SPECIALIST PERIODICAL REPORTS

Carbohydrate Chemistry

VOLUME 18

Part I

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

ROYAL SOCIETY OF CHEMISTRY

Specialist Periodical Reports

For almost 60 years, The Royal Society of Chemistry and its predecessor, The Chemical Society, have published 'Reports' in which acknowledged experts have charted developments in chemistry.

In 1967 it was realised that the old-established *'Annual Reports'* could no longer encompass the whole of chemistry in a single volume, so the title was split into two (more recently, three) annual volumes, and, in addition the series *'Specialist Periodical Reports'* was created. The aim of the *Specialist Periodical Reports* was to provide systematic and detailed review coverage of progress in the major areas of chemical research. The Society has been extremely fortunate in obtaining the services of leading experts in their specialist fields, and the series provides a unique service for the active specialist chemist in the shape of regular critical in-depth accounts of progress in most areas of chemistry.

Inevitably, there are changes in the degree of activity in the various fields of chemistry; some subject areas flourish and expand, others contract. Some titles in the SPR series have remained unchanged, others have changed their emphasis and their titles, some have been combined with others under a new name, and some have been discontinued. In recent years several entirely new titles have appeared, which emphasises the Society's commitment to continue as a major provider of specialist tertiary literature.

For more general coverage of the highlights in chemistry, *Annual Reports* remains a 'must'. It is available in three volumes: (*A*) Inorganic Chemistry; (*B*) Organic Chemistry; and (*C*) Physical Chemistry. For further details about *Specialist Periodical Reports* and *Annual Reports*, write to:

Sales and Promotion Department
The Royal Society of Chemistry
Burlington House
Piccadilly
London W1V 0BN

ISBN 0-85186-202-0
ISSN 0576-7172

Carbohydrate Chemistry

Volume 18
Part I

A Specialist Periodical Report

Carbohydrate Chemistry

Volume 18
Part I

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

A Review of the Literature Published during 1984

Senior Reporter
N. R. Williams, *Birkbeck College, University of London*

Reporters
B. E. Davison, *Polytechnic of North London*
R. J. Ferrier, *Victoria University of Wellington, New Zealand*
R. H. Furneaux, *D.S.I.R., Petone, New Zealand*
R. H. Wightman, *Heriot-Watt University, Edinburgh*

The Royal Society of Chemistry
Burlington House, London W1V 0BN

ISBN 0-85186-202-0
ISSN 0576-7172

Printed in Great Britain by
Antony Rowe Ltd, Chippenham, Wiltshire

Preface

This report covers the literature for 1984 available to us by February 1985. Fortunately, no untoward circumstance has served to delay publication of this report, and I wish to thank my colleagues for their conscientious efficiency and unstinted effort in its production. It has been a pleasure to welcome Dr. Richard Wightman as a new member of the team. I am also pleased to report that publication of this title of the Specialist Periodical Reports is not at present under threat and that at least one further volume will appear.

I would like to thank Mrs. A. Beattie, Ms. W. F. Janes, and Ms. S. J. Wharton for typing the chapters, and also Dr. P. G. Gardam and Mrs. R. H. Pape of the Royal Society of Chemistry for their advice and encouragement, and making our typescript into the published text.

February 1986 Neil R. Williams

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

1	Introduction and General Aspects	1
2	Free Sugars	3
	Theoretical Aspects	3
	Synthesis	4
	Physical Measurements	7
	Anomerization	9
	Oxidation	10
	Other Reactions	11
3	Glycosides and Disaccharides	15
	O-Glycosides	15
	Synthesis of Monosaccharide Glycosides	15
	Synthesis of Disaccharides and Their Derivatives	19
	O-Glycosides Isolated from Natural Products	25
	Hydrolysis and Other Reactions and Features	26
	S-Glycosides	29
	C-Glycosides	30
	Pyranoid Compounds	30
	Furanoid Compounds	34
	Glycosides Isolated from Natural Sources	36
4	Oligosaccharides	42
	General	42
	Trisaccharides	43
	Linear Homotrisaccharides	43
	Branched Homotrisaccharides	44
	Linear Heterotrisaccharides	44
	Branched Heterotrisaccharides	45
	Tetrasaccharides	46
	Linear Tetrasaccharides	46
	Branched Tetrasaccharides	46
	Higher Oligosaccharides	47
	Pentasaccharides	47
	Higher Saccharides	47
5	Ethers and Anhydro-sugars	50
	Ethers	50
	Methyl Ethers	50
	Other Alkyl and Aryl Ethers	51
	Silyl Ethers	53
	Intramolecular Ethers (Anhydro-sugars)	53
	Oxirans	53
	Other Anhydrides	54
6	Acetals	58
	Isopropylidene Acetals	58
	Other Acetals	60

7	Esters	63
	Carboxylic Esters	63
	Sulphonate Esters	68
	Phosphate and Related Esters	69
	Other Esters	73
8	Halogeno-sugars	78
9	Amino-sugars	88
	Natural Products	88
	Synthesis	88
	Reactions	97
	Di- and Tri-amino-sugars	101
10	Miscellaneous Nitrogen Derivatives	105
	Glycosylamines	105
	Azido-sugars	107
	Nitro- and Nitroso-sugars	108
	Nitriles, Isonitriles, Oximes, and Hydroxylamines	110
	Hydrazones, Osazones, and Derived Heterocycles	111
	Other Heterocyclic Derivatives	112
11	Thio-sugars	116
12	Deoxy-sugars	120
13	Unsaturated Derivatives	127
	Glycals	127
	Other Unsaturated Derivatives	130
14	Branched-chain Sugars	135
	Characterization of Natural Products	135
	Compounds with an R^1-C-OR^2 Branch	135
	Compounds with an R-C-N Branch	138
	Compounds with an R-C-H or R-C-R Branch	139
15	Aldosuloses and Dialdoses	145
16	Sugar Acids and Lactones	148
	Aldonic Acids	148
	Saccharinic Acids	151
	Ulosonic Acids	151
	Uronic Acids	153
	Ascorbic Acids	154
17	Inorganic Derivatives	157
	Carbon-bonded Phosphorus Derivatives	157
	Other Carbon-bonded Derivatives	160
	Oxygen-bonded Derivatives	160
18	Alditols and Cyclitols	163
	Alditols	163
	Cyclitols	169
19	Antibiotics	176
	Aminoglycoside and Aminocyclitol Antibiotics	176
	Macrolide Antibiotics	178
	Anthracycline Antibiotics	179
	Nucleoside Antibiotics	181
	Glycopeptide Antibiotics	184
	Miscellaneous Antibiotics	185

20	Nucleosides	190
	General	190
	Synthesis	190
	Anhydro- and Cyclo-nucleosides	194
	Deoxynucleosides	196
	Halogeno-sugar and Amino-sugar Nucleosides	197
	Thionucleosides	198
	Nucleosides and Unsaturated Sugars, Keto-sugars, and Uronic Acids	198
	C-Nucleosides	199
	Carbocyclic Nucleoside Analogues	201
	Nucleoside Phosphates and Phosphonates	202
	Ether, Acetal, and Ester Derivatives	204
	Miscellaneous Nucleoside Analogues	205
	Reactions	205
	Spectroscopic and Conformational Studies	206
21	N.M.R. Spectroscopy and Conformational Features	212
	Theoretical and General Considerations	212
	Acyclic Systems	214
	Furanose Systems	215
	Pyranose Systems	216
	Oligosaccharides	219
	Nucleosides	221
	Other Molecules	222
	N.M.R. of Nuclei Other Than ^{1}H or ^{13}C	222
22	Other Physical Methods	225
	I.r. Spectroscopy	225
	Mass Spectrometry	226
	X-Ray Crystallography	228
	E.S.R. Spectroscopy	232
	Polarimetry, Circular Dichroism, and Related Studies	232
23	Separatory and Analytical Methods	238
	Chromatographic Methods	238
	Gas-Liquid Chromatography	238
	Thin-layer Chromatography	239
	High-pressure Liquid Chromatography	240
	Column Chromatography	244
	Electrophoresis	244
	Other Analytical Methods	244
24	Synthesis of Enantiomerically Pure Non-carbohydrate Compounds from Carbohydrates	247
	Antibiotics and Their Components	247
	Enzyme Inhibitors	253
	Prostanoids and Related Compounds	254
	Lactones	255
	Miscellaneous Compounds	256
Author Index		262

Abbreviations

The following abbreviations have been used:

Ac	acetyl
Ad	adenin-9-yl
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
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
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
Py	pyridine
SIMS	secondary-ion mass spectrometry
TASF	tris(dimethylamino)sulphonium difluorotrimethyl silicate
Tf	trifluoromethanesulphonyl
THF	tetrahydrofuran
Thp	tetrahydropyranyl
TBDMS	t-butyldimethylsilyl
TMS	trimethylsilyl
TPP	triphenylphosphine
TPS	tri-isopropylbenzenesulphonyl
Tr	triphenylmethyl
Ts	toluene p-sulphonyl
U	uracil-1-yl

1
Introduction and General Aspects

This report follows the format of Volume 17 and reflects the continued wide interest in the chemistry of carbohydrates and their application to other areas of chemical and biochemical research. Three quarters of the chapters contain over 40 references, with particularly extensive interest being shown in glycosides, oligosaccharide synthesis, amino-sugars, antibiotics, nucleosides, and, increasingly, the use of carbohydrates as chiral synthons for a wide range of chiral natural products and their analogues. The demarkation between carbohydrate and non-carbohydrate compounds is increasingly difficult to see, and in particular we have had problems in the selection of references covering the necessarily vague boundary between mono-, di-, and tri-saccharides on the one hand and polysaccharides on the other. There does not seem to be any logical boundary between these two extremes, and hitherto we have somewhat arbitrarily concentrated on the synthesis and more chemical aspects of boundary compounds, including the structural analysis of naturally occurring oligosaccharides, while omitting degradation fragments of polysaccharides, or more purely biochemical aspects. Likewise our coverage of antibiotics and nucleosides focusses on the structure, synthesis, and reactions of the carbohydrate components of these materials. We would be interested to have your opinions both on the area and limits of coverage of Part I of this report, bearing in mind the overall cost effectiveness of the product, and also on the most sensible title for it; we are aware that the present title lacks precision, since we do mention some higher oligosaccharides in Chapter 4, and such units also occur in many antibiotics. It is much to be regretted that it has not proved possible to produce Part II of this report simultaneously, which might alleviate the problem.

An appreciation of the life of Dexter French has been published.[1]

A survey of regio-, stereo-, and chemo-selective reactions in carbohydrate chemistry includes discussion of phase transfer reactions in partial substitution reactions, selective halogenation and conversion to unsaturated sugars, and the selective cleavage of acetals giving partially substituted sugar derivatives.[2]

A statistical analysis of oxygen-hydrogen-oxygen hydrogen bonds in carbohydrate crystals has been made, indicating that all hydroxy groups and most oxygen atoms are involved in hydrogen bonding, and cooperative effects of these govern crystal structures.[3] A study of the anomeric effect has investigated 111 carbohydrate structures; relationships between bond lengths and bond angles in the C-O-C-O-C grouping were analysed, and interpreted in terms of the anomeric and exo-anomeric effect, aiding understanding of these effects and some hitherto problematic observations.[4]

References

1 J.H.Pazur, Advan. Carbohydr. Chem. Biochem., 1984, 42, 1.
2 P.J.Garegg, Pure Appl. Chem., 1984, 56, 845.
3 V.P.Panov and R.G.Zhbankov, Dokl. Akad. Nauk BSSR, 1984, 28, 441 (Chem. Abstr., 1984, 101, 152 199).
4 B.Fuchs, L.Schleifer, and E.Tartakovsky, Nouv. J. Chim., 1984, 8, 275.

2
Free Sugars

Reviews on the subjects of the composition of reducing sugars in solution,[1] hydrophobic nature of some sugar derivatives,[2] and aspects of the commercial chemical conversion of glucose, *e.g.* alkaline isomerism, oxidation, and degradative oxidation,[3] have appeared.

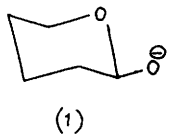
It has been shown that patients with multiple sclerosis have elevated levels of fructose and glucitol in their cerebrospinal fluid.[4]

1 Theoretical Aspects

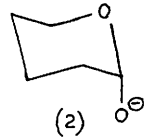
Ab initio SCF LCAO-MO calculations on β-D-fructopyranose and α-L-sorbopyranose using crystallographic data as the geometrical input have been carried out. Properties such as orbital energies, total energy, ionization potentials, Mulliken population analysis, and electrostatic potentials were considered in relation to sweetness; it was concluded that non-bonded overlap between oxygen and hydroxy hydrogen correlated with taste.[5] Force field calculations covering intra- and inter-molecular interactions have enabled the development of a model for α-D-glucose surrounded by specific water molecules.[6]

The relationship between molecular rotations and bond refractions has been used in calculations for a range of α-D-glucopyranose analogues with sulphur, nitrogen, or phosphorus as the hetero-ring atom.[7] Strengths of inter-molecular bonds in aqueous solutions have been calculated for D-glucopyranose, D-mannose, D-galactose, D-xylose, and maltose, confirming the effect of chiral centre interactions. The strengths of the bonds associated with α-anomers is greater than those of β-anomers.[8] A careful analysis of the reaction between 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose and trichloromethyl cyanide in the presence of sodium hydride yielding the anomeric imidate (see Chapter 7) led to the interesting conclusion that the anomeric β-D-oxide ion (1) is more nucleophilic than the corresponding α-oxide (2) because enhanced orbital repulsions in (1)

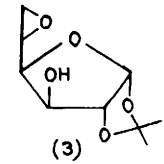
make the electrons on the anomeric oxygen more accessible; thus the anomeric effect operates kinetically as well as thermodynamically.[9]



(1)



(2)



(3)

2 Synthesis

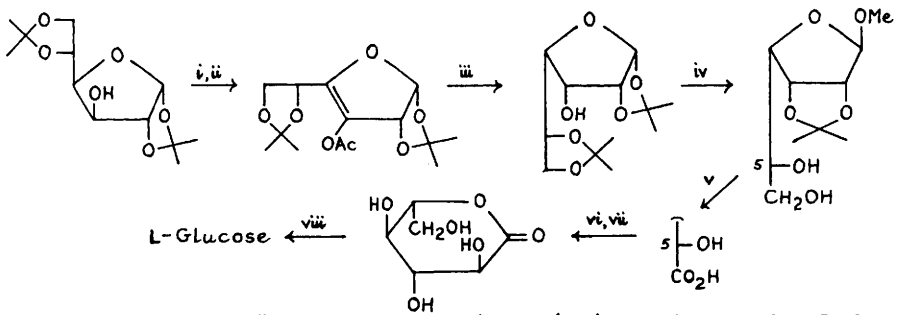
Reviews of the total synthesis of carbohydrates,[10] the synthesis of monosaccharides from non-cyclic compounds and their stereoselective glycosidations,[11] and of the use of carbon-carbon bond-forming reactions and stereoselective introduction of heteroatom functionality in the synthesis of free sugars, deoxysugars, aminosugars, alditols, and branched-chain sugars[12] have been published. The synthesis of monosaccharides from simple organic molecules such as 2,3-O-isopropylidene-D-glyceraldehyde and L-tartaric acid is the subject of a review, which includes new glycosylation reactions using glycosyl fluorides, internal cyclizations, and direct introduction of alkoxy groups to the 2-position of the keto-function in sugars.[13]

In a simulation of prebiotic conditions the formose reaction has been carried out using a wet discharge or u.v. irradiation. It was found that the presence of the mercury(II) ion increased the yield of sugars and their precursors, glycolaldehyde, glyoxal, and formic acid.[14] A comparison of photo- and X-irradiation in the formose reaction in the presence of base showed that the former produced penta-erythritol as a single product, while the latter resulted in glycolaldehyde as the main product.[15] When boric acid was used as the catalyst, the favoured formation of D,L-arabinitol in the formose reaction was shown by g.l.c. analysis.[16] Selective formation of DL-dendroketose in good yield in the formose reaction can be achieved by using thiazolium salts, followed by treatment with aqueous alkali. The course of the reaction is probably *via* the first-formed dihydroxyacetone, which is known to give dendroketose on reaction with base.[17] The products of the formose reaction using calcium hydroxide - bismethylene glycolate complex as catalyst have been analyzed by l.c., u.v., ^{13}C-n.m.r., and g.c.-m.s.[18] A kinetic analysis has led to the suggested mechanism for the formation of sugars from glycolaldehyde, glyceraldehyde, and dihydroxyacetone in

the calcium hydroxide-mediated final phase of the formose reaction.[19] Carrying out the formose reaction in the presence of thallium(I) hydroxide at pH>12 gave mainly pentoses, whereas lower pH values gave Cannizzaro products.[20] Twenty carbohydrates have been identified and a further nine tentatively identified in the mixture of linear, deoxy- and branched-chain carbohydrates formed in the formose reaction with the latter making up the major portion of the mixture.[21]

U.v. irradiation of the iron(III) complexes with monosaccharides gives rise to lower sugars. D-Fructose and D-arabinose both give D-erythrose in 80% yield, while D-glucose and D-mannose produced D-arabinose initially, which was then converted into D-erythrose. D-Ribose yielded D-erythrose and D-glyceraldehyde.[22] Aldehydo-sugars may be obtained by oxidative removal of the dithioacetal group from acetylated, methylated, tritylated, or N-tosylated sugars using N-bromosuccinimide in aqueous acetone or tert-butanol - acetone. The reaction, which was also applied to protected 2-acylamino-2-deoxy-sugars, proceeded rapidly at 0 °C, and generally gave yields equal to or better than the usual mercury(II) ion methods.[23]

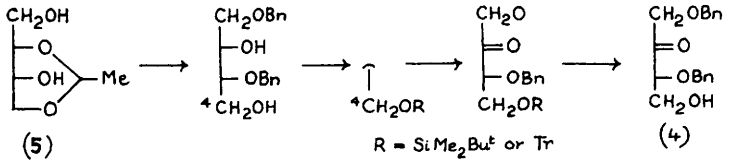
The best conditions for acid hydrolysis of 5,6-anhydro-1,2-O-isopropylidene-β-L-idofuranose (3), leading either to L-idose, or 1,2-O-isopropylidene-β-L-idofuranose, or 1,6-anhydro-L-idopyranose, have been determined.[24] L-Glucose has been synthesized from 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose by the route shown in Scheme 1,[25] 1,3-di-O-benzyl-D-glycero-tetrose (4) has been prepared[26] from the D-erythritol derivative (5) as summarized in Scheme 2, and L-fucose and [4-^{2}H]fucose have been synthesized from L-rhamnose as shown in Scheme 3.[27]



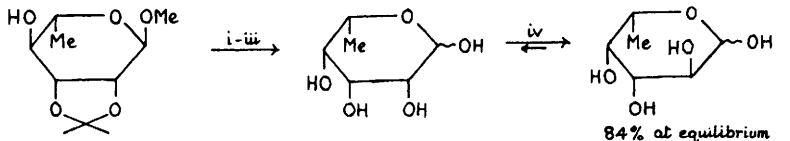
Reagents: i, RuO_4-KIO_4; ii, Ac_2O-Py; iii, H_2-Pd; iv, $Me_2C(OMe)_2$-Me_2CO-MeOH-HCl; v, Pt-O_2; vi, H^+(Resin)-H_2O; vii, H_2-Ni; viii, $NaBH_4$

Scheme 1

The Bilik molybdate reaction has been used to prepare labelled carbohydrates. Thus D-[U-^{14}C]glucose, from acid hydrolysis of the α-[U-^{14}C]glucan of the alga Chlorella sp grown in $^{14}CO_2$, was converted to D-[U-^{14}C]mannose. D-[U-^{14}C]-Erythrose, -threose, -galactose, -arabinose, -xylose, and -lyxose were also prepared.[28]

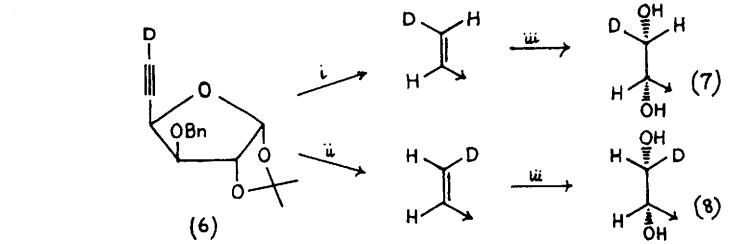


Scheme 2

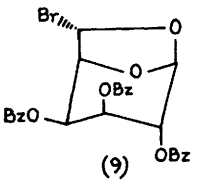


Scheme 3

The deuterated acetylene derivative (6) has been used to synthesize D-(6R)- and D-(6S)-[6-$^{2}H_{1}$]glucose by deprotection of the intermediates (7) and (8) shown in Scheme 4.[29] Regio- and stereo-



Scheme 4



specific photobromination of 1,6-anhydro-2,3,4-tri-O-benzoyl-β-D-galactopyranose to yield the (6S)-bromo-derivative (9) was the key step in the synthesis of D-(6S)-[6-$^{2}H_{1}$]galactose. Inversion of this via the 6-O-tosyl compound led to the (6R)-isomer.[30]

G.l.c.-m.s. of the isopropylidenated product mixture obtained by aldol condensation of glycolaldehyde and 1,3-dihydroxypropan-2-one allowed identification of erythro-2-pentulose, erythrose, threose, xylose, dendroketose and threo-2-pentulose. The ratio of these products varied with the base used, which included calcium, barium, and sodium hydroxides and the hydroxide ion form of Dowex-1 and Amberlite IRA-400.[31]

The formation of 1-deoxy-D- and -L-threo-pentulose by cell-free extracts of microorganisms has been reported. A new enzymatic acyloin-type condensation between pyruvate (or acetoin or methylacetoin) and D-glyceraldehyde was found to be catalyzed by cell-free extracts of a transketolase mutant of Bacillus pumilus IFO 12089, giving 1-deoxy-D-threo-pentulose. The same condensation using L-glyceraldehyde gave the L-isomer. Similar enzyme activities were detected in cell-free extracts of a variety of microorganisms, including yeasts, moulds, bacteria, and actinomycetes, suggesting that the enzyme responsible has an important role in the biosynthesis of thiamine, since the deoxy-pentulose is a precursor of the 5-carbon unit of the thiazole ring.[32]

3 Physical Measurements

Measurements of coupling constants and ^{13}C spin lattice times for ^{13}C-enriched tetroses and tetrofuranosides have enabled conformational changes and ring dynamics to be determined; a very thorough analysis of the furanose and acyclic species was made.[33]

The apparent ratios of β-pyranose and α- and β-furanose anomers in aqueous solutions have been determined by light scattering detection of h.p.l.c. peaks.[34]

Electro-osmosis and streaming potential measurements of aqueous D-glucose solutions across testosterone-plug membranes have been used to determine zeta potentials and to examine the influence of H-bonding between water molecules and those of D-glucose.[35]

The hydrogen-bonding in aqueous solutions of D-ribose and 2-deoxyribose has been examined by determining the enthalpies of transfer for these sugars from pure water to aqueous solutions of ethanol and urea, significant differences in enthalpies being observed between

the two sugars.[36] The excess enthalpies of nine aqueous ternary solutions of urea and monosaccharides have been determined by microcalorimetry, and it has been shown that there are differences between the behaviour of saccharides and that of cyclic or linear polyols.[37] The specific heat capacities of D-xylose and D-glucose in aqueous ethanol of different compositions have been measured.[38] A report of a study of the thermal behaviour of carbohydrates using heat flow calorimetry in the temperature range 20 - 270°C included enthalpy data for 44 sugars and polysaccharides. The temperature range for thermal decomposition varied widely for different carbohydrates.[39]

The mutarotation of α-D-glucopyranose is catalyzed by borate, tungstate, molybdate, and bicarbonate species. It was proposed that specific aquation around the anions enhances their nucleophilicity in the rate-determining formation of the aldehydo intermediate.[40] α-Aminoacids are widely held to be catalysts for sugar mutarotation, particularly histidine. However, 0.014M histidine only increased rate of glucose mutarotation by 3 - 4%, although in molar ratio of 1:10; it was also non-stereospecific with respect to the absolute stereochemistry of the amino-acid. Thus the action appears to be limited to general increase in buffer concentration and not to any concerted acid-base catalysis.[41] The use of a stopped flow polarimetry technique for the study of the base-catalyzed mutarotation of D-glucopyranoses in water is referred to in Chapter 22. In the presence of borate, there is a substantial increase in the proportion of the acyclic form of a number of sugars as determined by circular dichroism. The amount of acyclic form increased with alkalinity or temperature. In going from phosphate to borate buffer at 25° the open chain form increased 9.1 times for D-glucose, 2.9 times for galactose, and 2.2 times for D-mannose.[42]

Primary paramagnetic products of the radiolysis of β-L-arabinose between 77 and 430K were identified by e.s.r. as stabilized electron and alkoxy radicals with electrons localized at O-2. Free radicals, formed by thermal decomposition of primary products, were identified and their mechanism of formation and subsequent transformation proposed.[43] U.v., i.r., optical rotation, and magnetic susceptibility data on γ-irradiated fructose have been reported.[44] E.s.r. has been used to study production of free radicals during the autoxidation of simple monosaccharides *via* spin-trapping with 5,5-dimethyl-1-pyrroline *N*-oxide. The monosaccharides produced hydroxy and hydroxymethyl radical-derived spin adducts. At high pH, both hydroxy

and hydroxyalkyl radicals were formed, while at low pH only hydroxyalkyl radicals were detected. D-Ribose and D-glucose autoxidize very slowly without production of free radicals, whereas glycolaldehyde, glyceraldehyde, and dihydroxyacetone, which readily form the intermediate enediol, autoxidize with the production of radicals.[45]

The i.r. spectrum of D-fructose in deuterium oxide solution has been recorded; From the intensity of $\nu_{c=o}$, it was deduced that 0.9% open chain form was present. The assignment of bands to furanose and pyranose forms by Mathlouthi (see Vol.14, p.202, ref.8) were disputed since they were found to occur in the crystalline fructofuranose.[46]

The effect of crystallinity of lactose samples on their mechanical and structural properties has been examined.[47]

Temperature effects on rates of hydrolysis of sucrose in hydrochloric acid solution over the range 10 - 40 °C have been reinvestigated using polarimetry and h.p.l.c. analysis to measure sucrose concentration and g.l.c. analysis to estimate glucose. Activation energies were the same using all three methods and were temperature independent.[48] Values of pK_a for lactose and lactulose of use in the base-catalyzed isomerization of the former to the latter have been measured by means of ^{13}C-n.m.r. titration: the similarity of the values to those of D-glucose and D-fructose led to the conclusion that the extra galactose unit has little influence on the ionization.[49] G.l.c. analysis of monosaccharides involving dehydration by distillation followed by oximation has been used to show the presence of sugar impurities in commercial samples of sugars.[50]

4 Anomerization

A convenient, practical conversion of α-D-glucose to β-D-glucose in 92% yield, using mutarotation in acetic acid at 100 °C for one hour, and crystallization from acetic acid with seeding, has been described.[51] Pressure effects on the anomerization of α-D-glucose by the enzyme mutarotase over a pH range of 5.50 to 6.75 have been studied over the range 1 to 1000 Bar; the reaction was found to be unaffected, in contrast to the acid-base catalyzed isomerization, thus invalidating the accepted view that the two reactions have identical mechanisms. The Lineweaver-Burke values support a histidine unit being at the active site of the enzyme.[52]

5 Oxidation

Simple monosaccharides have been shown to autoxidize under physiological conditions to yield dicarbonyl compounds and hydrogen peroxide via reactive free radicals, the rate of enolization of the sugar being the rate-limiting step of this spontaneous process.[53]

The mechanism of oxidation of D-ribose[54] and of D-arabinose[55] by cerium(IV) in aqueous perchloric acid has been studied. In both cases, the reaction is first order in cerium(IV) and the pentose, with a fractional dependence on the concentration of perchloric acid, addition of which or of sodium perchlorate enhances the rate. From the Arrhenius parameters it was concluded that the rate determining step involves radical formation from the sugar. A similar rate dependence on oxidant and sugar has been found for the acid catalyzed oxidation of D-ribose by potassium permanganate.[56] The kinetics for the oxidation of L-arabinose to L-arabonic acid by Cu^{2+}, Ag^{2+}, Hg_2^{2+}, Fe^{3+}, Hg^{2+}, and Ce^{4+} at concentrations of 0.1 g ion L^{-1} of oxidant and 0.07 mol L^{-1} sugar at 100°C have been determined. The reaction was first order in both sugar and metal ion and the rate constants increased in the ion order given above.[57] The equation for the relationship of rate constants, free energy of equilibrium forms, and redox potentials of the oxidizing ions has been deduced from kinetic studies of the oxidation of D-ribose, D-xylose, and L-arabinose by Ag^{+}, Hg_2^{2+}, and Hg^{2+} ions.[58] The kinetics of the oxidation of aldoses by cerium(IV) sulphate in aqueous acid,[59] and by iron(III) iron in sulphuric acid[60] at 100-130°C, have been determined. The kinetics and mechanism of the oxidation of D-xylose, L-arabinose, and D-galactose by acidic aqueous chromium peroxydichromate, in which $HCrO_4^-$ is the primary oxidant, have been determined.[61]

Wet oxidation of D-xylose, D-glucose, D-glucitol, cellulose, and dextran by oxygen at 170 - 230°C has been studied. Relatively high yields of formic and acetic acids were obtained from all carbohydrates and these were further increased by addition of iron(II) sulphate as catalyst.[62] Oxidation of D-glucose to D-gluconic acid on a platinum electrode has been studied to obtain kinetic and hence mechanistic information.[63]

Measurements of the rate of oxidation of D-galactose by hexacyanoferrate(III) ions in the presence of ethylenediamine have shown that the reaction is first order in sugar and hydroxide ion, but zero order in the hexacyanoferrate(III) ion. A general mechanism in-

volving intermediate enediol was proposed.[64] An intermediate 1:1 complex between hexachloroiridate(IV) or tetrachloroaurate(III) and D-glucose 6-phosphate, which breaks down by fission of the anomeric C-H bond to give a free radical, is proposed in the mechanism of oxidation by these two complex species.[65] D-Fructose is oxidatively degraded to D-erythrose by oxygen under irradiation by Pyrex-filtered light in the presence of catalytic iron(III) chloride at near neutral pH. D-Glucose - iron(III) chloride and D-fructose - manganese(II) chloride were also shown to be susceptible to catalytic photooxidation.[66]

Thallium(III) in the presence of an essential catalytic amount of sulphuric acid in acetic acid oxidized maltose and lactose to the disaccharide aldonic acid, with activation enthalpies and entropies characteristic of second order reactions with non-cleavage of the parent molecule. The reaction was ionic but the rate was almost independent of ionic strength.[67] The mechanism of oxidation of trehalose by cerium(IV) in aqueous perchloric acid has been investigated and it has been shown that no initial complexation between oxidant and substrate occurs.[68] The kinetics and mechanism of oxidation of lactose and maltose by tetraamminecopper(II) in ammoniacal and buffered media have been further investigated.[69]

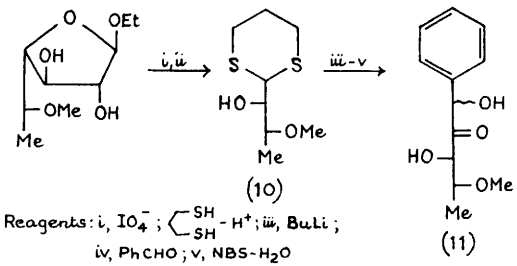
Oxidation of xylitol and glucitol by alkaline hexacyanoferrate-(III) under ruthenium(VIII) catalysis is believed to proceed by an activated polyol-ruthenium(VIII) oxide complex which slowly disproportionates to yield ruthenium(VIII) hydride, itself being reoxidized to the oxide.[70]

6 Other Reactions

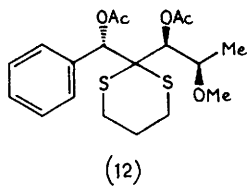
The carbon skeletal rearrangements of aldoses induced by molybdate have been reviewed.[71]

The effect of calcium ions on the rearrangement of aldos-2-uloses to aldonic acids is to enhance the reaction in all cases studied. It was suggested that complexation at O-2 and O-3 occurred and that the effect is greatest where the dihedral angle is close to zero for these two groups as in the $^{4}\underline{C}_{1}$ (D) conformations of cellobiose, glucose, maltose, mannose, and xylose.[72]

The chromomycinone side chain (10) has been synthesized[73] and converted[74] into 5-deoxy-1-C-phenyl-D-pentulose derivatives (11) as shown in Scheme 5. X-Ray analysis established the structure of the acetylated dithioacetal intermediate (12).[74]



Scheme 5



(12)

The catalytic disproportionation of D-glucose in DMF or DMA by dichlorotris(triphenylphosphine)ruthenium(II)produces inactive ruthenium complexes bearing carbon monoxide ligands derived primarily from aldehydo-D-glucose.[75] The same group has studied the disproportionation of D-glucose in tetrahydrofurfuryl alcohol catalyzed by hydridochlorocarbonyltris(triphenylphosphine)ruthenium(II) which was shown to involve transfer of hydride to a coordinated aldehydo-D-glucose.[76]

From a kinetic study of reactions involving hydrogen transfer from glutathione to glucose and deoxyribose radicals, it was shown that the incomplete repair of carbohydrate radicals is due to a competing unimolecular transformation of the sugar radical leading to damage which cannot be repaired by glutathione.[77]

Thirteen compounds have been identified in the reaction of D-glucose and L-lysine in slightly acidic aqueous solution; the reaction is of importance in nutritional loss during cooking, particularly in relation to the essential aminoacids such as lysine.[78]

References

1 S.J.Angyal, Advan. Carbohydr. Chem. Biochem., 1984, 42, 15.
2 M.Janado, Kagaku To Seibutsu, 1984, 22, 29 (Chem. Abstr., 1984, 100, 192 158).
3 A.P.G.Kieboom and H.Van Bekkum, Recl.: J.R. Neth. Chem. Soc., 1984, 103, 1 (Chem. Abstr., 1984, 100, 121 453).
4 S.L.Smith, M.Novotny, and A.Karmen, J. Chromatogr., 1984, 336, 351.
5 W.A.Szarek, S.-L.Korppi-Tommola, O.R.Martin, and V.H.Smith, Can. J. Chem., 1984, 62, 1506.
6 L.M.J.Kroon-Batenburg and J.A.Kanters, Acta Crystallogr., Ser. B, 1983, 39, 749.
7 B.-L.Poh, Aust. J. Chem., 1984, 37, 327.
8 I.A.Maslov and E.G.Martinovskaya, Zh. Fiz. Khim., 1984, 58, 925 (Chem. Abstr., 1984, 101, 111 300).
9 R.R.Schmidt and J.Michel, Tetrahedron Lett., 1984, 25, 821.

10 A.Zamojski and G.Grynkiewicz, Total Synth. Nat. Prod., 1984, 6, 141 (Chem. Abstr., 1984, 101, 55 429).
11 T.Mukaiyama, Nogucki Kenkyusho Jiho, 1983, 7 (Chem. Abstr., 1984, 100, 210 273).
12 G.J.McGarvey, M.Kimura, T.Oh, and J.M.Williams, J. Carbohydr. Chem., 1984, 3, 125.
13 T.Mukaiyama and S.Shoda, Yuki Gosei Kagaku Kyokaishi, 1984, 42, 474 (Chem. Abstr., 1984, 101, 111 278).
14 E.Miyoshi, A.Kobayashi, S.Yanagisawa, and T.Shirai, Nippon Kagaku Kaishi, 1983, 1449 (Chem. Abstr., 1984, 100, 19 551).
15 S.Irie, Chem. Lett., 1984, 2153.
16 Y.Shigemasa, A.Matsuba, N.Ueda, R.Nakashima, K.Harada, N.Takeda, M.Suzuki, and S.Saito, Carbohydr. Res., 1984, 134, C4.
17 T.Matsumoto, M.Yamane, and S.Inoue, Chem. Lett., 1984, 1819.
18 G.Harsch, M.Harsch, H.Bauer, and W.Voelter, Z. Naturforsch., B: Anorg. Chem., Org. Chem., 1983, 38, 1269 (Chem. Abstr., 1984, 100, 103 757).
19 G.Harsch, H.Bauer, and W.Voelter, Justus Liebigs Ann. Chem., 1984, 623.
20 G.V.Yakimova, O.E.Levanevskii, and A.A.Morozov, Izv. Akad. Nauk Kirg. S.S.R., 1984, 48 (Chem. Abstr., 1984, 101, 7529).
21 N.G.Medvedeva, V.I.Sukharevich, Ya.Ya.Stanek, and V.I.Yakovlev, Zh. Prikl. Khim. (Leningrad), 1983, 56, 2708 (Chem. Abstr., 1984, 100, 156 907).
22 K.Araki, M.Sakuma, and S.Shiraishi, Bull. Chem. Soc. Jpn., 1984, 57, 997.
23 M.Miljkovic, D.Dropkin, P.Hagel, and M.Habash-Marino, Carbohydr. Res., 1984, 128, 11.
24 N.Baggett and A.K.Samra, Carbohydr. Res., 1984, 127, 149.
25 W.A.Szarek, G.W.Hay, D.M.Vyas, E.R.Ison, and L.J.J.Hronowski, Can. J. Chem., 1984, 62, 671.
26 A.E.Wroblewski, Carbohydr. Res., 1984, 131, 325.
27 J.Defaye, A.Gadelle, and S.J.Angyal, Carbohydr. Res., 1984, 126, 165.
28 V.Bilik, P.Biely, and J.Kolina, Chem. Zvesti, 1984, 38, 491.
29 K.Kakinuma, Tetrahedron, 1984, 40, 2089.
30 H.Ohrui, Y.Nishida, and H.Meguro, Agric. Biol. Chem., 1984, 48, 1049.
31 S.Morgenlie, Carbohydr. Res., 1984, 132, 330,
32 A.Yokota and K.Sasajima, Agric. Biol. Chem., 1984, 48, 149.
33 A.S.Serianni and R.Barker, J. Org. Chem., 1984, 49, 3292.
34 I.N.Rabinowitz, O.Kou, D.K.King, and G.Kunberger, LC, Liq. Chromatogr. HPLC Mag., 1983, 1, 496 (Chem. Abstr., 1984, 100, 192 164).
35 M.L.Srivastava and B.Ram, Carbohydr. Res., 1984, 132, 209.
36 J.H.Stern and P.M.Hubler, J. Phys. Chem., 1984, 88, 1680 (Chem. Abstr., 1984, 100, 156 890).
37 V.Abate, G.Barone, G.Castronuova, V.Elia, and V.Savino, J. Chem. Soc., Faraday Trans. 1, 1984, 80, 759 (Chem. Abstr., 1984, 100, 198 587).
38 F.Kawaizumi, N.Sasaki, Y.Ohtsuka, H.Nomura, and Y.Miyahara, Bull. Chem. Soc. Jpn., 1984, 57, 3258).
39 A.Raemy and T.F.Schweizer, J. Therm. Anal., 1983, 28, 95 (Chem. Abstr., 1984, 101, 91 354).
40 C.J.O'Connor and A.A.T.Bailey, Aust. J. Chem., 1984, 37, 1411.
41 R.S.Shallenberger, Food Chem., 1984, 15, 1 (Chem. Abstr., 1984, 101, 211 580).
42 R.Roy, R.E.Williams, and H.J.Jennings, Carbohydr. Res., 1984, 127, 165.
43 S.L.Panasyuk and A.N.Fateev, Khim. Vys. Energ., 1984, 18, 291 (Chem. Abstr., 1984, 101, 192 312).
44 A.J.Dangre, Proc. Nucl. Chem. Radiochem. Symp., 1981 (Pub. 1983), 647 (Chem. Abstr., 1984, 101, 130 989).
45 P.J.Thornalley and A.Stern, Carbohydr. Res., 1984, 134, 191.
46 D.Steele, J.Lall, and J.Pamnani, Carbohydr. Res., 1984, 133, 313.
47 M.Morita, Y.Nakai, E.Fukuoka, and S.Nakajima, Chem. Pharm. Bull., 1984, 32, 4076.
48 S.Buchanan, D.G.Kubler, C.Meigs, M.Owens, and A.Tallman, Int. J. Chem.

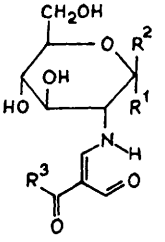
Kinet., 1983, 15, 1229 (Chem. Abstr., 1984, 100, 86 023).
49 G.de Wit, A.P.G.Kieboom, and H.van Bekkum, Carbohydr. Res., 1984, 127, 193.
50 I.Molnar-Perl, M.Pinter-Szakacs, A.Kovago, and J.Petroczy, J. Chromatogr., 1984, 295, 433.
51 P.E.Pfeffer, K.B.Hicks, M.H.Frey, S.J.Opella, and W.L.Earl, J. Carbohydr. Chem., 1984, 3, 197.
52 B.Andersen, Acta Chem. Scand., Ser. B., 1984, 38, 415.
53 S.P.Wolff, M.J.C.Crabbe, and P.J.Thornalley, Experientia, 1984, 40, 244 (Chem. Abstr., 1984, 100, 134 616).
54 A.Kale and K.C.Nand, Z. Phys. Chem. (Leipzig), 1983, 264,1023 (Chem. Abstr., 1984, 100, 6979).
55 K.C.Nand, Acta Cienc. Indica, [Ser.] Chem., 1983, 9, 193 (Chem. Abstr., 1984, 101, 55 439).
56 H.L.Gupta, S.C.Ameta, and S.K.Solanki, Cienc. Cult. (Sao Paulo), 1983, 35, 1512 (Chem. Abstr., 1984, 100, 68 613).
57 V.I.Krupenskii, Izv. Vyssh. Uchebn. Zaved., Lesn. Zh., 1983, 124 (Chem. Abstr., 1984, 100, 6976).
58 V.I.Krupenskii, Izv. Vyssh. Uchebn. Zaved., Khim, Khim. Tekhnol., 1983, 26, 917 (Chem. Abstr., 1984, 100, 34 752).
59 V.I.Krupenskii, Izv. Vyssh, Uchebn. Zaved., Khim. Khim. Tekhnol, 1984, 27, 178 (Chem. Abstr., 1984, 100, 192 166).
60 V.I.Krupenskii, Zh. Prikl. Khim. (Leningrad), 1983, 56, 2384 (Chem. Abstr., 1984, 100, 139 490).
61 K.Sharma, V.K.Sharma, and R.C.Rai, J. Indian Chem. Soc., 1983, 60, 747 (Chem. Abstr., 1984, 100, 121 469).
62 G.D.McGinnis, S.E.Prince, C.J.Biermann, and J.T.Lawrimore, Carbohydr. Res., 1984, 128, 51.
63 N.N.Nikolaeva, O.A.Khazova, and Yu.B.Vasil'ev, Elektrokhimiya, 1983, 19, 1476 (Chem. Abstr., 1984, 100, 139 491).
64 A.Srivastava, A.K.Singh, B.Singh, and B.Krishna, Proc. Natl. Acad. Sci., India, Sect. A., 1982, 52, 343 (Chem. Abstr., 1984, 101, 111 292).
65 K.K.Sen Gupta, V.Chatterjee, and S.N.Basu, Carbohydr. Res., 1984, 126, 321.
66 K.Araki and S.Shiraishi, Chem. Lett., 1984, 267.
67 S.N.Shukla and R.N.Kesarwani, Carbohydr. Res., 1984, 133, 319.
68 K.C.Nand, Cienc. Cult. (Sao Paulo), 1984, 36, 442 (Chem. Abstr., 1984, 101, 23 840).
69 K.C.Gupta and S.P.Pandey, Z. Phys. Chem. (Leipzig), 1984, 265, 365 (Chem. Abstr., 1984, 101, 23 839).
70 M.P.Singh and S.Kothari, Indian J. Chem., Sect. A., 1983, 22, 697 (Chem. Abstr., 1984, 100, 51 920).
71 S.Yano and S.Yoshikawa, Kagaku (Kyoto), 1983, 38, 890 (Chem. Abstr., 1984, 100, 139 488).
72 T.Vuorinen, Carbohydr. Res., 1984, 133, 329.
73 J.Thiem and H.-P.Wessel, Justus Liebigs Ann. Chem., 1983, 2173.
74 J.Thiem, H.-P.Wessel, M.Werk, and K.-H.Klaska, Justus Liebigs Ann. Chem., 1983, 2185.
75 S.Rajagopal, S.Vancheesan, J.Rajaram, and J.C.Kuriacose, J. Mol. Catal. 1983, 22, 131 (Chem. Abstr., 1984, 100, 121 464).
76 S.Rajagopal, S.Vancheesan, J.Rajaram, and J.C.Kuriacose, J. Mol. Catal. 1983, 22, 137 (Chem. Abstr., 1984, 100, 121 465).
77 M.Tamba and M.Quintiliani, Radiat. Phys. Chem., 1984, 23, 259 (Chem. Abstr., 1984, 100, 139 577).
78 R.Miller, K.Olsson, and P.-A.Pernemalm, Acta Chem. Scand., Ser. B., 1984, 38, 689.

3
Glycosides and Disaccharides

1 O-Glycosides

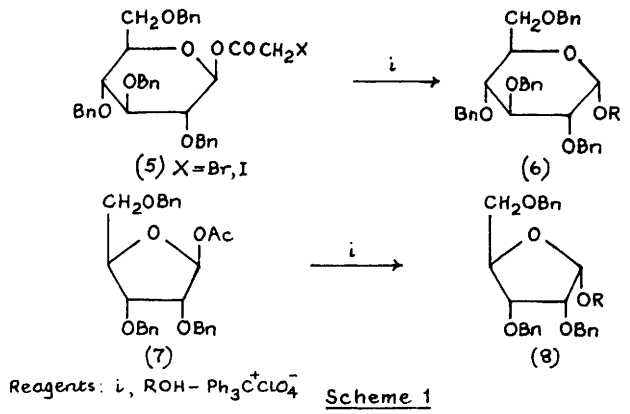
1.1 Synthesis of Monosaccharide Glycosides.- Reviews on this topic have dealt with issues involved in the synthesis of 1,2-cis-related glycosides generally[1] and of β-D-mannopyranosides and β-L-rhamnopyranosides specifically,[2] with new methods developed by Mukaiyama which depend upon the use of alkyl triflates, enol silyl ethers, and intramolecular cyclizations,[3] with stereoselective synthesis of sugars and their selective glycosidations,[4] and with many aspects of the cardiac glycosides.[5]

Compounds (1) and (2), readily prepared from 2-amino-2-deoxy-D-glucose, gave mainly the α-pyranoside (3) on treatment with methanolic HCl but also the β-anomer and minor amounts of the



	R^1	R^2	R^3
(1)	H	OH	OMe
(2)	OH	H	OMe
(3)	OMe	H	OMe
(4)	OH	H	Me

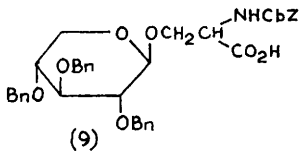
analogous α-furanoside; larger amounts of the last isomer were obtainable by use of resin as acid catalyst. Glycosidation of compound (4) was unsuccessful presumably because of the increased electron deficiency on the nitrogen atom.[6] Glycosyl esters are solvolysed by methanol in the presence of lithium iodide and 2,6-lutidine to give anomeric mixtures of methyl glycosides, whereas alkyl glycosides are not affected under these conditions.[7] More specifically, the esters (5) and (7) react with alcohols in the presence of trityl perchlorate to give the α-glycosidic products (6) and (8) with >90 and 70% selectivity, respectively (Scheme 1). In the latter case, molecular sieve and lithium perchlorate were added to inhibit α → β anomerization.[8] Methods of preparing methyl β-D- and β-L-ribofuranosides[9] and ethyl α-DL-lyxopyranoside and -arabinopyranoside[10] from non-carbohydrate



Scheme 1

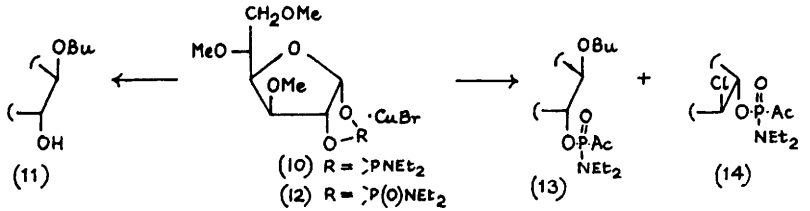
precursors have been reported.

