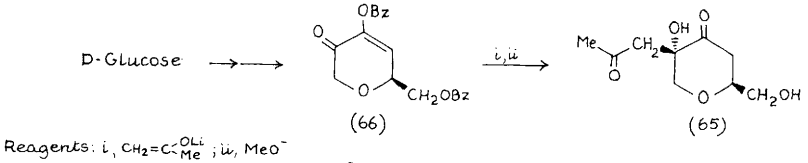
Reagents: i, TsCl; ii, MeO^-; iii, $\rightleftharpoons$MgBr-CuI; iv, I_2; v, Me_3N

Scheme 15



reported, starting from D-xylose (sugar carbons numbered).[66]

A full account has been given of Curran's synthesis of pseudomonic acid involving a Claisen rearrangement of a glycal derivative (see Vol. 18, p.247), together with further examples of such reactions and interesting observations and rationalizations concerning the relative rates of such processes.[67] The absolute configuration of bissetone, from a gorgonian coral, has been established as shown in (65) by a synthesis (Scheme 16) from D-glucose via the enone (66) which was obtained by an improved procedure.[68]

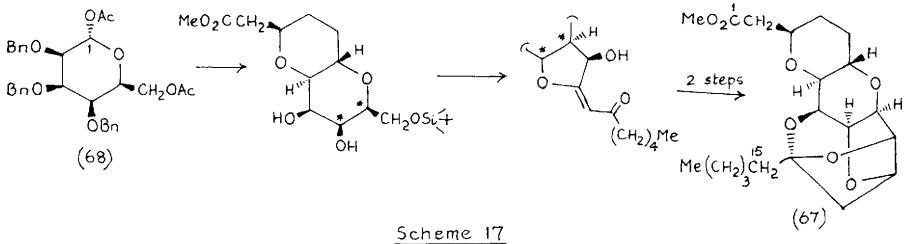


Reagents: i, $CH_2=C(Me)OLi$; ii, MeO^-

Scheme 16

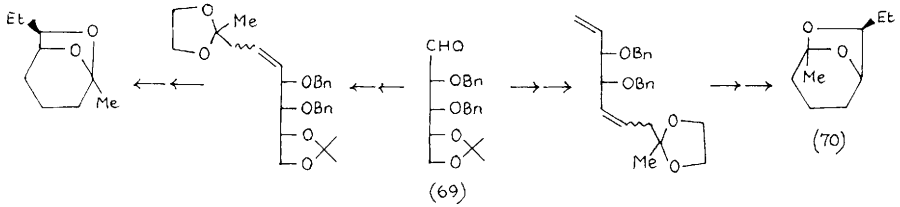
In synthetic studies directed towards the complex polyether systems of the halichondrins, a C(1) - C(15) unit (67) has been synthesized as outlined in Scheme 17. In this Scheme, the formulae shown are of the absolute chirality appropriate for the halichondrins, but the work was carried out using D-galactose as starting

material; this was converted into the enantiomer of (68) via the 3,4-acetonide of 1,6-anhydrogalactose. The reaction of (68) with allyltrimethylsilane and BF_3 ensured the correct stereochemistry at C-1 of the sugar (axial reagent approach).[69]

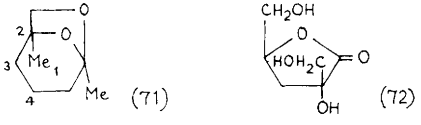


Scheme 17

Both enantiomers of endo-brevicomin have been synthesized from the D-ribose derivative (69), prepared from the sugar in 4 steps, by appropriate manipulation of the two ends of the chain; the (+)-isomer (70) was shown to be the natural pheromone of the southern pine beetle (Scheme 18).[70] The pheromone (-)-frontalin (71) has



Scheme 18

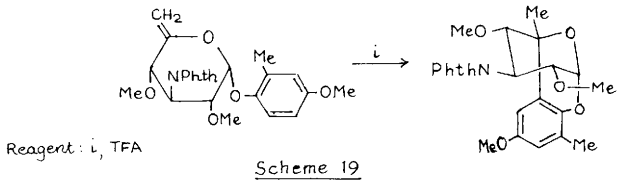


been made from α-D-isosaccharinolactone (72) (sugar numbers indicated) in 17% overall yield.[71]

The intramolecular Friedel-Crafts-type reaction shown in Scheme 19 has been accomplished, albeit in low yield, as a model for the attachment of the amino-sugar unit to the anthraquinone core of nogalamycin.[72]

6 Nitrogen heterocycles

A full account has been given of one of the syntheses reported last year (Vol.20 p.268) of unnatural (-)-sesbanimide A from D-sorbitol,