The anomeric selectivity observed in the synthesis of glucosides (including disaccharides) by reaction of 1-O-metallated 2,3,4-tri-O-benzyl-D-glucose compounds with alkyl triflates is dependent upon the substituent at O-6. Good β-selectivity was observed for the 6-benzyl ether, while for the monomethoxytrityl derivatives the α:β ratio was dependent upon the triflate employed.[11] The O-xylosyl serine derivative (9) has been made using the trichloroacetimidate method (also developed by Schmidt) for the syntheses of glycosylated peptides.[12]



The 1,2-orthoester method has been employed to prepare β-D-glucosides[13] and -maltosides[13,14] of 2-hydroxynaphthaquinones and β-D-glucosides of pregnenolone.[15] Treatment of the copper(I) bromide complex of the amidophosphite (10) (R = $>PNEt_2$) with butanol gave the furanoside (11) in 72% yield, while the phosphate (12) (R = $>P(O)NEt_2$) reacted with less anomeric selectivity. When (10) was treated with acetyl chloride before butanol, mixed products (13) and (14) were produced, with the former predominating (Scheme 2).[16]

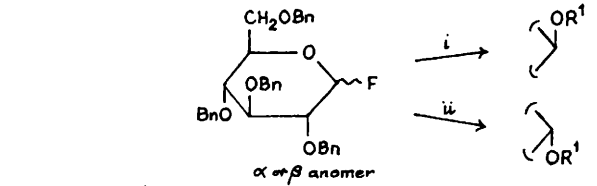
The use of glycals in the preparation of glycosides continues. A racemic anthracyclinone derivative has been resolved by treat-



Scheme 2

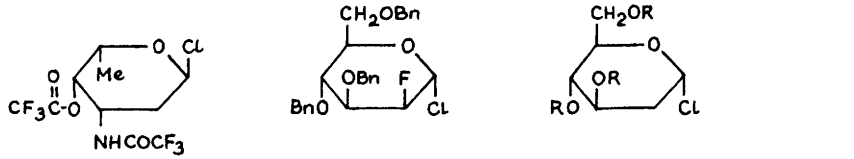
ment with 3,4-di-O-acetyl-L-rhamnal in the presence of N-iodosuccinimide, the resulting diastereoisomeric 2-deoxy-2-iodoglycosides being separated chromatographically.[17] The same addition reaction has been applied to methyl 3,4-di-O-acetyl-D-glucuronal and -D-galacturonal (and their 5-epimers which were derived by treatment of them with sodium methoxide) using cyclohexanol, and the stereochemistries of the addition reactions were considered.[18]

An interesting observation that the anomeric nature of the main glycosides formed by treatment of substituted glycosyl fluorides with silylated alcohols and catalytic trimethylsilyl triflate depends upon the solvent is illustrated in Scheme 3. Yields were



Scheme 3

in the 70-90% range with primary or secondary alcohols, including carbohydrate derivatives, and the anomeric ratios were 4-6:1.[19] Glycosyl chlorides (15)-(17) have been employed in glycoside



syntheses: the first afforded α-glycosides of the anthracycline series,[20] the second α-linked 2-deoxy-2-fluoro-D-mannopyranosides,[21] and the third was used together with four related

glycosyl halides in the synthesis of β-linked digitoxigenin compounds.[22]

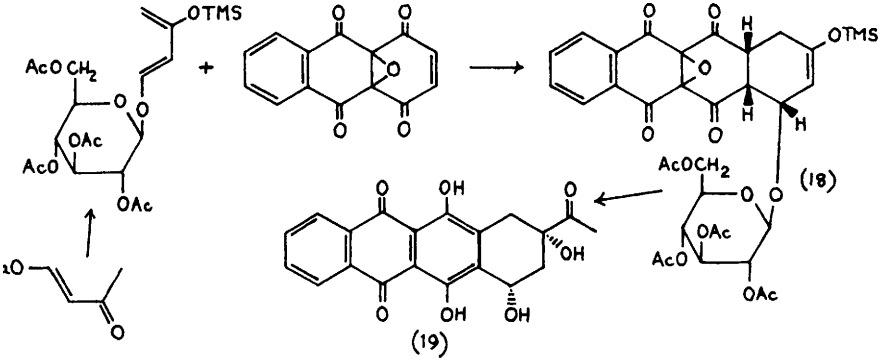
Acylated glycosyl bromides continue to be the most commonly used glycosylating agents. They have been employed to give glycosides of L-serine and L-threonine β-D-glucopyranoside[23] and α- and β-L-fucopyranosides,[24] tris(hydroxymethyl)aminomethane (tris-β-galactoside which was coupled to cholesterol via various spacers)[25] and the following steroids: β-sitosterol (β-glucoside),[26] five cardioactive steroid genins (β-glucosides and -galactosides),[27] 5-androsten-3β-ol with various side chains (β-glucosides),[28] 20α-cortol, 20α-cortolone and their 20-epimers,[29] estriol[30] and cortoic acids[31] (all β-D-glucuronides). Likewise, glycosides of the following have been reported: the triterpenes oleanolic acid and hederaginin (β-L-rhamnosides),[32] 9,10-dihydrolysergol (several glycosides),[33] fluorescein (β-D-glucuronide),[34] p-acrylamidophenol (β-glucoside of p-nitrophenol reduced and acylated)[35] and p-hydroxybenzyl alcohol (β-glucoside of p-hydroxybenzaldehyde reduced).[36]

The effects of free and polymer-bound crown ethers on the Koenigs Knorr reaction have been examined; with bulky alcohols the reaction is sensitive to the nature of the catalyst.[37,38] Details of the reaction applied with several 2-bromo-2-deoxyglycosyl bromides have been reported.[39]

A lactase from *Kluyveromyces lactis*, which causes *trans*-β-D-glucosylation from phenyl β-D-glucopyranoside, has been used to give β-glucosides. Yields depended on the primary, secondary or tertiary nature of the alcohols; for slightly soluble alcohols (*e.g.*, octanol) modest yields were obtained using a nitrobenzene-water two-phase system.[40] Likewise a β-galactosidase from *Aspergillus oryzae* causes efficient glycosylation of water-soluble or -insoluble alcohols using phenyl β-D-galactopyranoside as source in aqueous acetonitrile.[41] β-Glucosylation of rubusoside (a di-β-D-glucosyl derivative of steviol) was effected with a transferase from *B. megaterium* using soluble starch as donor, and mono- to hexa-glycosyl products were obtained. Their relative sweetnesses were measured and correlated with their structures.[42]

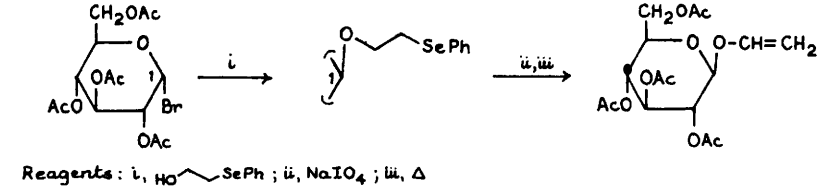
Many glycosides have been made by modification of other glycosidic compounds. The Diels-Alder reaction depicted in Scheme 4 gave mainly compound (18) which was converted into (+)-4-demethoxydaunomycinone (19). The sugar residue therefore

provided the desired stereoselection in the cycloaddition process.[43]



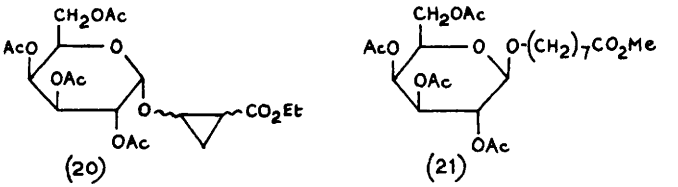
Scheme 4

Simple vinyl glycosides may be obtained via seleno intermediates (Scheme 5)[44] and, with the carbene derived from ethyl diazoacetate, can be converted into compounds such as (20).[45]



Scheme 5

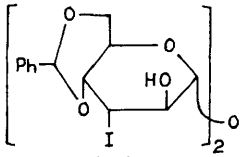
Several alkyl D-galactosides with terminal acid functions [e.g., that derived from the ester (21)] have been made by 2-carbon



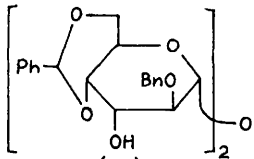
Wittig extension of corresponding aldehydes and then used for coupling to proteins.[46] The aglycone of a galacto-cerebroside has been converted into a diazoester derivative, making it a photo-labelling reagent which was used to show that water gained access to the reagent in phospholipid vesicles.[47] N-Acylation of the same cerebroside with complex hydrophobic groups has been reported.[48]

1.2 Synthesis of Disaccharides and Their Derivatives.- Coupling,

under the influence of boron trifluoride catalysis, of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranose with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl trichloroacetimidate followed by deacetylation gave β,β-trehalose in 58% yield.[49] By trans-diaxial opening of D-manno- and D-allo-epoxide derivatives of α,α-trehalose, respectively, the altro-compounds (22) and (23) were produced; some D-gluco-

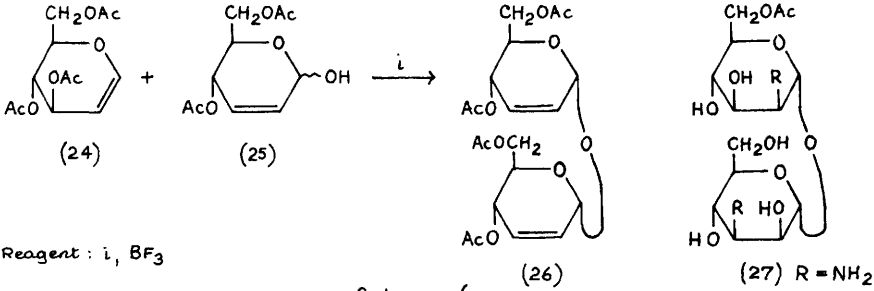


(22)



(23)

by-products were also detected during this work.[50] Reaction of tri-O-acetyl-D-glucal (24) with 4,6-di-O-acetyl-2,3-dideoxy-D-erythro-hex-2-enopyranose (25) afforded the non-reducing disaccharide derivative (26) as well as a previously described

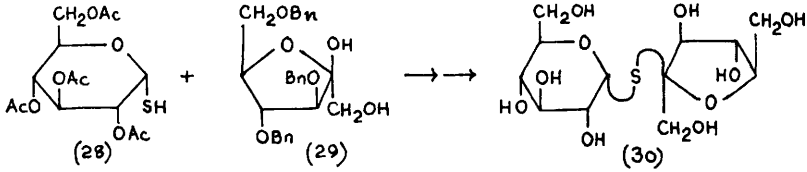


Reagent : i, BF_3

(24) (25) (26) (27) R = NH_2

Scheme 6

1',2-C-linked disaccharide analogue. The former product was then converted into α-D-mannopyranosyl α-D-mannopyranoside derivatives such as (27) and 3,3'- and 2,2'-diamino isomers (Scheme 6).[51] Lewis acid-catalysed condensation of the 1-thiol (28) and tetra-O-benzyl-D-fructose (29) afforded 1-thiosucrose (30) (Scheme 7) and



(28) (29) (30)

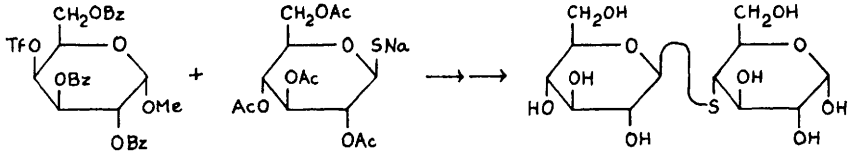
Scheme 7

the α,α-linked isomer; the other two diastereoisomers were obtained by similar treatment of the β-anomer of (28).[52] 6-Thiosucrose and 6-deoxysucrose were obtained by standard procedures starting from the 4,6-O-isopropylidene 2,3,1',3',4',6'-hexabenzoate.[53] Acetylated

L-rhamnopyranosyl bromide condensed with 2,3,4,6-tetra-O-acetyl-D-glucose gave access to the D-glucopyranosyl L-rhamnopyranosides.[54]

The following reducing disaccharides are categorized by the non-reducing sugar.

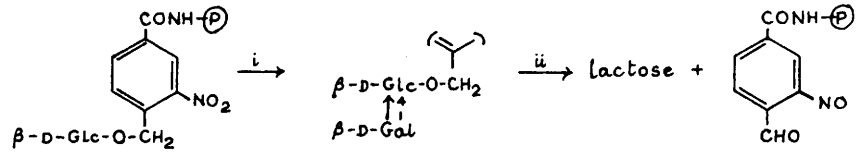
A thorough 1D and 2D ^1H n.m.r. study of cellulose and amylose disaccharide models in DMSO has been reported. The 2D technique allows complete signal assignment for the hydroxy protons.[55] Sophorose and kojibiose have been isolated from the products of treatment of 1,6-anhydro-β-D-glucopyranose with hydrogen chloride in DMF,[56] and thiocellobiose (and the 2-linked sophorose analogue) has been made according to Scheme 8.[57] Preparations have been



Scheme 8

reported of 3-O-β-D-glucopyranosyl-D-fructose (both chemical and by isolation from a fungal polysaccharide),[58] benzyl 2-azido-2-deoxy-4-O-β-D-glucopyranosyl-α-D-glucopyranoside and 1,6-anhydro-2-azido-2-deoxy-4-O-β-D-glucopyranosyl-β-D-glucopyranose,[59] and methyl 3-acetamido-3-deoxy-2-O-β-D-glucopyranosyl- (and -D-galactopyranosyl) -α-D-allopyranoside.[60]

Methyl 6-O-α- and β-D-galactopyranosyl-β-D-galactopyranoside have been made by standard procedures,[61] as have a set of differently substituted derivatives of the analogous allyl α-glycoside of the β-anomer,[62] and also methyl 4-deoxy-4-fluoro-6-O-(β-D-galactopyranosyl)-β-D-galactopyranoside.[63] Radioactive lactose has been obtained by enzymic trans-galactosylation from UDP-galactose to glucose attached to a water-soluble polymer (Scheme 9).[64] Considerable effort has gone into the preparation



Reagents: i, UDP-Gal-transferase ; ii, hν

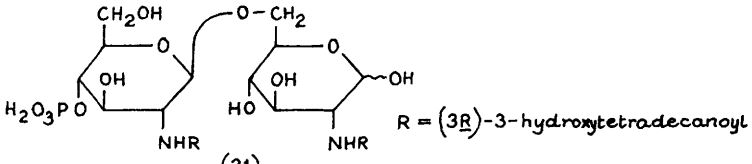
Scheme 9

of disaccharides comprising D-galactopyranose linked glycosidically to 2-amino-2-deoxyhexoses: 2-acetamido-2-deoxy-6-O-β-D-galactopyranosyl D-galactose (immobilized enzyme method[65] and Koenigs-

Knorr method[66]), 2-azido-2-deoxy-3-O-β-D-galactopyranosyl-D-galactose (as a glycoside perester[67] and as a glycosyl bromide derivative and hence α-linked L-serine and L-threonine glycosides[68]), and 2-amino-2-deoxy-4-O-β-D-galactopyranosyl-D-glucose (lactosamine) as the N-acetyl 3-O-methyl derivative ,[69] the N-acetyl-6'-tritiated derivative[70] and the 2-bromoethyl N-phthaloyl glycoside peracetate which was condensed with methyl propanoate 3-thiol and hence, after deprotection, to proteins.[71]

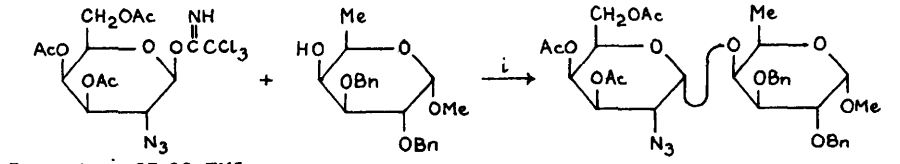
In the D-mannopyranose series, p-nitrophenyl 2- and 3-O-α-D-mannopyranosyl-α-D-mannopyranoside,[72] 2-O-α-D-mannopyranosyl-D-mannose (as the 1-glyceryl glycoside 2',3,3',4,4',6-hexaacetate[73]), 2-, 3-, 4- and 6-linked α-D-mannopyranosyl-D-glucoses (and their conversion to their α-1-phosphates and condensation with moraprenyl phosphate to give the moraprenyl pyrophosphates[74]), and 2-acetamido-2-deoxy-4-O-β-D-mannopyranosyl-β-D-glucopyranose (as the p-trifluoroacetamidophenyl glycoside prepared from a cellobiose derivative by specific oxidation and reduction[75]) were all reported.

Considerable interest continues to be shown in 2-aminohexose disaccharides and, in particular, several papers have focussed on the synthesis of the dimer (31), which is a major constituent of the hydrophobic region of bacterial endotoxins.[76-78] Closely related



(31)

work has led to analogues with five palmitoyl groups which are lipid A-related substances.[79,80] Some chitobiose derivatives have been described,[81] and mass spectral studies carried out on 7-O-(2-amino-2-deoxy-α-D-glucopyranosyl)-L-glycero-D-manno-heptose derivatives have been reported, the dimer having been isolated from a lipopolysaccharide of the Vibrionaceae family.[82]

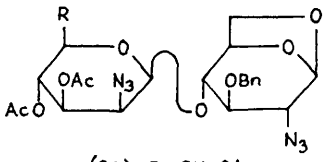


Reagent : i, CF_3SO_3TMS

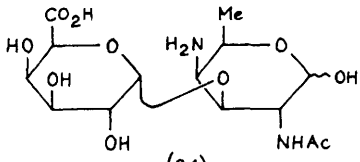
Scheme 10

A selection of disaccharides have been produced with good selectivity by use of 2-azido-2-deoxy trichloroacetimidates as

illustrated in Scheme 10.[83] Related compounds (e.g., 32) from which 2-amino-2-deoxy β-D-mannopyranosyl disaccharides are obtainable have been described, and in the same report corresponding D-mannuronic acid-based analogues (e.g., 33) were reported.[84] Also in the hexuronosyl series, a derivative of the Streptococcal polysaccharide component (34) has been prepared.[85]

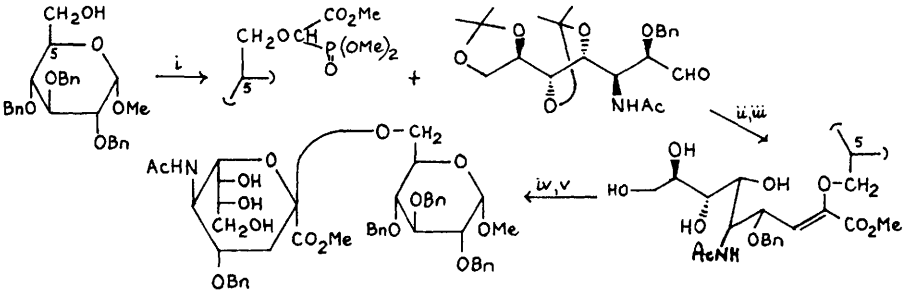


(32) R=CH_2OAc
(33) R=CO_2Me



(34)

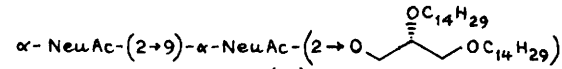
An ingenious new approach to the synthesis of sialic acid-based disaccharides is illustrated in Scheme 11; whereas the β-linkage was afforded from the Z-alkene, the E-isomer gave the α-linked product.[86] A more orthodox preparation of the same 1,6-linked



Reagents: i, $MeO_2CC(N_2)PO(OMe)_2$-$Rh(OAc)_4$; ii, NaH; iii, H^+; iv, $Hg(O_2CCF_3)_2$; v, Ph_3SnH

Scheme 11

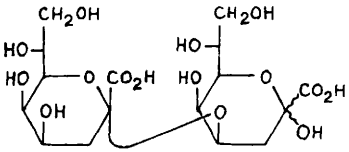
anomers used the acetylated glycosyl chloride and 2,3,4-tri-O-benzyl-D-glucose.[87] Related procedures led to the disialylglycerolipids (35) and the anomeric isomers.[88] N.m.r. and mass



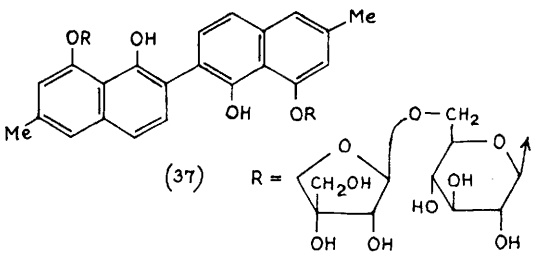
(35)

spectroscopic examinations of a 3-deoxy-D-manno-2-octulosonic acid disaccharide of a Salmonella godesberg mutant showed it to be the 2 → 4 linked compound (36).[89]

In the area of pentosyl disaccharides, the 1,2-O-(1-cyanoethylidene) method has been employed to obtain the 1,4-linked xylobioses;[90] trityl triflate led to high yields of the β-linked isomer.[91] Alternatively, the glycosyl bromide procedure was used



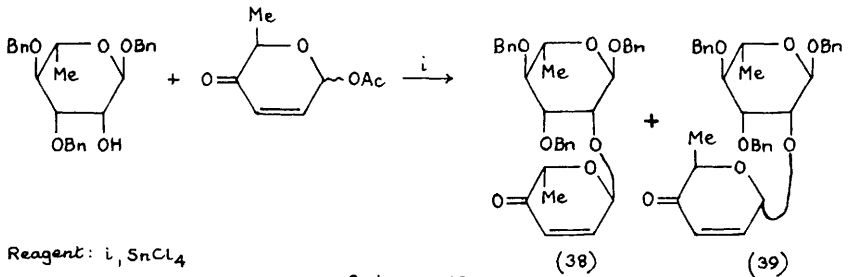
(36)



(37)

to give all possible xylopyranosylxyloses, and n.m.r. studies included ^{2}H-labelling procedures to distinguish between acetyl resonances in the reducing and non-reducing moieties.[92] The plant glycoside p-allylphenyl 6-O-β-D-xylopyranosyl-β-D-glucopyranoside has been prepared from p-allylphenyl 2,3,4-tri-O-acetyl-β-D-glucopyranoside,[93] and several 2-O-glycosylated α-L-arabinopyranosides have been made and examined closely by ^{1}H and ^{13}C n.m.r. spectroscopy.[94] The bis-O-(6-β-D-apiofuranosyl-β-D-glucopyranosyl) compound (37) has been isolated from the leaves of Diospyros mollis Griff.[95]

The interestingly isomeric disaccharides 2-O-α-L-rhamnopyranosyl-L-rhamnose and 2-O-α-D-rhamnopyranosyl-L-rhamnose have been made from compounds (38) and (39) (respectively) (Scheme 12), and the



Reagent: i, $SnCl_4$

(38) (39)

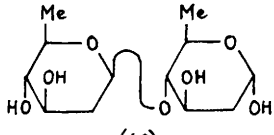
Scheme 12

3-linked analogues were similarly prepared.[96] 2-O-α-L-Rhamnopyranosyl-L-arabinose, required for specificity studies on a rhamnosidase, was made by standard procedures,[97] as was 5-O-α-L-rhamnopyranosyl-D-glucose.[54]

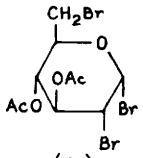
2-Bromoethyl 2-O-α-L-fucopyranosyl-D-galactoside has been coupled to different proteins through an extended spacer arm.[71]

In the area of dideoxyhexosyl disaccharides the dimer (40) has been made and oxidized to the corresponding aldonolactone, which is a product of the degradation of flambamycin.[98] The bromo-

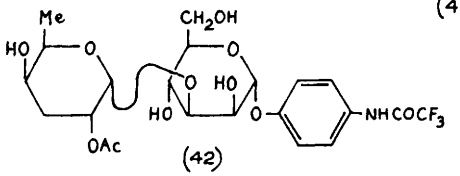
derivative (41) can be used in syntheses of such dideoxy-compounds,



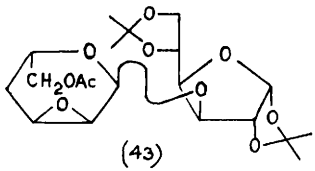
(40)



(41)



(42)



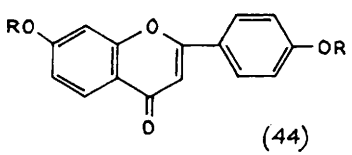
(43)

and its glycosidation reactions, together with those of related compounds (especially the α-manno-isomer), have been examined.[39] Compound (42), a glycoside of the Salmonella O-antigen 5, and deoxy derivatives of it were made to probe oligosaccharide-protein interactions,[99] and the anhydrodeoxy disaccharide diacetal (43) was obtained and examined by X-ray crystallography.[100]

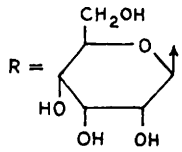
1.3 O-Glycosides Isolated from Natural Products.- As usual, this section is highly selective; many examples of simple and complex glycosides have been reported which contain unremarkable sugars and are here disregarded.

A revised structure has been proposed for the polygalloyl glucose tannic acid which, rather than having ester linked gallic acid, has it linked glycosidically through the C-3 phenolic group.[101] (2S)-1-O-β-D-Glucopyranosyl-sn-glycerol has been isolated from Lilium japonicum, and also synthesized from β-gentiobiose by specific degradation.[102]

D-Allose is proving to be widespread in plants. p-Hydroxyphenyl β-D-allopyranoside was isolated from a Viburnum species,[103] and the diglycoside (44), and mono- and di-acetates of it, from Thalictrum thumbergii.[104] The same sugar, its 6-deoxy derivative,



(44)

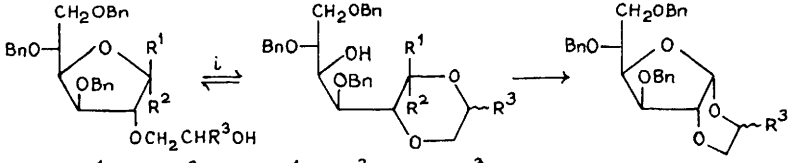


and 6-deoxy-D-glucose and -talose have been reported in cardioactive glycosides of Lophopetalum toxicum.[105] Coral has yielded pregnene -like glycosides of D-arabinose and D-xylose.[106]

1.4 Hydrolysis and Other Reactions and Features.- The pseudo first order rate constant for the hydrolysis of o-nitrophenyl β-D-glucopyranoside at pH 11.4 increases 10 fold on addition of phenylboronic acid in the presence of benzyl hexadecyl dimethylammonium chloride, whereas the enhancement factor for the corresponding galactoside is much less; the difference is attributed to the effects of micelles.[107] A quantum-chemical examination of aryl β-D-glucopyranosides indicates that the high reactivity of the p-nitrophenyl compound must be due to nucleophilic ipso-attack at C-1 of the benzene ring.[108]

A study of kinetic α-deuterium isotope effects for the enzymic and acidic hydrolysis of aryl β-D-glucopyranosides has indicated that there is considerable steric hindrance of the C-1—H bond in an early transition state for both kinds of reaction. Better leaving groups decrease the isotope effect for the acid-catalysed reaction - which is consistent with the predominant A-1 character of the reaction; the opposite holds for the enzymic reaction, suggesting considerable S_N2 character for the hydrolysis.[109] The glycosidic bond between a sugar unit and the ceramide portion of sphingolipids with unsaturated sphingosine can be cleaved by trifluoroacetolysis,[110] and nitrous acid cleaves the glycosidic bond of 1-(aminomethyl)pentyl β-D-galactoside, which represents a model for the selective cleavage under mild conditions of the hydroxylysine-bound glycosyl residues of collagen.[111]

A full report has appeared on the acid-catalysed solvolysis of 2-O-(2-hydroxypropyl)- and 2-O-(2-hydroxyethyl)-D-glucofuranose derivatives as is illustrated in Scheme 13. The β-anomer reacted

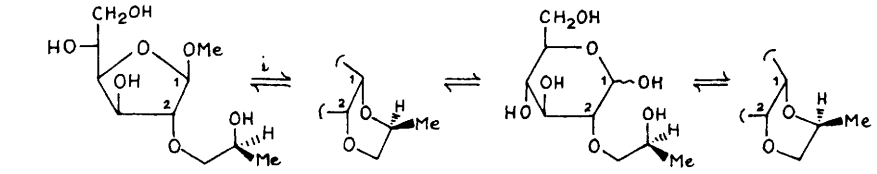


R^1=OMe, R^2=H or R^1=H, R^2=OMe ; R^3 = H or Me

Reagents: i, HCl-$CHCl_3$

Scheme 13

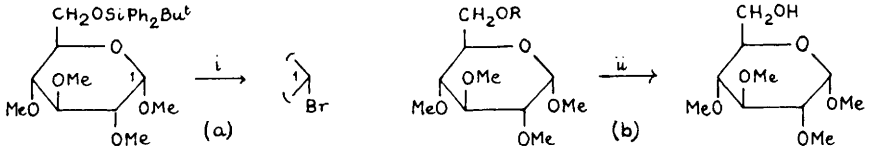
much faster, and in the intermediate one diastereoisomer is formed preferentially.[112] A closely related study examined the equilibria represented in Scheme 14 and those for the isomer with the alternative configuration in the substituent in what was a model study for the acid-catalysed hydrolysis of 2-O-(2-hydroxypropyl)cellulose.[113]



Reagent : i, H_2SO_4

Scheme 14

Dimethylboron bromide and diphenylboron bromide cleave acetals; carbohydrate examples are illustrated in Scheme 15a,b.[114]

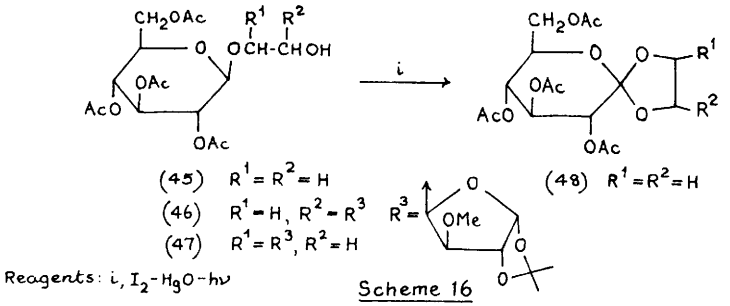


Reagents: i, Me_2BBr, 20°; ii, Me_2BBr, -78° R = MOM or MEM

Scheme 15

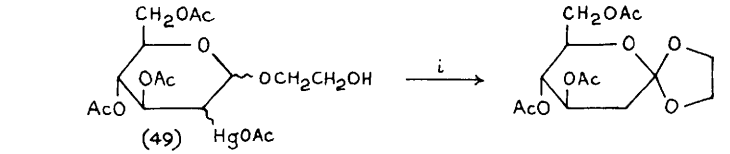
Reductive cleavage of glycosidic bonds of permethylated methyl α- and β-D-glucopyranoside, cyclohexa-amylose and cellulose has been effected with triethylsilyl deuteride and boron trifluoride or, better, with trimethylsilyl triflate as catalyst. 1-Deuterated 1,5-anhydro-D-glucitols were obtained with an α:β ratio of 95:5 and this was taken as evidence for the presence of free oxonium ions in the reactions.[115] The same reaction applied to permethylated 4-linked oligosaccharides gives 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol from the 4-linked units as expected, but in the presence of a little water the isomeric furanoid 1,4-anhydride is formed in up to 45% yield.[116]

Phenyl glycosides on photolysis at 350 nm in acetonitrile in the presence of 1,4-dicyanonaphthalene as sensitiser undergo hydrolysis in the presence of water or methanolysis to give methyl glycosides when methanol is present. Competing reactions include the formation of 1,6-anhydro-β-D-glucopyranose.[117,118] Alternatively, 2-hydroxyalkyl glycosides (e.g., 45-47), on irradiation in the presence of mercury(II) oxide and iodine, give spiro-orthoesters (e.g., 48), presumably by way of iodo-intermediates and by specific α-bond formation (Scheme 16). The same product was obtained from the α-anomer of compound (45) but the reaction was slower.[119] The 2-deoxy derivative of the spiro-product (48) is obtained from tri-O-acetyl-D-glucal by treatment with ethylene



Scheme 16

glycol and mercury(II) acetate and subsequent photolysis, in the presence of mercury(I) iodide and mercury(II) oxide, of the intermediate (49) (Scheme 17).[120]



Scheme 17

Two overlapping stages were detected in the thermal decomposition of anomeric glycopyranosides: at 200-300°, cleavage of the glycosidic bonds occurs with intramolecular and intermolecular reaction at the anomeric centres; at 310-340°, fragmentation ensues to give low molecular weight products.[121]

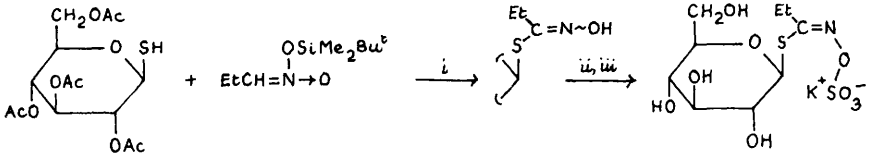
A very thorough ^{1}H and ^{13}C analysis involving ^{1}H-^{1}H, ^{13}C-^{1}H and ^{13}C-^{13}C coupling studies has been carried out on [^{13}C]-enriched tetrofuranosides. O-1 assumes the 4-axial orientation and ring dynamics and preferred conformations were studied.[122]

A review has appeared on carbohydrate liquid crystals based on alkyl O- and S-glycosides having hydrocarbon chains greater than hexyl;[123] some β-D-glucopyranosides and 1-thio-α-D-mannopyranosides have been examined in particular.[124]

There is enthalpy-entropy compensation in aqueous solutions of methyl D-pyranosides, and the positive excess free energies are interpreted in terms of favourable solute-solute interactions.[125]

Densities of sucrose-potassium chloride solutions have been examined.[126]

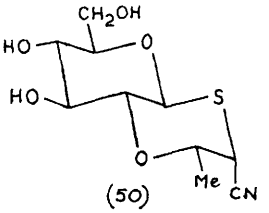
1-Thioglycosides can be made from protected glycosyl fluorides by use of thiols in the presence of boron trifluoride (as can acyl esters, phosphates, peroxides and various nitrogenous compounds) [127] or from compounds with free anomeric hydroxy groups, by treatment with diphenyldisulphide and tributylphosphine under light.[127a] More usually they are made from the 1-thio-sugars, and the S-trityl glycoside of 2-acetamido-2-deoxy-1-thio-D-glucose, made in this way, has been examined as a membrane binder in tumour



Reagents: i, Et_3N; ii, $Py-SO_3$; iii, NH_3-MeOH

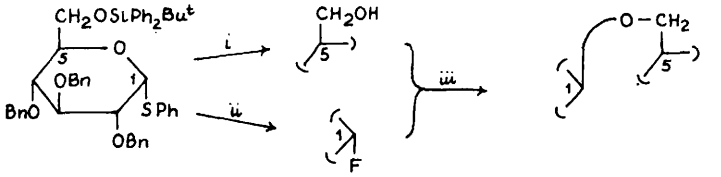
Scheme 18

chemotherapy.[128] A new route to glucosinolates has been developed, illustrated in Scheme 18.[129] In this field merosinigrin, the product of treatment of sinigrin with potassium methoxide, has been shown to have structure (50).[130]



(50)

Following the observation that 1-thiophenyl glycosides react with DAST or HF.pyridine complex-NBS to give glycopyranosyl or glycofuranosyl fluorides, the ingenious method illustrated in Scheme 19 for the derivation of 1,6-linked glucosans has been developed; at each stage further activation can be effected at

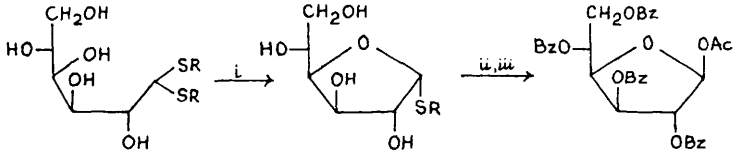


Reagents: i, F^-; ii, NBS-DAST; iii, $SnCl_2$-$AgClO_4$

Scheme 19

either end of the chain.[131]

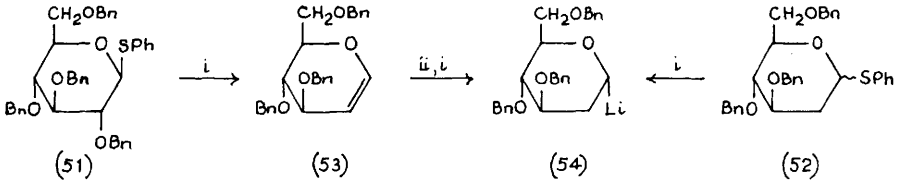
Aldose dithioacetals with phenylmercury acetate give 1,2-cis-related 1-thio furanosides and hence simple access to glycofuranosyl acetates on treatment with mercury(II) acetates in acetic acid (Scheme 20).[132]



Reagents: i, PhHgOAc-EtOH; ii, BzCl-Py; iii, $Hg(OAc)_2$-HOAc

Scheme 20

Reductive lithiation of compounds (51) and (52) gives the glycal (53) and the lithium derivative (54), respectively, and the (53) → (54) conversion can be made as indicated in Scheme 21.[133]



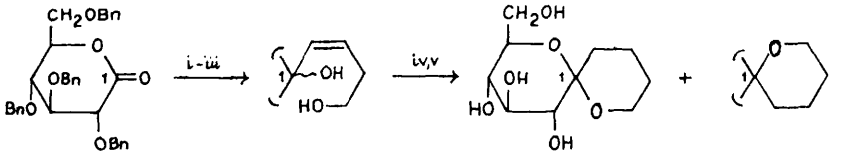
Reagents: i, Li naphthalenide-THF, -78°; ii, HCl

Scheme 21

3 C-Glycosides

Interest in this class of compounds continues at a high level, and a wide range of methods have been used in their preparation.

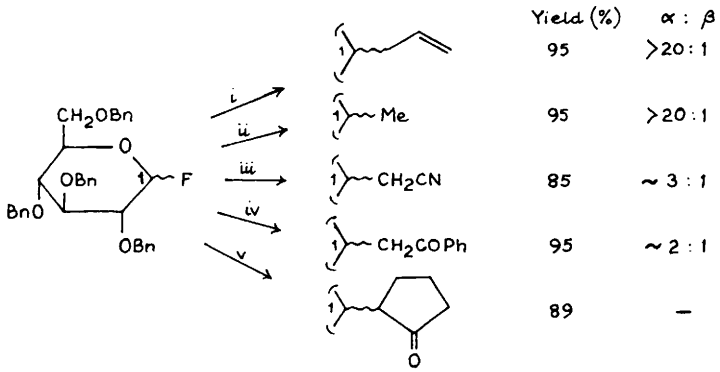
3.1 Pyranoid Compounds.- A route to spiro-compounds of the kind found in some antibiotics has been developed from aldonolactones (Scheme 22).[134]



Reagents: i, $LiC{\equiv}CCH_2CH_2OTMS$; ii, H^+; iii, H_2-Pd.$BaSO_4$; iv, H_2-PtO_2; v, H_2-$Pd(OH)_2$

Scheme 22

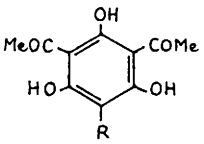
Substituted glycosyl halides have found frequent use, and a range of novel methods of considerable potential value starting from the fluorides are illustrated in Scheme 23.[135] C-



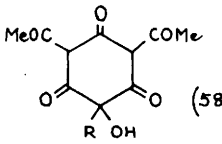
Reagents: i, $Me_3Si\text{-}CH_2CH{=}CH_2\text{-}BF_3$; ii, $AlMe_3$; iii, $Me_3SiCH_2CN\text{-}BF_3$; iv, $Me_3SiOC(Ph){=}CH_2\text{-}BF_3$; v, 

Scheme 23

Glycosylation of the phloroglucinols (55) and (56) with tetra-O-acetyl-D-glucosyl bromide gave low yields of compounds (57) and (58) which are related to the flower pigment carthamin.[136,137] Reaction of acetylated glycosyl bromides of various sugars with mercury(II) cyanide in nitromethane gives mainly the 1,2-trans-related glycosyl cyanides with about 10% of the cis-isomers and smaller amounts of the 1,2-O-cyanoethylidene isomers.[138] In related work, aromatic and heterocyclic C-glycosides have been

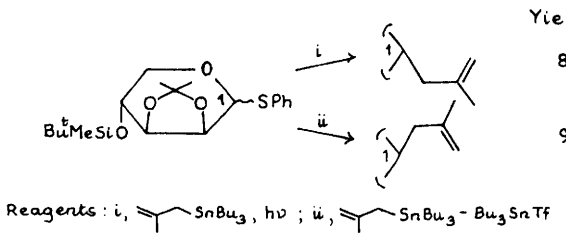


(55) R = H
(56) R = OH
(57) R = β-D-Glc-p



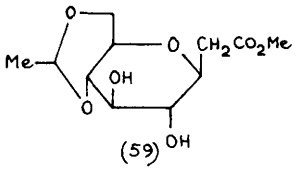
(58) R = β-D-Glc-p

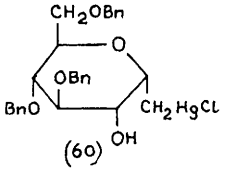
made from 2,3,4,6-tetra-O-benzyl-D-glucosyl acetate or halides using anisole, ferrocene, thiophene, furan and 1,3,5-trimethoxybenzene in the presence of Lewis acids.[139] The same glycosyl chloride and the analogous methyl glycoside have been converted into the C-allyl glycosides (c.f. Scheme 23) by use of allyltrimethylsilane and trimethylsilyl triflate or iodide. The yields were ca. 80% and the α:β ratios were high.[140] In the D-lyxose series methods of making both the C-butenyl glycosides with high selectivity from S-phenyl thioglycosides were developed (Scheme 24). Parallel work was carried out in the D-ribofuranose series; product ratios were dependent on the substituent group at O-5.[127a]



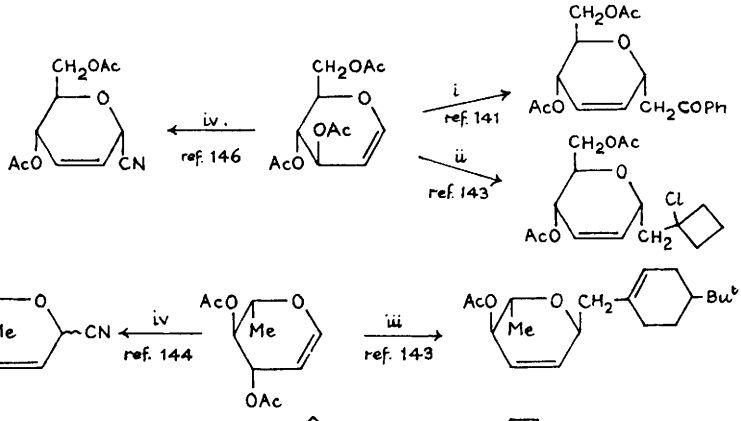
Scheme 24

Various C-glycosides have been made by cyclization of hydroxy-alkenes either with base to give (59)[141] or with mercury(II) salts



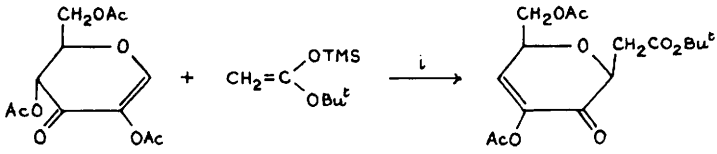


to give (60)[142] (a further example of this latter reaction is given in Chapter 17).



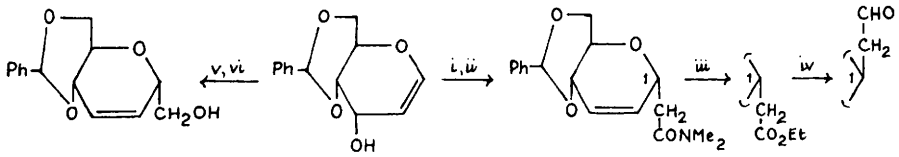
Scheme 25

Several examples have been reported of the synthesis of 2,3-unsaturated C-glycosides by application of the Lewis-acid catalysed rearrangement condensation with acylated glycals. These are illustrated in Scheme 25; a more complex reaction of a related kind is shown in Scheme 26.[145] An alternative route to 2,3-unsaturated C-glycosides involves a [3,3]-sigmatropic rearrangement



Scheme 26

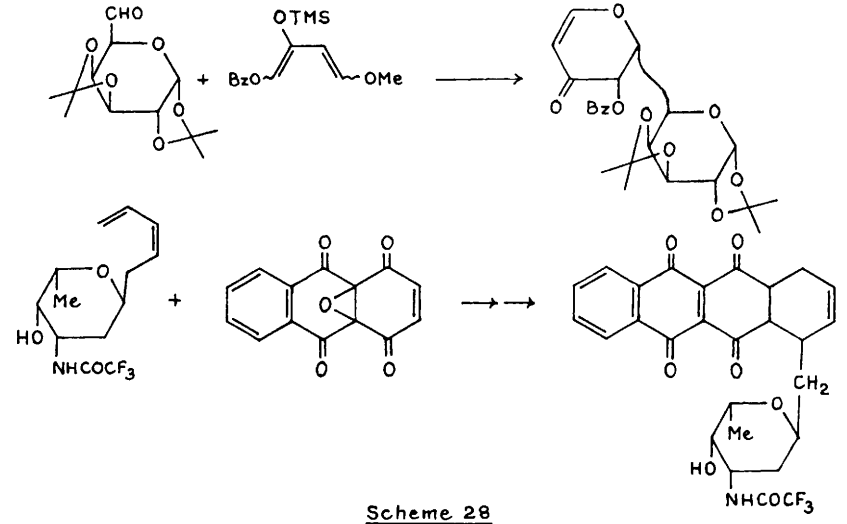
process effectively of 3-O-vinyl ethers or a (rather inefficient) [2,3]-sigmatropic rearrangement. It is notable that reduction of the α-ethyl acetate derivative gave mainly the product of anomerization (Scheme 27).[146] See Chapter 24 for further



Scheme 27

examples.

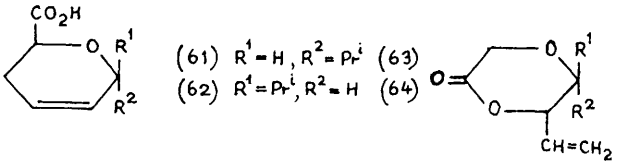
Complex C-glycosides based on disaccharide and anthracycline structures have been elaborated by [4+2]cycloaddition reactions as outlined in Scheme 28.[147,148]



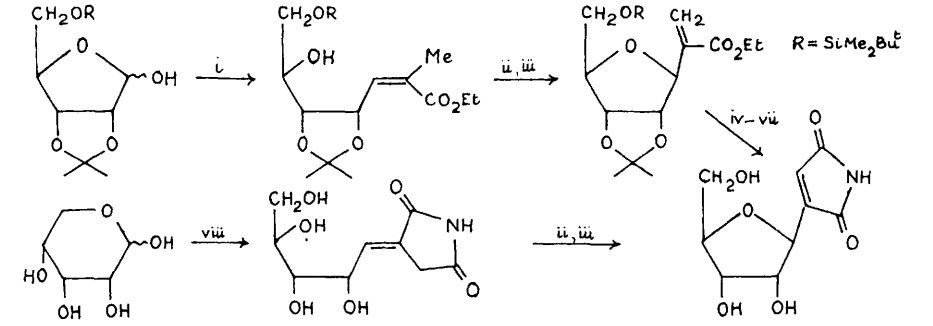
Scheme 28

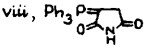
The racemic C-uronosides (61) and (62) and a range of related compounds have been synthesized from the 1,4-dioxans (63) and (64),

respectively, by intramolecular Cope rearrangement reactions, applied to the derived trimethylsilyl enol ethers.[149]



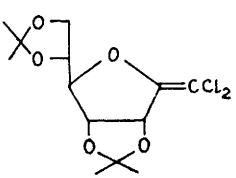
3.2 Furanoid Compounds.- As previously, a range of procedures have been developed for making compounds of this class. Free sugars offer a route following their reaction with Wittig reagents; in this way two complementary methods of making showdomycin (Scheme 29) have been reported.[150,151] In the latter, however, larger proportions of the α-anomer "epishowdomycin" were produced.



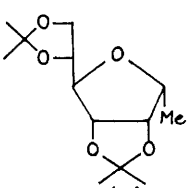
Reagents: i, $Ph_3P{=}C(Me)CO_2Et$; ii, PhSeCl; iii, H_2O_2; iv, O_3; v, Me_2S_2; vi, $Ph_3P{=}CHCONH_2$; vii, H^+; viii, 

Scheme 29

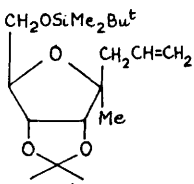
Aldonolactones can be used. For example, dichloromethylenation of 2,3:5,6-di-O-isopropylidene-D-allono-γ-lactone gives compound (65) in high yield and from this, by Raney nickel reduction, the C-methyl compound (66) can be obtained in high yield.[152] In related work, methylenation of a ribono-γ-lactone derivative followed by addition of an allyl radical by use of allyltri-



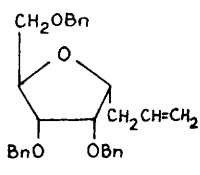
(65)



(66)



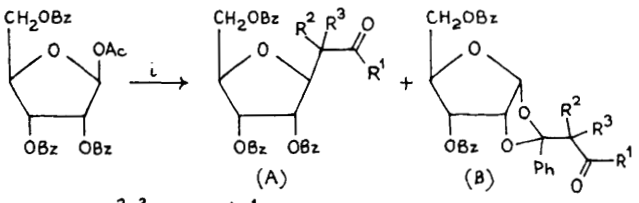
(67)



(68)

methylsilane in the presence of zinc chloride gave the "double C-glycoside" (67) of the type which occurs in some mycotoxins.[153]

Glycofuranosyl acetates treated with allyltrimethylsilane in the presence of trityl perchlorate afford allyl C-glycosides (e.g., 68),[154] and enol silyl ethers with tin(IV) chloride afford C-glycosides or 1,2-cyclic acetals according to the nature of the reagents used (Scheme 30).[155] In analogous work, tri-O-benzyl-D-

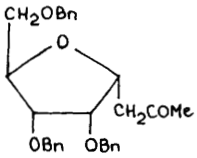


R^1	R^2	R^3	(A)	(B)
Et	H	Me	-	88%
EtO	H	PhS	-	82%
Me	H	PhS	83%	-
$(CH_2)_2$		TMSO	95%	
$(CH_2)_4$		H	95%	

Reagents: i, $R^2R^3C{=}C(OTMS)R^1$, $SnCl_4$

Scheme 30

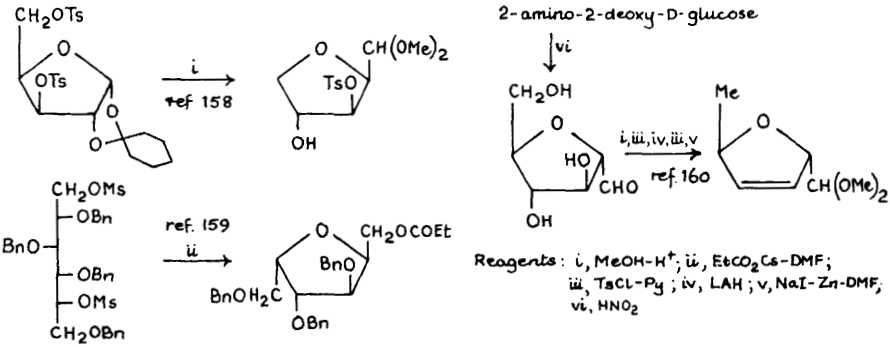
ribofuranosyl fluoride with the trisyl enol ether derived from acetone gave the α-compound (69) in high yield,[156] and the



(69)

corresponding glycosyl chloride and the analogous D-arabino-furanosyl bromide with aryl Grignard reagents gave the aryl C-glycosides, the anomers of which were separated.[157]

Cyclizations of simple sugar derivatives have been used to give C-glycosides as illustrated in Scheme 31. In the second example, O-2 seems to participate in the displacement at C-5,[159] and in the

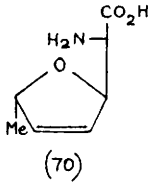


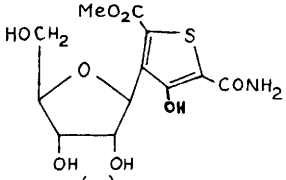
Reagents: i, MeOH-H^+; ii, $EtCO_2Cs$-DMF; iii, TsCl-Py; iv, LAH; v, NaI-Zn-DMF; vi, HNO_2

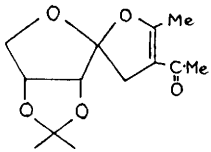
Scheme 31

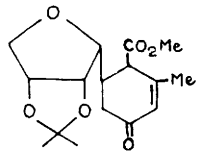
third the product was elaborated to give isomers of furanomycin (70).[160]

Elaboration of simple "aglycones" has led to the thiophene analogue (71) of the antiviral compound pyrazofurin[161] and, from 2,5-anhydro-3,4-O-isopropylidene-D-arabinose, the spiro-compound (72) and the cyclohexenone (73) by use of pentan-2,5-dione and

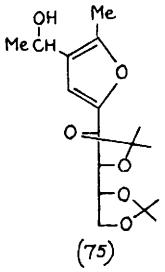

(70)

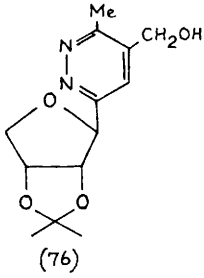

(71)

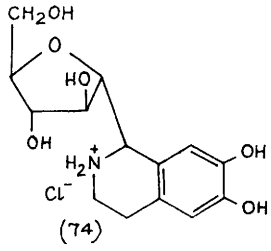

(72)


(73)

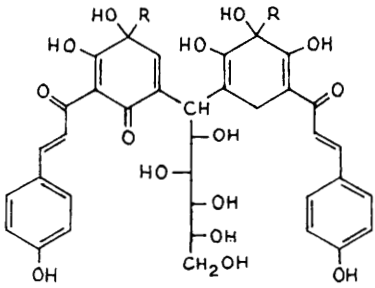
methyl acetoacetate (2 mols.).[162] Application of the Pictet-Spengler reaction to the corresponding aldehyde and dopamine hydrochloride gave the C-glycoside (74); a corresponding pentahydroxypentyl product was obtained from glucose.[163] Related acyclic compounds, e.g., (75), have been converted into pyridazines, e.g., (76), by photo-oxygenation followed by hydrazine treatment.[164] In the course of this work furanyl C-glycosides have been converted into O-glycosyl compounds by the photo-oxygenation process.[165] Other references to C-glycosidic compounds are given in Chapters 19 and 20.


(75)

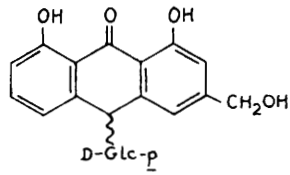

(76)


(74)

3.3 Glycosides Isolated from Natural Sources.- Safflor yellow B isolated from the flowers of Carthamus tinctorius is the C-glycoside-C-alditol derivative (77).[166] 6-C-β-D-Galactopyranosyl-8-C-β-D-glucopyranosylapigenin has been prepared by 6-C-galactosylation of vitexin and shown to differ from naturally occurring 6-C-β-D-glucopyranosyl-8-C-β-D-galactopyranosylapigenin.[167] A ^{1}H n.m.r. analysis of the aloins (78) has allowed the assignment of their stereochemistry.[168]



(77) R = β-D-Glc-p



(78)

References

1 V.Verez Bencomo and M.Basterrechea Rey, Rev. Cubana Farm., 1983, 17, 40 (Chem. Abstr., 1984, 100, 85 994).
2 V.Verez Bencomo and L.Konopski, Rev. Cubana Farm., 1983, 17, 55 (Chem. Abstr., 1984, 100, 85 995).
3 T.Mukaiyama and S.Shoda, Kagaku (Kyoto), 1983, 38, 881 (Chem. Abstr., 1984, 100, 85 998).
4 T.Mukaiyama, Noguchi Kenkyusho Jiho, 1983, 7 (Chem. Abstr., 1984, 100, 210 273).
5 J.Engel, Chem.-Ztg., 1984, 108, 195 (Chem. Abstr., 1984, 101, 111 270).
6 A.Gomez-Sanchez, P.Borrachero Moya, and J.Bellanato, Carbohydr. Res., 1984, 135, 101.
7 K.Ohtani, K.Muzutani, R.Kasai, and O.Tanaka, Tetrahedron Lett., 1984, 25, 4537.
8 T.Mukaiyama, S.Kobayashi, and S.Shoda, Chem. Lett., 1984, 907.
9 M.Ohno, Y.Ito, M.Arita, T.Shibata, K.Adachi, and H.Sawai, Tetrahedron, 1984, 40, 145.
10 R.M.Srivastava and R.K.Brown, Indian J. Chem., Sect. B, 1984, 23, 307 (Chem. Abstr., 1984, 101, 192 329).
11 R.R.Schmidt, M.Reichrath, and U.Moering, J. Carbohydr. Chem., 1984, 3, 67.
12 H.Kunz and H.Waldmann, Angew. Chem., Int. Ed. Engl., 1984, 23, 71.
13 S.G.Polonik, A.M.Tolkach, and N.I.Uvarova, Khim. Prir. Soedin., 1983, 324 (Chem. Abstr., 1984, 100, 6 983).
14 S.G.Polonik, A.M.Tolkach, and N.I.Uvarova, Khim. Prir. Soedin., 1984, 121 (Chem. Abstr., 1984, 101, 23 831).
15 N.F.Samoshina, V.A.Denisenko, V.L.Novikov, and N.I.Uvarova, Khim. Prir. Soedin., 1984, 191 (Chem. Abstr., 1984, 101, 230 869).
16 E.E.Nifant'ev, S.A.Rumyantseva, K.Sisneros, M.P.Koroteev, and N.K.Kochetkov, Zh. Obshch. Khim., 1984, 54, 200 (Chem. Abstr., 1984, 100, 210 286).
17 D.Horton, W.Priebe, and O.Varela, Carbohydr. Res., 1984, 130, C1.
18 J.Thiem and P.Ossowski, J. Carbohydr. Chem., 1984, 3, 287.
19 S.Hashimoto, M.Hayashi, and R.Noyori, Tetrahedron Lett., 1984, 25, 1379.
20 K.Krohn and E.Broser, J. Org. Chem., 1984, 49, 3766.
21 T.Ogawa and Y.Takahashi, J. Carbohydr. Chem., 1983, 2, 461.
22 D.S.Fullerton, M.Kihara, T.Deffo, E.Kitatsuji, K.Ahmed, B.Simat, A.H.Lfrom, and D.C.Rohrer, J. Med. Chem., 1984, 27, 256.
23 H.Kunz and S.Birnbach, Tetrahedron Lett., 1984, 25, 3567.
24 H.Matsue and M.Majima, J. Biochem. (Tokyo), 1983, 94, 1085 (Chem. Abstr., 1984, 100, 121 557).

25 H.J.M.Kempen, C.Hoes, J.H.Van Boom, H.H.Spanjer, J.De Lange, A.Langendoen, and T.J.C.Van Berkel, J. Med. Chem., 1984, 27, 1306.
26 V.F.Anufriev and N.I.Uvarova, Khim. Prir. Soedin., 1984, 119 (Chem. Abstr. 1984, 100, 210 293).
27 M.Kihara, K.Yoshioka, E.Kitatsuji, T.Hashimoto, D.S.Fullerton, and D.C.Rohrer, Steroids, 1983, 42, 37 (Chem. Abstr., 1984, 100, 192 170).
28 I.Cerny, V.Povzar, P.Drasar, M.Budesinsky, and M.Havel, Collect. Czech. Chem. Commun., 1984, 49, 881.
29 H.Hosoda, H.Yokohama, and T.Nambara, Chem. Pharm. Bull., 1984, 32, 4023.
30 M.Numazawa, M.Nagaoka, and M.Ogata, Chem. Pharm. Bull., 1984, 32, 618.
31 H.Hosoda, H.Yokohama, and T.Nambara, Chem. Pharm. Bull., 1984, 32, 1359.
32 N.Sh.Pal'yants and N.K.Abubakirov, Khim. Prir. Soedin., 1983, 652 (Chem. Abstr., 1984, 100, 156 895).
33 K.Seifert and S.Johne, Arch. Pharm. (Weinheim, Ger.), 1984, 317, 577 (Chem. Abstr., 1984, 101, 111 298).
34 I.Matsunaga, S.Nagataki, and Z.Tamura, Chem. Pharm. Bull., 1984, 32, 2832.
35 M.Aglietto, E.Ranucci, and G.Ruggeri, Conv. Ital. Sci. Macromol., [Atti], 6th, 1983, 2, 401 (Chem. Abstr., 1984, 101, 73 020).
36 Q.Pang and Y.Zong, Yiyao Gongye, 1984, 3 (Chem. Abstr., 1984, 101, 38 741).
37 J.Capillon, A.Ricard, and C.Quivoron, Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.), 1982, 23, 168 (Chem. Abstr., 1984, 100, 121 472).
38 A.Ricard, J.Capillon, and C.Quivoron, Polym. Sci. Technol. (Plenum), 1984, 24 (Crown Ethers Phase Transfer Catal. Polym. Sci.), 407 (Chem. Abstr., 1984, 101, 23 830).
39 K.Bock, E.Lundt, and C.Pedersen, Carbohydr. Res., 1984, 130, 125.
40 N.Mitsuo, H.Takeichi, and T.Satoh, Chem. Pharm. Bull., 1984, 32, 1183.
41 Y.Ooi, T.Hashimoto, N.Mitsuo, and T.Satoh, Tetrahedron Lett., 1984, 25, 2241.
42 M.Darise, K.Mizutani, R.Kasai, O.Tanaka, S.Kitahata, S.Okada, S.Ogawa, F.Murakami, and F.-H.Chen, Agric. Biol. Chem., 1984, 48, 2483.
43 R.C.Gupta, P.A.Harland, and R.J.Stoodley, Tetrahedron, 1984, 40, 4657.
44 P.Rollin, V.Verez Bencomo, and P.Sinaÿ, Synthesis, 1984, 134.
45 P.Ceccherelli, R.Coccia, M.Curini, and R.Pellicciari, Gazz. Chim. Ital., 1983, 113, 453 (Chem. Abstr., 1984, 100, 175 154).
46 P.M.Collins and H.Eder, J. Chem. Soc., Perkin Trans. 1, 1984, 1525.
47 J.Wydila and E.R.Thornton, J. Org. Chem., 1984, 49, 244.
48 E.V.Dokolina, A.S.Bushnev, E.N.Zvonkova, A.L.Lyutik, A.P.Kaplun, V.I.Shvets, and R.P.Evstigneeva, Biorg. Khim., 1983, 9, 1101 (Chem. Abstr., 1984, 100, 22 917).
49 S.J.Cook, R.Khan, and J.M.Brown, J. Carbohydr. Chem., 1984, 3, 343.
50 H.H.Baer and B.Radatus, Carbohydr. Res., 1984, 128, 165.
51 H.H.Baer, L.Siemsen, J.Defaye, and K.Burak, Carbohydr. Res., 1984, 134, 49.
52 J.Defaye, H.Driguez, S.Poncet, R.Chembert, and M.-F.Petit-Glatron, Carbohydr. Res., 1984, 130, 299.
53 T.P.Binder and J.F.Robyt, Carbohydr. Res., 1984, 132, 173.
54 S.Kahiya, S.Esaki, and R.Tanaka, Agric. Biol. Chem., 1984, 48, 2137.
55 R.Nardin, J.Saint-Germain, M.Vincendon, F.Taravel, and M.Vignon, Nouv. J. Chim., 1984, 8, 305.
56 P.A.Garcia Ruiz and A.Tarraga Tomas, An. Univ. Murcia, Cienc., 1980-1982, (Pub. 1983), 39-40, 207 (Chem. Abstr., 1984, 101, 91 364).
57 K.Hamacher, Carbohydr. Res., 1984, 128, 291.
58 A.Couto and R.M.de Ledercremer, Carbohydr. Res., 1984, 126, 313.
59 T.M.Shing and A.S.Perlin, Carbohydr. Res., 1984, 130, 65.
60 A.Temeriusz, J.Stepinski, B.Piekarska, and J.Radomski, Carbohydr. Res., 1984, 126, 331.
61 P.Kováč, E.A.Sokoloski, and C.P.J.Glaudemans, Carbohydr. Res., 1984, 128, 101.
62 H.A.El-Shenawy and C.Schuerch, Carbohydr. Res., 1984, 131, 227.
63 P.Kováč and C.P.J.Glaudemans, J. Carbohydr. Chem., 1984, 3, 349.

64 U.Zehavi and M.Herchman, Carbohydr. Res., 1984, 128, 160.
65 L.Hedbys, P.O.Larson, K.Mosbach, and S.Svensson, Biochem. Biophys. Res. Commun., 1984, 123, 8 (Chem. Abstr., 1984, 101, 147 274).
66 K.L.Matta, S.S.Rana, and S.A.Abbas, Carbohydr. Res., 1984, 131, 265.
67 H.Paulsen and M.Paal, Carbohydr. Res., 1984, 135, 53.
68 H.Paulsen and M.Paal, Carbohydr. Res., 1984, 135, 71.
69 K.L.Matta, R.Vig, and S.A.Abbas, Carbohydr. Res., 1984, 132, 119.
70 N.R.Plessas, D.A.Blake, and I.J.Goldstein, Carbohydr. Res., 1984, 129, 143.
71 J.Dahmén, T.Frejd, G.Magnusson, G.Noori, and A.-S.Carlström, Carbohydr. Res., 1984, 125, 237.
72 G.Ekborg and C.P.J.Glaudemans, Carbohydr. Res., 1984, 134, 83.
73 C.A.A.Van Boeckel, P.Westerduin, and J.H.Van Boom, Carbohydr. Res., 1984, 133, 219.
74 V.I.Torgov, V.N.Shibaev, and N.K.Kochetkov, Bioorg. Khim., 1984, 10, 946, (Chem. Abstr., 1984, 101, 230 887).
75 G.Ekborg and C.P.J.Glaudemans, Carbohydr. Res., 1984, 129, 287.
76 D.Charon, M.Mondange, and L.Szabó, J. Chem. Soc., Perkin Trans. 1, 1984, 2291.
77 D.Charon, C.Diolez, M.Mondange, S.R.Sarfati, L.Szabo, P.Szabo, and F.Trigalo, ACS Symp. Ser., 1983, 231, 301.
78 M.Imoto, H.Yoshimura, M.Yamamoto, T.Shimamoto, S.Kusumoto, Tetrahedron Lett., 1984, 25, 2667.
79 C.A.A.Van Boeckel, J.P.G.Hermans, P.Westerduin, J.J.Oltvoort, G.A.Van der Marel, and J.H.Van Boom, Recl. : J.R. Neth. Chem. Soc., 1983, 102, 438 (Chem. Abstr., 1984, 100, 121 493).
80 L.Anderson and M.A.Nashed, ACS Symp. Ser., 1983, 231, 255 (Chem. Abstr., 1984, 100, 103 782).
81 M.M.El Sadek, C.D.Warren, and R.W.Jeanloz, Carbohydr. Res., 1984, 131, 166.
82 J.H.Banoub, F.Michon, D.H.Shaw, and R.Roy, Carbohydr. Res., 1984, 128, 203.
83 G.Grundler and R.R.Schmidt, Justus Liebigs Ann.Chem., 1984, 1826.
84 H.Paulsen and J.P.Lorentzen, Carbohydr. Res., 1984, 133, C1.
85 H.Lönn and J.Lönngren, Carbohydr. Res., 1984, 132, 39.
86 F.Paquet and P.Sinaÿ, Tetrahedron Lett., 1984, 25, 3071.
87 H.H.Brandstetter and E.Zbiral, Monatsh. Chem., 1983, 114, 1247 (Chem. Abstr., 1984, 100, 192 196).
88 T.Ogawa and M.Sugimoto, Carbohydr. Res., 1984, 128, C1.
89 H.Brade, U.Zähringer, E.T.Rietschel, R.Christian, G.Schulz, and F.M.Unger, Carbohydr. Res., 1984, 134, 157.
90 L.V.Bakinovskii, N.E.Nifant'ev, and N.K.Kochetkov, Bioorg. Khim., 1983, 9, 1089 (Chem. Abstr., 1984, 100, 86 014).
91 L.V.Bakinovskii, N.E.Nifant'ev, and N.K.Kochetkov, Bioorg. Khim., 1984, 10, 226 (Chem. Abstr., 1984, 101, 38 739).
92 G.Excoffier, D.Gagnaire, and J.-P.Utille, Carbohydr. Res., 1984, 128, 217.
93 H.Ojika, H.Kuyama, H.Niwa, and K.Yamada, Bull. Chem. Soc. Jpn., 1984, 57, 2893.
94 K.Mizutani, A.Hayashi, R.Kasai, O.Tanaka, N.Yoshida, and T.Nakajima, Carbohydr. Res., 1984, 126, 177.
95 S.Paphassarang, M.Becchi, and J.Raynaud, Tetrahedron Lett., 1984, 25, 523.
96 A.Jaworska and A.Zamojski, Carbohydr. Res., 1984, 126, 191.
97 S.Kamiya, S.Esaki, and R.Tanaka, Agric. Biol. Chem., 1984, 48, 1353.
98 I.Lundt, J.Thiem, and A.Prahst, J. Org. Chem., 1984, 49, 3063.
99 B.Classon, P.J.Garegg, and T.Norberg, Acta Chem. Scand., Ser. B, 1984, 38, 195.
100 J.W.Krajewski, P.Gluzinski, Z.Urbanczyk-Lipkowska, A.Banaszek and M.Dobler, Carbohydr. Res., 1984, 134, 11.

101 M.Verzele, P.Delahaye, and C.Dewaele, Bull. Soc. Chim. Belg., 1984, 93, 151 (Chem. Abstr., 1984, 101, 130 990).
102 M.Kaneda, K.Kobayashi, K.Nishida, and S.Katsuta, Phytochemistry, 1984, 23, 795.
103 T.Iwagawa, H.Takahashi, K.Munesada, and T.Hase, Phytochemistry, 1984, 23, 468.
104 E.Shimizu, T.Tomimatsu, and T.Nohara, Chem. Pharm. Bull., 1984, 32, 5023.
105 H.Wagner, H.Habermeier, and H.-R.Schulten, Helv. Chim. Acta, 1984, 67, 54.
106 M.Kobayashi, Y.Kiyota, S.Orito, Y.Kyogoku, and I.Kitagawa, Tetrahedron Lett., 1984, 25, 3731.
107 M.Kodaka, Kagaku Gijutsu Kenkyusho Hokoku, 1984, 79, 169 (Chem. Abstr., 1984, 101, 171 614).
108 N.V.Khodyreva, S.G. Semenov, E.R.Novik, V.M.Sokolov, and T.V.Stolyarova, Zh. Obshch. Khim., 1983, 53, 2633 (Chem. Abstr., 1984, 100, 175 148).
109 E.Van Doorslaer, O.Van Opstal, H.Kersters-Hilderson, and C.K.De Bruyne, Bioorg. Chem., 1984, 12, 158 (Chem. Abstr., 1984, 101, 50 749).
110 A.Gunnarsson, J.Lundsten, and S.Svensson, Acta Chem. Scand., Ser. B, 1984, 38, 603.
111 P.W.Tang and J.M.Williams, J. Chem. Soc., Perkin Trans 1, 1984, 1199.
112 D.-S.Lee and A.S.Perlin, Carbohydr. Res., 1984, 125, 265.
113 D.-S.Lee and A.S.Perlin, Carbohydr. Res., 1984, 126, 101.
114 Y.Guindon, C.Yoakim, and H.E.Morton, J. Org. Chem., 1984, 49, 3912.
115 D.Rolf, J.A.Bennek, and G.R.Gray, J. Carbohydr. Chem., 1983, 2, 373.
116 J.A.Bennek, D.Rolf, and G.R.Gray, J. Carbohydr. Chem., 1983, 2, 385.
117 H.F.Davis, P.K.Das, G.W.Griffin, and J.D.Timpa, J. Org. Chem., 1983, 48, 5256.
118 J.D.Timpa and G.W.Griffin, Carbohydr. Res., 1984, 131, 185.
119 J.-P.Praly, G.Descotes, M.-F.Grenier-Loustalot, and F.Metras, Carbohydr. Res., 1984, 128, 21.
120 G.Descotes, H.Idmoumaz, and J.-P.Praly, Carbohydr. Res., 1984, 128, 341.
121 F.H.Hengemihle, G.D.McGinnis, S.Prince, and C.Templeton, J. Anal. Appl. Pyrolysis, 1984, 6, 317 (Chem. Abstr., 1984, 101, 211 585).
122 A.S.Serianni and R.Barker, J. Org. Chem., 1984, 49, 3292.
123 G.A.Jeffrey, Mol. Cryst. Liq. Cryst., 1984, 110, 221 (Chem. Abstr., 1984, 101, 141 193).
124 J.W.Goodby, Mol. Cryst. Liq. Cryst., 1984, 110, 205 (Chem. Abstr., 1984, 101, 141 513).
125 G.Barone, G.Castronuovo, V.Elia, and V.Savino, J. Solution Chem., 1984, 13, 209 (Chem. Abstr., 1984, 101, 192 323).
126 T.M.Herrington and R.J.Jackson, Int. Sugar J., 1983, 85, 364 (Chem. Abstr. 1984, 100, 141 112).
127 K.C.Nicolaou, A.Chucholowski, R.E.Dolle, and J.L.Randall, J. Chem. Soc., Chem. Commun., 1984, 1155.
127a G.E.Keck, E.J.Enholm, and D.F.Kachensky, Tetrahedron Lett., 1984, 25, 1867.
128 B.Paul and W.Korytnik, Carbohydr. Res., 1984, 126, 27.
129 T.H.Keller, L.J.Yelland, and M.H.Benn, Can. J. Chem., 1984, 62, 437.
130 J.F.Richardson and M.H.Benn, Can. J. Chem., 1984, 62, 1236.
131 K.C.Nicolaou, R.E.Dolle, D.P.Papahatjis, and J.L.Randall, J. Am. Chem. Soc., 1984, 106, 4189.
132 R.J.Ferrier and S.R.Haines, Carbohydr. Res., 1984, 127, 157.
133 J.-M.Lancelin, L.Morin-Allory, and P.Sinaÿ, J. Chem. Soc., Chem. Commun., 1984, 355.
134 S.Hanessian and A.Ugolini, Carbohydr. Res., 1984, 130, 261.
135 K.C.Nicolaou, R.E.Dolle, A.Chucholowski, and J.L.Randall, J. Chem. Soc., Chem. Commun., 1984, 1153.
136 H.Obara, M.Hattori, and Y.Matsui, Chem. Lett., 1984, 1039.
137 H.Obara, Y.Matsui, S.Namai, and Y.Machida, Chem. Lett., 1984, 1397.
138 R.W.Myers and Y.C.Lee, Carbohydr. Res., 1984, 132, 61.
139 G.Grynkiewicz and J.N.Be Miller, Carbohydr. Res., 1984, 131, 273.
140 A.Hosomi, Y.Sakata, and H.Sakurai, Tetrahedron Lett., 1984, 25, 2383.

141 R.D.Dawe and B.Fraser-Reid, J. Org. Chem., 1984, 49, 522.
142 F.Nicotra, R.Perego, F.Ronchetti, G.Russo, and L.Toma, Gazz. Chim. Ital., 1984, 114, 193 (Chem. Abstr., 1984, 101, 230 872).
143 J.Herscovici, K.Muleka, and K.Antonakis, Tetrahedron Lett., 1984, 25, 5653.
144 D.S.Grierson, M.Bonin, H.-P.Husson, C.Monneret, and J.-C.Florent, Tetrahedron Lett., 1984, 25, 4645.
145 H.Kunz, J.Weissmüller, and B.Müller, Tetrahedron Lett., 1984, 25, 3571.
146 D.B.Tulshian and B.Fraser-Reid, J. Org. Chem., 1984, 49, 518.
147 S.Danishefsky, C.J.Maring, M.R.Barbachyn, and B.E.Segmuller, J. Org. Chem., 1984, 49, 4564.
148 E.M.Acton, K.J.Ryan, and M.Tracy, Tetrahedron Lett., 1984, 25, 5743.
149 S.D.Burke, D.M.Armistead, and F.J.Schoenen, J. Org. Chem., 1984, 49, 4322.
150 P.D.Kane and J.Mann, J. Chem. Soc., Perkin Trans. 1, 1984, 657.
151 A.G.M.Barrett and H.B.Broughton, J. Org. Chem., 1984, 49, 3673.
152 Y.Chapleur, J. Chem. Soc., Chem. Commun., 1984, 449.
153 C.S.Wilcox, G.W.Long, and H.Suh, Tetrahedron Lett., 1984, 25, 395.
154 T.Mukaiyama, S.Kobayashi, and S.Shoda, Chem. Lett., 1984, 1529.
155 Y.S.Yokoyama, T.Inoue, and I.Kuwajima, Bull. Chem. Soc. Jpn., 1984, 57, 553.
156 Y.Araki, K.Watanabe, F.-H.Kuan, K.Itoh, N.Kobayashi, and Y.Ishido, Carbohydr. Res., 1984, 127, C5.
157 L.Li, D.Chen, S.Peng, and M.Cai, Huaxue Xuebao, 1984, 42, 288 (Chem. Abstr., 1984, 101, 38 737).
158 D.A.Miljkovic, V.J.Popsavin, and J.T.Hranisavljevic, Glas. Hem. Drus., Beograd, 1983, 48, 211 (Chem. Abstr., 1984, 100, 175 138).
159 V.S.Rao and A.S.Perlin, Can. J. Chem., 1984, 62, 886.
160 S.-Y.Chen and M.M.Joullie, J. Org. Chem., 1984, 49, 1769.
161 L.Huybrechts, D.Buffel, E.Freyne and G.Hoornaert, Tetrahedron, 1984, 40, 2479.
162 F.J.Lopez Herrera, M.Valpuesta Fernandez, and R.Garcia Segura, Carbohyr. Res., 1984, 127, 217.
163 I.M.Piper, D.B.MacLean, I.Kvarnström, and W.A.Szarek, Can. J. Chem., 1983, 61, 2721.
164 F.J.Lopez Aparicio, M.Plaza Lopez-Espinosa, and R.Robles Diaz, Carbohydr. Res., 1984, 132, 233.
165 F.J.Lopez Aparicio, J.A. Lopez Sastre, J.Isac Garcia, and R.Robles Diaz, Carbohydr. Res., 1984, 132, 19.
166 Y.Takahashi, K.Saito, M.Yanagiya, M.Ikura, K.Hikichi, T.Matsumoto, and M.Wada, Tetrahedron Lett., 1984, 25, 2471.
167 M.A.Dubois, A.Zoll, K.R.Markham, M.L.Bouillant, G.Dellamonica, and J.Chopin, Phytochemistry, 1984, 23, 706.
168 H.W.Rauwald and K.Roth, Arch. Pharm. (Weinheim, Ger.), 1984, 317, 362 (Chem. Abstr., 1984, 101, 7 540).

4
Oligosaccharides

1 General

As before, this Chapter deals with specific tri- and higher saccharides; most references related to their syntheses by specific chemical methods. It does not cover higher, non-specific compounds made by the oligomerisation of monosaccharide derivatives nor does it deal with the cyclodextrins. The synthesis of, e.g., pentasaccharides is dealt with under that heading and the required preparations of constituent parts are assumed and are not covered in their sections.

A lecture review on the synthesis of fragments of bacterial polysaccharides and their application in the preparation of antigens [1] and one on the synthesis of oligosaccharides of aureolic acids[2] have appeared.

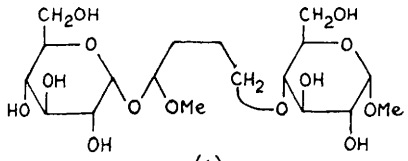
^{13}C n.m.r. chemical shifts of oligosaccharides have been tabulated,[3] and combinations of homo- and hetero-nuclear shift correlated 2-D n.m.r. techniques have been used to assign ^{1}H and ^{13}C signals of oligosaccharides related to arabinoxylan.[4] ^{1}H n.m.r. methods were used to determine the branching patterns in a ceramide pentadecasaccharide; differences were noted between the parent spectrum and that of partially degraded products.[5]

F.a.b. mass spectrometry has been shown to be a useful tool for the identification of cello- and malto-oligosaccharides and their alditol reduction products.[6] Permethylated sialo-oligosaccharides liberated from parent gangliosides can be usefully examined by chemical ionization mass spectrometry with ammonia as reagent gas. Molecular weights are revealed by the MH^+ and $(M+NH_4)^+$ ions and the fragmentation patterns indicate the linkage patterns.[7] Alternatively, the negative ion chemical ionization method as applied to oligosaccharides corresponds to the flash desorption technique. Stachyose, for example, gave not only the quasi-molecular ion but also cluster ions of glucose and sucrose.[8] Secondary ion mass spectra of oligosaccharides containing neutral or amino sugars and

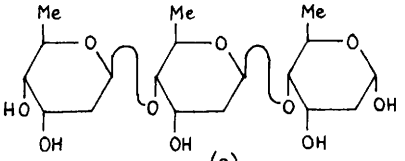
aminoglycoside antibiotics have been measured using various matrix materials; molecular adducts and fragments were observed.[9]

2 Trisaccharides

2.1 Linear Homotrisaccharides.- In connection with the characterization of an unknown trisaccharide from crocuses, the four possible linear β-D-glucopyranosyl derivatives of gentiobiose [β-D-Glcp(1 → 6)-D-Glc] were synthesized as their peracetates and their ^{1}H n.m.r. spectra were fully analysed.[10] Likewise, panose (O-α-D-Glcp(1 → 6)-O-α-D-Glcp(1 → 4)-D-Glc) has been prepared by rational synthesis,[11] as has compound (1) which is an analogue of methyl α-maltotrioside with a flexible central unit, being a competitive inhibitor for the hydrolysis of p-nitrophenyl α-maltotrioside by porcine α-amylase.[12] A study of the alkaline hydrolysis of methyl β-D-cellotrioside has been undertaken.[13]



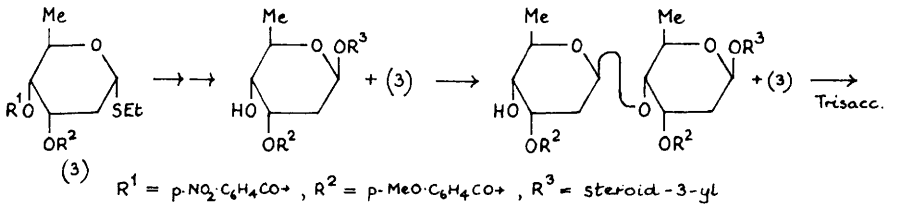
(1)



(2)

The α-propyl glycoside of O-β-D-Galp(1 → 4)-O-β-D-Galp-(1 → 4)-D-Galp has been prepared by use of allyl glycosides, and several unsuccessful approaches were discussed.[14] α-L-Rhamnopyranose trisaccharides with the following linkages have also been obtained synthetically: (1 → 4)(1 → 4), (1 → 4)(1 → 3), (1 → 4)(1 → 2)[15] and (1 → 2)(1 → 3);[16] in addition, O-α-D-Rhap(1 → 2)-α-L-Rhap-(1 → 3)-L-Rha was prepared.[16] In the pentose series, the methyl O-β-D-xylopyranosyl-(1 → 3)-β-D-xylopyranosyl-(1 → 2) and (1 → 3)-β-D-xylopyranosides have been synthesized by stepwise methods and examined by ^{13}C n.m.r. spectroscopy.[17]

The dideoxyhexose trisaccharide (2) has been isolated from twigs of Orthenthera viminea,[18] and also synthesized in the form of its β-steroidal glycoside, digitoxin. The outline of the synthesis is shown in Scheme 1, the use of the 1-thio S-ethylglycoside being very unusual, and the β-glycosidic bond formation being, it is proposed, consequent upon the intermediacy of a 1,3-acyloxonium ion.[19]



Scheme 1

2.2 Branched Homotrisaccharides.- O-β-D-Glcp-(1 → 2)-O-[β-D-Glcp-(1 → 6)]-D-Glc has been isolated from a crocus[20] and the isomer O-α-D-Glcp-(1 → 4)-O-[α-D-Glcp-(1 → 6)]-D-Glc has been synthesized by use of 2,3,4,6-tetra-O-benzyl-D-glucose in the presence of p-nitrobenzenesulphonyl chloride, silver triflate and triethylamine in N,N-dimethylacetamide.[21] Methyl O-α-D-Manp-(1 → 3)-O-[α-D-Manp-(1 → 6)]-α-D-Manp has been prepared with C-1 of both substituent sugars labelled with ^{13}C.[22]

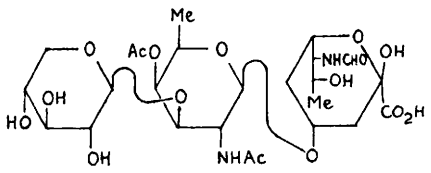
2.3 Linear Heterotrisaccharides.- Compounds are listed according to their reducing termini. Those with D-glucose at the reducing position are: O-β-D-Galp-(1 → 4)-O-β-D-Glcp-(1 → 4)-β-D-Glcp (prepared bound as a glycosylamine to a phenylalanine-containing polymer, the galactosyl unit being introduced by enzymic methods),[23] O-α-D-Galp-(1 → 4)-β-D-Galp-(1 → 4)-β-D-Glcp (linked through a spacer aglycone to two proteins),[24] α-D-Manp-(1 → 2)-α-D-Manp-(1 → 3)-α-D-Glcp (as α-methyl glycoside),[25] and O-α-L-Fucp-(1 → 2)-β-D-Galp-(1 → 4)-D-Glc (isolated from echidna milk).[26] Amino-sugar-containing trisaccharides of the series are O-β-D-GalNAc-(1 → 4)-β-D-Gal-(1 → 4)-β-D-Glcp (as the methyl 9-hydroxynonanoate glycoside),[27] and the same compound as a substituted methyl glycoside,[28] and O-β-D-GlcNH$_2$-(1 → 4)-β-D-Galp-(1 → 4)-D-Glc.[29]

With D-galactose at the reducing end the following were reported: O-α-D-Galp-(1 → 2)-α-D-Glcp-(1 → 2)-D-Gal,[30] O-β-D-Manp-(1 → 4)-α-L-Rhap-(1 → 3)-D-Gal (obtained as polymeric antigens by copolymerization of the β-allyl glycoside with acrylamide),[31] O-β-D-Galp-(1 → 4)-β-D-GlcNAc-(1 → 3)-D-Gal and O-β-D-Galp-(1 → 4)-β-D-GlcNAc-(1 → 6)-D-Gal (both synthesized with immobilized enzymes and UDP-Gal),[32] O-β-D-Galp-(1 → 3)-β-D-GlcNAc-(1 → 3)-D-Gal (a mucin fragment synthesized,[33] and various chemical interconversions carried out),[34] O-β-D-Fucp-(1 → 4)-β-D-GlcNAc-(1 → 6)-D-Gal.[35]

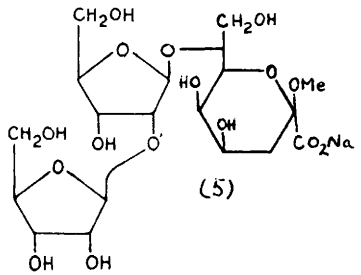
Those with 2-amino-2-deoxy-D-glucose carrying a disaccharide substituent are: O-α-D-Galp-(1 → 4)-β-D-Galp-(1 → 4)-D-GlcNH$_2$,[36] O-α-D-Manp-(1 → 3)-β-D-Manp-(1 → 4)-D-GlcNAc,[37] O-α-D-Manp-(1 → 6)-β-D-Manp-(1 → 4)-D-GlcNAc,[37] O-α-L-Fucp-(1 → 2)-α (- and β-) D-Galp-(1 → 3)-D-GlcNAc,[38,39] O-β-D-Manp-(1 → 4)-β-D-GlcNAcp-(1 → 4)-α-D-GlcNAc (as pyrophosphate dolechyl diesters),[40] α-D-GlcNH$_2$-(1 → 4)-β-D-GalUA-(1 → 4)-D-GlcNH$_2$ (a synthetic heparin trisaccharide as a pentasulphate ester),[41] and O-α-Neu5Ac-(2 → 6)-β-D-Galp-(1 → 4)-D-GlcNAc (a glycoprotein terminal unit).[42]

The D-galactosamine derivative O-β-D-GlcNAc-(1 → 3)-β-D-Galp-(1 → 3)-D-GalNAc has also been synthesized.[43]

The following miscellaneous compounds have also been reported: O-α-D-Galp-(1 → 2)-β-D-Manp-(1 → 4)-L-Rha (analogue of the repeating unit of *Salmonella* serogroups A, B and D),[44] O-α-L-Araf-(1 → 3)-β-D-Xylp-(1 → 4)-D-Xyl[45] and the ulosonic acid-containing compounds (4) (isolation of bacterial lipopolysaccharide fragment)[46] and (5) (synthesis of *E. coli* polysaccharide repeating unit).[47]



(4)



(5)

2.4 Branched Heterotrisaccharides.- Several compounds of this category have been synthesized: O-α-L-Fucp-(1 → 2)-O-[α-D-Galp-(1 → 3)]-D-Gal (a portion of the antigenic determinant of blood group B substance),[48] O-α-D-Galp-(1 → 2)-O-[α-D-Abep-(1 → 3)]-α-D-Manp (Abe = 3,6-dideoxy-D-*xylo*-hexose),[49] O-β-D-Fucp-(1 → 3)-O-[β-D-GlcNAc-(1 → 6)-]α-D-GalNAc (benzyl glycoside),[50] O-β-D-Galp-(1 → 3)-O-[β-D-GlcNAc-(1 → 6)]-α-D-GalNAc (benzyl glycoside, related to mucins and blood group substances),[51] O-α-L-Rhap-(1 → 2)-O-[α-D-Glc-(1 → 3)]-α-L-Rhap-OMe,[52] O-β-D-GlcNAc(1 → 2)-O-[α-D-Glc-(1 → 3)]-α-L-Rhap-OMe,[52] and O-α-L-Araf-(1 → 3)-O-[β-D-Xylp-(1 → 4)]-β-D-Xyl-OMe.[45]

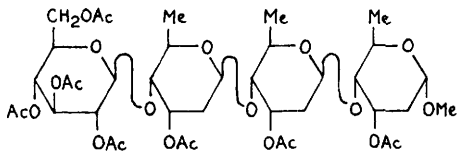
3 Tetrasaccharides

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

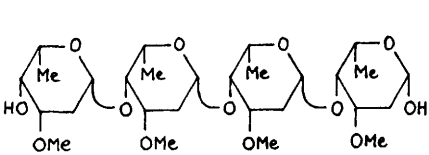
3.1 Linear Tetrasaccharides.- Reports of the preparation of the following have appeared: O-β-D-Galp-(1 → 3)-β-D-GalNAc-(1 → 4)-β-D-Galp-(1 → 4)-D-Glc,[27,29] O-α-L-Rhap-(1 → 2)-β-D-Glc-(1 → 2)-α-L-Arap-(1 → 6)-D-Glc,[53] and O-α-D-Glcp-(1 → 6)-α-D-Glcp-(1 → 4)-α-D-Glcp-(1 → 4)-D-Glc (coupled via spacer groups to proteins).[54]

Glucosamine derivatives are: O-α-D-Manp-(1 → 3)-β-D-Manp-(1 → 4)-β-D-GlcNAcp-(1 → 4)-α-D-GlcNAc (pyrophosphate dolichyl diester),[40] α-D-Manp-(1 → 2)-α-D-Manp-(1 → 3)-β-D-Manp-(1 → 4)-GlcNAc,[55] α-D-Manp-(1 → 3)-α-D-Manp-(1 → 6)-β-D-Manp-(1 → 4)-GlcNAc,[55] 4-methylcoumarin-7-yloxy tetra-N-acetyl-β-chitotetraoside (obtained from the tetraose peracetate which was produced by acetolysis of chitin),[56] O-α-Neu5Ac-(2 → 6)-β-D-Galp-(1 → 4)-β-D-GlcNAc-(1 → 2)-D-Man (and the β-Neu-5Ac isomer),[57] and O-α-D-OclAp-(2 → 4)-α-D-OclAp-(2 → 6)-β-D-GlcNAcp-(1 → 6)-D-GlcNAc(OclAp = 3-deoxy-D-manno-2-octulopyranosonic acid).[58]

Compound (6) is a derivative of the tetrasaccharide unit of lanatosides (cardiac glycosides) and has been synthesized by glycal addition procedures.[59] A tetrasaccharide of Orthenthera viminea twigs is the β-L-diginose tetramer (7).[60] A synthesis of the β-1,3-linked D-xylopyranose tetramer has been reported.[61]



(6)



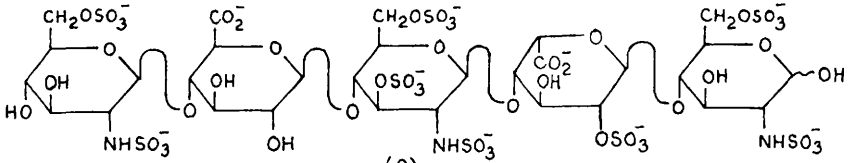
(7)

3.2 Branched Tetrasaccharides.- The following have been reported: O-α-D-GalNAc-(1 → 3)-[α-L-Fucp-(1 → 2)]-β-D-Galp-(1 → 4)-D-Glc (partial enzymic method),[62] O-α-L-Fucp-(1 → 2)-β-D-Galp-(1 → 4)-[α-L-Fucp-(1 → 3)]-D-Glc,[26] O-β-D-Glcp-(1 → 2)-O-[β-D-Xylp-(1 → 3)]-O-β-D-Glcp-(1 → 4)-D-Gal (lycotetraose),[63] α-D-Manp(1 → 3)-[α-D-Manp(1 → 6)]-β-D-Manp-(1 → 4)-D-GlcNAc[37] and α-D-Galp-(1 → 2)-α-D-

Manp-(1 → 4)-α-L-Rhap-O-$(CH_2)_8CO_2Me$ with the following sugars linked α-(1 → 3) to the mannose unit: 3,6-dideoxy-α-D-ribo- and arabino-hexose, 3,6-dideoxy-α-L-arabino-hexose, 2,3,6-trideoxy-α-D-threo-hexose and 3,4,6-trideoxy-α-D-erythro-hexose (units of Salmonella serogroup A and D and related antigens).[64]

4 Higher Oligosaccharides

4.1 Pentasaccharides.- The following have been obtained synthetically: β-D-Galp-(1 → 4)-β-D-GlcNAc-(1 → 6)-β-D-Gal-(1 → 4)-β-D-$GlcNH_2$-(1 → 6)-D-Gal (used to study the combining site of monochoral anti 1 Ma antibody),[35] β-D-Galp-(1 → 4)-β-D-GlcNAc-(1 → 2)-α-D-Manp-(1 → 6)-β-D-Manp-(1 → 4)-D-GlcNAc[65] and β-D-Galp-(1 → 4)-β-D-GlcNAc-(1 → 2)-α-D-Manp-(1 → 3)-β-D-Manp-(1 → 4)-GlcNAc[65] and α-D-Manp-(1 → 3)-[α-D-Manp-(1 → 6)]-β-D-Manp-(1 → 4)-β-D-GlcNAc (1 → 4)-D-GlcNAc[66] and the heparin pentasaccharide (8).[67]



(8)

4.2 Higher Saccharides.- Muscaroside B contains a novel branched-chain hexasaccharide which was structurally characterized using FAB m.s..[68]

The synthesis of the branched-chain octasaccharide (9), a glycoprotein structural unit, has been achieved.[65]

β-D-Galp-(1 → 4)-β-D-GlcNAc-(1 → 2)-α-D-Manp-(1 → 3)-β-D-Manp-(1 → 4)-D-GlcNAc
6
↑
1
β-D-Galp-(1 → 4)-β-D-GlcNAc-(1 → 2)-α-D-Manp

(9)

References

1 N.K.Kochetkov, Pure Appl. Chem., 1984, 56, 923.

2 J.Thiem, Nachr. Chem., Tech. Lab., 1984, 32, 6 and 10 (Chem. Abstr., 1984, 100, 121 454).

3 K.Bock, C.Pedersen, and H.Pedersen, Advan. Carbohydr. Chem. Biochem., 1984, 42, 193.

4 J.Schraml, J.Hirsch, E.Petrakova, E.Krahe, and C.Bliefert, Collect. Czech. Chem. Commun., 1984, 49, 1605.
5 U.Dabrowski, P.Hanfland, H.Egge, S.Kuhn, and J.Dabrowski, J. Biol. Chem., 1984, 259, 7648.
6 C.Bosso, J.Defaye, A.Heyraud, and J.Ulrich, Carbohydr. Res., 1984, 125, 309.
7 Y.Tanaka, R.K.Yu, S.Ando, T.Ariga, and T.Itoh, Carbohydr. Res., 1984, 126, 1.
8 K.Tsujimoto, Y.Shida, M.Ohashi, and Y.Yamada, Shitsuryo Bunseki, 1984, 32, 115 (Chem. Abstr., 1984, 101, 152 218).
9 K.I.Harada, F.Occhiai, M.Suzuki, and H.Kambara, Org. Mass. Spectrom., 1983, 18, 447 (Chem. Abstr., 1984, 100, 68 623).
10 M.Rychener, P.Bigler, and H.Pfander, Helv. Chim. Acta, 1984, 67, 378.
11 K.Takedo and K.Shinmitsu, Carbohydr. Res., 1984, 133, 135.
12 S.Jegge and J.Lehmann, Carbohydr. Res., 1984, 133, 247.
13 I.Simkovic, A.Ebringerova, J.Konigstein, V.Mihalov, and F.Janecek, Chem. Zvesti, 1984, 38, 223.
14 H.A.El-Shenawy and C.Schuerch, Carbohydr. Res., 1984, 131, 239.
15 A.Liptak, J.Harangi, G.Batta, O.Seligmann, and H.Wagner, Carbohydr. Res., 1984, 131, 39.
16 A.Jawarska and A.Zamojski, Carbohydr. Res., 1984, 126, 205.
17 J.Hirsch and E.Petrakova, Chem. Zvesti, 1984, 38, 409.
18 K.N.Tiwari, N.K.Khare, A.Khare, and M.P.Khare, Carbohydr. Res., 1984, 129, 179.
19 T.Y.R.Tsai, H.Jin, and K.Wiesner, Can. J. Chem., 1984, 62, 1403.
20 M.Rychener, P.Bigler, and H.Pfander, Helv. Chim. Acta, 1984, 67, 386.
21 S.Koto, N.Morishima, M.Owa,and S.Zen, Carbohydr. Res., 1984, 130, 73.
22 F.M.Winnik, J.P.Carver, and J.J.Krepinsky, J. Labelled Comp. Radiopharm., 1983, 20, 983 (Chem. Abstr., 1984, 100, 68 622).
23 U.Zehavi and M.Herchman, Carbohydr. Res., 1984, 133, 339.
24 J.Dahmén, T.Frejd, G.Magnusson, G.Noori, and A.-S. Carlström, Carbohydr. Res., 1984, 127, 15.
25 V.Verez Bencomo, G.Garcia Fernandez, M.Basterrechea Rey, F.Coll Manchado, and M.E.Rodriguez Fernandez, Rev. Cubana Farm., 1983, 17, 36 (Chem. Abstr., 1984, 100, 34 761).
26 G.A.Jenkins, J.H.Bradbury, M.Messer, and E.Trifonoff, Carbohydr. Res., 1984, 126, 157.
27 S.Sabesan and R.U.Lemieux, Can. J. Chem., 1984, 62, 644.
28 H.-P.Wessel, T.Iversen, and D.R.Bundle, Carbohydr. Res., 1984, 130, 5.
29 H.Paulsen, M.Paal, D.Hadamczyk, and K.-M.Steiger, Carbohydr. Res., 1984, 131, C1.
30 B.Doboszewski and A.Zamojski, Carbohydr. Res., 1984, 132, 29.
31 A.Ya.Chernyak, A.B.Levinsky, B.A.Dmitriev, and N.K.Kochetkov, Carbohydr. Res., 1984, 128, 269.
32 C.Augé, S.David, C.Mathieu, and C.Gautheron, Tetrahedron Lett., 1984, 25, 1467.
33 K.Kohata, S.H.Abbas, and K.L.Matta, Carbohydr. Res., 1984, 132, 127.
34 K.Kohata, S.A.Abbas, and K.L.Matta, Carbohydr. Res., 1984, 132, 345.
35 T.C.Wong and R.U.Lemieux, Can. J. Chem., 1984, 62, 1207.
36 J.Dahmén, T.Frejd, G.Magnusson, G.Noori, and A.-S.Carlström, Carbohydr. Res., 1984, 129, 63.
37 H.Paulsen, T.Peters, V.Sinnwell, R.Lebuhn, and B.Meyer, Justus Liebigs Ann. Chem., 1984, 951.
38 K.L.Matta, S.S.Rana, C.F.Piskorz,and S.A.Abbas, Carbohydr. Res., 1984, 131, 247.
39 N.V.Bovin and A.Ya.Khorlin, Bioorg. Khim., 1984, 20, 853 (Chem. Abstr., 1984, 101, 211 588).
40 C.D.Warren, M.-L. Milat, C.Augé, and R.W.Jeanloz, Carbohydr. Res., 1984, 126, 61.
41 J.-C.Jacquinet, M.Petitou, P.Duchaussoy, I.Lederman, J.Choay, G.Torri, and P. Sinäy, Carbohydr. Res., 1984, 130, 221.