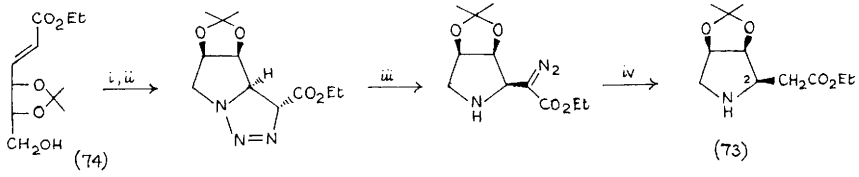


Reagent: i, TFA

Scheme 19

and these workers have also prepared the (+)-isomer from D-xylose in a manner very similar to other groups (see Vols. 19 and 20).[73]

The synthesis of chiral hydroxylated pyrrolidines, piperidines, and indolizidines continues to attract attention. The synthon (73) can be prepared stereospecifically from the E-alkene (74) as outlined in Scheme 20; the Z-alkene, produced together with (74) by Wittig reaction with 2,3-O-isopropylidene- D-erythrose, gave, by the same sequence of reactions, the C-2 epimer of (73).[74] The same group has given a full account of other routes to synthons such as



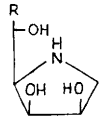
Reagents: i, Tf_2O-Py; ii, N_3^-; iii, EtO^-; iv, H_2-Pd/C

Scheme 20

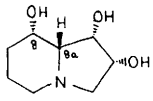
(73) (see Vol. 18, p.256), and their use in the preparation of pyrrolizidine alkaloids such as retronecine and crotanecine.[75]

Full papers have appeared giving details of the syntheses by Fleet's group of (2R, 3S, 4R)-3,4-dihydroxyproline,[76] (2R, 3R, 4R, 5S)-trihydroxypipecolic acid, its (2S)-isomer, and (2R, 3R, 4R)-3,4-dihydroxyproline,[77] (2S, 4S, 5S)-dihydroxypipecolic acid and bulgecinine (see Vol. 20, p.267-68),[78] 1,4-dideoxy-1,4-imino-D-mannitol (Vol. 18, p.168), 1,4-dideoxy-1,4-imino-D-lyxitol (Vol. 19, p.170), and swainsonine (Vol. 18,p.253).[79] The same group has also described the synthesis of 1,4-dideoxy-1,4-imino-L-gulitol (75), 1,4-dideoxy-1,4-imino-D-lyxitol (76), and (-)-8-epi-swainsonine (77),[80] by methods similar to those used earlier by Suami's group for the synthesis of (77) (Vol. 20, p.267), and the Japanese workers have given a full account of their synthesis of (-)-8a-epi-swainsonine (Vol. 20, p.267).[81]

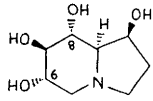
A new route to castanospermine (78) involves as a key step the



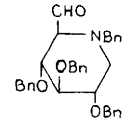
(75) R = CH_2OH
(76) R = H



(77)

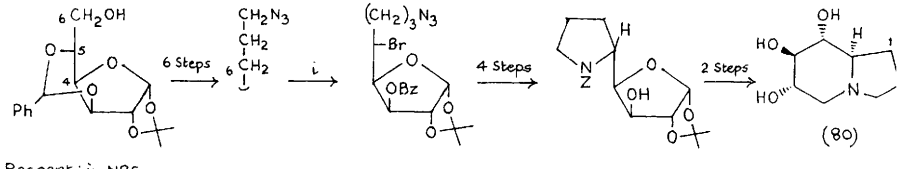


(78)



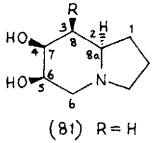
(79)

diastereoselective addition of allyl trimethylsilane to the aldehyde (79), produced by oxidation of a previously-reported intermediate (Vol. 19, p.170); the analogous manno- and galacto-precursors gave rise to 8- and 6-epi-castanospermine, and the authors claim that natural 6-epi-castanospermine is the enantiomer of the material prepared.[82] 1-Deoxycastanospermine (80) has been prepared from D-glucose via the key intermediates shown in Scheme 21; the product was not an effective glucosidase inhibitor, indicating the need for the 1-hydroxy group for the efficacy of castanospermine itself.[83] The same workers have also devised routes from D-glucose to (6R, 7S, 8aR)-dihydroxyindolizidine (81) and (6R, 7R, 8S 8aR)-trihydroxyindolizidine (82) (glucose numbering exocyclic), involving ring-closure between N-2 and C-6 of a 2-

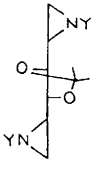


(80)

Scheme 21



(81) R = H
(82) R = OH



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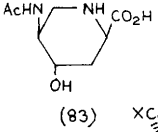

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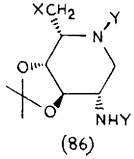

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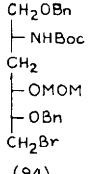
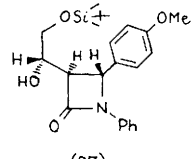