42 H.Paulsen and H.Tietz, Carbohydr. Res., 1984, 125, 47.
43 S.A.Abbas and K.L.Matta, Carbohydr. Res., 1984, 132, 137.
44 K.Bock and M.Meldal, Acta Chem. Scand., Ser. B., 1983, 37, 775.
45 J.Hirsch, E.Petrakova, and J.Schraml, Carbohydr. Res., 1984, 131, 219.
46 Y.A.Knirel, E.V.Vinogradov, V.L.L'vov, N.A.Kocharova, A.S.Shashkov, B.A.Dmitriev, and N.K.Kochetkov, Carbohydr. Res., 1984, 133, C5.
47 P.Kosma, G.Schulz, and F.M.Unger, Carbohydr. Res., 1984, 132, 261.
48 C.Subero, M.L.Jimeno, A.Alemany, and M.Martin-Lomas, Carbohydr. Res., 1984, 126, 326.
49 B.M.Pinto and D.R.Bundle, Carbohydr. Res., 1984, 133, 333.
50 C.F.Piskorz, S.A.Abbas, and K.L.Matta, Carbohydr. Res., 1984, 131, 257.
51 C.F.Piskorz, S.A.Abbas, and K.L.Matta, Carbohydr. Res., 1984, 126, 115.
52 L.V.Bakinovskii, A.R.Gomtsyan, N.E.Bairamova, and N.K.Kochetkov, Bioorg. Khim., 1984, 10 , 79 (Chem. Abstr., 1984, 100, 210 297).
53 M.Adinolfi, G.Barone, R.Lanzetta, G.Laonigro, L. Mangoni, and M.Parrilli, Can. J. Chem., 1983, 61, 2633.
54 J.Dahmén, T.Frejd, G.Magnusson, G.Noori, and A.-S.Carlström, Carbohydr. Res., 1984, 127, 27.
55 Y.Itoh and S.Tejima, Chem. Pharm. Bull., 1984, 32, 957.
56 T.Inaba, T.Ohgushi, Y.Iga, and E.Hasegawa, Chem. Pharm. Bull., 1984, 32, 1597.
57 T.Kitajima, M.Sugimoto, T.Nukada, and T.Ogawa, Carbohydr. Res., 1984, 127, C1.
58 R.Christian, G.Schulz, P.Waldstatten, and F.M.Unger, Tetrahedron Lett., 1984, 25, 3433.
59 J.Thiem and P.Ossowski, Justus Liebigs Ann. Chem., 1983, 2215.
60 K.N.Tiwari, A.Khare, and M.P.Khare, J. Carbohydr. Chem., 1984, 3, 315.
61 D.Dupeyre, G.Excoffier, and J.-P.Utille, Carbohydr. Res., 1984, 135, C1.
62 A.D.Yates, J.Feeney, A.S.R.Donald, and W.M.Watkins, Carbohydr. Res., 1984, 130, 251.
63 K.Takeo, T.Nakaji, and K.Shinmitsu, Carbohydr. Res., 1984, 133, 275.
64 K.Bock and M.Meldal, Acta Chem. Scand., Ser. B, 1984, 38, 255.
65 H.Paulsen and R.Lebuhn, Carbohydr. Res., 1984, 125, 21.
66 H.Paulsen and R.Lebuhn, Carbohydr. Res., 1984, 130, 85.
67 P.Sinäy, J.-C.Jacquinet, M.Petitou, P.Duchaussoy, I.Lederman, J.Choay, and G.Torri, Carbohydr. Res., 1984, 132, C5.
68 M.Adinolfi, L.Mangoni, G.Marino, M.Parrilli, and R.Self, Biomed. Mass Spectrom., 1984, 11, 310 (Chem. Abstr., 1984, 101, 192 337).

5
Ethers and Anhydro-sugars

1 Ethers

Methyl Ethers.- Oligoglycoside diterpenes with 3-O-methylated α-L-rhamnopyranosyl, β-D-quinovopyranosyl, and β-D-glucopyranosyl moieties have been isolated from Scypholepia hookeriana fronds.[1]

The role of the dimsyl anion ($MeSOCH_2^-$) in the Hakamori methylation procedure has been questioned, hydroxide and hydride anions being shown to be the effective bases. An alternative procedure employing solid hydroxides as bases (i.e. NaOH or KOH -DMSO-MeI) has thus been developed and demonstrated for the permethylation of sucrose and eleven reducing sugars. It proved to be simple, rapid (6-7 min), high yielding (98±2%), and to have none of the side reactions found in the Hakamori method.[2] A modification of the Hakamori permethylation has been described in which silver nitrate was added with excess methyl iodide, precipitated silver iodide was removed by filtration, and traces of silver salts were removed by treatment with aqueous potassium cyanide.[3] A compilation of carbohydrate methylations employing methyl triflate has appeared.[4]

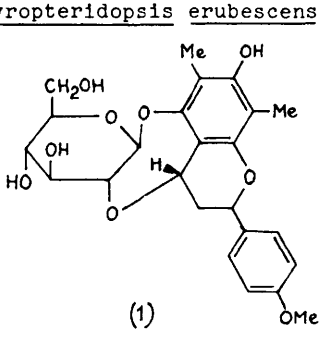
Further detailed investigation of the selective monoalkylation of diols in D-gluco-, D-manno-, and D-galacto-pyranoside derivatives by formation of copper(II) chelates ($NaH-CuCl_2$ in ether solvents) then reaction with allyl, benzyl, or methyl iodide has revealed a number of synthetically useful examples (c.f. Vol. 16, p.51). Thus methyl 4,6-O-benzylidene-α-D-glucopyranoside provided 2- and 3-monomethyl ethers in 20 and 60% yield, respectively.[5] Reaction of methyl 6-O-trityl-α-D-mannopyranoside with diazomethane-tin(II) chloride led selectively to mixtures of the 2- and 3-O-monomethyl ethers, the ratio of products depending upon the solvent employed.[6]

Partial methylation of methyl β-D-xylopyranoside followed by column chromatographic separation of the products has been claimed to be a better method for obtaining all seven possible products

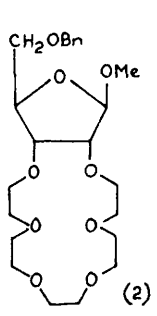
than employing standard syntheses of the individual compounds. Fair yields (7-22%) of all derivatives were obtained from a single reaction, and literature data on the 2,3- and 2,4-diethers were revised.[7] Partial methylation of methyl 4,6-dideoxy-α- and β-L-ribo-hexopyranoside led primarily to their 2-O-monomethyl ethers; these results have been discussed in relation to those obtained with other configurational isomers.[8] The proportions of the mono- to tri-O-methyl ethers in the complex mixture obtained on dimolar methylation of methyl 6-O-trityl-α-D-mannopyranoside have been determined.[9] Conventional syntheses[10] and ^{13}C-n.m.r. spectra[11] of the 3-mono, 2,3- and 3,4-di-, and 2,3,4-tri-O-methyl ethers of methyl (methyl α-D-mannopyranosid) uronate have been reported.

The sulphate ester group has been used as a temporary blocking group in a synthesis of 3,4,6-tri-O-methyl-D-glucose. Treatment of methyl 4,6-O-benzylidene-α- or β-D-glucopyranoside with pyridine-sulphur trioxide complex led mainly to the 2-sulphate, which was sequentially hydrolysed selectively to remove the acetal, methylated, and desulphated.[12] Unambiguous syntheses of the 2,4- and 3,4-di-O-methyl ethers of methyl α-D-mannopyranoside involved methylation-debenzylation of 3,6-di-O-benzyl and 2,6-di-O-benzyl derivatives obtained by reductive acetal cleavage ($NaBH_3CN$-HCl) of 3-O-benzyl-4,6-O-benzylidene and 3-O-benzoyl-2-O-benzyl-4,6-O-benzylidene derivatives, respectively.[13]

Other Alkyl and Aryl Ethers.- Two references to allylation and benzylation appear in the section on methyl ethers. The intramolecularly etherified flavan-4-ol glucoside (1) has been isolated from Glaphyropteridopsis erubescens.[14]



(1)



(2)

A compilation of carbohydrate benzylations and other alkylations employing alkyl triflates has appeared.[4] Application of David's procedure to the preparation and selective monoalkylation

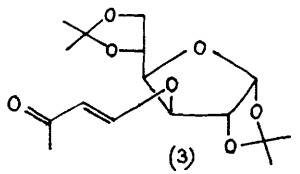
of methyl 4,6-O-benzylidene 2,3-O-(dibutylstannylene)-β-D-gluco-pyranoside led to the following monoethers product mixtures: 2- and 3-O-allyl (60 and 33%), 2- and 3-O-benzyl (29 and 61%), and 2- and 3-O-methyl (22 and 66%), respectively.[15]

The compatibility of benzyl, 4-methoxybenzyl, and 3,4-dimethoxybenzyl ether protecting groups has been demonstrated, benzyl ethers being selectively removed by hydrogenolysis with Raney nickel,[16] but 3,4-dimethoxybenzyl ethers being more readily removed by DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) oxidation.[17] Reductive cleavage of methyl 4,6-O-(4-methoxybenzylidene)-α-D-gluco- and galacto-pyranoside derivatives with sodium cyanoborohydride can lead regioselectively and in good yields to the 6-O-(4-methoxybenzyl) ethers using trifluoroacetic acid as catalyst, or to the 4-O-(4-methoxybenzyl) isomers using trimethylsilyl chloride. Such 4-methoxybenzyl ether groups can be selectively cleaved in the presence of benzyl ethers using cerium(IV) ammonium nitrate in aqueous acetonitrile.[18,19]

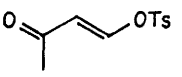
Further crown ethers incorporating carbohydrate diol units have been reported, including a range of compounds such as (2) which incorporate triose and pentose derivatives.[20] Spectroscopically indistinguishable [18]-crown-6 isomers with two methyl 4,6-O-benzylidene-α-D-galactopyranoside moieties aligned *syn*- or *anti*- with respect to each other have been synthesized; their *gluco*-analogues were reported previously by other workers (Vol.16, p.55).[21] The syntheses of chiral diaza-crown ethers and corresponding [2.2.1]cryptands incorporating the 2,3-diol moieties of α-D-gluco-, -galacto-, and -manno-pyranosides (Vol. 17,p.57) have now been published in full,[22,23] while an alternative preparation of the diaza-crown ether incorporating a methyl 4,6-O-benzylidene-α-D-glucopyranoside unit has been reported.[24]

Mixtures of mono- to tetra-O-(pentyloxymethyl) ethers of methyl α-D-glucopyranoside have been synthesized and separated conventionally.[25]

3-Oxobut-1-enyl ethers, *e.g.*, (3), required for hetero-Diels-Alder chemistry, have been obtained by reacting the tosylate (4)



(3)



(4)

with alkoxides obtained from mono-hydroxy sugar derivatives.[26]

Monophenylation of carbohydrate diols has been effected in yields ≤42% using triphenylbismuth diacetate; 1,2-cis-diols on pyranosyl rings gave mainly axial monoethers, while 1,2-trans-diols reacted slowly and with little selectivity.[27] Syntheses of compounds with methoxycarbonylmethyl and 1-(methoxycarbonyl)ethyl ether moieties appear in Chapters 9 and 18, respectively.

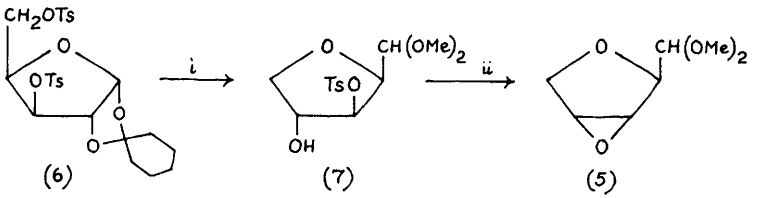
Silyl Ethers.- The tert-butylmethoxyphenylsilyl ether protecting group has been shown to have the following favourable properties: i) it can be introduced selectively at primary positions, ii) it is more sensitive to fluoride ion than tert-butyldimethylsilyl (TBDMS) or tert-butyldiphenylsilyl ethers, and iii) it can be formed with tertiary alcohols. It is, however, less stable to acid hydrolysis than the TBDMS ether.[28] In the presence of base, it has been shown that the TBDMS group is capable of migrating between two trans-diaxial carbohydrate hydroxy groups.[29]

Selective 2-O-allyloxycarbonylation of methyl 4,6-O-(tetraisopropyldisiloxane-1,3-diyl)-α-D-glucopyranoside and its benzyl β-glucoside analogue has provided access to the 2-O-allyl ether derivatives by decarboxylation [$Pd(OAc)_2$-Ph_3P], or to a variety of protected derivatives via migration of the disiloxane-1,3-diyl group from the 4,6- to the 3,4-position.[30]

3',5'-Cyclic dimethylsilanediyl and tetramethyldisiloxanediyl derivatives of deoxynucleosides are covered in Chapter 20.

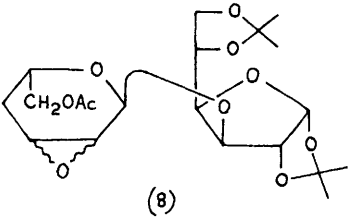
2 Intramolecular Ethers (Anhydro-sugars)

Oxirans.- The acid-catalyzed hydrolysis of 5,6-anhydro-1,2-O-isopropylidene-β-L-idofuranose has been re-examined, because the conditions reported previously for the preparation of L-idose were found not to give a pure product; conditions for optimum production of L-idose, 1,2-O-isopropylidene-β-L-idofuranose, or 1,6-anhydro-L-idopyranose were found.[31] The 2,5:3,4-dianhydride (5) has been synthesized from 1,2-O-cyclohexylidene-α-D-xylofuranose via the ditosylate (6) (Scheme 1). Sulphonyloxy groups at C-3 in acetals such as (7) are reported to be readily displaced with the formation of a 3,4-epoxide, even using weak bases, the tosylates reacting 2.5-3 times faster than their mesylate analogues.[32] A mixture of disaccharide epoxides (8) has been obtained by epoxidation (MCPBA) of the corresponding olefin.[33]

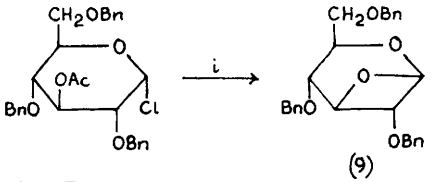


Reagents: i, MeOH-TsOH ; ii, Bu^tOK

Scheme 1



Other Anhydrides.- Improved six-step syntheses of 2,4,6-tri-O-benzyl-1,3-anhydro-β-D-glucopyranose (9), or its 4-bromobenzylated or 4-methylbenzylated analogues, from 3-O-allyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose have been reported, the crucial final step being shown in Scheme 2.[34]

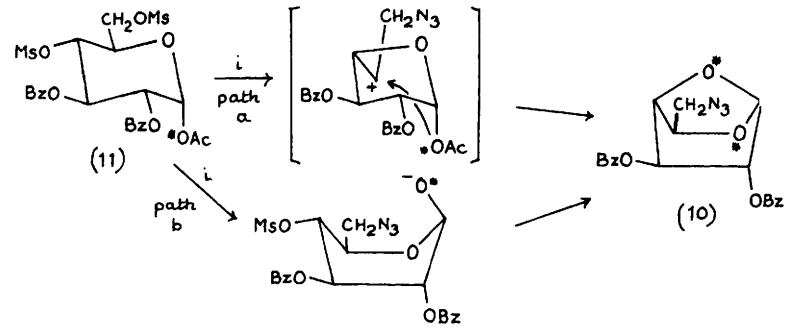


Reagents: i, LiOEt-THF

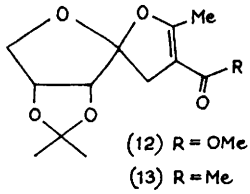
Scheme 2

The mechanism by which the 1,4-anhydro-D-galactose derivative (10) is formed on reaction of the 4,6-dimesylate (11) with azide has been investigated using ^{17}O-n.m.r. and ^{18}O induced isotopic shifts in the ^{13}C-n.m.r. spectra. The two pathways elucidated (Scheme 3) differ in giving products with O*-1 bonded to C-5 (path a, involving ring contraction) or to C-4 (path b).[35]

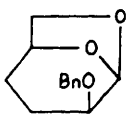
Knoevenagel reaction of 2,5-anhydro-3,4-O-isopropylidene-D-arabinose with methyl acetoacetate or acetylacetone led to mixtures of alkenes, from which the spiro-acetals (12) or (13) could be obtained on treatment with acid.[36]



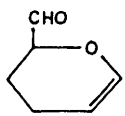
Scheme 3



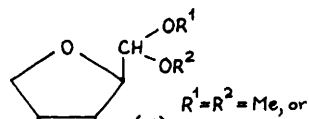
A simple, one-flask, two-step synthesis of 1,6-anhydro-β-D-mannopyranose from D-mannose has been described, although the scale reported was relatively small (1 g). A 6-O-tosyl group was selectively introduced into D-mannose in pyridine solution, and then intramolecularly displaced by addition of aqueous alkali to pH9.[37] Selective removal of the isopropylidene group in 1,6-anhydro-2,3-O-isopropylidene-β-D-mannopyranose derivatives having 4-O-allyl, -tert-butyl, -trichloroacetyl, or -tert-butyldiphenylsilyl groups has been effected by heating in methanol containing pyridinium tosylate.[38] The racemic 1,6-anhydride (14) has been synthesized in eight steps from the acrolein dimer (15), and its cationic ring-opening polymerization to form a (1→6)-glycan has been studied.[39]



DL-(14)



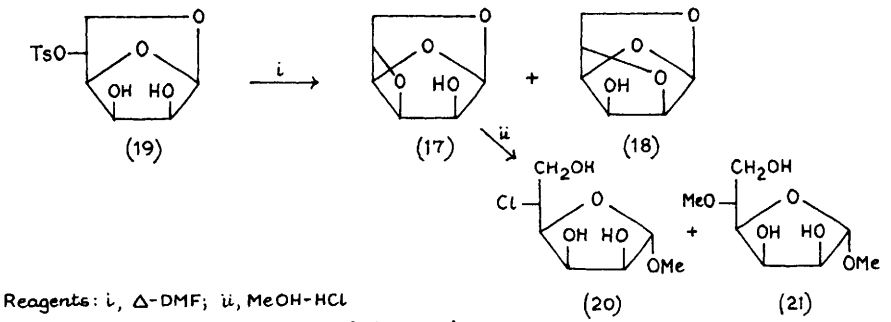
DL-(15)



The 2,5-anhydrohexose derivatives (16) have been obtained from

their C-3 epimers using sulphonate displacement reactions.[40] A 2',5'-anhydro-β-D-arabinofuranosyl nucleoside and other anhydronucleosides appear in Chapter 20.

A 40:1 mixture of the 1,6:3,5- and 1,6:2,5-dianhydrides (17) and (18), respectively, was obtained on heating 1,6-anhydro-5-O-tosyl-β-D-mannofuranose (19) in DMF; the major component yielded the ring-cleavage products (20) and (21) on methanolysis (Scheme 4).[41]



Reagents: i, Δ-DMF; ii, MeOH-HCl

Scheme 4

References

1 T.Kuraishi, K.Ninomiya, T.Murakami, N.Tanaka, Y.Saiki, and C.-M.Chen, Chem. Pharm. Bull., 1984, 32, 4883.
2 I.Ciucanu and F.Kerek, Carbohydr. Res., 1984, 131, 209.
3 T.Zhu, Y.Pei, and S.Wang, Zhongcaoyao, 1983, 14, 339 (Chem. Abstr., 1984, 100, 34 754).
4 R.W.Binkley and M.G.Ambrose, J. Carbohydr. Chem., 1984, 3, 1.
5 R.Eby, K.T.Webster, and C.Schuerch, Carbohydr. Res., 1984, 129, 111.
6 R.Toman, P.Capek, J.Rosik, and A.Kardosova, Chem. Zvesti, 1984, 38, 669.
7 J.Stanek, Jr., J.Jerabkova, and J.Jary, Collect. Czech. Chem. Commun., 1984, 49, 2922.
8 K.Kefurt, Z.Kefurtova, and J.Jary, Collect. Czech. Chem. Commun., 1984, 49, 2130.
9 V.I.Grishkovets and V.Ya.Chirva, Khim. Prir. Soedin., 1983, 432 (Chem. Abstr., 1984, 100, 22 920).
10 V.I.Grishkovets, A.E.Zemlyakov, and V.Ya.Chirva, Khim. Prir. Soedin., 1983, 555 (Chem. Abstr., 1984, 100, 139 534).
11 A.S.Shashkov, V.I.Grishkovets, A.E.Zemlyakov, and V.Ya.Chirva, Biorg. Khim., 1984, 10, 88 (Chem. Abstr., 1984, 100, 175 185).
12 A.Liav and M.B.Goren, Carbohydr. Res., 1984, 131, C8.
13 K.Noumi, S.Kitagawa, Y.Kondo, and S.Hirano, Carbohydr. Res., 1984, 134, 172.
14 N.Tanaka, T.Sada, T.Murakami, Y.Saiki, and C.-M.Chen, Chem. Pharm. Bull., 1984, 32, 490.
15 K.Takeo and K.Shibata, Carbohydr. Res., 1984, 133, 147.
16 Y.Oikawa, T.Tanaka, K.Horita, and O.Yonemitsu, Tetrahedron Lett., 1984, 25, 5397.
17 Y.Oikawa, T.Tanaka, K.Horita, T.Yoshioka, and O.Yonemitsu, Tetrahedron Lett., 1984, 25, 5393.

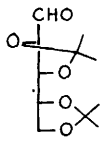
18 R.Johansson and B.Samuelsson, J. Chem. Soc., Chem. Commun., 1984, 201.
19 R.Johansson and B.Samuelsson, J. Chem. Soc., Perkin Trans. 1, 1984, 2371.
20 R.Aldag and G.Schröder, Justus Liebigs Ann. Chem., 1984, 1036.
21 W.Hain, R.Lehnert, B.Walz and G.Schröder, Justus Liebigs Ann. Chem., 1984, 1046.
22 M.Pietraszkiewicz and J.Jurczak, Tetrahedron, 1984, 40, 2967.
23 M.Pietraszkiewicz, P.Salanski, and J.Jurczak, Tetrahedron, 1984, 40, 2971.
24 P.Bako, L.Fenichel, and L.Toke, Acta Chim. Acad. Sci. Hung., 1984, 116, 323.
25 J.Staniewski and J.Szymanowski, Staerke, 1984, 36, 176 (Chem. Abstr., 1984, 101, 171 606).
26 A.Lubineau and A.Malleron, Tetrahedron Lett., 1984, 25, 1053.
27 S.David and A.Thieffry, J. Org. Chem., 1983, 48, 441.
28 Y.Guindon, R.Fortin, C.Yoakim, and J.W.Gillard, Tetrahedron Lett., 1984, 25, 4717.
29 C.A.A.Van Boekel, S.F.Van Aelst, and T.Beetz, Recl., J.R. Neth. Chem. Soc., 1983, 102, 415 (Chem. Abstr., 1984, 100, 22 909).
30 J.J.Oltvoort, M.Kloosterman, and J.H.Van Boom, Recl., J.R. Neth. Chem. Soc., 1983, 102, 501 (Chem. Abstr., 1984, 100, 121 474).
31 N.Baggett and A.K.Samra, Carbohydr. Res., 1984, 127, 149.
32 D.A.Miljkovic, V.J.Popsavin, and J.T.Hranisavljevic, Glas. Hem. Drus. Beograd, 1983, 48, 211 (Chem. Abstr., 1984, 100, 175 138).
33 J.W.Krajewski, P.Gluzinski, Z. Urbanczyk-Lipkowska, A.Banaszek, and M.Dobler, Carbohydr. Res., 1984, 134, 11.
34 F.Good and C.Schuerch, Carbohydr. Res., 1984, 125, 165.
35 A.Dessinges, S.Castillon, A.Olesker, T.T.Thang, and G.Lukacs, J. Am. Chem. Soc., 1984, 106, 450.
36 F.J.Lopez Herrera, M.Valpuesta Fernandez, and R.Garcia Segura, Carbohydr. Res., 1984, 127, 217.
37 M.Georges and B.Fraser-Reid, Carbohydr. Res., 1984, 127, 162.
38 R.van Rijsbergen, M.J.O.Anteunis, and A.De Bruyn, J. Carbohydr. Chem., 1983, 2, 395.
39 H.Sumitomo and K.Ogasawara, Polym. J. (Tokyo), 1983, 15, 821 (Chem. Abstr., 1984, 100, 192 183).
40 D.A.Miljkovic, V.J.Popsavin, and B.S.Slavica, Glas. Hem. Drus. Beograd, 1983, 48, 219 (Chem. Abstr., 1984, 100, 86 012).
41 P.Köll, U.Lendering, J.O.Metzger, W.Schwarting, and H.Komander, Justus Liebigs Ann. Chem., 1984, 1597.

6
Acetals

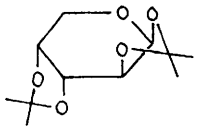
1 Isopropylidene Acetals

Pyridinium p-toluenesulphonate in methanol at reflux has been shown to be effective in selective removal of the isopropylidene groups of 1,6-anhydro-2,3-O-isopropylidene-β-D-mannopyranose derivatives bearing 4-O-allyl, -tert-butyl, -trichloroacetyl, and -tert-butyldiphenylsilyl groups.[1]

Acetonation of the diethyl dithioacetals of D- and L-arabinose gave the 2,3:4,5-di-O-isopropylidene acetals as oils; the reaction was shown to proceed *via* the first-formed 4,5-acetal. Demercaptalation with mercury(II) chloride - cadmium carbonate gave 2,3:4,5-di-O-isopropylidene-aldehydo-D-arabinose (1), whereas the literature procedure employing mercury(II) chloride - mercury(II) oxide gave a mixture of (1) and 1,2:3,4-di-O-isopropylidene-β-D-arabinose (2). A trace of acid rapidly and completely converted (1) to (2).[2]



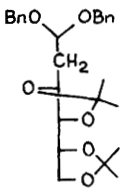
(1)

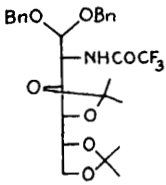


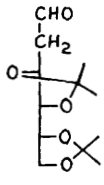
(2)

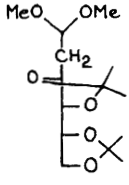
Treatment of methyl α- and β-D-glucopyranoside with two moles of 2-methoxypropene in DMF gave the expected 4,6-O-isopropylidene derivatives; on reaction with a further 2.5 moles of the reagent, a 73% yield of the 2,3:4,6-di-O-isopropylidene-glucoside was obtained. The yields of the diacetal were lower when the glycoside was treated directly with excess 2-methoxypropene.[3] A mixture of the dibenzyl acetals of 2,3:5,6- and 3,4:5,6-di-O-isopropylidene-D-glucose was obtained on reaction of D-glucose with 2,2-dibenzyloxypropane in the presence of tosic acid in dioxan at 65°C. The products were difficult to separate chromatographically, so an indirect procedure of acetylation, partial hydrolysis to 5,6-diols which could be separated, followed by re-acetalation, was adopted.[4] Similar findings were reported for the reaction of D-glucose with dimethoxypropane in the presence of tosic acid.[5] Reference to further conversions of these acetals will be found in Chapter 9. In similar acetalations by

the same research group, 2-deoxy-D-glucose and N-substituted derivatives of glucosamine gave the expected dibenzyl acetals of the 3,4:5,6-di-O-isopropylidene compounds (3) and, e.g., (4). Hydrogenolysis of (3) using palladium catalyst gave the aldehydo-2-deoxy-3,4:5,6-di-O-isopropylidene-D-glucose (5). Dimethoxypropane also gave similar products with 2-deoxy-D-arabino-hexose, and it was shown that the 5,6-acetal could be selectively hydrolysed to yield the diacetal (6) by means of 80% acetic acid.[6]

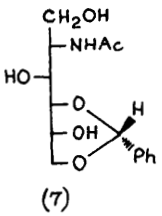

(3)

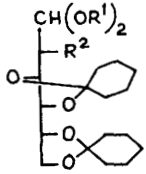

(4)


(5)


(6)

A re-investigation of the structure of the tri-O-isopropylidene-D-glucitol by means of the Bruker AG reiterative n.m.r. programme, PANIC, at 250 MHz, has shown that it is the 1,3:2,4:5,6-triacetal and not the 1,2:3,5:4,6-triacetal as previously claimed.[7] The three products from acetalation of D-mannitol with 2-methoxypropene in DMF with tosic acid catalyst have been shown to be 1,2:5,6-, 1,2:4,6-, and 1,2:3,6-di-O-isopropylidene-D-mannitol.[8] The preparation of 1,2:5,6-di-O-isopropylidene-D-mannitol by three alternative procedures for acetonation of D-mannitol has been investigated, using acetylation and capillary g.l.c. to monitor the products. The highest yield was obtained by propanone-zinc chloride, whereas 2,2-dimethoxypropane - tin(II) chloride and 2-methoxypropene - tosic acid gave more complex mixtures contrary to claims in the literature. A new triacetal, 1,2:3,6:4,5-tri-O-isopropylidene-D-mannitol, was isolated and its graded hydrolysis compared with that of 1,2:3,4:5,6-triacetal.[9] Acetal-


(7)


(8) R^1 = Me
(9) R^1 = Bn
R^2 = H, NHAc, $NHCOCF_3$

ation of 2-acetamido-4,6-(R)-O-benzylidene-2-deoxy-D-glucitol (7), prepared by borohydride reduction of the corresponding free sugar, was

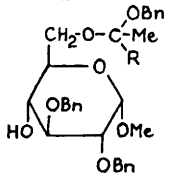
found to be best accomplished by means of 2,2-dimethoxypropane - sulphuric acid. Full assignments of the ^{1}H- and ^{13}C-n.m.r. spectra of the triacetate of (7) were made.[10]

2 Other Acetals

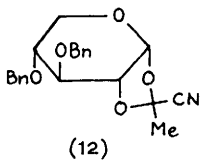
The major products from the tosic acid-catalysed reactions of 2-deoxy-D-arabino-hexose, 2-acetamido-2-deoxy-D-glucose, and 2-deoxy-2-trifluoroacetamido-D-glucose with 1,1-dimethoxycyclohexane were the acyclic 3,4:5,6-di-O-cyclohexylidene acetals of the 1,1-dimethyl acetals (8). With 1,1-dibenzyloxycyclohexane, the analogous 1,1-dibenzyl acetals (9) were obtained, which could be converted into the acyclic aldehydo derivative on hydrogenolysis (c.f. ref. 6 above).[11] Reaction of cyclohexanone diethylacetal and D-mannitol in DMSO or DMF with camphorsulphonic acid as catalyst yielded 1,2:5,6- and 1,2:4,6-di-O-cyclohexylidene-D-mannitol in 80 and 20% yield, respectively; the former product could be obtained pure by direct crystallization and the latter from column chromatography. Periodate cleavage of the symmetrical diacetal gave 2,3-O-cyclohexylidene-D-glyceraldehyde, a stable and more tractable derivative than the corresponding isopropylidene acetal.[12]

2-Furylidene acetals have been prepared from methyl α- and β-D-glucopyranoside, methyl α-D-galactopyranoside, and methyl α-D-mannopyranoside by reaction with 2-furaldehyde and tosic acid with azeotropic removal of water; the expected 4,6-mono or 2,3:4,6-di-acetals were formed.[13]

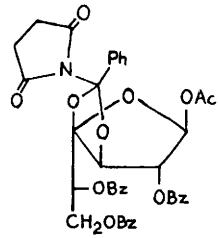
2',3'-O-Ethylidene and -(dimethylamino)methylidene acetals of nucleosides have been prepared using either triethylorthoformate or $(MeO)_2CHNMe_2$ (see also Chapter 20).[14]



(10) R=Me
(11) R= CH_2F



(12)



(13)

Mixed acetals of the type shown in (10)[15] and (11)[16] have been prepared in high yield by reaction of 2-benzyloxypropene or 2-benzyloxy-3-fluoropropene with the corresponding 2,3-di-O-benzyl glycoside.

Regeneration of the alcohol from (10) was accomplished by catalytic hydrogenation under neutral conditions,[15] while the fluorinated analogue (11) was stable to acid under conditions where the non-fluorinated mixed acetal (10) and a TBDMS group are cleaved.[16]

The 1,2-O-(1-cyano)ethylidene xylopyranose (12) has been prepared using standard methods from the 1,2-O-benzylidene compound.[17] Reaction of N-bromosuccinimide with 1-O-acetyl-2,3,5,6-tetra-O-benzoyl-β-D-glucofuranose in the presence of light gave in 74% yield the phenylsuccinimidyl acetal (13), which was characterized by X-ray crystallography. The reaction was also carried out on a related β-D-ribofuranose ester and adenosine pentabenzoate.[18]

Lithium aluminium hydride complexed to 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose has been used to reduce Schiffs' bases to optically active amines with enantiomeric excesses of 10 - 25%.[19] A similar complex between lithium aluminium hydride and 1,2-O-cyclohexylidene-3-O-cyclohexylmethyl-α-D-glucofuranose has been used to reduce ketones and ketoximes to alcohols and amines with (S)configuration of up to 52% optical purity.[20]

Reduction of 4,6-O-(4-methoxybenzylidene)hexopyranosides to 4-methoxybenzyl ether groups[21,22] is referred to in Chapter 4, and oxidation of benzylidene acetals to hydroxybenzoates in Chapter 5.

References

1 R.van Rijsbergen, M.J.O.Anteunis, and A.De Bruyn, J. Carbohydr. Chem., 1983, 2, 395.
2 D.Horton and O.Varela, Carbohydr. Res., 1984, 134, 205.
3 J.-L.Debost, J.Gelas, D.Horton, and O.Mols, Carbohydr. Res., 1984, 125, 329.
4 M.Kiso, H.Ishida, A.Kawaide, and A.Hasegawa, Carbohydr. Res., 1984, 127, 129.
5 M.Kiso, A.Yasui, and A.Hasegawa, Carbohydr. Res., 1984, 127, 137.
6 M.Kiso, A.Kondo, Y.Kondo, and A.Hasegawa, Carbohydr. Res., 1984, 127, 121.
7 P.Sohar and J.Kuszmann, Org. Magn. Reson., 1983, 21, 694 (Chem. Abstr., 1984, 100, 103 778).
8 J.Kuszmann, E.Tomori, and P.Dvortsak, Carbohydr. Res., 1984, 132, 178.
9 J.Kuszmann, E.Tomori, and I.Meerwald, Carbohydr. Res., 1984, 128, 87.
10 C.Morin, Carbohydr. Res., 1984, 128, 345.
11 M.Kiso, A.Yasui, and A.Hasegawa, J. Carbohydr. Chem., 1983, 2, 449.
12 T.Sugiyama, H.Sugawara, M.Watanabe, and K.Yamashita, Agric. Biol. Chem., 1984, 48, 1841.
13 J.Maslinska-Solich and I.Rudnicka, Carbohydr. Res., 1984, 132, 150.
14 E.Albano-Garcia and L.U.Colmenares, Nat. Appl. Sci. Bull., 1982, 34, 211 (Chem. Abstr., 1984, 100, 139 541).
15 T.Mukaiyama, M.Ohshima, and M.Murakami, Chem. Lett., 1984, 265.
16 T.Mukaiyama, M.Ohshima, H.Nagaoka, and M.Murakami, Chem. Lett., 1984, 615.

17 N.E.Nifant'ev and L.V.Bakinovskii, Izv. Akad. Nauk SSSR, Ser. Khim., 1983, 2400 (Chem. Abstr., 1984, 100, 51 908).
18 R.J.Ferrier, S.R.Haines, G.J.Gainsford, and E.J.Gabe, J. Chem. Soc., Perkin Trans. 1, 1984, 1683.
19 S.R.Landor, O.O.Sonola, and A.R.Tatchell, Bull. Chem. Soc. Jpn., 1984, 57, 1658.
20 S.R.Landor, Y.M.Chan, O.O.Sonola, and A.R.Tatchell, J. Chem. Soc., Perkin Trans. 1, 1984, 493.
21 R.Johansson and B.Samuelsson, J. Chem. Soc., Chem. Commun., 1984, 201.
22 R.Johansson and B.Samuelsson, J. Chem. Soc., Perkin Trans. 1, 1984, 2371.

7
Esters

Reviews in Japanese on the reactivity of hydroxy groups in monosaccharides towards direct acylation, and the methods for hydroxy group modification without recourse to blocking-deblocking strategies by using tin intermediates, have appeared. O-Acyl migration in D-glucose and L-arabinose is also discussed.[1,2] Neighbouring group participation in nucleophilic displacements of carbohydrates has been the subject of a review in Polish.[3]

1 Carboxylic Esters

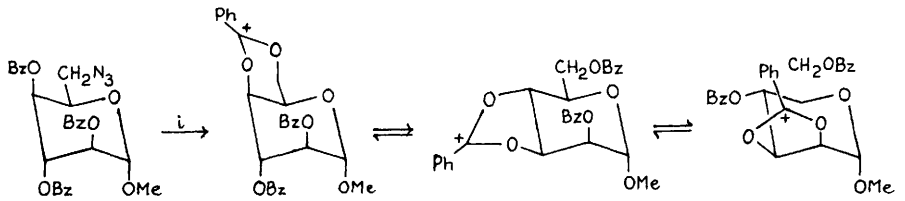
Improved preparations of 1,2,3,4-tetra-O-acetyl-β-D-gluco- and -manno-pyranose have been described.[4]

Substituted D-gluco, -manno, and -galacto derivatives having two free hydroxy groups have been converted to metal chelates by reaction with sodium hydride and the appropriate metal chloride in either oxolane or 1,2-dimethoxyethane. Reaction of these with acetic anhydride or benzoyl chloride gave mixtures of di-, mono-, and un-substituted products, in which one monosubstituted derivative predominated. Appropriate choice of metal ion (copper or mercury) and organic reagent led to selective substitutions, illustrated by many examples.[5] Reference to the same reaction used for alkylation will be found in Chapter 5. Partial hydrolysis of peracetyl and perbenzoyl 1,6-anhydro-β-D-glucopyranose using methanolic hydrogen chloride or hydrazine hydrate has allowed the synthesis of all possible partially esterified derivatives, owing to the selectivity exhibited. Thus the ester group at C-3 is more stable than those at C-2 and C-4 towards the acid reagent, but is most labile in hydrazine hydrate.[6] Reaction of 1,2-cis-1-thioglucofuranoside esters with mercury(II) acetate in acetic acid produced the 1-O-acetate trans to the ester group at C-2, in good yield; e.g., ethyl 2,3,5,6-tetra-O-benzoyl-1-thio-α-D-glucofuranoside gave 1-O-acetyl-2,3,5,6-tetra-O-benzoyl-β-D-glucofuranose.[7]

The selective benzoylation of 1,5-anhydro-L-arabinitol using benzoyl chloride in pyridine at -40°C has been studied; O-2 is

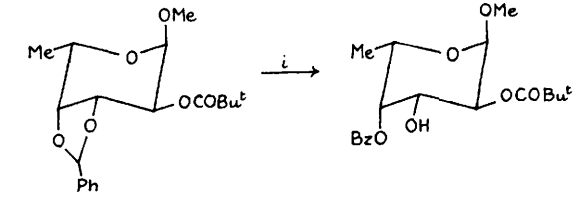
somewhat less reactive than O-3 or O-4.[8] The methods described by David using dibutylstannylene derivatives of diols have been applied to methyl 4,6-O-benzylidene-β-D-glucopyranoside. Treatment of this derivative with benzoyl chloride in benzene gave 49% 2-benzoate and 39% 3-benzoate, in contrast to the result when tosyl chloride was used in which the major product (63%) was the 3-tosylate, with only 21% 2-tosylate produced.[9] Alkylations of this type are mentioned in Chapter 5. Six monosaccharides, two diols and four triols, containing only secondary hydroxy groups, have been mono- and di-benzoylated with high regioselectivity using bis(tributyltin) oxide and dibutyltin oxide. The applicability of the method is enhanced by the the fact that the product ratios may be drastically altered by changes in coordinating ability of the solvent or the presence of Lewis bases. The factors governing the selectivity were discussed.[10] The selective benzoylation of secondary hydroxy groups in 6,1',6'-tri-O-tritylsucrose by the same reagent system has enabled the preparation of mono- and dibenzoyl derivatives, which were characterized by 500 MHz ^{1}H n.m.r. spectroscopy.[11]

Treatment of peracyl 6-azido-6-deoxy-hexopyranosides with nitrosyl hexafluorophosphate in acetonitrile leads to dioxolanium ions which may rearrange when there is a vicinal, axially oriented ester group, as shown in Scheme 1. Where this condition is not met, no rearrangement occurs, thus explaining the results reported in Vol. 15, p.69-70.[12]



Reagents: i, $NO^+PF_6^-$, 0°

Scheme 1

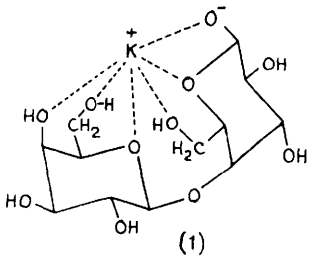


Reagents: i, NBS-H_2O-$BaCO_3$-hν

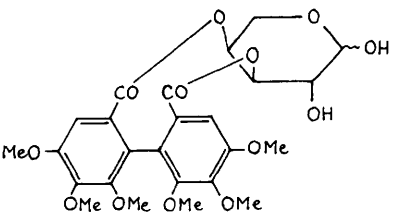
Scheme 2

Cyclic benzylidene acetals derived from cis-related vicinal diols on pyranosyl rings, on irradiation in the presence of N-bromosuccinimide and water, react to give the corresponding axially oriented monobenzoate, illustrated in Scheme 2.[13]

The ^{1}H n.m.r. spectra of some benzoylated derivatives of β-lactose, β-maltose, and β-cellobiose have been reported.[14] The selectivities of hydroxy groups in sucrose towards pivaloylation have been shown to vary with conditions. On acetylation, most of the possible partially esterified derivatives between sucrose and the octa-ester could be isolated in yields between 30 and 52% by suitable selection of conditions.[15] Lactose has been found not to react with fatty acid esters in the presence of potassium carbonate in DMF, in contrast to the findings with sucrose. The fact that there is a shift in the α,β-ratio from 35:65 to 15:85 on increasing concentration of potassium carbonate was cited as evidence for the formation of a stable chelated ion pair (1). Methyl β-lactoside, on treatment with ethyl myristate under these conditions, gave 10% 3',6'-diester, 15% 6,6'-diester, 35% 3'-monoester, and 40% 6'-monoester.[16]



(1)

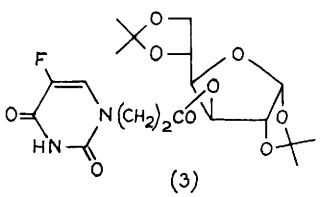


(2)

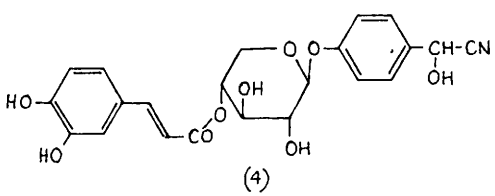
2,3-Di-O-galloyl-D-glucose has been isolated from the flowers of Tamarix nilotica.[17] The roots of Sanguisorba officinalis produce galloyl esters of the rarely encountered natural methyl β-D-glucopyranoside.[18] Galloyl esters of the branched-chain sugar hamamelose have been found to be present in the bark of Castanea crenata.[19] Quercus stenophylla bark, on extraction, yielded eight new di- to penta-O-galloyl protoquercitol derivatives[20] and two new ellagitannins.[21] Additive parameters of chemical shifts in ^{13}C n.m.r. of galloyl or hexahydroxydiphenoyl-sugars may be used to locate the position of these groups on the D-glucopyranosyl rings from hydrolysable tannins. The FAB-m.s. of the tannins allows determination of their molecular weights without prior formation of derivatives.[22,23] 3,4-O-(3,3',4,4',5,5'-Hexamethoxybiphenoyl)-L-

arabinopyranose (2) has been synthesized by condensing 1-O-(3,4,5-tri-O-methylgalloyl)-L-arabinose with hexamethoxybiphenoyl chloride and subsequently removing the galloyl protecting groups, and was shown to be identical to the isolated natural product.[24] Penta-O-galloyl-β-D-glucopyranose and related ellagitannins display remarkably strong inhibition of the mutagenicity of potent dibenzopyrene diol epoxide and 3-hydroxyamino-1-methyl-5H-pyrido[4,3-b]indole mutagens.[25]

Four new acylated sugars, 2-O-cinnamoyl-β-D-glucose, 2-O-cinnamoyl-1,6-di-O-galloyl-β-D-glucose, 2-O-p-coumaroyl-1-O-galloyl-β-D-glucose and a mixture of 1-O-galloyl-β-D-fructopyranose and 1-O-galloyl-α-,and β-D-fructofuranose, were found in Japanese rhubarb.[26] 4-O-Coumaroyl-D-glucose and its 2-acetate have been isolated from Plagiogyria euphlebia and Microlepia spetuncae, respectively.[27] Methyl 2,3-di-O-glycyl- and 4,6-di-O-glycyl-2,3-di-O-methyl-α-D-glucopyranosides have been synthesized by DCC-induced coupling of N-benzyloxycarbonyl or N-t-butyloxycarbonyl protected glycine with the corresponding glucose derivative, followed by N-deprotection. These model compounds containing the O-(aminoacyl) protecting groups could be deprotected by alkaline hydrolysis with aqueous sodium hydroxide – N-methylmorpholine or Pronase E. Thus O-glycyl groups offer the advantages of simple hydrolytic or enzymic removal and the presence of an ionizable amine function suitable for isolation by, e.g., ion exchange chromatography.[28] The synthesis of the 5-fluorouracil-1-ylpropanoyl ester (3) has been achieved by Michael addition of the corresponding 2-acryloyl derivative and the fluorouracil.[29]



(3)

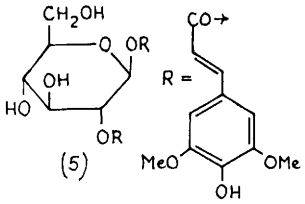


(4)

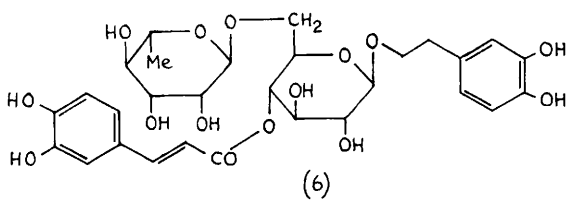
The first cyanogenic glycoside with an acyl substituent on the sugar, nandinin (4), has been isolated from the leaves of Nandina domestica.[30] The related 1,2-di-O-sinapoyl-β-D-glucopyranose (5) has been isolated from the cotyledons of red radish,[31] and forsythoside A (6) containing the 4-O-caffeoyl-nitinose moiety has been described.[32]

A new sesquiterpene glucoside from Mortonia gregii contains a

2,6-di-O-acetyl-β-D-glucopyranosyl unit.[33] Derivatives of stevioside (the sweet principle of Stevia rebaudiana), in which the β-D-glucopyranose unit is replaced by β-D-xylose, α-L-arabinose, α-D-

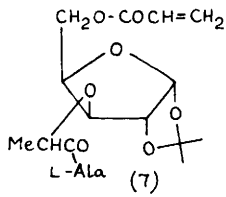


(5)



(6)

mannose, β-L-glucose, α-L-rhamnose, or β-L-quinovose, have been prepared conventionally and tested for sweetness. In all cases, the compounds were 110-285 times as sweet as sucrose.[34] An immunoassay for paeniflorin has been developed using synthetic 6'-hemisuccinyl- and 6'-hemiglutaryl-paeniflorin derivatives (ester attached at O-6 in the β-D-glucopyranosyl unit) as haptens, coupled to the β-D-galactosidase and bovine serum.[35] Branched-chain cyclic esters from Plagiogyria sp. are referred to in Chapter 14. The 6-O-acryloyl, -3-O-lactyl-L-alanine derivative (7) has been synthesized, homopolymerized, or co-polymerized with styrene to provide, after removal of protecting groups, a polymer with pendant MDP analogues.[36]



(7)

A monoterpene glycoside isolated from the fruits of Gymnocladus chinensis has been shown to contain the acylated disaccharide 3-O-β-D-glucopyranosyl-4-O-(2-methylbutanoyl)-α-L-arabinosyl moiety.[37] Sucrose fatty acid polyesters, e.g., sucrose octapalmitate, have been synthesized in high yield by alkali metal catalysed transesterification of sucrose octaacetate with the appropriate methyl esters of the fatty acid in the absence of solvents.[38] Dithiocarbonation of sucrose in sodium hydroxide-pyridine, which allows product acetylation without isolation, has been achieved using carbon disulphide. Chromatography yielded an anticipated range of partially xanthated, otherwise acetylated sucrose derivatives in pure form.[39] 6,6'-Di-O-

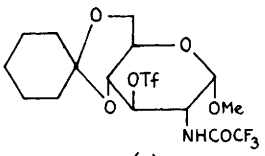
palmitoyl-sucrose and -trehalose, cord factor analogues, have been synthesized in good yield by direct dimolar acylation of the disaccharide under Mitsunobu conditions (Ph_3P,($Pr^iO_2CN=)_2$,$C_{15}H_{31}CO_2H$, DMF). Monomolar palmitoylation of sucrose gave 6-O-palmitoyl-sucrose; this is in contrast to t-butyldiphenylsilylation, in which the etherification occurs on the 6-hydroxy group of the fructose unit (see Vol. 16, p.55, ref.35).[40] The synthesis of 6-O-mycolyl- and 6-O-corynomycolyl-α,α-trehalose, related to the trehalose mycolates widely distributed in mycobacteria, has been achieved *via* the key step of mesylate displacement with potassium mycolate or corynomycolate (see also refs.48 and 49).[44]

N-2'-Acetoxybenzoyl (aspirin) derivatives of chitosan, N-desulphated heparin, and D-glucosamine have been synthesized and tested as pro-drugs for aspirin.[42]

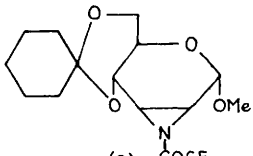
2 Sulphonate esters

A review of the synthesis and reactions of carbohydrate-triflates included a comprehensive compilation of all reported triflates.[43]

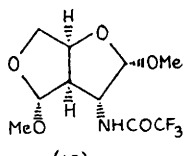
The partial tosylation of 1,6-anhydro-D-mannofuranose with one molar tosyl chloride in pyridine gives 79% 5-tosylate, 3.5% 2,5-ditosylate, 1.2% 3,5-ditosylate, and 0.4% 3-tosylate.[44] The complex mixtures obtained on selective mono- and di-molar tosylation of 1,5-anhydro-L-arabinitol have been investigated and the influences of intramolecular hydrogen bonding and gauche-related tosyloxy groups on the ratios of products discussed.[45] Reactions of methyl 4,6-O-cyclohexylidene-2-deoxy-2-trifluoroacetamido-3-O-triflyl-α-D-glucopyranoside (8) with various reagents have been examined. Lithium chloride and sodium iodide were found to give S_N2 displacements, sodium benzoate in DMF gave various products derived from the 2,3-allo-epimine (9), while solvolysis of (8) with hot methanol gave a ring-contraction product (10).[46]



(8)



(9)



(10)

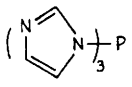
The substitution pattern in the reaction of sucrose with 2,4,6-

tri-isopropylbenzenesulphonyl chloride in pyridine showed that the ratio of 6':6:1' monoesters was 3.5:1.0:0.16. The 6'-monoester could be prepared crystalline in 39% yield by direct procedures.[47] Selective triflation of 4,6,4',6'-di-O-benzylidene-α,α-trehalose gave the 2,2'-triflate, which was used to prepare 2,3:2',3'-tetra-O-benzyl-4,6:4',6'-di-O-benzylidene-α-D-mannopyranosyl α-D-mannopyranoside by treatment with sodium nitrite in HMPT followed by benzylation. Debenzylidenation and tosylation led to a separable mixture of the 6,6'-di- and the 6-monotosyl esters, which were converted into the corresponding mycolates and corynomycolates (see also ref. 44 above).[48] Extension of this idea to the α-D-galactosyl α-D-galactoside was achieved by inversion of 2,3,2',3'-tetra-O-benzyl-4,6,4'6'-tetra-O-mesyl-α,α-trehalose with sodium benzoate, debenzoylation, and selective tosylation, or mesylation to give 6,6'-diesters. These were converted to the dimycolate and dicorynomycolate.[49]

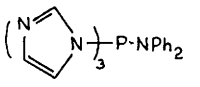
3 Phosphate and Related Esters

A review of phosphates and phosphonates of biological interest, with particular reference to carbohydrates, has appeared.[50] Phosphorylation in the synthesis of mono- and oligonucleotides has been the subject of a review.[51]

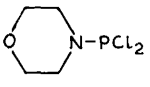
Four new phosphorylating agents have been described which show regioselectivity in ribose: tri-imidazolylphosphine (11), (diphenyl)-amino tri-imidazolyl phosphonate (12), which react at the primary hydroxy group, and N-dichlorophosphinyl-morpholine (13) and di-isopropylaminophosphorus dichloride (14), which react at the cis-glycol group.[52]



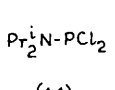
(11)



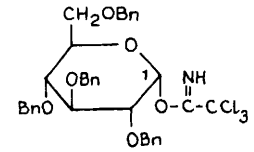
(12)

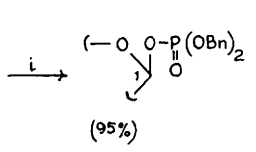


(13)



(14)

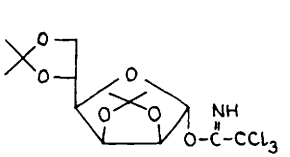




(95%)

Reagent: i, $(BnO)_2P(O)OH$

Scheme 3

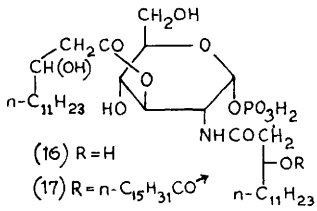


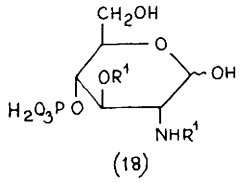
(15)

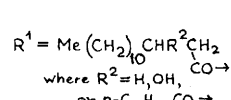
Glycosyl trichloroacetimidates have been used to prepare glycosyl phosphates by treatment with mono- or di-esters of phosphoric acid; the reaction normally proceeded with predominant inversion (Scheme 3) but in the case of the trichloroimidate (15) with monocetyl phosphate retention was observed.[53]

Intermediates in the recently discovered L-type pentose phosphate pathway, characterized by ^{13}C n.m.r. (see also Chapter 21 for anomeric and ring-size composition), have been shown to be D-*altro*-heptulose 1,7-diphosphate, D-*glycero*-D-*altro*-octulose 1,8-diphosphate, and D-*glycero*-D-*ido*-octulose 1,8-diphosphate.[54]

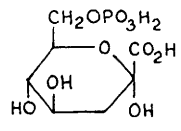
A review of the isolation and separation of phosphatides and glycolipids, by solvent fractionation, preparative column chromatography, and h.p.l.c., has appeared.[55] Lipid X (16) and Lipid Y (17), related to lipid A and found in *E. coli* mutants, have been synthesized.[56] Biologically active monosaccharide Lipid A analogues (18) have been synthesized from the appropriate *N*-substituted butyl glucosaminide.[57] Reference is made to tri- and tetrasaccharide pyrophosphate esters, intermediates in *N*-glycoprotein biosynthesis,

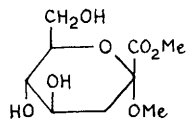


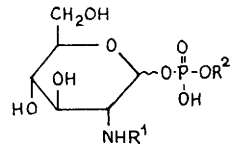




in Chapter 4. 3-Deoxy-D-*arabino*-2-heptulosonic acid 7-phosphate (19), an intermediate in the shikimic acid pathway, has been synthesized by phosphorylation of the methyl glycoside of the heptulosonic ester (20), followed by deprotection.[58] The syntheses of the



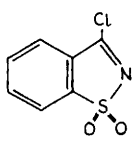




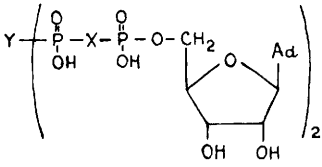
N-substituted glucosamine 1-phosphate (21) and the corresponding diphosphate aminoethyl ester (22) have been described.[59] Attempts to phosphorylate *myo*-inositol with various polyphosphates or urea phos-

phate under aqueous conditions according to published procedures were unsuccessful. The easiest method for complete phosphorylation was to heat myo-inositol with phosphoric acid under reduced pressure at 150°C for 6 hours.[60] Moraprenyl pyrophosphates of β-D-galactose, β-D-glucose, and 4-deoxy-α-D-xylo-hexose have been synthesized by glycosidation of moraprenyl phosphoimidazolide with the corresponding glycosyl phosphates.[61]

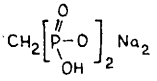
3-Chloro-1,2-benzisothiazole 1,1-dioxide (23) is an excellent coupling reagent for the preparation of phosphodiester derivatives, nucleosides, and phosphoric monoesters.[62] A range of diadenosine



(23)



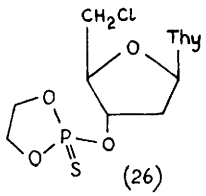
(24) X=Y=O; X=O, Y=CH_2; X=CH_2, Y=O



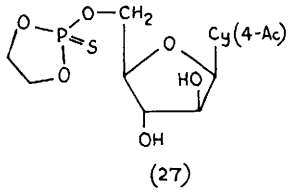
(25)

tetraphosphate and phosphonates of type (24) have been prepared by treatment of the disodium phosphonate (25) with N,N'-carbonyldiimidazole, followed by appropriate combinations of protected adenosines.[63]

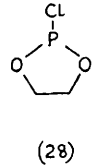
Cycloethylenephosphothioates such as (26) and (27) have been synthesized by treatment of the hydroxy compound with the chlorophosphite (28) followed by sulphuration with elemental sulphur.[64] Reference to other nucleotides will be found in Chapter 20.



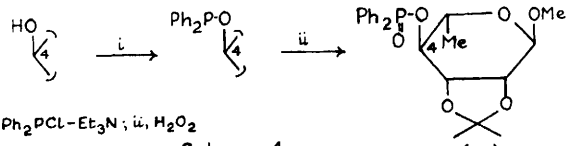
(26)



(27)



(28)



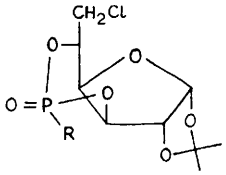
Reagents: Ph_2PCl-Et_3N; ii, H_2O_2

Scheme 4

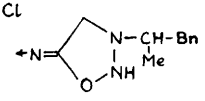
(29)

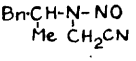
The phosphinate (29), synthesized as shown in Scheme 4, has been

used in homogeneous asymmetric hydrogenation reactions; optical yield using $Rh_2Cl_2(C_8H_{12})_2$-triethylamine at atmospheric pressure, varied between 80% and 48%.[65] Treatment of the chlorophosphinate (30) with the N-cyanomethyl N-nitroso compound (31) in triethylamine gave the cyclic amidophosphinate (32).[66] Reaction of phosphorus trichloride with D-mannitol in dry dioxan gave 43% cyclic diphosphite



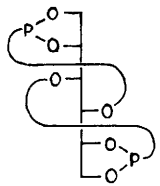
(30) R=Cl

(32) R= 

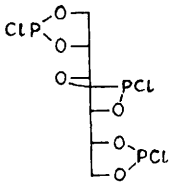


(31)

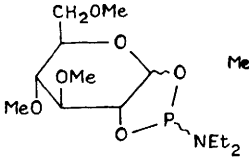
(33) and the tri(chlorophosphite) (34).[67] 1,2-Cycloamidophosphites e.g., (35), have been obtained as stereoisomeric mixtures from the corresponding 1,2-diols in D-ribose and D-glucose derivatives by reaction with tris(diethylamino)phosphine;(35) was converted to the corresponding thiophosphate on reaction with sulphur. Also obtained were glycosyl phosphorodiamidites such as (36).[68] Cyclic phosphites (37) and (38) have been synthesized by treating the corresponding triols with tris(dimethylamino)phosphine, while (39) was obtained from (38) by desilylation, rearrangement and acetylation. Chlorination of (37) gave the 5-chloro-derivative (40), which was aminated by piperidine to yield (41).[69]



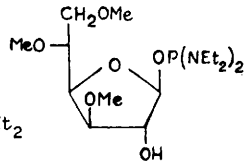
(33)



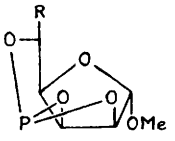
(34)



(35)

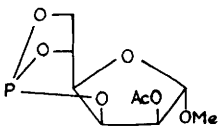


(36)

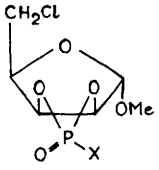


(37) R=H

(38) R=CH_2OSiPh_3



(39)

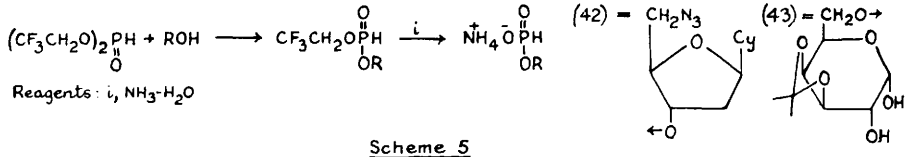


(40) X = Cl

(41) X= 

Included in a general method for the preparation of mono- and mixed diesters of phosphorous acid are some examples of carbohydrate

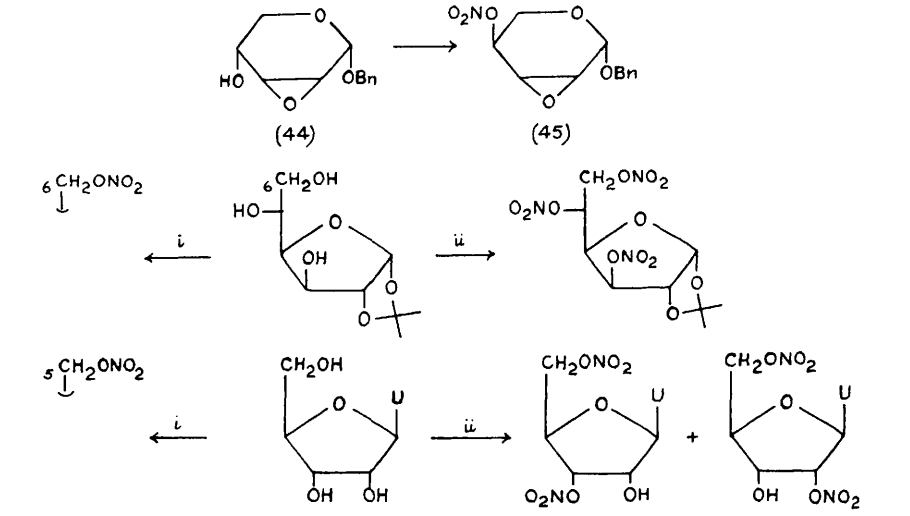
and nucleosides; thus the two ammonium phosphites (42) and (43) were prepared *via* the reaction sequence shown in Scheme 5.[70]



Scheme 5

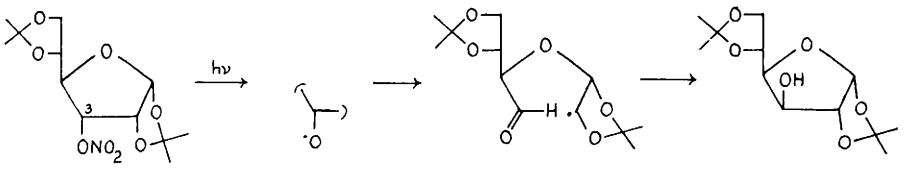
4 Other Esters

A one-step synthesis of sugar mono- and di-nitrates used triflation of partially protected sugars, followed by reaction with tetra-*n*-butylammonium nitrate. The method was mild, convenient, and did not affect highly acid labile groups; *e.g.*, the anhydrosugar (44) was converted in 90% yield into the nitrate (45) with inversion.[71] Selective nitration has been achieved using one molar thionyl chloride and one molar silver nitrate in THF; when two moles silver nitrate were used per mole of thionyl chloride, nitration was less selective (Scheme 6).[72] A range of nitrates of methyl α-D-glucopyranoside, prepared by nitration of suitably protected starting materials, have been examined using ^{13}C n.m.r.; the chemical shift differences due to nitrate groups were useful for distinguishing between isomers.[73]



Scheme 6

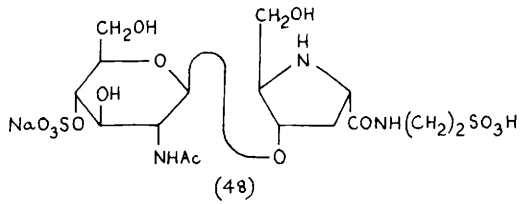
Photolytic cleavage of sugar nitrates by irradiation at $\lambda > 240$ n.m. in propan-2-ol gave the parent alcohol in most cases; with the allo-nitrate (46) the product was the epimer glucofuranose (47). A mechanism driven by dipole-dipole interactions between the C-2-O and C-3-O bonds was suggested (Scheme 7).[74]



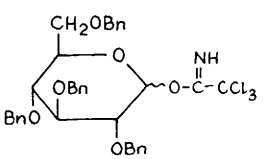
(46) (47)

Scheme 7

Reaction of 4,6:4',6'-di-O-benzylidene-α,α-trehalose with sulphur trioxide in pyridine, followed by deprotection gave, as the major product, α,α-trehalose 2-sulphate and, as the minor, the 3-sulphate. The 2-sulphate was shown to be identical to that produced by solvolysis of the principal sulphatide of *Micobacterium tuberculosis*, implicated in the virulence of the pathogen.[75] The structure of the biologically active *Pseudomonas* metabolite bulgecin A has been established as the sulphated glycopeptide (48).[76] Reference to the



(48)



(49)

use of cyclic sulphates in the synthesis of fluoro-sugars is made in Chapter 8.

Potentiometric studies of chelates of phenylboronic acid and pentoses in acid solution showed only the presence of 1:1 species.[77] FAB-m.s. has been used to examine negatively charged boronate cage compounds formed by boronic acids and trifunctional molecules such as sugars and nucleosides on the probe tip; the method is useful for the analysis of such polyhydroxy compounds, and for the determination of the affinity constants of the complexes.[78]

Reaction of lactose with long chain isocyanates in pyridine gave the 1-O-β-carbamates, while lactosylamine gave the 1-lactosylureas. An analogous reaction with isothiocyanate to give lactosylthioureas

was carried out.[79] The rate constants for the second order reaction of laevo-glucosan with phenyl isocyanate with catalysis by triethylamine and diethyltinbisheptonate to yield the 2,3,4-tricarbamate have been determined. An induction period was confirmed.[80] When 2,3,4,6-tetra-O-benzyl-D-glucopyranose was reacted with trichloroacetonitrile and sodium hydride to give the imidate (49), the initially formed β-anomer was rapidly anomerized to give the α-anomer in 96% isolated yield. In presence of potassium carbonate, anomerization was suppressed, leading to a 79% yield of the β-anomer.[81]

References

1 Y.Tsuda and K.Yoshimoto, Yuki Gosei Kagaku Kyokaishi, 1984, 42, 479 (Chem. Abstr., 1984, 101, 111 279).
2 Y.Tsuda, K.Yoshimoto, E.Hague, and M.Taru, Tennen Yuki Kagobutsu Toronkai Koen Yoshishu, 1983, 523 (Chem. Abstr., 1984, 100, 192 156).
3 Z.Smiatacz and A.Moczulska, Wiad. Chem., 1983, 37, 37 (Chem. Abstr., 1984, 100, 51 896).
4 V.G.Bukharov, S.N.Golovach, and V.M.Aver'yanova, Nukleofil'nye Reakts Karbonil'nykh. Soedin., 1982, 101 (Chem. Abstr., 1984, 101, 192 345).
5 R.Eby, K.T.Webster, and C.Schuerch, Carbohydr. Res., 1984, 129, 111.
6 S.Kucar, J.Zamocky, J.Zemek, D.Anderle, and M.Matulova, Collect. Czech. Chem. Commun., 1984, 49, 1780.
7 R.J.Ferrier and S.R.Haines, Carbohydr. Res., 1984, 127, 157.
8 Y.Kondo, Carbohydr. Res., 1984, 134, 167.
9 K.Takeo and K.Shibata, Carbohydr. Res., 1984, 133, 147.
10 C.W.Holzapfel, J.M.Koekemoer, and C.F.Marais, S. Afr. J. Chem., 1984, 37,19 (Chem. Abstr., 1984, 101, 111 285)
11 C.W.Holzapfel, J.M.Koekemoer, and C.F.Marais, S. Afr. J. Chem., 1984, 37, 57 (Chem. Abstr., 1984, 101, 131 003).
12 S.Jacobsen, Acta Chem. Scand., B, 1984, 38, 157.
13 R.W.Binkley, G.S.Goewey, and J.C.Johnston, J. Org. Chem., 1984, 49, 992
14 I.M.Vazquez, N.B.D'Accorso, I.M.E.Thiel, and A.M.Schueller, An. Asoc. Quim. Argent., 1984, 72, 239 (Chem. Abstr., 1984, 101, 192 338).
15 M.S.Chowdhary, L.Hough, and A.C.Richardson, J. Chem. Soc., Perkin Trans. 1, 1984, 419.
16 R.A.Munavu, B.Nasseri-Noori, and H.H.Szmant, Carbohydr. Res., 1984, 125, 253.
17 M.A.M.Nawwar, A.M.A.Souleman, J.Buddrus, H.Bauer, and M.Linscheid, Tetrahedron Lett., 1984, 25, 49.
18 T.Tanaka, G.Nonaka, and I.Nishioka, Chem. Pharm. Bull., 1984, 32, 117
19 G.Nonaka, K.Ishimaru, T.Tanaka, and I.Nishioka, Chem. Pharm. Bull., 1984, 32, 483.
20 H.Nishimura, G.Nonaka, and I.Nishioka, Chem. Pharm. Bull., 1984, 32, 1741.
21 H.Nishimura, G.Nonaka, and I.Nishioka, Chem. Pharm. Bull., 1984, 32, 1750.
22 T.Yoshida, T.Hatano, T.Okuda, M.U.Memon, T.Shingu, K.Inoue, and K. Fukushima, Tennen Yuki Kagobutsu Toronkai Koen Yoshishu, 1983, 158 (Chem. Abstr., 1984, 100, 175 141).
23 T.Yoshida, T.Hatano, T.Okuda, M.U.Memon, T.Shingu, and K.Inoue, Chem. Pharm. Bull., 1984, 32, 1790.

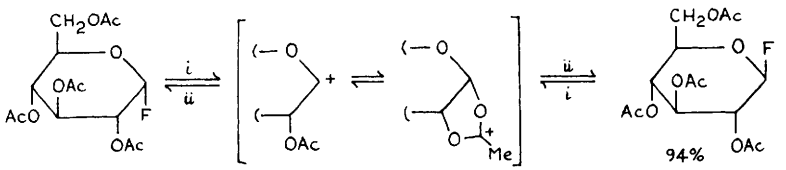
24 K.K.Trivedi, G.Kochak, and K.Misra, Indian J. Chem., Sect. B, 1983, 22, 925 (Chem. Abstr., 1984, 100, 156 887).
25 T.Okuda, K.Mori, and H.Hayatsu, Chem. Pharm. Bull., 1984, 32, 3755.
26 Y.Kashiwadi, G.Nonaka, and I.Nishioka, Chem. Pharm. Bull., 1984, 32, 3461.
27 T.Kuraishi, T.Kimura, T.Murakami, Y.Saiki, and C.-M.Chen, Chem. Pharm. Bull., 1984, 32, 1998.
28 K.Kinomura, M.Tamura, T.Oga, and H.Okai, J. Carbohydr. Chem., 1984, 3, 229.
29 T.Ouchi, S.Jokei, H.Fujie, H.Chikashita, and T.Inoi, J. Heterocycl. Chem., 1984, 21, 1023.
30 J.D.Olechno, J.E.Poulton, and E.E.Conn, Phytochemistry, 1984, 23, 1784.
31 D.Strack, B.Dahlbender, L.Grotjahn, and V.Wray, Phytochemistry, 1984, 23, 657.
32 K.Endo and H.Kikino, Can. J. Chem., 1984, 62, 2011.
33 M.Martinez, B.Esquivel, and L.Rodriquez-Hahn, Phytochemistry, 1984, 23, 1651.
34 S.Esaki, R.Tanaka, and S.Kamiya, Agric. Biol. Chem., 1984, 48, 1831.
35 M.Kanaoka, S.Yano, H.Kato, K.Nakanishi, and M.Yoshizaki, Chem. Pharm. Bull., 1984, 32, 1461.
36 T.Ouchi, Y.Sakamoto, S.Jokei, and H.Chikashita, Makromol. Chem., 1984, 185, 255 (Chem. Abstr., 1984, 100, 192 401).
37 T.Konoshima and T.Sawada, Chem. Pharm. Bull., 1984, 32, 2617.
38 G.Mieth, A.Elsner, and A.Weiss, Nahrung, 1983, 27, 747 (Chem. Abstr. 1984, 100, 156 898).
39 G.Descotes, G.Muller, and J.Mentech, Carbohydr. Res., 1984, 134, 313.
40 S.Bottle and I.D.Jenkins, J. Chem. Soc., Chem. Commun., 1984, 385.
41 A.Liav and N.B.Goren, Carbohydr. Res., 1984, 125, 323.
42 S.Hirano and Y.Ohe, Carbohydr. Polym., 1984, 4, 15 (Chem. Abstr., 1984, 100, 73 853).
43 R.W.Binkley and M.G.Ambrose, J. Carbohydr. Chem., 1984, 3, 1.
44 P.Köll, H.Komander, B.Meyer, and U.Lendering, Justus Liebigs Ann. Chem., 1984, 1591.
45 Y.Kondo, Carbohydr. Res., 1984, 128, 175.
46 T.Tsuchiya, K.Ajito, S.Umezawa, and A.Ikeda, Carbohydr. Res., 1984, 126, 45.
47 S.Singh, C.M.Maynard, R.J.Doyle, and K.G.Taylor, J. Org. Chem., 1984, 49, 976.
48 A.Liav and M.B.Goren, Carbohydr. Res., 1984, 129, 121.
49 A.Liav, H.M.Flowers, and M.B.Goren, Carbohydr. Res., 1984, 133, 53.
50 D.W.Hutchinson, Organophosphorus Chem., 1983, 14, 157 (Chem. Abstr., 1984, 100, 68 606).
51 Z.J.Lesnikowski, Wiad. Chem., 1983, 37, 91 (Chem. Abstr., 1984, 100, 51 897).
52 T.Shimidzu, K.Yamana, S.Maikuma, and Y.Oikawa, Nucleic Acids Symp. Ser., 1983, 12, 55 (Chem. Abstr., 1984, 100, 210 341).
53 R.R.Schmidt and M.Stumpp, Justus Liebigs Ann. Chem., 1984, 680.
54 F.P.Francke, M.Kapuscinski, J.K.Macleod, and J.F.Williams, Carbohydr. Res., 1984, 125, 177.
55 I.Viden, Chem. Listy, 1983, 77, 971 (Chem. Abstr., 1984, 100, 6959).
56 S.Kusamoto, M.Yamamoto, and T.Shiba, Tetrahedron Lett., 1984, 25, 3727.
57 M.Kiso, H.Ishida, and A.Hasegawa, Agric. Biol. Chem., 1984, 48, 251.
58 M.Adlersberg and D.B.Sprinson, Carbohydr. Res., 1984, 127, 9.
59 D.Charon, C.Diolez, M.Mondange, S.R.Sarfati, L.Szabo, P.Szabo, and F. Trigalo, ACS Symp. Ser., 1983, 231, 301.
60 J.Emsley and S.B.Niazi, Soil. Biol. Biochem., 1984, 16, 73 (Chem. Abstr., 1984, 101, 38 749).
61 S.D.Mal'tsev, N.N.Yurchenko, L.L.Danilov, and V.N.Shibaev, Bioorg. Khim., 1983, 9, 1097 (Chem. Abstr., 1984, 100, 6986).
62 S.Ueda and H.Takaku, Kenkyu Hokoku-Chiba Kogyo Daigaku, Riko-hen, 1984, 29, 139 (Chem. Abstr., 1984, 101, 131 025).

63 N.B.Tarusova, V.V.Shumyantseva, A.C.Krylov, M.Ya.Karpeiskii, and R.M. Khomutov, Bioorg. Khim., 1983, 9, 838 (Chem. Abstr., 1984, 100, 7026).
64 S.Parekh, A.Patel, C.J.McNeal and J.Nagyvar, Nucleosides Nucleotides, 1983, 2, 91 (Chem. Abstr., 1984, 100, 7045).
65 M.Yamashita, M.Kobayashi, K.Tsunekawa, M.Sugiura, T.Oshikawa, S.Inokawa, and H.Yamamoto, Carbohydr. Res., 1984, 131, C6.
66 A.K.Akhlebinin, E.V.Borisov, M.P.Koroteev, N.M.Pugashova, and E.E. Nifant'ev, Zh. Obshch. Khim., 1983, 53, 2141 (Chem. Abstr., 1984, 100, 51 905).
67 I.A.Litvinov, V.D.Cherepinskii-Malov, Yu.T.Struchkov, B.A.Arbuzov, L.I. Gurarii, A.Kh. Plyamovatyi, and E.T.Mukmenev, Izv. Akad. Nauk SSSR, Ser. Khim., 1983, 2068 (Chem. Abstr., 1984, 100, 51 921).
68 E.E.Nifant'ev, S.A.Rumyantseva, X.Cisneros, M.P.Koroteev, A.I.Lutsenko, and N.K.Kochetkov, Zh. Obshch. Khim., 1983, 53, 2619 (Chem. Abstr., 100, 175 137).
69 M.P.Koroteev, A.I.Lutsenko, and E.E.Nifant'ev, Zh. Obshch. Khim. 1984, 54, 279 (Chem. Abstr., 1984, 100, 210 292).
70 D.E.Gibbs and C.Larsen, Synthesis, 1984, 410.
71 N.Afza, A.Malik, and W.Voelter, Z. Naturforsch., B: Anorg. Chem., Org. Chem., 1984, 39, 840 (Chem. Abstr., 1984, 101, 211 565).
72 G.H.Hakimelahi, H.Sharghi, H.Zarrinmayeh, and A.Khalafi-Nezhad, Helv. Chim. Acta, 1984, 67, 906.
73 S.I.Firgang, A.S.Shashkov, and A.I.Usov, Bioorg. Khim., 1983, 9, 1082 (Chem. Abstr., 1984, 100, 34 750).
74 R.W.Binkley and D.J.Koholic, J. Carbohydr. Chem., 1984, 3, 85.
75 A.Liav and M.B.Goren, Carbohydr. Res., 1984, 127, 211.
76 S.Shinagawa, F.Kasahara, Y.Wada, S.Harada, and M.Asai, Tetrahedron, 1984, 40, 3465.
77 E.Huttunen, Fin. Chem. Lett., 1983, 169 (Chem. Abstr., 1984, 100, 210 278).
78 M.E.Rose, C.Longstaff, and P.D.G.Dean, Biomed. Mass Spectrom., 1983, 10, 512 (Chem. Abstr., 1984, 100, 121 506).
79 D.Plusquellec, F.Roulleau, and E.Brown, Tetrahedron Lett., 1984, 25, 1901.
80 R.Pernikis, E.Plepis, and V.Karlivans, Latv. P.S.R. Zinat. Akad. Vestis, Kim. Ser., 1984, 197 (Chem. Abstr., 1984, 101, 55 437).
81 R.R.Schmidt and J.Michel, Tetrahedron Lett., 1984, 25, 821.

8
Halogeno-sugars

A review, in Japanese, on the synthesis of fluoro-sugars, together with their ^{1}H and ^{19}F n.m.r. spectroscopy, has appeared.[1]

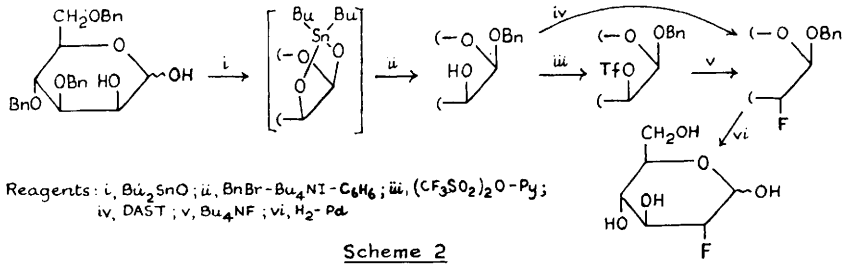
Although monosaccharides with a free anomeric hydroxy group react with pyridinium poly(hydrogen fluoride) to yield predominantly α-glycosyl fluorides,[2] better yields have been obtained by using the 1-acetate.[3] In the latter case, the presence of a participating group at C-2 leads to the β-fluoride as the kinetic product which anomerizes under forcing conditions.[3] Thus 2,3,4,6-tetra-O-acetyl-α,β-D-glucopyranose with the reagent in dichloromethane at 25°C yields 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl fluoride,[2] and 1-O-acetyl-2,3,4,6-tetra-O-benzyl-α-D-glucopyranose at 0°C gives 89% α-fluoride and 2% β-fluoride.[3] Pyranosyl and furanosyl fluorides have been prepared by the action of hydrogen fluoride-pyridine complex - NBS or DAST reagent on the phenyl 1-thio-glycoside; the reaction has been extended to oligosaccharide and glycoside synthesi (see Chapter 3).[4] Liquid hydrogen fluoride reacts with 1,2,3,4,6-penta-O-acetyl-α,β-D-glucopyranose to yield the α-glucosyl fluoride. The deacetylated product showed no inhibitory action on glucose isomerase.[5] The anomerization of glycosyl fluorides under silver fluoroborate catalysis has been studied. The reaction, which was carried out by the addition of a trace of boron trifluoride etherate to a solution of the sugar and silver fluoroborate in nitromethane, was generally complete in ten minutes; the reaction is illustrated for D-glucose in Scheme 1, which also indicates the yields of β-



Scheme 1

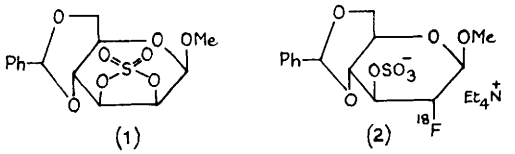
fluoride for other sugars.[6] A large scale synthesis of 2-deoxy-2-fluoro-D-arabinofuranose derivatives in good overall yield from D-

glucose has been described.[7] A gas-solid phase microchemical method for the synthesis of acetyl hypofluorite and hence tetra-O-acetyl-2-deoxy-2-fluoro-D-glucose from 3,4,6-tri-O-acetyl-D-glucal in 68% yield (and the ^{18}F-labelled analogue) uses a column of alkali metal acetate through which a stream of fluorine in nitrogen is passed.[8] The rapid stereoselective synthesis of fluorinated carbohydrates by the addition of acetyl hypofluorite to six unsaturated carbohydrates which contain a vinyl ether group has been reported. All reactions were complete in less than five minutes at -78°C, giving, with one exception, high yields of the isomerically pure cis-addition product, with a strong preference for reaction from one face of the double bond.[9] Fluorine-18 acetyl hypofluorite reacts with D-glucal in water to give a radiochemical yield of 40% 2-deoxy-2-[^{18}F]-fluoro-D-glucose with greater than 95% radiochemical purity. The synthesis was complete in about 15 minutes. The reagent is useful in other aqueous fluorination reactions, over a wide range of acidity.[10] An automated method for preparing 2-deoxy-2-[^{18}F]fluoro-D-glucose, designed for routine use in clinical laboratories, has been described, the whole sequence of operations being controlled by microcomputers.[11] 2-Deoxy-2-fluoro-D-glucose has also been prepared as shown in Scheme 2. The substitution and debenzylation steps were very rapid, enabling the fluorine-labelled product to be isolated (^{18}F has $t_{\frac{1}{2}}$ 110 min).[12] The product was used to study cerebral glucose metabolism. The same product, prepared by addition of $^{18}F_2$ in fluorotrichloromethane to triacetyl-D-glucal,



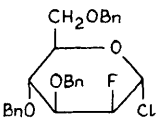
Reagents: i, Bu_2SnO; ii, BnBr-Bu_4NI-C_6H_6; iii, $(CF_3SO_2)_2O$-Py; iv, DAST; v, Bu_4NF; vi, H_2-Pd

Scheme 2

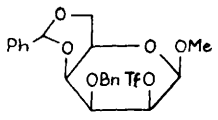


(1) (2)

followed by deacetylation, has been used to determine the biodistribution of 2-deoxy-2-fluoro-D-glucose in mice.[13] The reaction of the cyclic sulphate (1) with [^{18}F]-tetraethylammonium fluoride gave the 2-deoxy-2-[^{18}F]-fluoro-glucose derivative (2) which was deprotected with tris(trifluoroacetyl)borate to give the parent labelled compound.[14] 2-Deoxy-2-[^{18}F]-fluoro-3-O-methyl-D-glucose has been synthesized *via* displacement of a 2-O-triflate in a methyl β-D-mannopyranoside derivative with caesium hydrogen $^{18}F_2$-difluoride and used in animal biodistribution studies.[15] Displacement of a triflate has also been used to synthesize 2-deoxy-2-fluoro-D-mannose methyl 3-O-acetyl-4,6-O-benzylidene-2-O-triflyl-β-D-glucopyranoside was treated with tetrabutylammonium fluoride in acetonitrile, followed by acid hydrolysis. The procedure was suitable for preparing the analogues with radioactive fluorine substituents. The behaviour of the sugar triflates with 3-O-benzyl and 3-O-methyl substituents in both anomeric forms towards various fluoride sources was also studied.[16] A similar displacement to prepare the same fluoromannose has been applied to perbenzylated 2-O-triflyl-β-D-glucopyranoside. The product was converted to the glycosyl chloride (3), which was then used to prepare glycosides and disaccharides with an α-linkage (see Chapter 2).[17] 2-Deoxy-2-fluoro-D-galactose has been

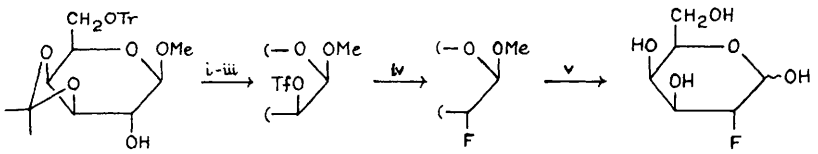


(3)



(4)

synthesized as shown in Scheme 3. By contrast, attempted displacement of the triflate (4) with tetraethylammonium fluoride led to elimination.[18] A modified literature method has been used to synthesize

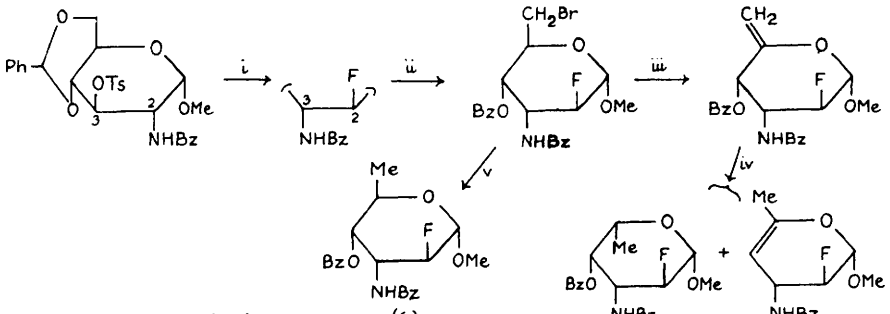


Reagents : i, DMSO-Ac_2O ; ii, LAH ; iii, Tf_2O-Py ; iv, Et_4NF-MeCN ; v, H_3O^+

Scheme 3

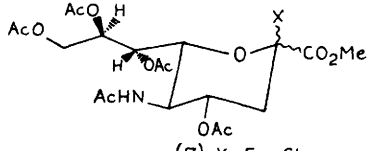
methyl 3-benzamido-4-O-benzoyl-2,3,6-trideoxy-2-fluoro-β-L-galactopyranoside (5) *via* unsaturated derivatives as shown in Scheme 4. The 6-deoxy-altrose derivative (6) was also prepared.[19]

The 2-α- and -β-fluoro- and 2-β-chloro-derivatives of tetra-O-



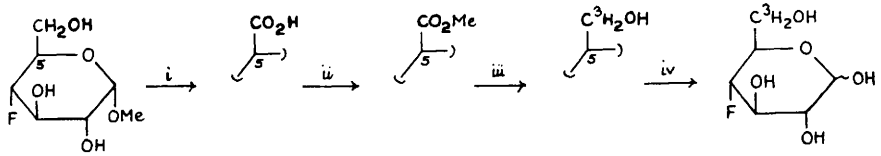
Scheme 4

acetyl-N-acetyl neuraminic acid have been prepared. All compounds adopted the $^{2}C_{5}$ (L) conformation shown in formula (7). The fluoro-compounds were O-deprotected and hydrolyzed to the free acid.[20]



(7) X = F or Cl

4-Deoxy-4-fluoro-D-[6-^{3}H]glucose has been synthesized from methyl 4-deoxy-4-fluoro-α-D-glucopyranoside as shown in Scheme 5.[21]



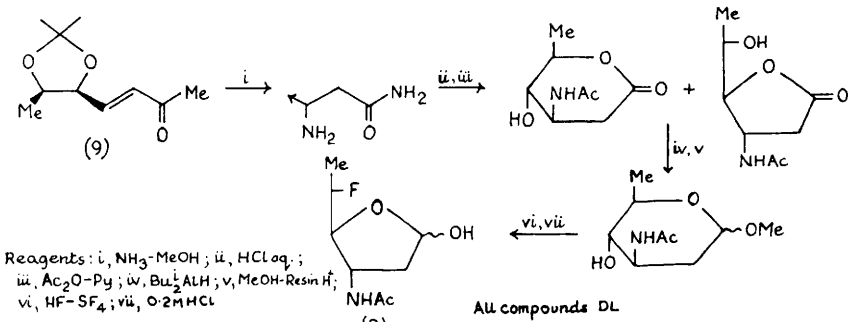
Scheme 5

Enzymatic dehydrogenation of 3-deoxy-3-fluoro-D-mannitol using enzymes of Gluconobacter oxydans provides a route to 4-deoxy-4-fluoro-D-fructose, whose structure was confirmed by ^{1}H, ^{13}C, and ^{19}F n.m.r. spectroscopy. The molecule adopts the $^{2}C_{5}$ (D) conformation in aqueous solution.[22]

Direct fluorinative dehydroxylation of methyl 3-acetamido-2,3,6-

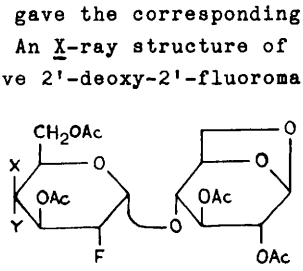
trideoxy-D,L-arabino-hexopyranoside with sulphur tetrafluoride - hydrogen fluoride has been used as the key step in the preparation of the 5-fluoro-furanose (8). The whole route from the non-carbohydrate ester (9) is depicted in Scheme 6. The α-p-nitrobenzoate of (8) was characterized by X-ray crystallography.[23]

6-Deoxy-6-fluorosucrose and hexabenzyl-6-deoxy-6-fluoro-galacto-sucrose have been prepared by conventional steps from 1',2,2',3,3',6' hexa-O-benzyl-4,6-O-isopropylidene-sucrose.[24] The mesylate displacement by tetra-n-butylammonium fluoride used in this synthesis has also been used to prepare 4-deoxy-4-fluoro-galacto-sucrose and its 4,6-difluoro-analogue.[25] 1'-Deoxy-1'-fluoro-sucrose has been obtained by treatment of 1-deoxy-1-fluoro-D-fructose with UDP-glucose The fluorofructose was obtained by reaction of 2,3:4,5-di-O-isopropylidene-1-O-triflyl-D-fructopyranose with tris(dimethylamino)sulphonium difluorotrimethylsilicate (TASF). 1'-Deoxy-1'-fluorosucrose is transported by the sucrose carrier protein but is not a substrate for invertase.[26] Coupling of 3,4,6,-tri-O-acetyl-2-deoxy-2-fluoro-



Scheme 6

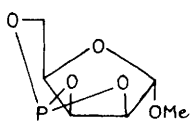
α-D-glucosyl and -galactosyl bromides with 1,6-anhydro-2,3-di-O-acetyl-β-D-glucopyranose in the presence of silver carbonate and silver triflate gave the corresponding 4-fluoro-α-(1→4)-disaccharide (10) and (11). An X-ray structure of (11) was carried out and its deprotection gave 2'-deoxy-2'-fluoromaltose.[27]