(84)

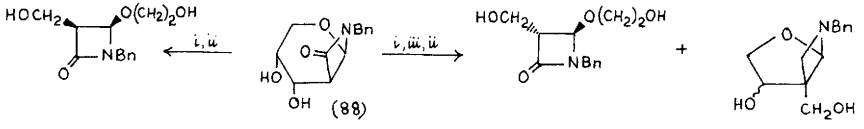


(87)

amino-2-deoxy-D-altrose derivative as the key step.[84] The pipecolic acid derivative (83) has been synthesized as a potential sialidase inhibitor; the route proceeded from D-glucosamine via intermediate (84), which was cyclized between N-2 and C-6, and nitrogen introduced at C-5 with inversion of configuration.[85] In

certain cases, when diaziridines of type (85) (Vol. 20, p.271) are treated with nucleophiles X^-, piperidines of type (86) are produced.[86] Some other papers dealing with hydroxylated nitrogen heterocycles are mentioned in Chapter 18.

The β-lactam (87) has been prepared by a route analogous to that reported for a similar case last year (Vol. 20, p.268-9),[87] and the glycal cycloadduct (88) (c.f. Vol. 20, p.268-9) was subjected to the chemistry outlined in Scheme 22 to give products of potential use in the synthesis of 1-oxapenem and 1-oxacephem systems.[88]



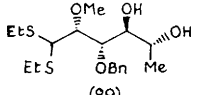
Reagents: i, $NaIO_4$; ii, $NaBH_4$; iii, $NaHCO_3$

Scheme 22

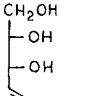
7 Acyclic Compounds

Octadecane -1,2,3,4-tetraols of D-lyxo, L-ribo and L-xylo configurations have been synthesized by Wittig elongation of aldehydo-pentose derivatives; the natural product guggultetrol-18 was shown to have D-xylo- configuration.[89] Similar work by others was reported last year (Vol. 20, p.271-72). A full account has been given of the synthesis of (+)- and (-)- indicine -N- oxides (see Vol. 20, p.271) by linking chiral pyrrolizidines with chiral carboxylic acids derived from D- or L- arabinose; the diastereomeric intermedine- N-oxides were also prepared.[90] The synthon (89), representing the acyclic portion of the aureolic acid antibiotics, has been prepared from D-glucose, with an inversion of configuration at C-4.[91]

A number of chiral building-blocks such as (90) and (91) can be prepared via the zinc-copper cleavage of 5-bromo-5-deoxy-2,3-O-isopropylideneribonolactone (see Vol. 20, p.272),[92] and in the case of (90) the optical purity via this method was found to be

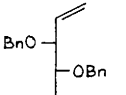


(89)



(90)

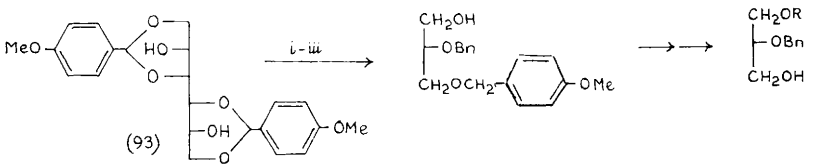
(91)



(92)

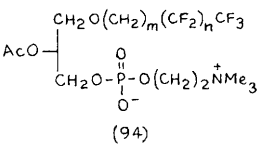
superior to that of material prepared by Sharpless epoxidation of divinyl carbinol.[93] D-Mannitol has been converted into the R,R-

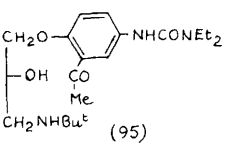
synthon (92),[94] and both R- and S- isomers of α-hydroxy-β-aminopropionaldehyde and -propionic acid have been made from D-mannitol by appropriate manipulation of 1,2 : 5,6-diepoxides, followed by central oxidative cleavage.[95] The D-mannitol derivative (93) can be used to provide optically-active glycerol derivatives in either enantiomeric series, the products being known precursors of platelet-activating factor (Scheme 23),[96] and various fluorinated analogues of the factor (94) have been prepared from 3-O-benzyl-1,2-O-isopropylidene-D-threitol.[97] A range of 2,3-O-diprotected-D-glyceraldehyde derivatives have been synthesized from D-mannitol,[98] as have various (S)-1-alkylamino-3-aryloxy-2-propanols;[99] the absolute configuration of a compound of this class, (+)-celiprolol (95) has been established as (R)- by a synthesis from isopropylidene-D-glyceraldehyde.[100]



Reagents: i, BnBr-NaH ; ii, $NaBH_3CN$-TFA ; iii, $NaIO_4$, $NaBH_4$

Scheme 23





Papers covering the use of carbohydrates as chiral auxiliaries in enantioselective syntheses are mentioned in Chapters 6,7, and 10.

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