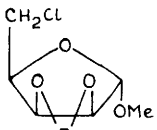


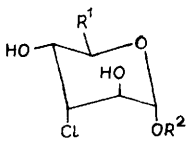
(10) X = OAc, Y = H
(11) X = H, Y = OAc

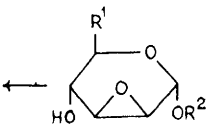
Reference to nucleosides containing halogeno-sugars is made in

Chapter 20, and to n.m.r. spectroscopy of fluorinated oligosaccharides in Chapter 21. The 4",6"-dideoxy-4",6"-difluoro-, 4",6"-dideoxy-4"-fluoro-, 6"-deoxy-6"-fluoro-, and 6"-deoxy-derivatives of 4"-epi-kanamycin A have been synthesized from the 4",6"-ditriflate and 6"-brosylated-4"-triflate derivatives of kanamycin A and their antibacterial properties examined.[28] A discussion of the conversion of hydroxy groups into chloro-, bromo-, and iodo-deoxy groups is included in a review of regio-, stereo-, and chemo-selective reactions of carbohydrates.[29] Chlorination of the cyclic phosphite (12) gave rise to the 5-deoxy-5-chloro-chlorophosphite (13).[30] Whereas tosyl chloride in 4-dimethylaminopyridine gives the normal tosylate ester of secondary hydroxy groups, it reacts at the anomeric centre to yield glycosyl chlorides.[31] Regioselective one-pot synthesis of chlorodeoxy sugars has been realized by the trans diaxial cleavage of oxiran sugar derivatives with $PdCl_2(PhCN)_2$, e.g., the 3-chloro-sugars (14) are obtained from the oxirans (15). No epoxide migration was observed and the method was found to be satisfactory in the presence of acid labile functions.[32] Reaction


(12)

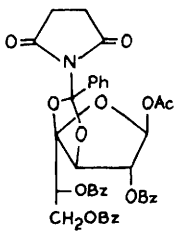

(13)

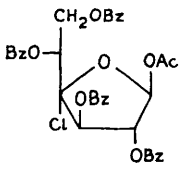

(14)


(15)

$R^1 = CH_2OH$ or H
R^2 = Me or Bn

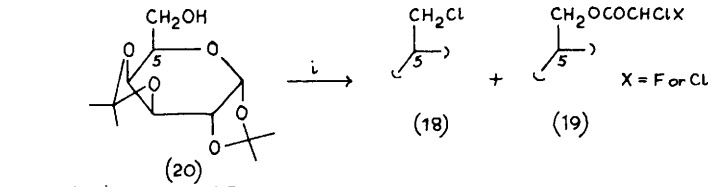
of the succinimido acetal (16) with dichloromethoxymethane in the presence of boron trifluoride gave the 4-chloro-4-dehydro-glucose derivative (17).[33] Direct conversion of hydroxy groups into chloro


(16)


(17)

groups has been achieved using triphenylphosphorus dichloride-imidazole or triphenylphosphine-carbon tetrachloride-imidazole. Thus

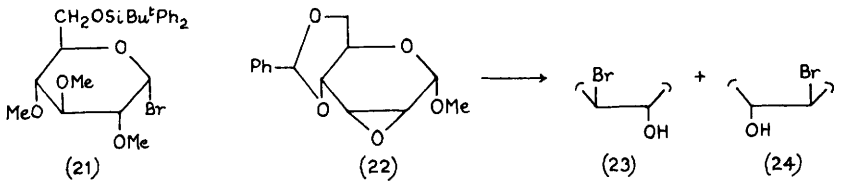
methyl α-D-glucopyranoside with either of these reagents in mixed pyridine-acetonitrile at 70°C for 3.5 h followed by acetylation gave 89% methyl 2,3-di-O-acetyl-4,6-dichloro-4,6-dideoxy-α-D-galact pyranoside, whereas at 25°C for 1 to 2 hours and acetylation gave 80% of the 2,3,4-triacetate of the 6-chloro-6-deoxy-derivative. Th reagent, which was similarly applied to the manno system, was found to be more sensitive to steric hindrance than the corresponding brc inating or iodinating reagents (see Vol. 16, p. 86, ref. 21, and al



Scheme 7

ref. 40 below).[34] Mixtures of the 6-chloro- and 6-O-dihaloacetyl derivatives (18) and (19) have been obtained on treatment of the D-galactose derivative (20) with chlorofluorotriethylamines in DMF (Scheme 7).[35]

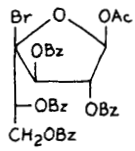
Treatment of methyl 6-O-(tert-butyl)diphenylsilyl-2,3,4-tri-O-methyl-α-D-glucopyranoside with dimethylboron bromide at 25°C[36] cleaves the glycoside to yield the α-glycosyl bromide (21). The

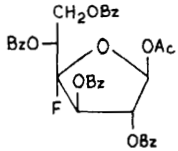


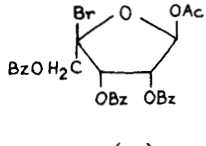
(21) (22) (23) (24)

claim (see Vol.15, p.88, ref.25) that reaction of the anhydro-alloside (22) reacts with magnesium bromide to yield mainly the abnormal diequatorial 3-bromo-glucose derivative (23) has been disputed; a reinvestigation has shown that the main product (78%) is the expected 2-bromo-altroside (24) with only 15% (23) being formed.[37] Bromination of 1-O-acetyl-2,3,5,6-tetra-O-benzoyl-β-D-glucofuranose with bromine in the presence of light gave the 4-bromo-glycosulose derivative (25). Reaction of (25) with silver fluoride gave the inverted fluoride (26), while mixtures of (26) and its 4-epimer were obtained with silver fluoroborate. Similar reactions on 1-O-acetyl-2,3,5-penta-O-benzoyl-β-D-ribofura

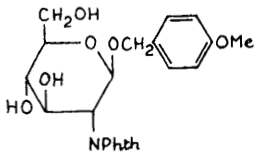
ose yielded the 4-bromo-pentosulose derivative (27), and adenosine pentabenzoate was also examined.[38] 5-Bromo-5-deoxy-3-O-acetyl-1,2-

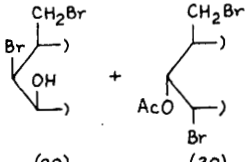

(25)

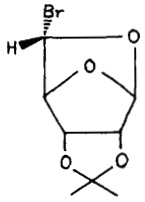

(26)


(27)

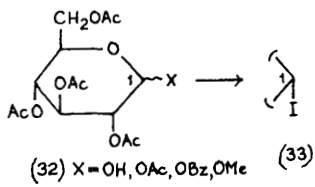
O-cyclohexylidene-α-D-xylofuranose has been prepared conventionally from 1,2-O-cyclohexylidene-α-D-xylofuranose; solvolysis of the product caused migration of the 3-O-acetyl group to the 5-position.[39] Triphenylphosphine - tribromoimidazole has been shown to be rather unselective in conversion of hydroxy groups to bromo-deoxy groups; e.g., the p-methoxybenzyl glycoside (28) gives a mixture of the 4,6-dibromo- and the 3,6-dibromo-sugars (29) and (30), isolated as their acetates in 63% and 26% yield respectively. Reaction of p-methoxybenzyl glycosides with either bromine or NBS in anhydrous dichloromethane gave the glycosyl bromides directly.[40] Photobromination of 1,5-anhydro-2,3-O-isopropylidene-β-D-ribofuranose using NBS gave stereoselectively the 5(S)-bromo-derivatve (31) which was converted into 5(S)- and 5(R)-deutero-riboses by reduction with triphenyltin deuteride.[41]

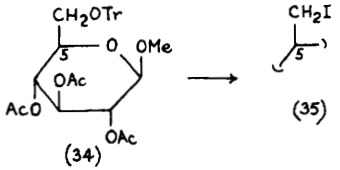

(28)

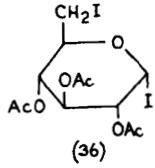

(29) (30)


(31)

The iodinating properties of trimethylsilyl iodide have been investigated: the various 2,3,4,6-tetra-O-acetyl-glucose derivatives (32) all yielded the α-iodide (33), while the 6-O-trityl derivative (34) gave the 6-iodo compound (35), and the 6-iodo-glycosyl iodide


(32) X = OH, OAc, OBz, OMe (33)


(34) (35)


(36)

(36) was obtained from 1,2,3,4-tetra-O-acetyl-β-D-glucopyranose.[42]

References

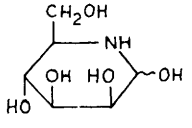
1 T.Tsuchiya, Yuki Gosei Kagaku Kyokaishi, 1984, 42, 544 (Chem. Abstr., 1984, 101, 111 271).
2 W.A.Szarek, G.Grynkiewicz, B.Doboszewski, and G.W.Hay, Chem. Lett., 1984, 1751.
3 M.Hayashi, S.Hashimoto, and R.Noyori, Chem. Lett., 1984, 1747.
4 K.C.Nicolaou, R.E.Dolle, D.P.Papahatjis, and J.L.Randall, J. Am. Chem. Soc., 1984, 106, 4189.
5 T.Goto, T.Kasumi, and N.Tsumura, Shokuhin Sogo Kenkyusho Kenkyu Hokoku, 1983, 50 (Chem. Abstr., 1984, 101, 171 601).
6 Y.V.Voznij, L.N.Koikov, and A.A.Galoyan, Carbohydr. Res., 1984, 132, 339.
7 M.W.Chun, M.H.Kim, D.Kim, and W.K.Chung, Yakhak Hoechi, 1984, 28, 191 (Chem. Abstr., 1984, 101, 230 856).
8 D.M.Jewett, J.F.Potocki, and R.E.Ehrenkaufer, J. Fluorine Chem., 1984, 24, 477 (Chem. Abstr., 1984, 101, 152 201).
9 M.J.Adam, J.R.Neeser, L.D.Hall, and B.D.Pate, Report 1983, TRI-PP-83-2, (Chem. Abstr., 1984, 101, 130 982).
10 R.E.Ehrenkaufer, J.F.Potocki, and D.M.Jewett, J. Nucl. Med., 1984, 25, 333 (Chem. Abstr., 1984, 101, 55 431).
11 R.Iwata, T.Ido, T.Takahashi, and M.Monma, Int. J. Appl. Radiat. Isot., 1984, 35, 445 (Chem. Abstr., 1984, 101, 171 599).
12 A.Dessinges, A.Olesker, G.Lukacs, and T.T.Thang, Carbohydr. Res., 1984, 126, C6.
13 C.Y.Shiue, C.D.Arnett, and A.P.Wolf, Eur. J. Nucl. Med., 1984, 9, 77 (Chem. Abstr., 1984, 100, 210 285).
14 T.J.Tewson, J. Nucl. Med., 1983, 24, 718 (Chem. Abstr., 1984, 100, 6969).
15 S.Levy, E.Livni, D.R.Elmaleh, D.A.Varnum, and G.L.Brawnell, Int. J. Appl. Radiat. Isot., 1983, 34, 1560 (Chem. Abstr., 1984, 100, 121 462).
16 T.Haradahira, M.Maeda, H.Omae, Y.Yano, and M.Kojima, Chem. Pharm. Bull., 1984, 32, 4758.
17 T.Ogawa and Y.Takahashi, J. Carbohydr. Chem. 1983, 2, 461.
18 T.Haradahira, M.Maeda, Y.Yano, and M.Kojima, Chem. Pharm. Bull., 1984, 32, 3317.
19 M.K.Gurjar, V.J.Patil, J.S.Yadav, and A.V.Rama Rao, Carbohydr. Res., 1984, 135, 174.
20 M.N.Sharma and R.Eby, Carbohydr. Res., 1984, 127, 201.
21 J.Samuel and N.F.Taylor, Carbohydr. Res., 1984, 133, 168.
22 M.Budesinsky, M.Cerny, J.Dolezalova, M.Kulhanek, J.Pacak, and M.Tadra, Collect. Czech. Chem. Commun., 1984, 49, 267.
23 J.T.Welch, B.-M.Svahn, S.Eswarakrishnan, J.P.Hutchinson, and J.Zubieta, Carbohydr. Res., 1984, 132, 221.
24 L.Hough, A.K.M.S.Kabir, and A.C.Richardson, Carbohydr. Res., 1984, 125, 247.
25 P.J.Card and W.D.Hitz, J. Am. Chem. Soc., 1984, 106, 5348.
26 L.Hough, A.K.M.S.Kabir, and A.C.Richardson, Carbohydr. Res., 1984, 131, 335.
27 J.G.Shelling, D.Dolphin, P.Wirz, R.E.Cobbledick, and F.W.B.Einsten, Carbohydr. Res., 1984, 132, 241.
28 R.Albert, K.Dax, and A.E.Stütz, J. Carbohydr. Chem., 1984, 3, 267.
29 P.J.Garegg, Pure Appl. Chem., 1984, 56, 845.
30 M.P.Koroteev, A.I.Lutsenko, and E.E.Nifant'ev, Zh. Obshch. Khim., 1984, 54, 279 (Chem. Abstr., 1984, 100, 210 292).
31 C.K.Hwang, W.S.Li, and K.C.Nicolaou, Tetrahedron Lett., 1984, 25, 2295.

32 N.Afza, A.Malik, and W.Voelter, Chimia, 1983, 37, 422 (Chem. Abstr., 1984, 100, 103 769).
33 R.J.Ferrier, S.R.Haines, G.J.Gainsford, and E.J.Gabe, J. Chem. Soc., Perkin Trans. 1, 1984, 1683.
34 P.J.Garegg, R.Johansson, and B.Samuelsson, Synthesis, 1984, 168.
35 R.Zeisig, D.Cech, F.Liska, and V.Dedek, Z. Chem., 1983, 23, 375 (Chem. Abstr., 1984, 100, 139 492).
36 Y.Guindon, C.Yoakim, and H.E.Morton, J. Org. Chem. 1984, 49, 3912.
37 M.K.Gurjar, J.S.Yadav, and A.V.R.Rao, Indian. J. Chem., Sect. B, 1983, 22, 1139 (Chem. Abstr., 1984, 101, 91 377).
38 R.J.Ferrier and S.R.Haines, J. Chem. Soc., Perkin Trans. 1, 1984, 1675.
39 D.Miljkovic, N.Vukojevic, and L.Milenkovic, Glas. Hem. Drus. Beograd, 1983, 48, 303 (Chem. Abstr., 1984, 100, 86 013).
40 B.Classon, P.J.Garegg, and B.Samuelsson, Acta Chem. Scand., Ser. B, 1984, 38, 419.
41 H.Ohrui, T.Misawa, and H.Meguro, Agric. Biol. Chem., 1984, 48, 1825.
42 A.Klemer and M.Bieber, Justus Liebigs Ann. Chem., 1984, 1052.

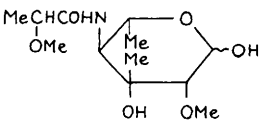
9
Amino-sugars

1 Natural Products

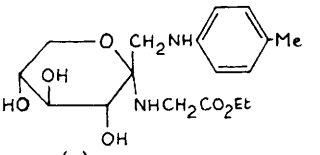
Nojirimycin B (5-amino-5-deoxy-D-mannopyranose, 1), the 2-epimer of nojirimicin, has been isolated from *S. lavendulae*, and converted to the corresponding δ-lactam by microbiological oxidation (*Gluconobacter suboxydans*). Both were powerful α-mannosidase and β-glucosidase inhibitors.[1] A novel aminosugar, *N*-acyl-kanosamine, has been isolated from the antigenic lipo-oligosaccharide of *Mycobacterium kansasii* and proposed to be 4,6-dideoxy-2-*O*-methyl-3-*C*-methyl-4-(2'-methoxypropionamido)-L-mannopyranose (2).[2]



(1)



(2)



(3)

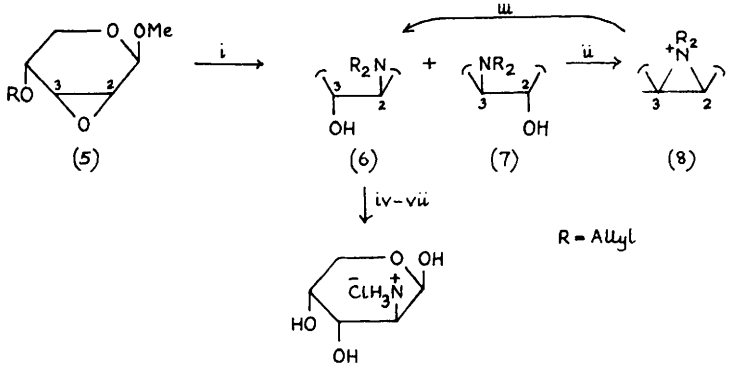
2 Synthesis

Reviews on the following topics have appeared: i) the synthesis, reactions, and spectroscopic properties of carbohydrate isocyanides,[3] ii) the synthesis of sialic acid derivatives, including control of the stereochemistry at C-2,[4] and iii) the synthesis of isoxazolines and their conversion into naturally occurring amino-compounds, including amino-sugars.[5]

The glucose-lysine Amadori compounds monofructosyl-lysine and difructosyl-lysine have been isolated, and the kinetics of their formation studied.[6] 1-Deoxy-1-tolylamino-D-fructopyranose has been obtained by amination of fructose with *p*-toluidine, and shown to form an acyclic oxime and, on reaction with glycine ethyl ester, the glycosylamine derivative (3).[7]

2-Amino-2-deoxy-D-arabinopyranose (4) has been synthesized from

D-arabinose via the readily obtained epoxide (5) (Scheme 1). Opening of epoxide (5) with diallylamine gave a 1:1 mixture of the

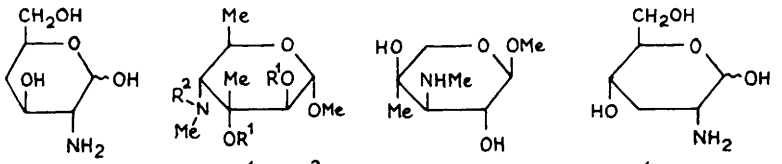


(5) (6) (7) (8) (4)

Reagents : i, R_2NH ; ii, MsCl-Et_3N; iii, H_2O ; iv, Pd-C-H_3O^+ ; v, HCO_3^- ; vi, Ac_2O ; vii, H_3O^+

Scheme 1

xylo- and arabino-isomers (6) and (7). Both could be converted into the same lyxo-aziridinium ion (8), however, which was then regioselectively cleaved at C-3 by water to regenerate compound (6) alone.[8] Cleavage of the epoxide ring in 1,6:2,3-dianhydro-4-deoxy-D-lyxo-hexopyranose with azide has been used to obtain 2-amino-2,4-dideoxy-D-glucose (9); the reaction solvent influenced the proportion of diaxial vs. diequatorial ring opening products.[9] The branched-chain amino-sugar methyl glycosides (10) and (11) of N-acetyl-3-epi-sibirosamine[10] and garosamine,[11] respectively, have been obtained from known sugar epoxides by multistep procedures (see Chapter 14). The 2,3-di-O-methyl-3-epi-sibirosamine derivative (12) has been prepared by a standard 12-step synthesis from methyl 2,3-anhydro-4,6-O-benzylidene-α-D-altropyranoside, but attempted de-O-methylation (using BCl_3 or BBr_3) was not successful.[12]

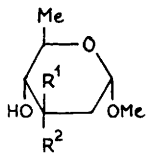


(9) (10) R^1=H, R^2=Ac (11) (13)

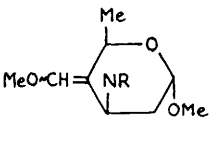
(12) R^1=Me, R^2=H

Introduction of nitrogen functionality by sulphonate displacement continues to be a popular strategy. D-Lividosamine (2-amino-2,3-dideoxy-D-glucose, 13) has been obtained from 1,6-anhydro-3-

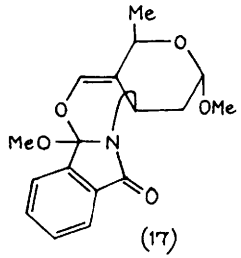
deoxy-2-O-tosyl-β-D-arabino-hexopyranose via an azide intermediate.[9] A further synthesis of a D-lividosamine derivative is covered in Chapter 12. Methyl 3-amino-2,3,6-trideoxy-α-D-arabino-hexopyranoside (14) has been synthesized from 2-deoxy-D-glucose via the mesylate (15) and converted into a mixture of chiral intermediates (16) and (17), required for a thienamycin synthesis,



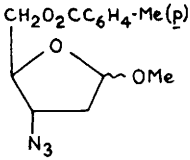
(14) $R^1=NH_2, R^2=H$
(15) $R^1=H, R^2=OMs$



(16)
R = Phthalimido

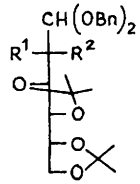


(17)

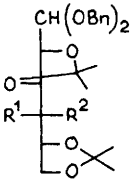


(18)

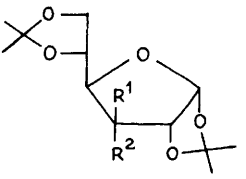
by olefination [$(MeO)_2P(O)C\bar{H}N_2.K^+$] of a 4-keto-intermediate.[13] A new synthesis of methyl 3-azido-2,3-dideoxy-5-O-(p-methylbenzoyl)-D-ribofuranoside (18), a potential precursor of 3-amino-3-deoxy-nucleosides, has been achieved in 9 steps from 1,2:3,5-di-O-isopropylidene-α-D-xylofuranose, key steps being 2-deoxygenation by the Barton-McCombie procedure and azide displacement of a 3-triflate.[14] New routes to derivatives of 2-amino-2-deoxy-D-mannose and 4-amino-4-deoxy-D-galactose, e.g. (19) and (20), have utilized the mixtures of 3,4:5,6- and 2,3:5,6-di-O-isopropylidenated dialkylacetals, e.g. (21) and (22), obtained on direct acetalation of D-glucose [e.g. $(BnO)_2CMe_2$-TsOH], the lone hydroxy groups being triflated and displaced with azide.[15,16] Tri-



(19) $R^1=NHAc, R^2=H$
(21) $R^1=H, R^2=OH$

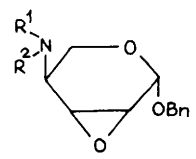


(20) $R^1=N_3, R^2=H$
(22) $R^1=H, R^2=OH$

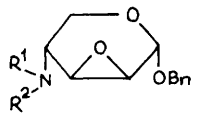


(23) $R^1=OTf, R^2=H$
(24) $R^1=H, R^2=NH_2$

flates may advantageously be displaced with ammonia in chlorinated hydrocarbon solution, the difficult conversion of the glucose 3-triflate derivative (23) into the 3-amino-3-deoxy-allose derivative (24) being effected in 58% yield.[17] Conventional syntheses of the 4-aminoacid-2,3-anhydro-β-L- and α-D-lyxopyranosides, (25) and (26), involved displacements of 4-O-triflate esters with inversion.[18] A novel synthesis of the 6-amino-6-deoxy-D-galactose

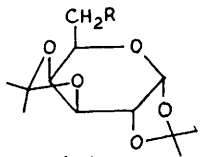


(25)



(26)

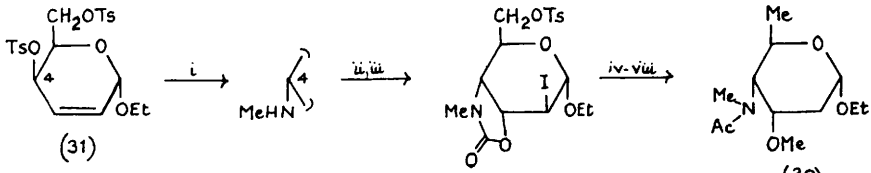
NR^1R^2 = L-Aminoacid esters of Leu, Ala, Phe, Met, Pro, Glu, and Lys



(27) R = NH_2
(28) R = NH·NPh$_2$
(29) R = OTf

derivative (27) involved preparation of the 6-(N,N-diphenyl-hydrazino)-derivative (28) from the 6-triflate (29), and photochemical elimination of carbazole. Product yields, however, were considered to be too low for this approach to be of general value.[19]

Several amino-sugars have been prepared from hex-2-enopyranoside 4,6-ditosylates. The halocosamine derivative (30) has been synthesized from the D-threo-alkene (31) (Scheme 2).[20] Malik and



(31) (30)

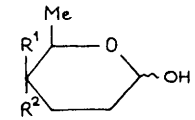
Reagents: i, $MeNH_2$; ii, EtO_2CCl; iii, I(Collidine)$_2ClO_4$; iv, NaI; v, Bu_3SnH; vi, KOH; vii, Ac_2O-MeOH; viii, NaH-MeI-Bu_4NI

Scheme 2

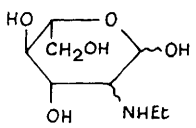
co-workers have reviewed their syntheses of 4-amino-4-deoxy-pentoses and -hexoses and 4,6-diamino-4,6-dideoxy-hexoses, which include sulphonate displacements with azide.[21] Details on their syntheses of D-ossamine (32),[22] D-tolyposamine (33),[22] and D-forosamine (34)[23] via the D-erythro-isomer of alkene (31) have also appeared. Further examples where azido- or amino-functionality has been introduced by sulphonate displacement are covered in Chapters 10 and 24.

A key step in the synthesis of 3-acetamido-3-deoxy-D-galactose involved the use of a reagent system (DEAD-TPP-HN_3) to introduce an azido-function with inversion in place of the 3-hydroxy group of 1,2:5,6-di-O-isopropylidene-α-D-gulofuranose, the latter being obtained by a modification of a known procedure from its D-gluco-isomer.[24]

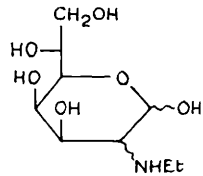
Using the aminonitrile synthesis, in which hydrogen cyanide is added to an N-alkyl -glycosylamine and the product is catalytically



(32) $R^1 = NMe_2$, $R^2 = H$
(33) $R^1 = H$, $R^2 = NH_2$
(34) $R^1 = H$, $R^2 = NMe_2$



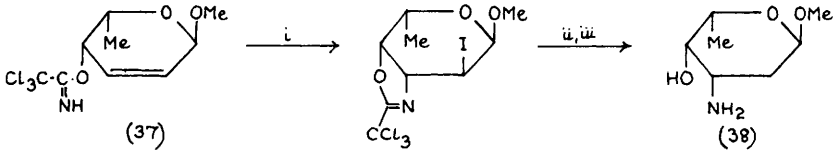
(35)



(36)

reduced, the epimeric 2-deoxy-2-ethylamino-L-manno- and -L-gluco-pyranoses (35) have been prepared from L-arabinose,[25] and the epimeric 2-deoxy-2-ethylamino-D-glycero-D-galacto- and -D-glycero-D-talo-heptoses (36) have been prepared from D-mannose.[26] Reactions of these products with arylisothiocyanates to produce glycofurano-imidazolidine-2-thione derivatives are referred to in Chapter 10.

Intramolecular delivery of an amino-function has been effected in the halocyclization of the allylic trichloroacetimidate (37), the product being converted to methyl α-L-daunosaminide (38) (Scheme 3).[27]

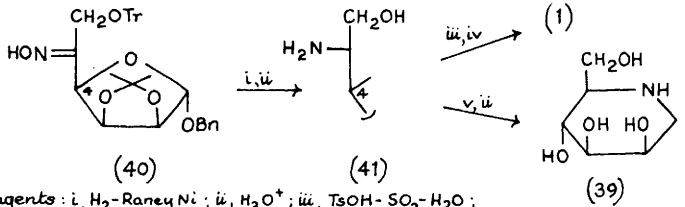


(37) (38)

Reagents: i, NIS ; ii, H^+ ; iii, Bu_3SnH

Scheme 3

5-Amino-5-deoxy-D-mannopyranose (1), whose natural occurrence is reported in Section 1, and 1,5-dideoxy-1,5-imino-D-mannitol (39) have been prepared as shown in Scheme 4 and their ability to inhibit α- and β-D-mannosidases studied. Reduction of the oxime (40) led to a separable mixture of D-manno-amine (41) and its L-gulo-isomer, compound (41) being either hydrolyzed in the presence



(40) (41) (1) (39)

Reagents: i, H_2-Raney Ni ; ii, H_3O^+ ; iii, TsOH-SO_2-H_2O ; iv, Resin (OH^-) ; v, H_2-$Pd(OH)_2$-C

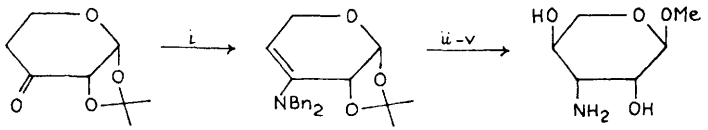
Scheme 4

of sulphur dioxide to protect the acid-labile product (1) as its

hydrogen sulphite addition product or hydrogenolyzed to the 1-deoxy-derivative (39).[28] A related synthesis of 1,4-dideoxy-1,4-imino-D-mannitol is covered in Chapter 18.

Fluorogenic malto-oligosaccharides with 6-deoxy-6-(2-pyridyl)-amino-substituted non-reducing terminal units and their corresponding alditol derivatives (from $NaBH_4$ reduction), required as α-amylase substrates, have been synthesized by reductive amination ($NaBH_3CN$) of partially 6-aldehydo-amylose with 2-amino-pyridine, enzymic digestion, and separation of the resulting oligomers (D.P. 4-6) by ion-exchange chromatography.[29]

3-Amino-sugars have been synthesized from pyranosidulose derivatives. Methyl 3-amino-3-deoxy-α-DL-lyxopyranoside (42) was obtained by hydroboration of the enamine (43) derived from 3-ulose (44) (Scheme 5).[30] The hexopyranosid-2-ulose derivative (45) was

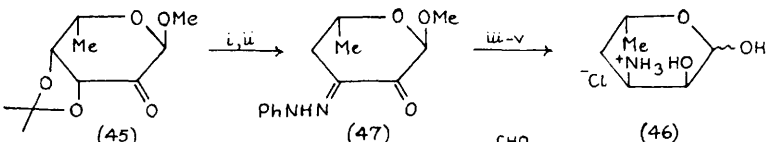


DL-(44) DL-(43) DL-(42)

Reagents: i, Bn_2NH ; ii, B_2H_6 ; iii, H_2O_2 ; iv, MeOH-HCl ; v, H_2-Pd/C

Scheme 5

converted into the 3-amino-3,4,6-trideoxy-L-ribo-hexopyranose (46) by way of the monohydrazone (47) (Scheme 6); 3-amino-3,4-dideoxy-



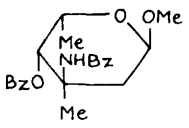
(45) (47) (46)

Reagents: i, NaOH ; ii, $PhNHNH_2$; iii, H_2-PtO_2-HOAc ; iv,  ; v, H_3O^+

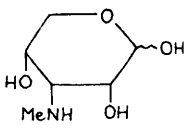
Scheme 6

D-erythro-pentopyranose was similarly obtained from a pento-pyranosid-2-ulose analogue.[31] The L-xylo branched-chain amino-sugar (48) was synthesized from a 3-keto-precursor via a spiro-aziridine intermediate.[32] The syntheses of 4"-sulphonamido-oleandomycin derivatives via a 4"-keto-derivative are covered in Chapter 19.

Several amino-sugar syntheses have employed 3- and 4-carbon chiral starting materials. The synthesis of DL-daunosamine from a tartaric acid derivative (Vol.17, p.95) has been detailed, along with an analogous synthesis of 3-epigentosamine (49) from 2,3-O-

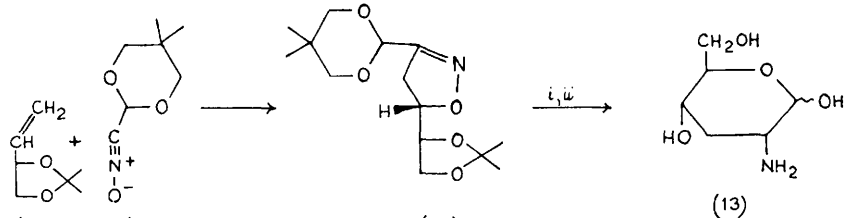


(48)



(49)

isopropylidene-D-glyceraldehyde.[33] A 3.5:1 mixture of D-lividosamine (13) and its C-2 epimer has been obtained on reduction of the major dipolar cycloadduct (50) from reaction of the 2,3-di-O-isopropylidene-D-glyceraldehyde-derived alkene (51) and nitrile oxide (52) (Scheme 7); the desired isomer (13) was isolated

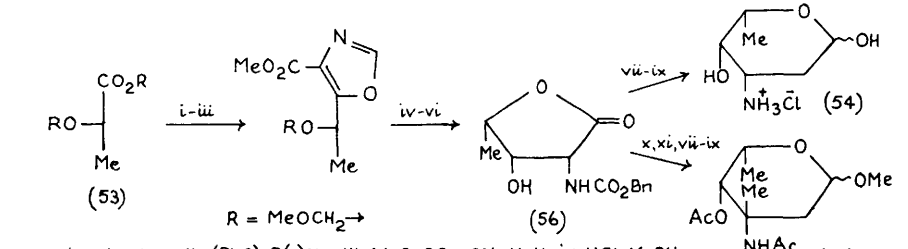


(51) (52) (50) (13)

Reagents: i, LAH ; ii, H_3O^+

Scheme 7

chromatographically as its acetylated methyl glycoside. Extensive model studies on the racemic analogues and related hexitol derivatives were also reported.[34] The L-lactic acid derivative (53) has been elaborated into L-daunosamine (54)[35] and into the branched-chain L-vancosamine derivatives (55),[36] via the common pentonolactone intermediate (56) (Scheme 8). N-Benzoyl-L-



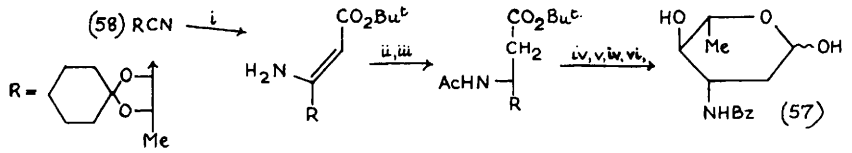
(53) (56) (54) (55)

R = $MeOCH_2$→

Reagents: i, LiOH ; ii, $(PhO)_2P(O)N_3$; iii, MeO_2CCH_2CN-NaH ; iv, HCl-MeOH ; v, $(BnOCO)_2O$; vi, H_2-Rh/Al_2O_3 ; vii, DIBAL ; viii, Ph_3P CHOMe ; ix, HCl ; x, LDA ; xi, MeI

Scheme 8

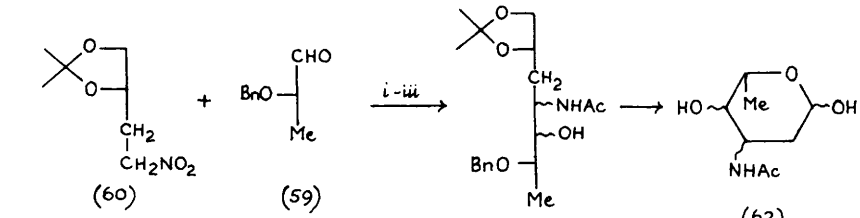
acosamine (57) has been stereoselectively synthesized from the tetrononitrile (58) (Scheme 9), which is available from either L-lactic or L-tartaric acids;[37] the same route has been used to obtain the N-benzoyl derivative of L-daunosamine (54) from the C-2



Reagents: i, CH_2=CH(OBu^t)OMgX ; ii, Ac_2O-Py ; iii, H_2-Rh/C ; iv, H^+; v, BzCl ; vi, DIBAL

Scheme 9

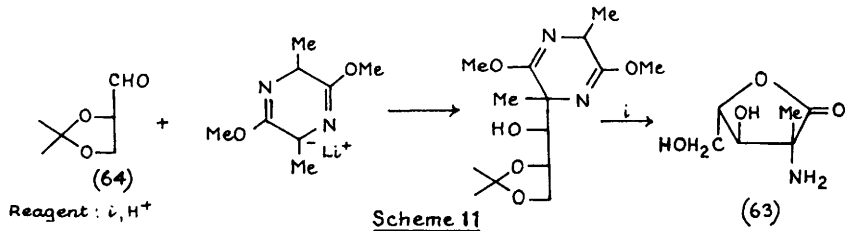
epimer of compound (58).[38] Henry reaction of the chiral aldehyde (59) with the nitro-derivative (60) has provided a chromatographically separable mixture (61) of (2S,4R,5S,6S)-, (2S,4S,5R,6S)- and (2S,4R,5R,6S)-4-amino-1,2,5,6-heptanetetrols, isolated in 16,



Reagents: i, KF-MeCN; ii, H_2-Raney Ni ; iii, Ac_2O

Scheme 10

22, and 16% yields (Scheme 10), from which 3-acetamido-2,3,5-trideoxy-L-hexopyranose derivatives (62) with the xylo-, arabino- [i.e., L-acosamine, c.f. (57)], and ribo- (i.e., L-ristosamine) configurations, respectively, could be separately synthesized by a procedure involving release and periodate cleavage of the terminal diol moiety. The synthesis of the nitro-derivative (60) in 10 steps and 16% overall yield, from 3,4-O-isopropylidene-1,2,5,6-tetra-O-mesyl-D-mannitol, was also reported.[39] The branched-chain amino-lactone (63) has been synthesized from 2,3-O-isopropylidene-L-glyceraldehyde (64) as shown in Scheme 11.[40]

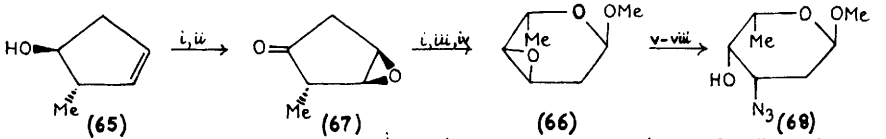


Reagent: i, H^+

Scheme 11

A variety of non-carbohydrate starting materials have been elaborated into amino-sugars. An extensive review on acyclic

stereoselective synthesis of carbohydrates from non-carbohydrates has included amino-sugar examples.[41] The cyclopentene (65), prepared by asymmetric hydroboration, has been converted into the known 3,4-anhydro-L-ribo-hexopyranoside (66) by Baeyer-Villiger oxidation of cyclopentanone (67),[42] and then into the L-daunosamine derivative (68) by conventional azide ring-opening of the epoxide

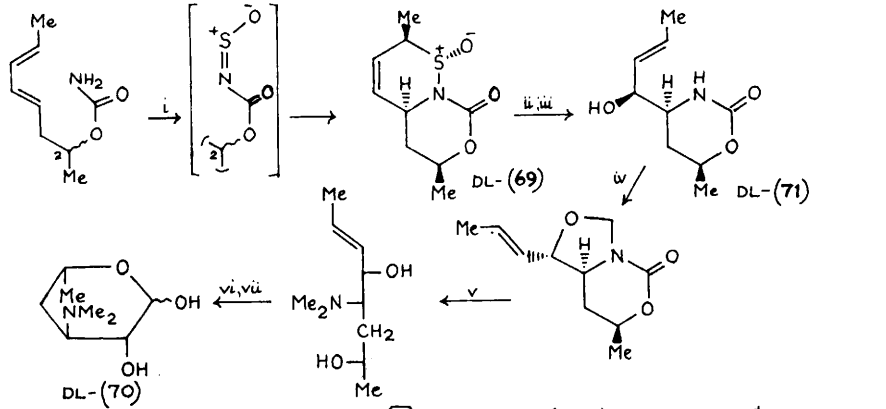


Reagents: i, MCPBA ; ii, CrO_3-Py ; iii, Bu^i_2AlH ; iv, MeOH-BF_3; v, NaN_3 ; vi, MsCl-Py; vii, NaOBz ; viii, NaOH

Scheme 12

and inversion of configuration at C-4 by sulphonate displacement (Scheme 12).[43]

A variety of conjugated dienes have been used as starting materials. The synthesis of racemic N-benzoyl-DL-daunosamine from (E)-1,3-pentadiene (Vol.15, p.96) has been detailed, and resolution of the enantiomers by crystallization with an optically active acid has been described.[44] The hetero-Diels-Alder cycloadduct (69) has been converted into DL-5-epi-desosamine (70) by the route shown in Scheme 13, involving cleavage to an allylic sulphoxide by a

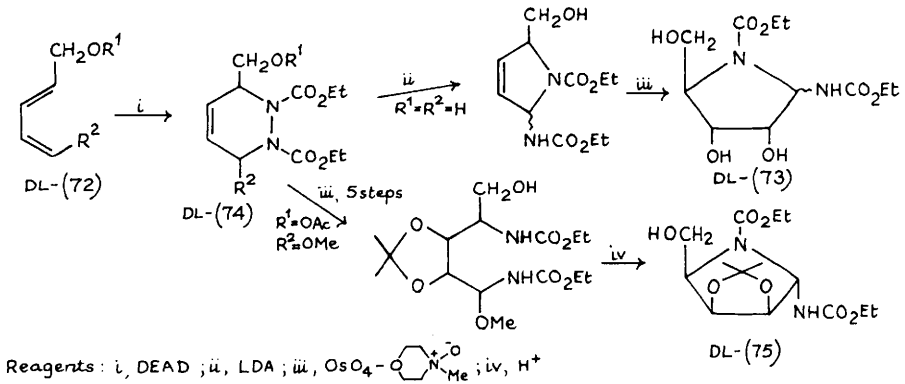


Reagents: i, $SOCl_2$-Py ; ii, PhMgBr ; iii, NH-EtOH ; iv, $(CH_2O)_n$; v, LAH ; vi, H^+ ; vii, O_3-Zn

Scheme 13

Grignard reagent, [2,3]-sigmatropic rearrangement of this to a sulphenate ester, and desulphurization to give the urethane derivative (71).[45] Racemic 4-amino-4-deoxy-pentofuranosylamine derivatives, which have ring-nitrogen atoms, have been synthesized by coupling dienes (72) with diethyl azodicarboxylate, the ribo-

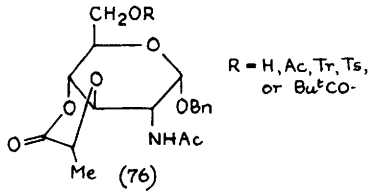
isomers (73) being obtained via ring contraction of the carbanion of (74),[46] the lyxo-isomer (75) by acid-catalyzed cyclization (Scheme 14).[47]

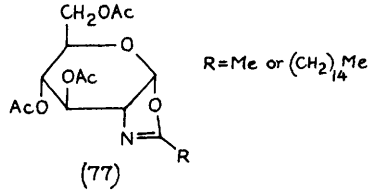


Scheme 14

3 Reactions

N-Acetyl-muramoyl-L-alanyl-D-isoglutamine (MDP) analogues continue to be popular synthetic targets. MDP itself has been synthesized by standard procedures from a 2-acetamido-2-deoxy-D-glucose derivative, and its FAB mass spectrum recorded.[48] Similarly, Hasegawa and co-workers have prepared and tested the immunoadjuvant activity of sulphur-containing MDP-analogues, including lipophilic N-octadecanoyl-1-thio-derivatives, some with additional octadecanoyl moieties on S-1 and/or O-6,[49] 3-deoxy 3-thio-MDP,[50] and 6-S-acetyl, -octadecyl, and -octadecanoyl-6-deoxy -6-thio-MDP derivatives.[51] The N-acetyl-muramic acid lactones (76) yield the corresponding HO-4 unsubstituted methyl esters with retention of the D-gluco-configuration, on silica gel-catalyzed methanolysis; in the presence of imidazole, lactones (76, R = H or Ac) condense with amino acids and peptide esters to give N-acetylmuramylamide derivatives.[52] N-Peptidyl-N'-glycosyl-thiourea

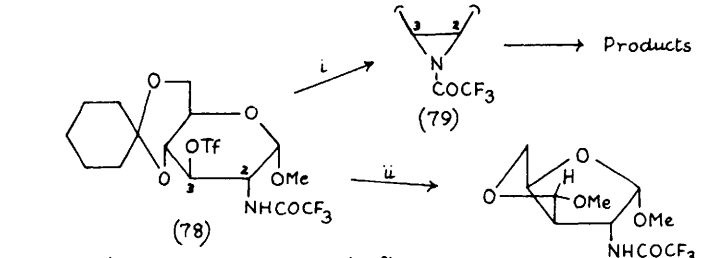




MDP-analogues with immunoadjuvant activity (see Chapter 10) [53] and an acryloyl-type polymer with pendant MDP-analogues (see Chapter 7) [54] have also been reported.

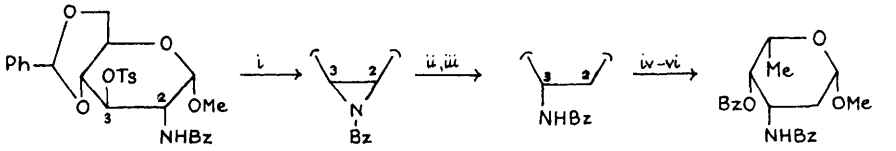
1,2-Fused oxazoline derivatives (77) have been obtained in high yield upon attempted phosphorylation of 3,4,6-tri-O-acetyl-2-acylamino-2-deoxy-D-glucopyranoses with 2-chlorophenylphosphorodi-(1,2,4-triazolide) in the presence of triethylamine.[55]

The 3-triflate group in the 2-trifluoroacetamido-derivative (78) can be displaced by the following alternate pathways depending upon the reagents used: i) conventional displacement with inversion (using LiCl or NaI-DMF), ii) formation and subsequent reaction of the 2,3-allo-epimine (79), or iii) ring contraction, involving



Scheme 15

migration of the C4-C5 bond, to give the 3-C-formyl derivative (80) (Scheme 15).[56] An analogous ring contraction of a diamino-sugar derivative was also reported and is covered in Section 4. A synthesis of methyl 3-N-benzoyl-4-O-benzoyl-β-L-daunosaminide (81) from 2-amino-2-deoxy-D-glucose has employed a 2,3-epimine intermediate (82) as a way of transferring nitrogen from C-2 to C-3 (Scheme 16).[57] A related displacement of a 3-tosylate by

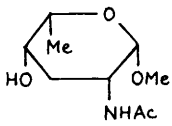


Scheme 16

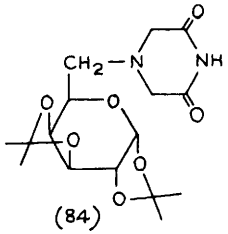
fluoride, involving a 2,3-epimine intermediate, is covered in Chapter 8. Methyl 2-acetamido-2,3,6-trideoxy-β-L-lyxo-hexo-pyranoside (83) has been synthesized conventionally by a C-6 deoxy-

genation, C-5 epimerization sequence similar to steps iv-vi in Scheme 16.[58]

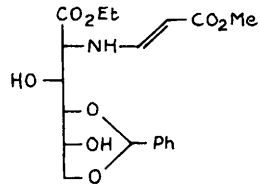
The N,N,N-trimethyl derivatives of 2-amino-2-deoxy-D-glucose and -D-galactose and of mycosamine (3-amino-3,6-dideoxy-D-mannose) have been synthesized.[59] In search of sugar-dioxopiperazine derivatives that might have anti-tumour activity, galactose-derivatives such as (84) have been synthesized by reaction of a



(83)

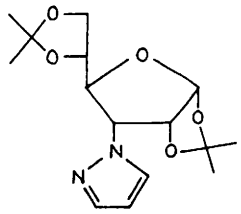


(84)

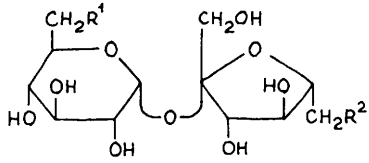


(85)

6-amino-precursor with sodium chloroacetate [to give a 6-amino-6-N,N-bis(carboxymethyl) derivative] then urea.[60] Michael addition of ethyl 2-amino-4,6-O-benzylidene-2-deoxy-D-gluconate to acetylenic esters has yielded enamines, e.g., (85) from methyl propiolate; the reaction has possible applications in N-protection.[61] Deoxy-(pyrazol-1-yl)-sugar derivatives such as the allofuranose derivative (86) have been synthesized as pseudo-N-nucleosides by reaction of deoxy-hydrazino derivatives with N-methylpyrimidinium methyl sulphate.[62]



(86)



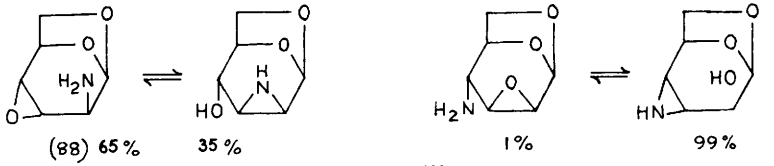
(87) R^1, R^2 = H, NHCON(NO)CH_2CH_2Cl

2-Amino-2-deoxy-D-glucose hydrochloride has been converted to the N-hexadecanoyl derivative using 3-hexadecanoyl-1,3-thiazolidine-2-thione, a reagent with high chemoselectivity for N- over O-acylation,[63] and has also been coupled with N-carboxy α-amino acid anhydrides sequentially to the N-tripeptidyl level.[64] Methyl 3-DL-alanylamido-3,6-dideoxy-α-D-glucopyranoside, which shows greater antibacterial activity than the corresponding 3-L-glyceroylamido derivative, has been synthesized conventionally from the 3-amino-precursor.[65] Two 2-chloroethylnitrosourea derivatives (87) of sucrose, synthesized by carbamoylation of

6-amino-6-deoxy- and 6'-amino-6'-deoxy-sucrose, have exhibited significant antitumour activity.[66]

The Maillard degradation of a large range of N-substituted 1-amino-1-deoxy-fructoses has been investigated, but the sometimes claimed correlation between the yield of pyrolyzate and the basicity of the amine moiety was not found.[67]

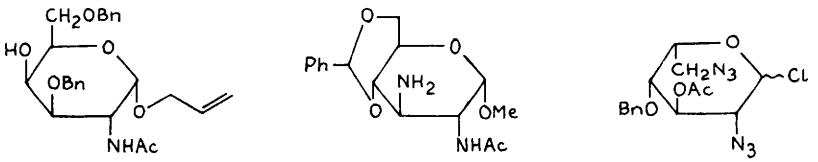
Cerny and co-workers have prepared four 2-amino-1,6-anhydro-dideoxy-β-D-hexopyranoses (the 2,3-dideoxy-arabino and -ribo and 2,4-dideoxy-lyxo and -xylo isomers) and have compared their ^{1}H- and ^{13}C-n.m.r. spectroscopic properties. The 2,3-dideoxy-arabino isomer was synthesized from 1,6-anhydro-D-mannosamine via the N-benzyloxycarbonyl derivative of 3,4-epoxide (88). These authors also examined the epoxide ⇌ epimine equilibria shown in Scheme 17 and demonstrated that greater stability was conferred by



Scheme 17

i) an exo-three-membered ring and ii) an aziridine compared to an epoxide ring.[68]

The partially protected 2-acetamido-2-deoxy-D-galactoside (89), a building block for oligosaccharide synthesis, has been conveniently prepared by standard methods from allyl 2-acetamido-2-deoxy-α-D-glucopyranose, the required inversion at C-4 being effected by sulphonate displacement.[69] 6-Amino-6-deoxy-2,3,4,5-tetra-O-methyl-D-gluconic acid has been prepared conventionally from 6-azido-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose for a study of the biological properties of ω-aminoaldonic acids.[70]

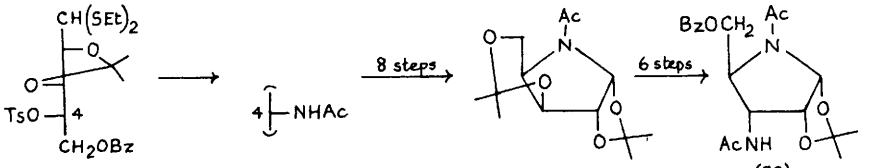


Syntheses of the alkaloid swainsonine (see Chapter 24) have employed methyl 3-amino-3-deoxy-α-D-mannopyranoside derivatives made either from D-glucose via dialdehyde-nitromethane condensation [71] or from a 3-amino-3-deoxy-D-glucose derivative, the required inversion at C-2 being effected by sulphonate

displacement.[72]

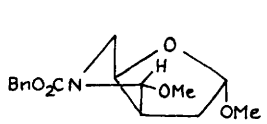
4 Di- and Tri-Amino-sugars

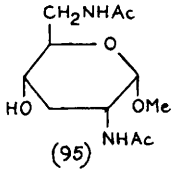
Sulphonate displacement with azide has been used to prepare several diamino-sugars. The 2,3-diamino-2,3-dideoxy-D-glucose derivative (90) was obtained after phase-transfer catalyzed displacement of a 3-mesylate from a 2-acetamido-2-deoxy-D-allopyranoside precursor.[73] The 2,6-diazido-2,6-dideoxy-L-idopyranosyl chloride (91), required for the synthesis of neomycin B, has been synthesized in 13 steps from a D-glucofuranose derivative, using a reduction-oxidation sequence to invert the sugar chain. Chloride (91) was converted into the unprotected methyl 2,6-diamino-2,6-dideoxy-α-L-idopyranose.[74] The ring-nitrogen containing derivative (92), regarded as a chiral precursor for 7,11-diazaprostanoids, has been synthesized stereospecifically from L-arabinose via the dithioacetal derivative (93) (Scheme 18).[75]



Scheme 18

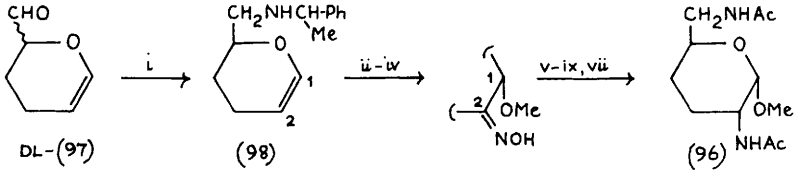
The 3-C-formyl derivative (94) has been formed by elimination of a 3-triflate from a 2,6-diamino-D-glucoside derivative with ring-contraction, in a fashion analogous to that shown earlier in Scheme 15.[56]





A synthesis of di-N-acetyl-α-D-tobrosaminide (95) from a 2-acetamido-4,6-O-benzylidene-2,3-dideoxy-precursor involved generation of a 6-bromide using N-bromosuccinimide and displacement of bromide by azide.[58]

The methyl α-D-purpurosaminide C derivative (96) has been synthesized from acrolein dimer (97) as shown in Scheme 19. Reductive amination with (R)-α-methylbenzylamine provided a pair



Reagents: i, $PhCH(Me)NH_2$–$NaBH_4$; ii, Tf_2O–Py; iii, NOCl; iv, MeOH; v, $NaBH_3CN$–HOAc; vi, Pd/C; vii, Ac_2O; viii, $NaBH_4$; ix, $Pd(OH)_2$–H_2

Scheme 19

of diastereoisomeric 6-amino-derivatives from which the desired isomer (98) could be isolated as its 3,5-dinitrobenzoate.[76] The synthesis of a 3,4-unsaturated purpurosamine C derivative is covered in Chapter 13.

References

1 T.Niwa, T.Tsuruoka, H.Goi, Y.Kodama, J.Itoh, S.Inouye, Y.Yamada, T.Niida, M.Nobe, and Y.Ogawa, J. Antibiot., 1984, 37, 1579.
2 S.W.Hunter, T.Fujiwara, R.C.Murphy, and P.J.Brennan, J. Biol. Chem., 1984, 259, 9729.
3 Z.J.Witczak, J. Carbohydr. Chem., 1984, 3, 359.
4 H.Ogura and K.Furuhata, Yuki Gosei Kagaku Kyokai Shi, 1984, 42, 536 (Chem. Abstr., 1984, 101, 152 192).
5 V.Jaeger, H.Grund, V.Buss, W.Schwab, I.Mueller, R.Schohe, R.Franz, and R.Ehrler, Bull. Soc. Chim. Belg., 1983, 92, 1039 (Chem. Abstr., 1984, 100, 139 561).
6 C.M.Lee, B.Sherr and Y.N.Koh, J. Agric. Food Chem., 1984, 32, 379 (Chem. Abstr., 1984, 100, 121 563).
7 L.Kroh and G.Westphal, Z. Chem., 1983, 23, 293 (Chem. Abstr., 1984, 100, 103 784).
8 I.Drivas, D.Picq, D.Anker, and H.Pacheco, J. Carbohydr. Chem., 1984, 3, 243.
9 I.Cerny, T.Trnka, and M.Cerny, Collect. Czech. Chem. Commun., 1984, 49, 433.
10 M.Georges, D.MacKay, and B.Fraser-Reid, Carbohydr. Res., 1984, 130, 115.
11 H.W.Pauls and B.Fraser-Reid, Can. J. Chem., 1984, 62, 1532.
12 Atta-ur-Rahman, N.Hong, and J.Yoshimura, J. Chem. Soc. Pak., 1983, 5, 253 (Chem. Abstr., 1984, 101, 111 318).
13 A.O.Stewart and R.M.Williams, Carbohydr. Res., 1984, 135, 167.
14 N.B.Dyatkina and A.V.Azhayev, Syhthesis, 1984, 961.
15 M.Kiso, H.Ishida, A.Kawaide, and A.Hasegawa, Carbohydr. Res., 1984, 127, 129.
16 M.Kiso, A.Yasui, and A.Hasegawa, Carbohydr. Res., 1984, 127, 137.
17 A.Malik, N.Afza, M.Roosz, and W.Voelter, J. Chem. Soc., Chem. Commun., 1984, 1530.
18 A.Malik, W.Kowollik, P.Scheer, N.Afza, and W.Voelter, J. Chem. Soc., Chem. Commun., 1984, 1229.
19 T.W.Flechtner and H.Pohlid, J. Carbohydr. Chem., 1984, 3, 107.
20 M.Georges, D.Mackay, and B.Fraser-Reid, Can. J. Chem., 1984, 62, 1539.
21 A.Malik, N.Afza, and W.Voelter, Biol. Act. Princ. Nat. Prod., 1984, 230 (Chem. Abstr., 1984, 101, 111 319).
22 A.Malik, N.Afza, and W.Voelter, Justus Liebigs Ann. Chem., 1984, 636.
23 W.Voelter, A.Malik and A.Afza, Z. Naturforsch., B: Anorg. Chem., Org. Chem., 1984, 39B, 405 (Chem. Abstr., 1984, 101, 55 462).

24 W.Schmid and E.Zbiral, Monatsh. Chem., 1983, 114, 1253 (Chem. Abstr., 1984, 100, 210 306).
25 J.A.Galbis Perez, J.C.Palacios Albarran, J.L.Jiminez Requejo, M.Avalos Gonzalez, and J.M.Fernandez-Bolaños, Carbohydr. Res., 1984, 129, 131.
26 J.A.Galbis Perez, J.C.Palacios Albarran, J.L.Jimenez Requejo, M.Avalos Gonzalez, and J.M.Fernandez-Bolaños, Carbohydr. Res., 1984, 131, 71.
27 G.Cardillo, M.Orena, S.Sandri, and C.Tomasini, J. Org. Chem., 1984, 49, 3951.
28 G.Legler and E.Jülich, Carbohydr. Res., 1984, 128, 61.
29 K.Omichi and T.Ikenaka, J. Chromatogr., 1984, 336, 368.
30 D.Picq, D.Anker, and H.Pacheco, Carbohydr. Res., 1984, 128, 283.
31 P.M.Collins, W.G.Overend, and V.M.Racz, J. Chem. Soc., Perkin Trans. 1, 1984, 733.
32 T.Yasumori, K.-i.Sato, H.Hashimoto, and J.Yoshimura, Bull. Chem. Soc. Jpn., 1984, 57, 2538.
33 P.DeShong, C.M.Dicken, J.M.Leginus, and R.R.Whittle, J. Am. Chem. Soc., 1984, 106, 5598.
34 V.Jäger and R.Schohe, Tetrahedron, 1984, 40, 2199.
35 Y.Hamada, A.Kawai, and T.Shioiri, Tetrahedron Lett., 1984, 25, 5409.
36 Y.Hamada, A.Kawai, and T.Shioiri, Tetrahedron Lett., 1984, 25, 5413.
37 T.Hiyama, K.Nishide, and K.Kobayashi, Tetrahedron Lett., 1984, 25, 569.
38 T.Hiyama, K.Nishide, and K.Kobayashi, Chem. Lett., 1984, 361.
39 T.Suami, K.Tadono, A.Suga, and Y.Ueno, J. Carbohydr. Chem., 1984, 3, 429.
40 J.-C.Depezay and A.Dureault, Tetrahedron Lett., 1984, 25, 1459.
41 G.J.McGarvey, M.Kimura, T.Oh, and J.M.Williams, J. Carbohydr. Chem., 1984, 3, 125.
42 G.Grethe, J.Sereno, T.H.Williams, and M.R.Uskokovic, J. Org. Chem., 1983, 48, 5315.
43 G.Grethe, T.Mitt, T.H.Williams and M.R.Uskokovic, J. Org. Chem., 1983, 48, 5309.
44 F.M.Hauser, R.P.Rhee, and S.R.Ellenberger, J. Org. Chem., 1984, 49, 2236.
45 S.W.Remiszewski, R.R.Whittle, and S.M.Weinreb, J. Org. Chem., 1984, 49, 3243.
46 A.K.Forrest and R.R.Schmidt, Tetrahedron Lett., 1984, 25, 1769.
47 A.K.Forrest, R.R.Schmidt, G.Huttner, and I.Jibril, J. Chem. Soc., Perkin Trans. 1, 1984, 1981.
48 L.R.Phillips, O.Nishimura, and B.A.Fraser, Carbohydr. Res., 1984, 132, 275.
49 A.Hasegawa, E.Seki, Y.Hioki, M.Kiso, and I.Azuma, Carbohydr. Res., 1984, 131, 61.
50 A.Hasegawa, M.Ozaki, M.Kiso, and I.Azuma, J. Carbohydr. Chem., 1984, 3, 331.
51 A.Hasegawa, E.Seki, Y.Hioki, M.Kiso, and I.Azuma, Carbohydr. Res., 1984, 129, 271.
52 D.Keglevic and M.Pongracic, Carbohydr. Res., 1984, 135, 85.
53 Yu.P.Abashev, T.M.Andronova, S.E.Zurabyan, V.P.Mal'kova, I.B.Sorokina, and Ya.A.Khorlin, Bioorg. Khim., 1984, 10, 18 (Chem. Abstr., 1984, 100, 192 252).
54 T.Ouchi, Y.Sakamoto, S.Jokei, and H.Chikashita, Makromol. Chem., 1984, 185, 255 (Chem. Abstr., 1984, 100, 192 401).
55 J.J.Oltvoort, C.A.A.Van Boeckel, G.A.Van der Marel, and J.H.Van Boom, Recl.: J.R.Neth. Chem. Soc., 1983, 102, 475 (Chem. Abstr., 1984, 100, 103 791).
56 T.Tsuchiya, K.Ajito, S.Umezawa, and A.Ikeda, Carbohydr. Res., 1984, 126, 45.
57 M.K.Gurjar, V.J.Patil, J.S.Yadav, and A.V.R.Rao, Carbohydr. Res., 1984, 129, 267.
58 M.M.Abuaan, J.S.Brimacombe, and L.C.N.Tucker, Carbohydr. Res., 1984, 132, 51.
59 L.Falkowski, M.Beszczynski, A.Jarzebski, and B.Stefanska, Pol. J. Chem., 1983, 57, 1353.

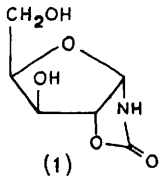
60 K.Capek, J.Capkova, J.Jary, and P.Trska, Collect. Czech. Chem. Commun., 1984, 49, 1914.
61 L.M.Vázquez de Miguel, J.A.Serrano Blázquez, F.J.Garciá Barros, and M.Gómez Guillén, Carbohydr. Res., 1984, 126, 81.
62 P.Smit, G.A.Stork, and H.C.Van der Plas, Recl.: J.R.Neth. Chem. Soc., 1983, 102, 453 (Chem. Abstr., 1984, 100, 121 505).
63 Y.Nagao, K.Seno, K.Kawabata, T.Miyasaka, S.Takao, and E.Fujita, Chem. Pharm. Bull., 1984, 32, 2687.
64 M.Oya and T.Negishi, Bull Chem. Soc. Jpn., I984, 57, 439.
65 I.Jezo and J.Zemek, Chem. Zvesti, 1984, 38, 405.
66 T.Suami, T.Kato, K.Kanai, S.Ohki, and H.Yamashita, J. Carbohydr. Chem., 1984, 3, 417.
67 E.J.Birch, J.Lelievre, and E.L.Richards, Carbohydr. Res., 1984, 128, 351.
68 I.Černý, M.Buděšínský, T.Trnka, and M.Černý, Carbohydr. Res., 1984, 130 103.
69 M.A.Nasheed, R.I.El-Sokkary, and L.Rateb, Carbohydr. Res., 1984, 131, 47.
70 K.Kefurt, Z.Kefurtova, and J.Jary, Collect. Czech. Chem. Commun., 1984, 49, 2665.
71 M.H.Ali, L.Hough, and A.C.Richardson, J. Chem. Soc., Chem. Commun., 1984, 447.
72 T.Suami, K.Tadano, and Y.Iimura, Chem. Lett., 1984, 513.
73 A.Calvo-Mateo, M.J.Camarasa, and F.G.De las Heras, J. Carbohydr. Chem., 1984, 3, 461.
74 T.Usui, Y.Takagi, T.Tsuchiya, and S.Umezawa, Carbohydr. Res., 1984, 130, 165.
75 I.Coetzee, C.W.Holzapfel, J.M.Koekemoer, and A.E.Von Platen, S. Afr. J. Chem., 1984, 37, 11 (Chem. Abstr., 1984, 101, 131 013).
76 B.Schwesinger, R.Schwesinger, and H.Prinzbach, Tetrahedron Lett., 1984, 25, 1979.

10
Miscellaneous Nitrogen Derivatives

1 Glycosylamines

N-(p-Chloro- and p-methoxy-phenyl) α- and β-D-lyxo-pyranosylamines and their O- and/or N-acetylated derivatives have been synthesized; while the α-tetraacetate adopted the $^{1}C_{4}$-conformation, the β-tetraacetate adopted the $^{4}C_{1}$-conformation.[1] Glucopyranosylamine derivatives have been synthesized by Lewis acid ($AlMe_3$ or $MgBr_2.OEt_2$)-catalyzed reactions of 2,3,4,6-tetra-O-benzyl-α,β-D-glucopyranosyl fluoride with amines; aniline gave a 1:1 mixture of anomers, but morpholine favoured the β-anomer by 10:1.[2] A ^{1}H- and ^{13}C-n.m.r. study has shown that the reaction of D-ribose, or its 2,3-O-isopropylidene derivative, with secondary amines furnishes mixtures containing only β-pyranosylamines and β-furanosylamines and, in some instances, Amadori rearrangement products (2-30%).[3] The glycosylamine formed on reaction of 1-deoxy-1-tolylamino-D-fructopyranose with glycine ethyl ester has been characterized.[4]

The synthesis of α-D-xylo- and α-D-gluco-pyranosyl pyridinium bromides has permitted their conformations in D_2O solution ($^{1}C_{4}$ and $^{1}S_{3}$ respectively) to be determined by ^{1}H-n.m.r. spectroscopy and the kinetics of their acid catalyzed hydrolysis to be studied in detail. The antiperiplanar lone pair hypothesis is discussed and considered not to be applicable.[5] Similarly, the N-β-D-glucuronides of pyridine and 3-methylpyridine have been synthesized by standard Koenigs-Knorr methods, and their base- and β-glucuronidase-catalyzed hydrolysis has been studied. Hydrogenation of the former compound caused glycosidic cleavage, but reduction of its methyl ester peracetate yielded the correspondingly protected N-D-glucuronide of piperidine.[6]



(1)

α-D-Xylo-furano[1,2-d]oxazolidin-2-one (1) has been isolated as the major monomeric product from reaction of equimolar amounts of xylose and urea in water at 68° for six weeks.[7] Reaction of benzosulphimide or succinimide, as their silver salts, with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide gave the expected β-glucosylated imides, whereas phthalimide gave the corresponding ortho-ester derivative.[8]

Carboxy-activated aminoacids have been coupled with unprotected glycosylamines to prepare both anomers of N-(L-β-aspartoyl)-D-glucopyranosylamine,[9] di- and tri-peptidyl β-glycosylamines having D-glucopyranosyl, cellobiosyl, or 2-acetamido-2-deoxy-D-glucopyranosyl sugar moieties,[10] and N-glycidoyl-α-D-glucopyranosylamine.[11] The amido-linkage between D-glucopyranosylamine and aspartic acid, glutamic acid, and glycine can be cleaved by hydroxide-form anion exchange resin in water, α-linkages being more readily cleaved than β-linkages. This treatment did not cleave the analogous linkage between 2-acetamido-2-deoxy-D-glucopyranosylamine and asparagine or glutamine.[11]

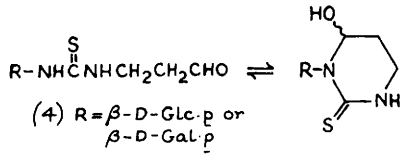
A new procedure for the synthesis of glycosyl isothiocyanates involves the action of potassium thiocyanate and a tetrabutylammonium salt as catalyst on per-O-acetylated, -benzoylated or -benzylated glycosyl halides in acetonitrile, e.g., 2,3,4-tri-O-acetyl-β-D-ribofuranosyl isothiocyanate (55% yield).[12]

N-Lactosyl-urea and -thiourea derivatives have been obtained by condensation of lactosylamine with long chain isocyanates and isothiocyanates respectively.[13] Muramoyl dipeptide analogues (2) and (3) in which the sugar is joined to the peptide by a glycosylamine

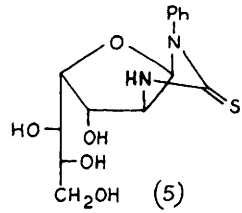
(2) (3)

n = 0-2
X = Ala, L-Ala-D-Glu, L-Ala-D-iso-Gln, or D-Ala-L-Ala-D-iso-Gln

linkage have been synthesized by coupling acetylated glycosyl isothiocyanates with alanine or unprotected peptides and shown to have immunoadjuvant activity.[14] N-β-D-Galactosyl- and glucosyl-N'-(propanal-3-yl)-thioureas (4), which exist as equilibrium mixtures of ring-chain tautomers, have similarly been synthesized from acetylated glycosyl isothiocyanates.[15] Per-O-acetylated β-D-gluco- or α-D-arabino-pyranosyl isothiocyanates have been used as chiral reagents for the preparation of diastereoisomeric thiourea deriva-



(4) R = β-D-Glc-p or β-D-Gal-p

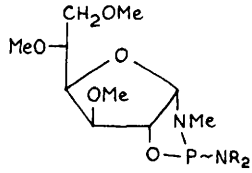


(5)

tives of enantiomeric amino acids (c.f. Vol.15, p.108)[16] and amphetamines (1-phenyl-2-aminopropane derivatives)[17,18] that are separable by h.p.l.c.

Glycofurano-imidazolidine-2-thiones such as the D-glycero-L-gluco-derivative (5) have been obtained by reactions of aryl isothiocyanates with 2-deoxy-2-ethylamino-hexoses and -heptoses, whose synthesis is referred to in Chapter 9.[19,20]

The 1,2-N,O-cycloglycosylamidophosphites (6) have been synthesized by reaction of N-methyl-2,4,6-tri-O-methyl-D-glucofuranosyl-



(6) R = Me or Et

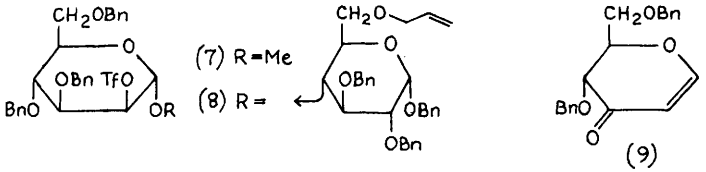
amine with tris(dialkylamino)phosphines; subsequent oxidation with nitric oxide or sulphur furnished the corresponding amidophosphates and amidothiophosphates respectively.[21]

2 Azido-sugars

Azido-sugars encountered as intermediates in syntheses of amino-sugars are covered in Chapter 9.

A mixture of 2,3,4,6-tetra-O-benzyl-α- and β-D-glucopyranosyl azides in the ratio 10:1 has been obtained in 90% yield from the corresponding anomeric mixture of glycosyl fluorides on treatment with trimethylsilyl azide in the presence of boron trifluoride as catalyst.[2]

Sulphonate displacement reactions are frequently used for introducing azide substituents, but in the case of the α-D-mannosides (7) and (8) displacement (LiN_3-DMF) of the 2-O-triflate could be achieved only in low yield, the major product being the enone (9) in both cases. By contrast, the β-anomer of (7) gave a

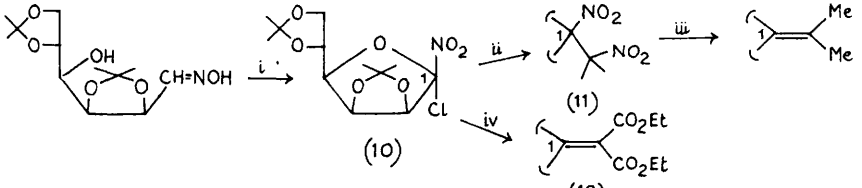


(9)

2-azido-glucoside in 90% yield, presumably because in this case the anomeric substituent does not hinder the approaching nucleophile.[22] A new synthesis of methyl 3-azido-2,3-dideoxy-4-O-(p-methylbenzoyl)-α,β-D-ribofuranose in 9 steps from 1,2:3,5-di-O-isopropylidene-α-D-xylofuranose involved displacement of a triflate group by azide; the product is a potential precursor of 2,3-dideoxy-3-amino-nucleosides.[23]

3 Nitro- and nitroso-sugars

1-C-Nitroglycosyl chlorides such as (10) have been synthesized from sugar oximes [24] and used for the synthesis of chain-extended sugar derivatives using both photoinduced free radical coupling reactions [to give (11)] or displacement of halide by a weakly basic carbanion [to give (12)] (Scheme 1).[25] The α-chloronitro-

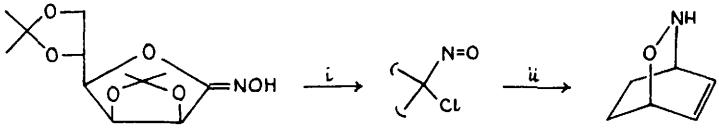


(10) (11) (12)

Reagents: i, NaOCl-Bu_4NHSO_4-H_2O; ii, $\rangle=N^{+}_{O^-}$ K^+-hν; iii, Na_2S; iv, $(EtO_2C)_2CH^-$-hν

Scheme 1

derivative (10) is presumed to be formed by oxidation of the cyclized form of the oxime to the known D-mannonolactone oxime (13) (see Section 4, ref.35) and then to the α-chloronitroso compound (14). This latter transformation has been separately reported en route to the optically pure hetero-Diels-Alder adduct (15)

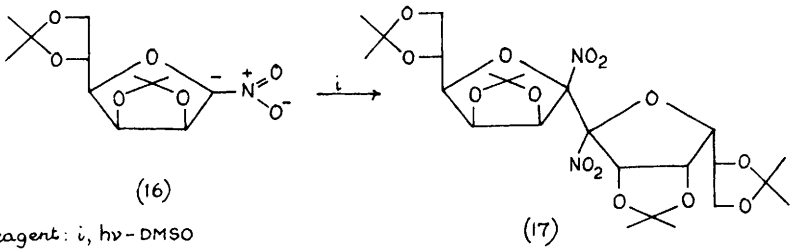


(13) (14) (15)

Reagents: i, Bu^tOCl; ii, ⬡ - MeOH

Scheme 2

(Scheme 2).[26] Photo-induced dimerization of the carbanion (16) derived from the bromo-analogue of (10) led to dinitro-derivative (17) in high yield (Scheme 3).[25]

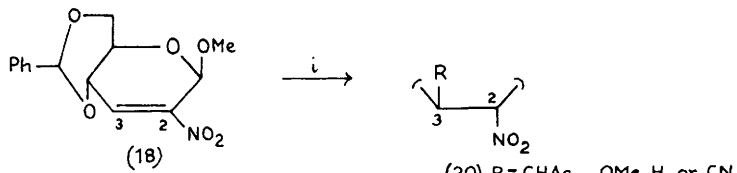


(16) (17)

Reagent: i, hν - DMSO

Scheme 3

Sakakibara and co-workers have reported in full (c.f. Vol.16, p.112) on the synthesis of, and Michael addition of nucleophiles to, the anomeric methyl 2,3-dideoxy-2-nitro-β-D-erythro-hex-2-eno-pyranosides (18) and (19). In the case of the β-anomer (18), nucleophiles added predominantly in an equatorial fashion at C-3,

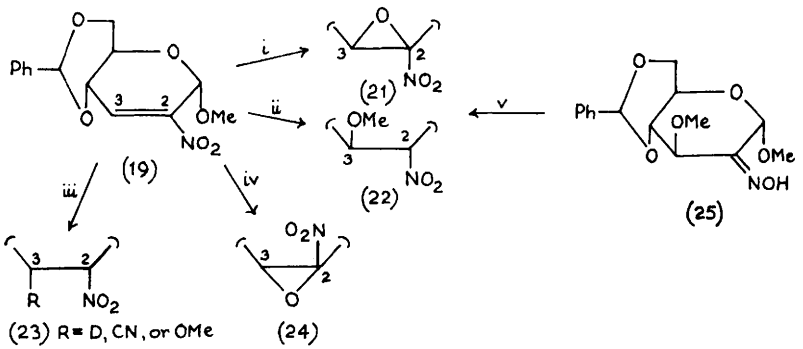


(18) (20) R = $CHAc_2$, OMe, H, or CN

Reagents: i, Ac_2CHNa, MeOH, $NaBH_4$, or HCN

Scheme 4

leading mainly to products with a β-D-gluco-configuration, e.g. (20), (Scheme 4).[27] In the case of the α-anomer (19), products were dependent upon the nature of the nucleophile (Scheme 5). The



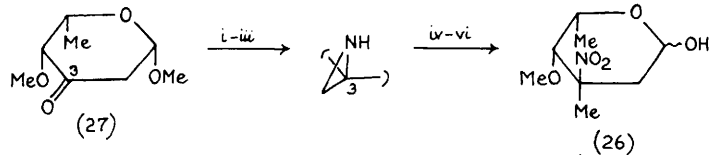
(19) (21) (22) (23) R = D, CN, or OMe (24) (25)

Reagents: i, But_2O_2; ii, NaOMe; iii, $NaBD_4$, HCN, or MeOH; iv, H_2O_2-NaOH; v, CF_3CO_3H - $NaHCO_3$ - $CO(NH_2)_2$

Scheme 5

bulky di-tert-butyl peroxide and the charged sodium methoxide led to products of equatorial C-3 attack, i.e., the 2-nitro-manno-epoxide (21) and the 3-O-methyl-α-D-gluco-derivative (22), respectively. Other reagents, however, added predominantly by axial C-3 attack to give α-D-allo-derivatives (23) accompanied by lesser amounts of their C-2 epimeric α-D-altro-isomers or, in the case of alkaline hydrogen peroxide, the 2-nitro-allo-epoxide (24). The 3-O-methyl-α-D-gluco-derivative (22) was also obtained by oxidation of the oxime (25).[28]

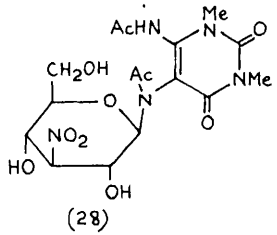
The branched-chain nitro-sugar L-rubranitrose (26) has been elaborated from the 3-keto-derivative (27) as shown in Scheme 6.[29]

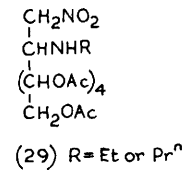


Reagents: i, HCN-Py; ii, MsCl; iii, LAH; iv, H_2-Ni; v, MCPBA; vi, H_3O^+

Scheme 6

The 3-nitro-nucleoside analogue (28) has been synthesized from the corresponding D-glucosyl nucleoside by conventional periodate oxidation - nitromethane condensation procedures.[30] 2-Alkylamino-1-nitro-heptitols (29) have been synthesized by addition of ethylamine or n-propylamine to 1,2-dideoxy-1-nitro-hept-1-enitol tetra-

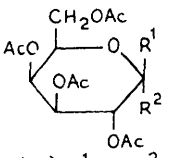




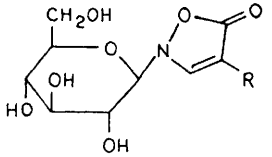
acetates with D-gluco-, D-manno, and D-galacto-configurations.[31]

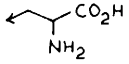
4 Nitriles, Isonitriles, Oximes and Hydroxylamines

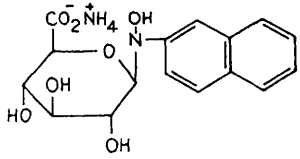
2,4,5,6-Tetra-O-benzoyl-D-gluconononitrile has been identified as a byproduct frequently encountered in the synthesis of the perbenzoylated D-gluconononitrile.[32] Reaction of the per-O-acetylated D-galacto-, D-xylo- and D-arabino-pyranosyl bromides of hept- and hexulononitriles, e.g., (30), with silver or mercury(II) acetate in acetic acid-acetic anhydride solution has provided the corresponding inverted pyranosyl acetates, e.g., (31), in good yields.[33]



(30) R^1=CN, R^2=Br
(31) R^1=OAc, R^2=CN



(32) R= H or 



(33)

The synthesis, reactions and spectroscopic properties of carbohydrate isonitriles, including both glycosyl and ring-substituted derivatives, have been reviewed.[34]

Reaction of 2,3:5,6-di-O-isopropylidene-D-mannose oxime with N-chlorosuccinimide in pyridine gave the N-hydroximinolactone (13) (see Scheme 2) rather than the isomeric ring-opened nitrile oxide. Conditions under which this lactone oxime would act as a precursor of the nitrile oxide for dipolar cycloaddition to alkenes were not found.[35]

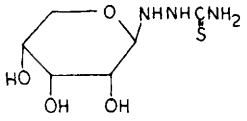
The levels of isoxazolin-5-ones, including the glucosyl derivatives (32), present in the plant Lathyrus odoratus at various stages of development have been determined.[36] The N-glucuronides of the carcinogenic N-hydroxyarylamines, N-hydroxy-4-aminobiphenyl, N-hydroxy-2-aminofluorene, and N-hydroxy-2-aminonaphthalene, e.g., (33), have been prepared in good yields by direct condensation of glucuronic acid with the appropriate hydroxylamine.[37]

D-Ribose and its 2,3-O-isopropylidene derivative condense with hydroxylamine to give primarily the acyclic oximes, as shown by ^{1}H- and ^{13}C-n.m.r. studies;[3] e.g., 2,3-O-isopropylidene-D-ribose gave an 8:1:1-mixture of the E- and Z-acyclic isomers and the β-furanose form respectively.

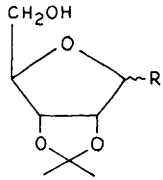
5 Hydrazones, Osazones and Derived Heterocycles

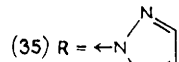
The products formed on reaction of D-ribose and its 2,3-O-isopropylidene derivative with secondary amines (see Section 1), hydroxylamine (see Section 4), hydrazine and thiosemicarbazide have been determined by ^{1}H- and ^{13}C-n.m.r. studies. Hydrazine gave primarily the acyclic hydrazones, whereas thiosemicarbazide afforded mainly cyclic derivatives. Thus D-ribose and thiosemicarbazide gave the pyranose derivatives (34) along with its β-furanose, and E-acyclic isomers in the ratio 54:9:37 respectively.[3] Reaction of N-methylpyrimidinium methyl sulphate with the hydrazone of 2,3-O-

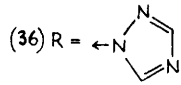
isopropylidene-D-ribose led to the 1-N-ribofuranosyl-pyrazole and -(1,2,4-triazole) derivatives, (35) and (36), in 10 and 17% yield respectively.[38]

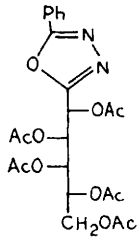


(34)



(35) R = 

(36) R = 



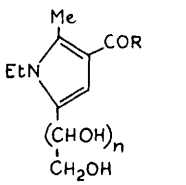
(37)

Emission and excitation spectra of D-arabino-hexulose phenylosazone have been measured to determine the singlet and triplet excited state energy levels for the planar and twisted conformations.[39]

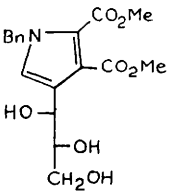
Mono- and bis-hydrazones have been formed sequentially by reaction of dehydroascorbic acid and m-chlorophenylhydrazine. The bis-hydrazone was converted into a pyrazole derivative on treatment with base (c.f. Vol.15, p.113).[40] The cyclization of the N-benzoylhydrazones of galactose, arabinose, and 6-deoxygalactose to oxadiazole derivatives, e.g., (37), has been described.[41] The D-gluconoylhydrazones of 5-nitrofurfural and 3-(5-nitro-2-furyl)-propenal have been synthesized by condensation of D-gluconic acid hydrazide with the corresponding aldehydes.[42]

6 Other Heterocyclic Derivatives

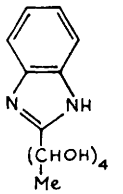
Several tetritol-1-yl- and pentitol-1-yl-pyrrole derivatives (38) have been prepared by condensation of 2-deoxy-2-ethylamino-hexoses or -heptoses with 2,4-pentanedione or ethyl 3-oxobutyrate,[43] while the 4-(D-threo-trihydroxypropyl)pyrrole (39) has been synthesized by addition of dimethyl acetylenedicarboxylate to 1-benzylamino-1-



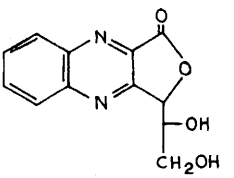
(38) R = Me or OEt
n = 2 or 3



(39)



(40)

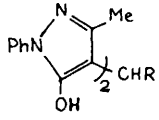


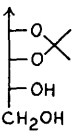
(41)

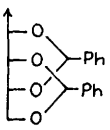
deoxy-D-threo-pentulose.[44]

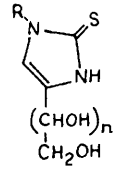
In a continuing study of the reaction of sugars with o-phenylenediamine under acidic conditions (c.f. Vol.17, p.112), D-ribose, D-xylose,[45] L-rhamnose and L-fucose[46] have been shown to give mixtures of 2-(alditol-1-yl)-quinoxaline derivatives, accompanied in the case of the latter two sugars by benzimidazole derivatives (40). The quinoxaline derivative (41) has similarly been obtained by reaction of dehydro-D-arabino-ascorbic acid with o-phenylenediamine and subjected to further conversions.[47]

Five 1,1-di-C-substituted 1-deoxy-D-ribitol derivatives, including compounds (42) and (43), and two 1-deoxy-D-glucitol analogues have been synthesized by condensation of aldehydo-sugar derivatives with 3-methyl-1-phenyl-5-pyrazolone and shown to have high antiviral activity with relatively low cytotoxicity.[48]



(42) R = 

(43) R = 

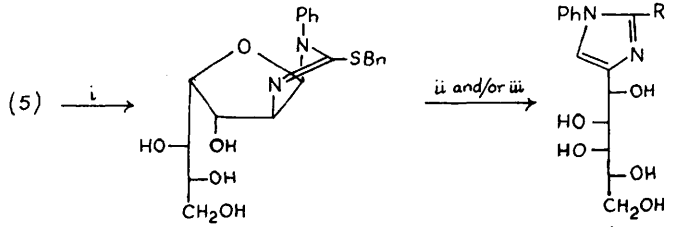


(44) R = $C_6, C_8 \cdots C_{16}$ (alkyl)

n-2 or 3

4-(Polyhydroxyalkyl)-1-N-alkyl-1,3-dihydro-2H-imidazole-2-thiones (44) have been synthesized by condensation of 1-alkylamino-1-deoxy-pent- or hex-2-uloses with potassium thiocyanate, while several 3-N-alkyl isomers were obtained from 2-alkylamino-2-deoxy-D-glucose by the same procedure.[49]

The (D-glycero-L-gluco-heptofurano)-imidazoline derivative (5) (see Section 1) has been converted into the 4-(D-galacto-pentitol-1-yl)imidazole derivatives (45), which are acyclic C-nucleoside analogues, as shown in Scheme 7.[50,51] Analogous 1-deoxy-1-C-



Reagents: i, BnCl-$NaHCO_3$; ii, Raney Ni; iii, CF_3CO_2H

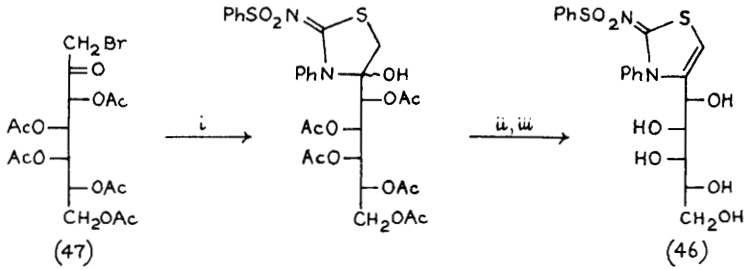
(45) R=H or SBn

Scheme 7

(substituted Δ^4-thiazolinylidene)-D-galactitols, e.g.,(46), have been synthesized by condensation of the 1-bromo-1-deoxy-heptulose

derivative (47) with thiourea derivatives, followed by dehydration of the initial adducts (Scheme 8).[52]

Other heterocyclic derivatives are referred to in Chapter 9.



(47) (46)

Reagents: i, $PhSO_2NHCSNHPh$; ii, $POCl_3$; iii, deacetylation

Scheme 8

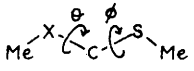
References

1 Z.Smiatacz and A.Moczulska, Carbohydr. Res., 1984, 128, 227.
2 K.C.Nicolaou, A.Chucholowski, R.E.Dolle, and J.L.Randall, J. Chem. Soc., Chem. Commun., 1984, 1155.
3 C.Chavis, C.De Gourcy, and J.-L.Imbach, Carbohydr. Res., 1984, 135, 13.
4 L.Kroh and G.Westphal, Z. Chem., 1983, 23, 293 (Chem. Abstr., 1984, 100, 103 784).
5 L.Hosie, P.J.Marshall, and M.L.Sinnott, J. Chem. Soc., Perkin Trans. 1, 1984, 1121.
6 L.Dalgaard, Acta Chem. Scand., 1983, B37, 923.
7 L.Benzing-Purdie and J.H.Nikiforuk, J. Carbohydr. Chem., 1983, 2, 439.
8 J.A.Serrano Blazquez and F.Marquez Archilla, An. Quim., Ser. C, 1984, 80, 17 (Chem. Abstr., 1984, 101, 211 571).
9 M.Tamura, H.Nishizaki, C.Miyazaki, and H.Okai, Bull. Chem. Soc. Jpn., 1984, 57, 3167.
10 M.Tamura and H.Okai, Carbohydr. Res., 1984, 133, 207.
11 M.Sawaki, T.Takeda, Y.Ogihara, and S.Shibata, Chem. Pharm. Bull., 1984, 32, 3698.
12 M.J.Camarasa, P.Fernandez-Reza, M.T.Garciá-López, F.G.de las Heras, P.P.Mendez-Castrillón, and A.San Feliz, Synthesis, 1984, 509.
13 D.Plusquellec, F.Roulleau and E.Brown, Tetrahedron Lett., 1984, 25, 1901.
14 Yu.P.Abashev, T.M.Andronova, S.E.Zurabyan, V.P.Mal'kova, I.B.Sorokina, and Ya.A.Khorlin, Bioorg. Khim., 1984, 10, 18 (Chem. Abstr., 1984, 100, 192 252).
15 A.D.Shutalev, L.A.Ignatova, and B.V.Unkovskii, Khim. Geterotsikl. Soedin, 1984, 548 (Chem. Abstr., 1984, 101, 55 448).
16 N.Nimura, A.Toyama, and T.Kinoshita, J. Chromatogr., 1984, 316, 547.
17 J.Gal, J. Chromatogr., 1984, 307, 220.
18 K.J.Miller, J.Gal, and M.M.Ames, J. Chromatogr., 1984, 307, 335.
19 J.A.Galbis Perez, J.C.Palacios Albarran, J.L.Jimenez Requejo, M.Avalos Gonzalez, and J.M.Fernandez-Bolaños, Carbohydr. Res., 1984, 131, 71.
20 J.A.Galbis Perez, J.C.Palacios Albarran, J.L.Jiminez Requejo, M.Avalos Gonzalez, and J.M.Fernandez-Bolaños, Carbohydr. Res., 1984, 129, 131.
21 S.A.Rumyantseva, X.Cisneros, M.P.Koroteev, and E.E.Nifant'ev, Zh. Obshch. Khim., 1984, 54, 204 (Chem. Abstr., 1984, 100, 175 145).
22 J.N.Vos, J.H.van Boom, C.A.A.van Boeckel, and T.Beetz, J. Carbohydr. Chem., 1984, 3, 117.
23 N.B.Dyatkina and A.V.Azhayev, Synthesis, 1984, 961.
24 R.Meuwly and A.Vasella, Helv. Chim. Acta, 1984, 67, 1568.

25 B.Aebischer, R.Meuwly, and A.Vasella, Helv. Chim. Acta, 1984, 67, 2236.
26 H.Felber, G.Kresze, H.Braun, and A.Vasella, Tetrahedron Lett., 1984, 25, 5381.
27 T.Sakakibara, Y.Tachimori, and R.Sudoh, Tetrahedron, 1984, 40, 1533.
28 T.Sakakibara, Y.Tachimori, and R.Sudoh, Carbohydr. Res., 1984, 131, 197.
29 J.Yoshimura, T.Yasumori, T.Kondo, and K.Sato, Bull. Chem. Soc. Jpn., 1984, 57, 2535.
30 M.Melgarejo Sampedro and R.Rico Gomez, Ars. Pharm., 1982, 23, 481 (Chem. Abstr., 1984, 100, 34 767).
31 J.A.Galbis Perez and J.A.Serrano Blazquez, An. Quim., Ser. C, 1983, 79, 33 (Chem. Abstr., 1984, 100, 7 011).
32 R.D.G.Lastres, I.M.E.Thiel, and A.M.Schueller, An. Asoc. Quim. Argent., 1984, 72, 247 (Chem. Abstr., 1984, 101, 211 572).
33 L.Somsak, G.Batta, and I.Farkas, Carbohydr. Res., 1984, 132, 342.
34 Z.J.Witczak, J. Carbohydr. Chem., 1984, 3, 359.
35 K.E.Larsen and K.B.G.Torssell, Tetrahedron, 1984, 40, 2985.
36 F.Ikegami, F.Lambein, Y.-H.Kuo, and I.Murakoshi, Phytochemistry, 1984, 23, 1567.
37 M.S.Lee and C.Y.Wang, Carcinogenesis (London), 1984, 5, 73 (Chem. Abstr., 1984, 100, 192 197).
38 P.Smit, G.A.Stork, and H.C.Van der Plas, Recl: J.R. Neth. Chem. Soc., 1983, 102, 453 (Chem. Abstr., 1984, 100, 121 505).
39 A.Maciejewski, J.Wojtczak, and M.Szymanski, J. Chem. Soc., Faraday Trans. 2, 1984, 80, 411.
40 Y.El Kilany, H.A.Hamid, and E.S.H.El Ashry, Carbohydr. Res., 1984, 125, 77.
41 M.A.M.Nassr, Org. Prep. Proced. Int., 1984, 15, 329 (Chem. Abstr., 1984, 100, 86 008).
42 V.I.Veksler, Zh. Obshch. Khim., 1983, 53, 2799 (Chem. Abstr., 1984, 100, 156 916).
43 J.A.Galbis Perez, J.C.Palacios Albarran, J.L.Jimenez Requejo, and M.Avalos Gonzalez, Carbohydr. Res., 1984, 132, 153.
44 E.Pando, M.C.Garcia Bala and C.Martin Madero, Afinidad, 1983, 40, 445 (Chem. Abstr., 1984, 100, 156 451).
45 N.Morita, Y.Daido, and M.Takagi, Agric. Biol. Chem., 1984, 48, 3161.
46 N.Morita, Y.Daido, and M.Takagi, Agric. Biol. Chem., 1984, 48, 2753.
47 M.A.El Sekily, S.Mancy, and K.Fahmy, Carbohydr. Res., 1984, 133, 324.
48 E.Breuer, D.Melumad, S.Sarel, E.Margalith, and E.Katz, Eur. J. Med. Chem. - Chim. Ther., 1983, 18, 481 (Chem. Abstr., 1984, 100, 156 883).
49 J.Fernandez-Bolaños, R.Ruiz Contreras, M.P.Gimenez Gracia, and F.Zamora Mata, An. Quim., Ser. C, 1984, 80, 102 (Chem. Abstr., 1984, 101, 230 920).
50 J.A.Galbis Perez, P.Areces Pravo, F.Rebolledo Vicente, J.I.F.Garcia-Hierro, and J.Fuentes Mota, Carbohydr. Res., 1984, 126, 91.
51 J.Fuentes Mota, P.Areces Bravo, F.Rebolledo Vicente, J.I.F.Garcia-Hierro, and J.A.Galbis Perez, Nucleosides Nucleotides, 1984, 3, 115.
52 L.Somsak, I.Farkas, I.Romhanyi, and K.Peseke, Pharmazie, 1983, 38, 719 (Chem. Abstr., 1984, 100, 156 922).

11
Thio-sugars

Theoretical studies have been applied to the stereochemistry of methoxy(methylthio)methane[1] and di(methylthio)methane[2] as models of of the thioacetal segment in thioglycosides. The MNDO technique was used in each case, and the results used to assess the magnitude of the anomeric and exo-anomeric effects in 1-thio- and 5-thio-pyranosides. By considering the torsion angles shown in (1), the calculations for the oxythio compound gave the thermodynamic ratios 92:5:2:1:0 for the (sc,sc), the (ap,sc), the (sc,ap), the (ac,ac), and the (ap,ap) conformers respectively in the absence of solvent,[1] while the dithio model gave 78:21:1 for the corresponding (sc,sc), (sc,ap), and (ap,ap) conformers.[2] Increasing the solvent polarity was shown to increase the proportion of (ap) conformation for the methyl groups.

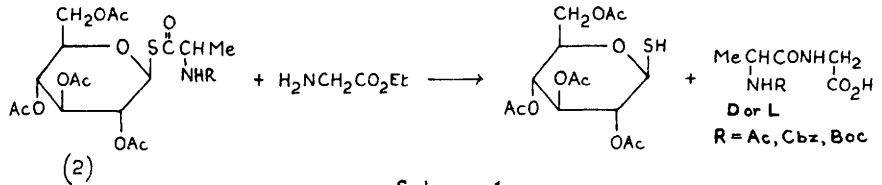


(1) X = O or S

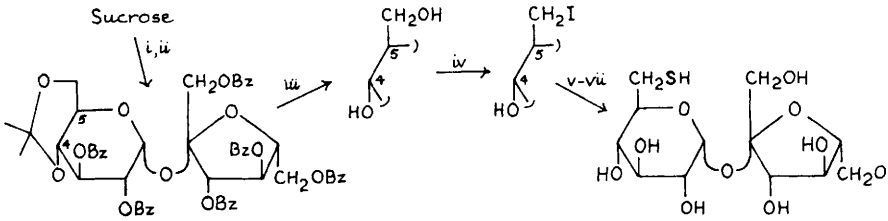
A stereoselective synthesis of 1,2-trans-related 1-thioglycoses utilized the reaction of thioacetic acid with peracetylated sugars in the presence of zirconium chloride. Application to standard peracetylated aldopyranoses (β-D-xyl, β-D-glc, β-D-gal, α-D-man) gave excellent yields of the corresponding 1,2-trans-peracetyl 1-thiosugars with no observable anomerization.[3] The preparation of some lipophilic derivatives of 1-thiomuramoyl-L-alanyl-D-isoglutamine has been described; products included 2-N-octadecanoyl derivatives of 1-S-acetyl-, 1-S-octadecanoyl-, and 6-O-octadecanoyl derivatives of 1-thiomuramoyl-L-alanyl-D-isoglutamine.[4] The kinetics of the peptide-forming aminolysis reaction of 1-thio-D-glucopyranosyl alanyl esters (2) with ethyl glycinate, in which (2) acts as an aminoacid transfer agent, have been investigated and shown to vary with the nature of the N-protecting group and with th configuration of the alanine (Scheme 1).[5]

Zirconium chloride - catalyzed condensation of 2,3,4,6-tetra-O-acetyl-1-thio-α-D-glucopyranose with 1,3,4,6-tetrabenzyl-β-D-fructo

furanose, followed by l.c. separation of the deprotected disaccharide, led to 1-thiosucrose and α-D-fructofuranosyl 1-thio-α-D-glucopyranoside in 15 and 22% yields respectively. Condensation of the fructofuranose derivative with the corresponding β-glucose anomer gave, in 1:6 ratio, α-D-fructofuranosyl 1-thio-β-D-glucopyranoside (1-thioisosucrose) and its β,β-anomer.[6] The synthesis of 6-thiosucrose (3) has been achieved as shown in Scheme 2. The

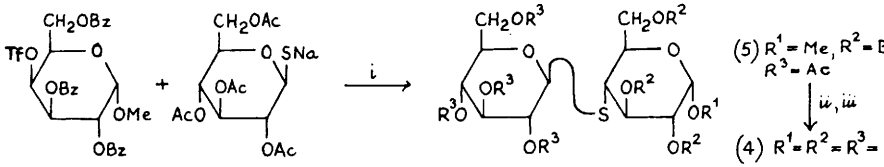


Scheme 1



Reagents: i, $(MeO)_2CMe_2$-TsOH-DMF; ii, BzCl-Py; iii, AcOH-H_2O-Me_2CO (70°); iv, Imidazole-PPh_3-I_2; v, KSAc-Me_2CO; vi, NaOMe-MeOH; vii, 1,4-Dithiothreitol-EtOH

Scheme 2



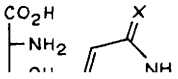
Reagents: i, Kryptofix-21; ii, Ac_2O-AcOH-H_2SO_4; iii, NaOMe-MeOH

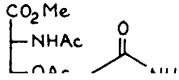
Scheme 3

route also provided 6-deoxysucrose in improved yields (see Chapter 12).[7] 3,3',4',6'-Tetra-O-acetylsucrose in DMF, on treatment with thioacetic acid, triphenylphosphine and DEAD followed by deacetylation, also gave good yields of 6-thiosucrose. 6'-Thiosucrose was similarly obtained from 4,6:2,1'-di-O-isopropylidenesucrose.[8] The o-nitrophenyl and p-nitrophenyl 4-thio-α-maltosides have been prepared by condensation of S-acetyl-1-thio-α-D-glucopyranose with

the appropriate nitrophenyl 2,3,6-tri-O-benzoyl-4-O-triflyl-α-D-galactopyranoside followed by isolation as the tetraacetate and deprotection. The S-linked maltosides were shown to be poorer substrates than their oxygen counterparts for pig pancreatic α-amylase, with cleavage occurring exclusively at the chromogenic sites.[9] Thiocellobiose (4) has been synthesized *via* the intermediate (5) as shown in Scheme 3; a similar reaction of the sodium thiolate with 1,3,4,6-tetra-O-acetyl-α-D-mannopyranose yielded thiosophorose.[10] The 3-thio-MDP-analogue, N-[2-S-(2-acetamido-2,3-dideoxy-D-glucopyranose-3-yl)-2-thio-D-lactoyl]-L-alanyl-D-isoglutamine, has been synthesized from allyl 2-acetamido-2-deoxy-β-D-glucopyranoside, using a double inversion sequence to introduce sulphur at C-3. The compound had less immunoadjuvant activity than the oxygen analogue.[11] The same research group has also prepared several 6-thio-MDP analogues.[12] A review, which includes some previously unpublished results, on the introduction of 7-S-alkylthio substituents into the antibiotic lincomycin structure has appeared. The main method involved the attack of a wide variety of sulphur nucleophiles on a 6,7-N-acetylepimine intermediate.[13]

Various nucleoside analogues have been synthesized from 1-O-acetyl-2,3-O-phenylboronyl-4-thio-D-erythrose by standard procedures.[14] The thionucleosides (6) and (7) have been obtained[15] by enzymic cleavage of albomycin δ_1 and δ_2, and chemical reactions of (7) gave rise to the sulphoxide (8) which was characterized by X-ray crystallography.[16]

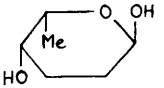




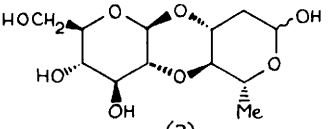
3 J.Defaye, H.Driguez, E.Ohleyer, C.Orgeret, and C.Viet, Carbohydr. Res., 1984, 130, 317.
4 A.Hasegawa, E.Seki, Y.Hioki, M.Kiso, and I.Azuma, Carbohydr. Res., 1984, 131, 61.
5 S.Horvat, S.Tomic, and Z.Jericevic, Tetrahedron, 1984, 40, 1047.
6 J.Defaye, H.Driguez, S.Poncet, R.Chambert, and M.-F.Petit-Glatron, Carbohydr. Res., 1984, 130, 299.
7 T.P.Binder and J.F.Robyt, Carbohydr. Res., 1984, 132, 173.
8 I.D.Jenkins and S.Thang, Aust. J. Chem., 1984, 37, 1925.
9 M.Blanc-Muesser, J.Defaye, H.Driguez, G.Marchis-Mouren, and C.Seigner, J. Chem. Soc., Perkin Trans. 1, 1984, 1885.
10 K.Hamacher, Carbohydr. Res., 1984, 128, 291.
11 A.Hasegawa, M.Ozaki, M.Kiso, and I.Azuma, J. Carbohydr. Chem., 1984, 3, 331.
12 A.Hasegawa, E.Seki, Y.Hioki, M.Kiso, and I.Azuma, Carbohydr. Res., 1984, 129, 271.
13 B.Bannister, Tetrahedron, 1984, 40, 1633.
14 J.E.McCormick and R.S.McElhinney, Proc. R. Ir. Acad., Sect. B, 1983, 83, 125 (Chem. Abstr., 1984, 100, 22 947).
15 G.Benz, Justus Liebigs Ann. Chem., 1984, 1399.
16 G.Benz, Justus Liebigs Ann. Chem., 1984, 1408.

12
Deoxy-sugars

Vimose, a tetrasaccharide composed of β-(1→4)-linked L-diginose (i.e., 2,6-dideoxy-3-O-methyl-L-lyxo-hexose) units, has been isolated from Orthenthera viminea twigs.[1] Full details have been published for the determination of the absolute configuration of the potent prolyl hydroxylase inhibitor P-1894B, which has L-aculose (2,3,6-trideoxy-L-glycero-hex-2-enopyranose-4-ulose) and L-rhodinose (2,3,6-trideoxy-L-threo-hexopyranose, 1) as constituent sugars (c.f. Vol.16, p.199).[2] A review, in Japanese, has described work on the oligosaccharides released on hydrolysis of biologically



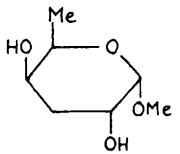
(1)



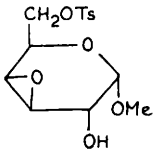
(2)

active Asclepiadaceous plant glycosides (c.f. Vol.16, p.232; Vol.17, p.120). These oligosaccharides incorporate D- and L-cymarose, D-oleandrose, 6-deoxy-3-O-methyl-D-allose, and the unusual ether-linked glucosyl olivose wilforibiose (2) as constituent sugars, and their ^{1}H- and ^{13}C-n.m.r. characteristics have been tabulated.[3]

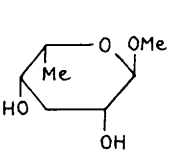
Super-hydride ($LiBEt_3H$) has been shown to be more effective than other reagents (e.g., LAH) for reductive cleavage of epoxides and sulphonate esters. Thus methyl α-abequioside (3) was obtained in 94% yield on reduction of the epoxy-sugar sulphonate (4), while



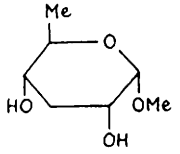
(3)



(4)



(5)



(6)

methyl 3,6-dideoxy-α-L-lyxo-hexopyranoside (5) was obtained on reduction of methyl 3,4-anhydro-6-deoxy-α-L-talopyranoside.[4]

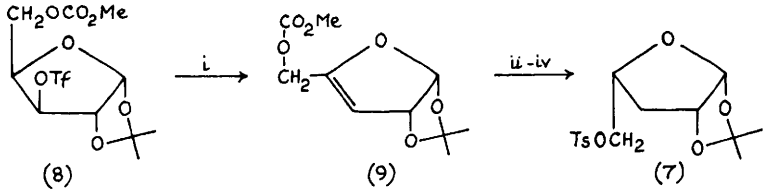
Another 3,6-dideoxy-sugar glycoside, methyl α-D-paratoside (6), has been synthesized from methyl 3,6-di-O-pivaloyl-α-D-mannopyranoside by sequential selective oxidation-reduction at C-2, followed

by photolytic deoxygenation at C-3 and C-6; selective oxidation of other partially esterified sugar derivatives was reported.[5]

Deoxy-sugar derivatives could also be obtained by reaction of triflates with sodium borohydride in acetonitrile. 1,2:3,4-Di-O-isopropylidene-6-O-triflyl-α-D-galactopyranose and 1,2:5,6-di-O-isopropylidene-3-O-triflyl-α-D-allofuranose gave the corresponding 6- and 3-deoxy-derivatives, respectively, but the gluco-isomer of the latter underwent competitive hydrolysis and 3,4-elimination of the 3-triflate as well as deoxygenation. Other limitations of the reaction were noted.[6]

An improved six-step synthesis of 6-deoxy-sucrose from sucrose,[7] a routine synthesis of 6,6'-dideoxy-lactose,[8] and a multi-step synthesis of methyl N-acetyl-3-epi-sibirosaminide, a branched-chain 4-amino-4,6-dideoxy-D-altropyranoside (see Chapter 14),[9] have each involved the synthesis and reductive dehalogenation (using H_2-Pd/C or Bu_3SnH) of primary iodides.

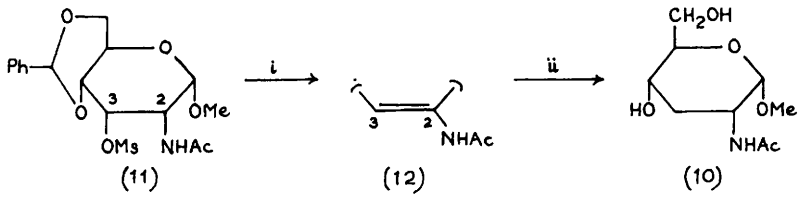
A variety of deoxy-sugars have been synthesized by procedures involving the catalytic hydrogenation of double bonds. The 3-deoxy-β-L-threo-pentofuranose derivative (7) was conveniently prepared from the xylofuranose 3-triflate (8) via the 3,4-ene (9) (Scheme 1).[10] Methyl 2-acetamido-2,3-dideoxy-α-D-ribo-hexopyranoside (10) was obtained from the D-allo mesylate (11) via the



Reagents: i, DBU ; ii, H_2-Pd/$BaSO_4$; iii, NaOMe-MeOH ; iv, TsCl-Py

Scheme 1

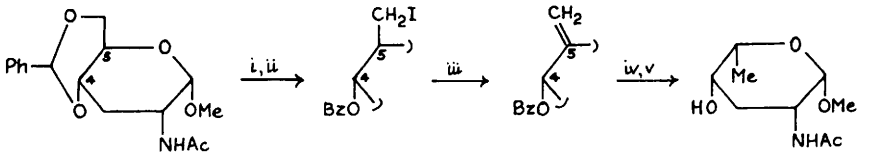
2,3-ene (12) (Scheme 2).[11] Methyl 2-acetamido-2,3,6-trideoxy-β-L-



Reagents: i, NaH-$MeOCH_2CH_2OMe$; ii, H_2-Pd/C

Scheme 2

lyxo-hexopyranoside (13) was synthesized from the 3-deoxy-derivative (14) via the 5,6-ene (15) (Scheme 3).[12] The 2,3,6-

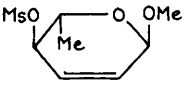


(14) (15) (13)

Reagents: i, NBS ; ii, NaI ; iii, AgF-Py ; iv, MeONa-MeOH ; v, H_2-Raney Ni

Scheme 3

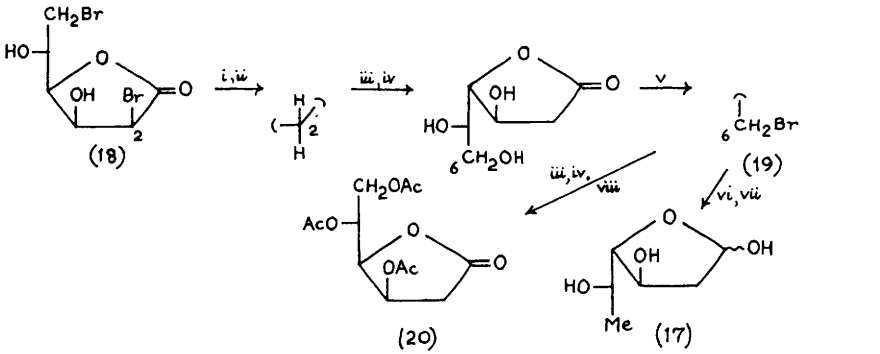
trideoxy-sugar L-rhodinose (1) has been obtained from the allylic mesylate (16) by sequential C-4 inversion (CO_3^{2-}-form resin),



(16)

hydrogenation, and hydrolysis.[13] Purpurosamine C is theoretically available by hydrogenation-hydrolysis of a 2,6-diamino-3,4-unsaturated derivative described in Chapter 13.

Deoxy-sugars can be synthesized from aldonolactones via β-elimination or bromination procedures. 3-Deoxy-D-arabino-hexono-1,5-lactone, readily available from D-glucono-1,5-lactone by sequential acetylation, β-elimination, hydrogenation, and deprotection, has been converted to 2-deoxy-D-erythro-pentose in 92% yield by indirect electrochemical oxidation.[14] 3-Deoxy-D-arabino-hexose, which exists as a 53:30:17 mixture of the α- and β-pyranose, and α-furanose forms in aqueous solution, has been synthesized by reduction of the 2,4,6-tri-O-benzoyl derivative of



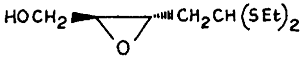
(18) (19) (20) (17)

Reagents: i, N_2H_4 ; ii, Br_2 ; iii, KOH ; iv, H_3O^+ ; v, HBr-HOAc ; vi, H_2-Pd/C ; vii, Disiamylborane ; viii, Ac_2O-H^+

Scheme 4

3-deoxy-D-arabino-hexono-1,5-lactone with disiamylborane.[15] L-Digitoxose (17) has been synthesized from the 2,6-dibromo-2,6-dideoxy-D-mannono-1,4-lactone (18) as shown in Scheme 4, involving selective C-2 dehalogenation, inversion at C-4 and C-5 (the mechanism being discussed in terms of epoxide migrations), selective C-6 bromination [to give (19)], and reduction. The 2-deoxy-D-arabino-hexono-1,4-lactone derivative (20) was similarly obtained from the 6-bromide (19) by inversion at C-4 and C-5.[16] Other deoxy-lactones are covered in Chapter 16.

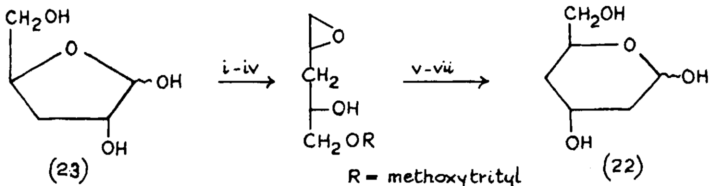
The five-carbon chiral epoxide (21) has been synthesized in 7



(21)

steps from L-arabinose via 2-deoxy-4,5-O-isopropylidene-L-threo-pentose.[17]

Both chemical and biochemical strategies have been described for synthesizing deoxy-sugars by sugar-chain extension. 2,4-Dideoxy-D-erythro-hexopyranose (22), useful for the synthesis of mevinolin, has been prepared from D-glucose via 3-deoxy-D-erythro-pentose (23) (Scheme 5).[18] Various 1-deoxy-ketoses have been obtained by an

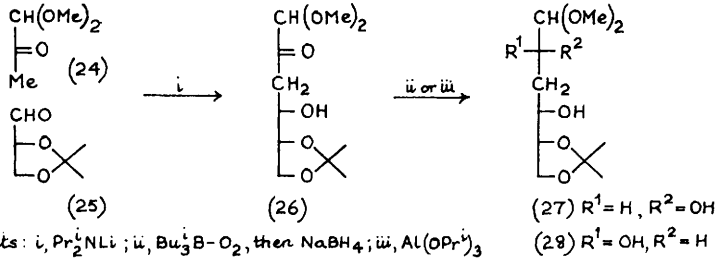


Reagents: i, Methoxytritylation; ii, NaBH4; iii, TsCl-Py; iv, KOH-MeOH; v, Li⟨S S⟩; vi, NBS; vii, H_3O^+

Scheme 5

acyloin-type condensation induced by enzymes in cell-free extracts of bacteria and actinomycetes, particularly a transketolase mutant from Bacillus pumilis. Thus coupling of pyruvate with D-erythrose, glycolaldehyde, and D- or L-glyceraldehyde led to 1-deoxy-D-fructose, 1-deoxy-D-glycero-tetrulose, and 1-deoxy-D- or -L-threo-pentulose respectively.[19,20]

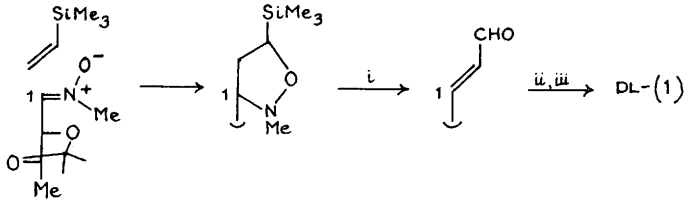
An extensive review on the acyclic stereoselective synthesis of carbohydrates from non-carbohydrate starting materials, which covers both carbon-carbon bond forming reactions and stereoselective introduction of heteroatom functionality, has included deoxy-sugar examples.[21] Aldol condensation of pyruvaldehyde and D-glyceraldehyde derivatives (24) and (25) has led to the adduct (26), from which 3-deoxy-D-ribo- and arabino-hexoses have been obtained by



Scheme 6

reduction and acid hydrolysis (Scheme 6).

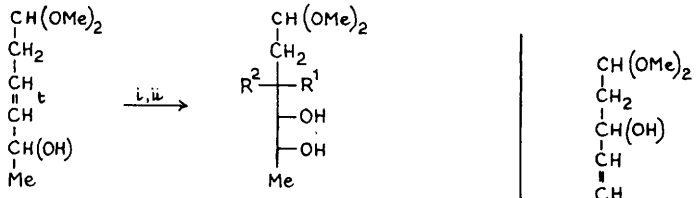
Reduction of adduct (26) by treatment of its di-isobutylborinic ester with sodium borohydride provided the 2,4-syn-diol (27) as the predominant product, whereas direct reduction of adduct (26) with aluminium tri-isopropoxide yielded mainly the 2,4-trans-diol (28).[22] A further synthesis of rhodinose (1) (see ref.13), in this instance as a racemate, utilized the dipolar cycloaddition shown in Scheme 7 to construct the six-carbon sugar chain.[23]



Scheme 7

Syntheses of isomeric 3-acetamido-2,3,5-trideoxy-L-hexopyranoses, utilizing the Henry reaction for coupling 4-nitro-butane-1,2-diol and 2-oxypropanal derivatives, are covered in Chapter 9.

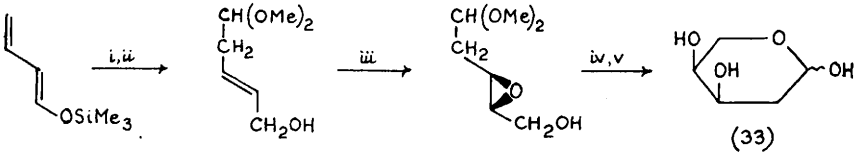
Several five- and six-carbon non-carbohydrate derivatives have been converted into deoxy-sugars. An epoxidation-hydrolysis sequence has been utilized to convert the racemic trans-isomer of alkene (29) into an ∿4:1 mixture of DL-digitoxose (ribo) and DL-oliose (lyxo) dimethyl acetals (30) and (31) (Scheme 8). The cis-isomer of alkene (29), however, yielded an ∿4:1 mixture of analogous DL-canarose (arabino) and DL-boivinose (xylo) derivatives. Similar treatment of the cis- and trans-isomers of the related alkene (32) provided ∿4:1 mixtures of DL-digitoxose and DL-canarose derivatives and of DL-oliose and DL-boivinose derivatives, respectively.[24] Chiral products have been obtained using the Sharpless asymmetric epoxidation procedure. 2-Deoxy-L-



Reagents: i, Bu^tO_2H–Vanadyl pentane-2,4-dionate; ii, NaOH–H_2O

Scheme 8

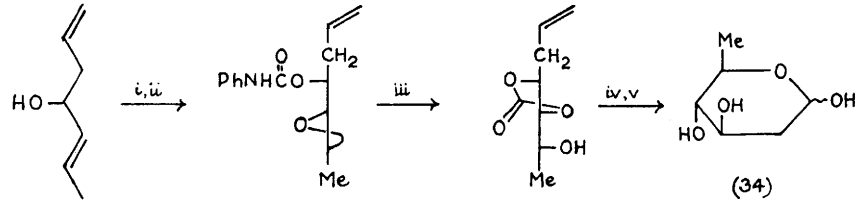
ribose (33) has been synthesized as shown in Scheme 9,[25] while five



Reagents: i, $(MeO)_3CH$; ii, LAH; iii, Bu^tO_2H–$Ti(OPr^i)_4$–(+)-diisopropyltartrate; vi, OH^-; vii, H_3O^+

Scheme 9

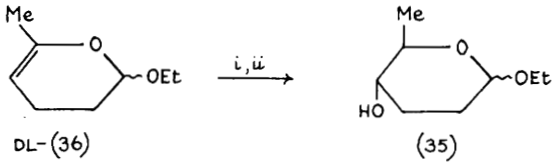
2,6-dideoxy-hexoses [D-olivose (34), D-digitoxose, D-oliose, D-cymarose, and DL-boivinose] have been obtained by synthesis and ring opening of acylated 2,3-epoxyalcohols with neighbouring-group participation, preferably involving a phenylurethane moiety, as exemplified by the synthesis of D-olivose (34) in Scheme 10.[26]



Reagents: i, Bu^tO_2H–$Ti(OPr^i)_4$–(–)diisopropyltartrate; ii, PhNCO–Py; iii, Et_2AlCl; iv, NaOMe–MeOH; v, O_3

Scheme 10

Ethyl amicetosides (35) have been synthesized by hydroboration of the dihydropyran (36) using diisopinocampheylborane (Scheme 11); the use of 1R,5R-pinene (63% e.e.) led to D-series sugars (45.5% e.e.)[27] Synthesis of a racemic 1,6-anhydro-3,4-dideoxy-hexose from acrolein is mentioned in Chapter 5, as is the partial methylation of methyl 4,6-dideoxy-α- and β-L-ribo-hexopyranosides.



DL-(36) (35)

Reagents : i, diisopinocampheylborane ; ii, oxidation

Scheme 11

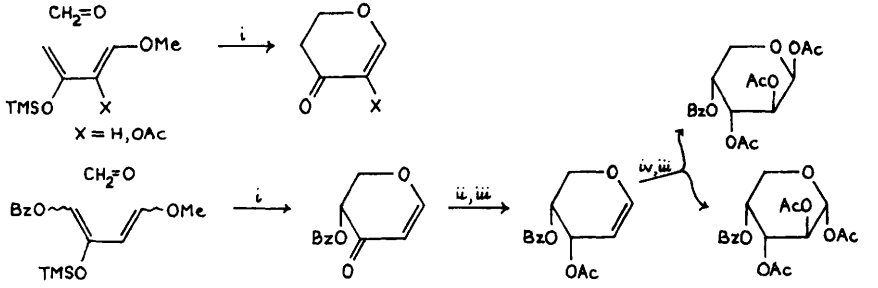
References

1 K.N.Tiwari, A.Khare, and M.P.Khare, J. Carbohydr. Chem., 1984, 3, 315.
2 K.Ohta, E.Mizuta, H.Okazaki, and T.Kishi, Chem. Pharm. Bull., 1982, 32, 4350.
3 K.Hayashi, T.Nakagawa, K.Wada, S.Yoshimura, S.Tsukamoto, H.Narita, and H.Mitsuhashi, Tennen Yuki Kagobutsu Toronkai Koen Yoshishu, 1983, 204 (Chem. Abstr., 1984, 100, 135 778).
4 H.H.Baer and D.J.Astles, Carbohydr. Res., 1984, 126, 343.
5 A.Klausener, J.Runsink, and H.-D.Scharf, Justus Liebigs Ann. Chem., 1984, 783.
6 E.-P.Barrette and L.Goodman, J. Org. Chem., 1984, 49, 176.
7 T.P.Binder and J.F.Robyt, Carbohydr. Res., 1984, 132, 173.
8 I.Jezo and J.Zemek, Chem. Zvesti, 1984, 38, 715.
9 M.Georges, D.MacKay, and B.Fraser-Reid, Carbohydr. Res., 1984, 130, 115.
10 L.M.Lerner, Carbohydr. Res., 1984, 132, 168.
11 A.Calvo-Mateo, M.J.Camarasa, and F.G.De las Heras, J. Carbohydr. Chem., 1984, 3, 461.
12 M.M.Abuaan, J.S.Brimacombe, and L.C.N.Tucker, Carbohydr. Res., 1984, 132, 51.
13 G.Cardillo, M.Orena, S.Sandri, and C.Tomasini, Gazz. Chim. Ital., 1984, 114, 325 (Chem. Abstr., 1984, 101, 230 865).
14 Y.Nakamura, Noguchi Kenkyusho Jiho, 1983, 31 (Chem. Abstr., 1984, 101, 73 018).
15 C.du Mortier and R.M.de Lederkremer, J. Carbohydr. Chem., 1984, 3, 219.
16 K.Bock, I.Lundt, and C.Pedersen, Acta Chem. Scand., Ser. B, 1984, 38, 555.
17 C.Morin, J. Chem. Res., Synop., 1983, 275 (Chem. Abstr., 1984, 100, 120 787).
18 P.-T.Ho and S.Chung, Carbohydr. Res., 1984, 125, 318.
19 A.Yokota and K.-I.Sasajima, Agric. Biol. Chem., 1984, 48, 149.
20 A.Yokota and K.-I.Sasajima, Agric. Biol. Chem., 1984, 48, 1643.
21 G.J.McGarvey, M.Kimura, T.Oh, and J.M.Williams, J. Carbohydr. Chem., 1984, 3, 125.
22 K.Narasaka and F.-C.Pai, Tetrahedron, 1984, 40, 2233.
23 P.De Shong and J.M.Leginus, Tetrahedron Lett., 1984, 25, 5355.
24 Yu.E.Raifel'd, L.L.Zil'berg, B.M.Arshava, and S.M.Makin, Zh. Org. Khim., 1984, 20, 52 (Chem. Abstr., 1984, 100, 175 143).
25 S.M.Makin, Yu.E.Raifel'd, L.L.Zil'berg, and B.M.Arshava, Zh. Org. Khim., 1984, 20, 210 (Chem. Abstr., 1984, 100, 175 144).
26 W.R.Roush, R.J.Brown, and M.DiMare, J. Org. Chem., 1983, 48, 5083 and 5093.
27 A.Konowal and A.Zamojski, Bull. Acad. Pol. Sci., Ser. Sci. Chim., 1984, 32, 65.

13
Unsaturated Derivatives

1 Glycals

Hetero-Diels-Alder reactions between various oxygen-substituted butadienes and formaldehyde in the presence of zinc chloride have been used to produce racemic glycal derivatives and hence D,L-pentoses (Scheme 1).[1]

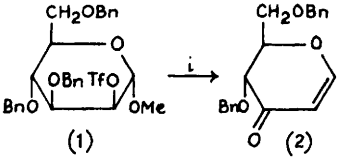


Reagents: i, $ZnCl_2$; ii, $NaBH_4$-$CeCl_3$; iii, Ac_2O-Py; iv, OsO_4-N-Methylmorpholine N-oxide

Scheme 1

Methyl 3,4-di-O-acetyl-D-glucuronal and -galacturonal have been prepared conventionally and converted by base treatment into mixtures with their C-5 epimers; the conformational equilibria of the four glycuronals and a number of related glycals were determined by ^1H n.m.r. spectroscopy.[2]

The major product obtained on treatment of the α-mannoside 2-triflate (1) with azide ion was the enone (2) (Scheme 2) whereas

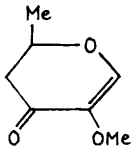


Reagents: i, LiN_3

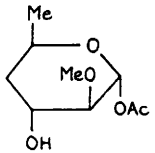
Scheme 2

similar treatment of the β-mannoside analogue gave the 2-azido-D-gluco-product.[3] A related enone (3), produced on oxidation of the

hydroxy group of (4) and treatment of the product with DBU, is the



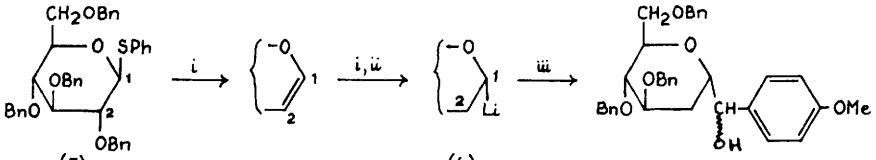
(3)



(4)

methyl ether of a degradation product of the Calotropis cardenolide,[4] which is thus configurationally characterized.

Addition of hydrogen chloride to tri-O-benzyl-D-glucal and reductive lithiation of the product gave the glycosyl lithium (6) which, with aldehydes or ketones, afforded C-glycosides (Scheme 3). The starting glycal was made from the thiophenyl glycoside (5)

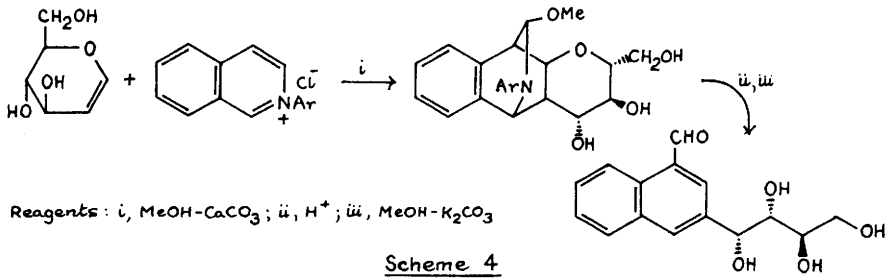


(5) (6)

Reagents : i, Lithium naphthalenide; ii, HCl; iii, p-$MeOC_6H_4CHO$

Scheme 3

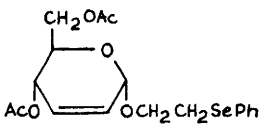
also by reductive lithiation.[5] A further novel addition reaction of D-glucal is illustrated in Scheme 4.[6]



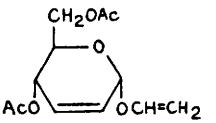
Reagents : i, MeOH-$CaCO_3$; ii, H^+; iii, MeOH-K_2CO_3

Scheme 4

Rearrangement reactions of glycal derivatives continue to be of interest, tri-O-acetyl-D-glucal giving the α-glycoside (7) under standard conditions with boron trifluoride as catalyst and the appropriate alcohol. Periodate oxidation gave the α-vinyl

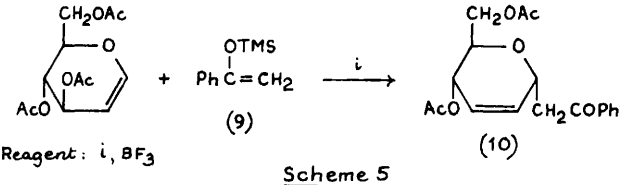


(7)



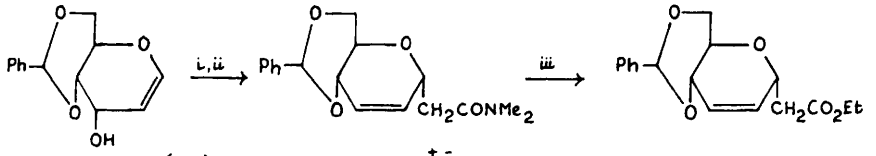
(8)

glycoside (8).[7] The same glycal ester and the vinyl ether (9) in the presence of the same catalyst gave the C-glycoside (10) and a small proportion of the β-anomer (Scheme 5).[8] A related reaction which proceeds via a sigmatropic rearrangement is illustrated in



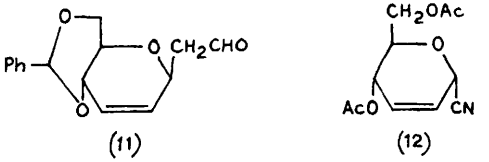
Scheme 5

Scheme 6. Reduction of the final product with lithium triethoxyaluminium hydride afforded mainly the aldehyde product of

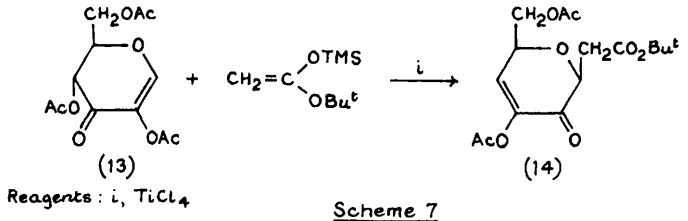


Scheme 6

anomerization (11). A further means of making α-compounds of this series involves treatment of tri-O-acetyl-D-glucal with diethylaluminium cyanide, which gives the cyanide (12) in almost quantitative yield.[9]

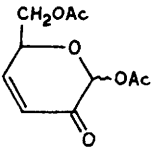


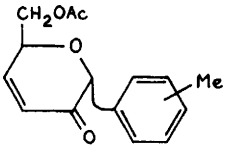
A related rearrangement of the enolone (13) gave the unsaturated C-glycoside derivative (14) in 40% yield (Scheme 7),[10] and prolonged treatment of tetra-O-acetyl-2-hydroxy-D-glucal or -galactal with

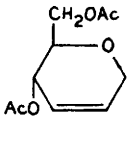


Scheme 7

boron trifluoride gave the enones (15). When the reaction was carried out in toluene, the C-glycosides (16) were produced in competing reactions.[11]

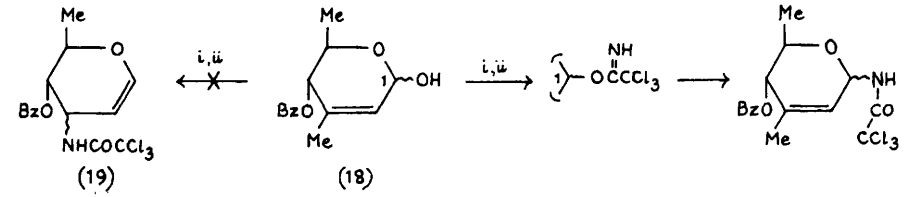

(15)


(16)


(17)

2 Other Unsaturated Derivatives

Rearrangements of acylated glycals to 2,3-unsaturated pyranoid compounds are mentioned above, and others appear in Chapter 3; an unusual further example relates to the synthesis of analogues with carboranes as aglycones, the anomers of which were separated by HPLC.[12] Reaction of tri-O-acetyl-D-glucal or ethyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside with triethylsilane and boron trifluoride gave compound (17) in near quantitative yield.[12a] Reaction of the branched-chain, unsaturated compound (18) occurs at -40°C as shown in Scheme 8 via the glycosyl trichloroacetimidates, and does not give the 3-aminoglycal products (19) as previously reported (I.Dyong, J. Weigand, and H.Merten, Tetrahedron Lett., 1981, 22, 2965). 4-O-Benzoylpyranose to 5-O-



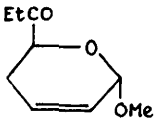
(19) (18)

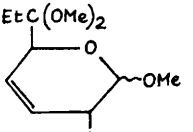
Reagents: i, NaH ; ii, CCl_3CN

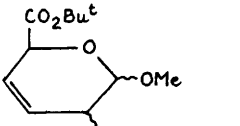
Scheme 8

benzoylfuranose isomerizations occur easily in this series.[13]

Zamojski and his group have reported the conversion of the racemic ketone (20) into the 3,4-ene (21) by way of epoxides and then 3-dimethylamino compounds, which were subjected to Cope degradations,[14] and the same group have examined the conformational equilibria of racemic esters (22), finding that the half

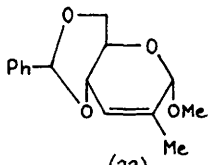

(20)

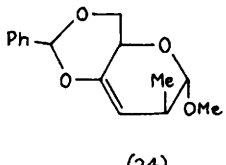

(21)

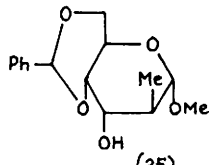

(22) R=H,Ac

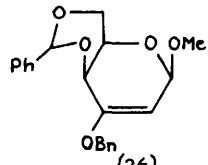
chairs with quasi-axial ester functions contribute significantly (see Chapter 21).

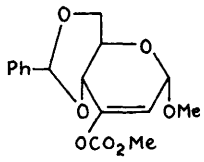
The alkenes (23) and (24) have been prepared from the D-altrose derivative (25) (see Chapter 14), and the enol ether (26) was the product formed by treatment of the corresponding D-talose 2-triflate with tetraethyl ammonium fluoride in acetonitrile.[15] The analogous enol carbonate (27) was made from methyl 2,3:4,6-di-O-benzylidene-α-D-mannoside by treatment with butyllithium followed by methyl chloroformate. With related C-glycosides, such enol acylation can be effected by way of the 3-ulosides.[16]

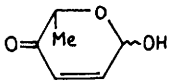

(23)

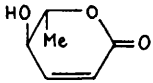

(24)

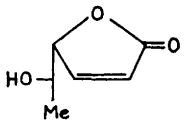

(25)


(26)


(27)

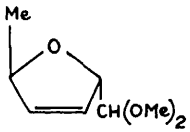

(28)

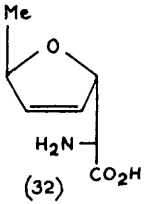

(29)

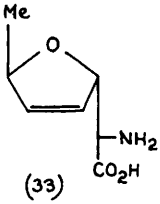

(30)

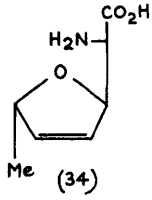
The prolyl hydroxylase inhibitor P-1894B contains the enone (28) (L-aculose) and also a reduction product L-rhodinose (2,3,6-trideoxy-L-threo-hexose).[17] The closely related unsaturated aldonolactones (29) and (30) are present in Osmunda japonica and are antifeedants for butterfly species.[18] Diels-Alder additions to pyranoid enones are noted in Chapters 14 and 24; see also Chapter 15 for another report on enones.

2,5-Anhydro-D-mannose, produced from 2-amino-2-deoxy-D-glucose with nitrous acid, has been converted by standard procedures into the dihydrofuran (31) and hence into the isomers (32) and (33) of


(31)

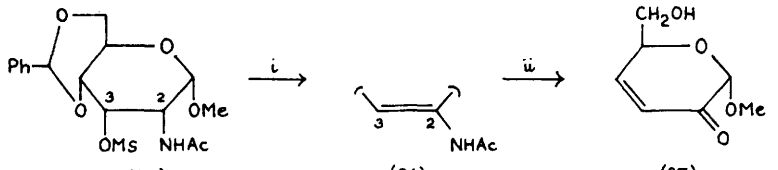

(32)


(33)

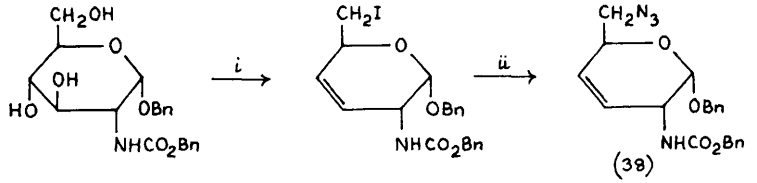

(34)

furanomycin (34).[19] A corrected structure for a trienonic acid lactone derived from a heptono-1,4-lactone is noted in Chapter 16.

Treatment of the mesylate (35) with sodium hydride gives the enamine (36) about quantitatively, and this hydrolyses with mild acid to the enone (37) (Scheme 9).[20] Compound (38), from which purpurosamine C can be obtained, was prepared in good yield as shown in Scheme 10.[21]

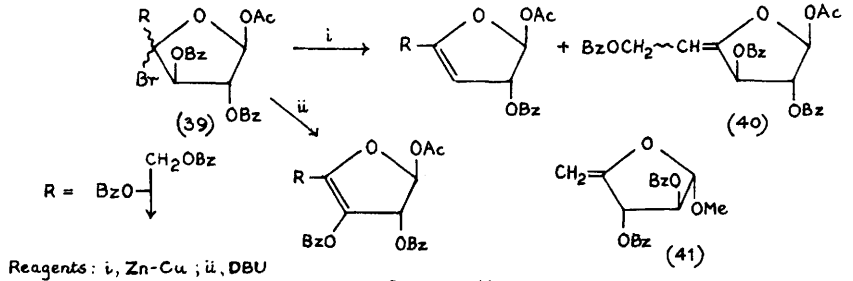


Scheme 9



Scheme 10

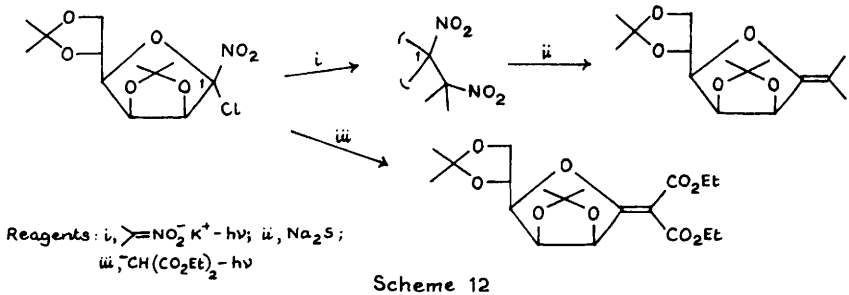
Elimination reactions applied to the 4-bromofuranose derivative (39) are outlined in Scheme 11. Compound (40) and the simpler 4,5-ene analogue (41) do not rearrange to cyclopentanes on treatment with mercury(II) salts in aqueous media, but give acyclic



Scheme 11

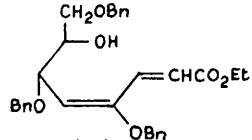
species.[22] In Chapter 24 mention is made of the use of 3,4-unsaturated furanoid compounds in the synthesis of cyclopentenes and cyclohexanes.

Some exocyclic furanoid alkenes were produced during studies of 1-C-nitroglycosyl halides (Scheme 12).[23]



Scheme 12

2,3,4,6-Tetra-O-benzyl-D-glucose is reported to react with the appropriate Wittig reagent to give the dienonate (42), whereas no elimination was noted for manno-, altro-, allo- or galacto-isomers. 4,6-O-Benzylidene-2,3-di-O-benzyl-D-glucose and the 2,3-diacetate were reported to give C-glycosidic products.[24] In the present



(42)

author's experience such results may prove difficult to reproduce because several variables contribute importantly in determining the nature of the products of such reactions, e.g., the presence of basic impurities in the Wittig reagent used.

References

1 S.Danishefsky and R.R.Webb, J. Org. Chem., 1984, 49, 1955.
2 J.Thiem and P.Ossowski, J. Carbohydr. Chem., 1984, 3, 287.
3 J.N.Vos, J.H.van Boom, C.A.A.van Boeckel, and T.Beetz, J. Carbohydr. Chem., 1984, 3, 117.
4 H.Kunz and J.Weissmüller, Justus Liebigs Ann. Chem., 1984, 66.
5 J.-M.Lancelin, L.Morin-Allory and P. Sinaÿ, J. Chem. Soc., Chem. Commun., 1984, 355.
6 R.W.Franck and R.B.Gupta, J. Chem. Soc., Chem. Commun., 1984, 761.
7 P.Rollin, V.Verez Bencomo, and P.Sinaÿ, Synthesis, 1984, 134.
8 R.D.Dawe and B.Fraser-Reid, J. Org. Chem., 1984, 49, 522.
9 D.B.Tulshian and B.Fraser-Reid, J. Org. Chem., 1984, 49, 518.
10 H.Kunz, J.Weissmüller, and B.Müller, Tetrahedron Lett., 1984, 25, 3571.
11 P.Köll, K.Klenke, and D.Eisermann, J. Carbohydr. Chem., 1984, 3, 403.
12 A.J.Serino and M.F.Hawthorne, J. Chromatogr., 1984, 291, 384.
12a G.Grynkiewicz, Carbohydr. Res., 1984, 128, C9.
13 I.Dyong, H.Merten, and J.Thiem, Tetrahedron Lett., 1984, 25, 277.
14 M.Chmielewski, O.Achmatowicz,Jr., and A.Zamojski, Bull. Pol. Acad. Sci., Chem., 1984, 32, 19 (Chem. Abstr., 1984, 101, 230 879).
15 T.Haradahira, M.Maeda, Y.Yano, and M.Kojima, Chem. Pharm. Bull., 1984, 32, 3317.

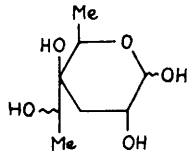
16 R.Tsang and B.Fraser-Reid, J. Chem. Soc., Chem. Commun., 1984, 60.
17 K.Ohta, E.Mizuta, H.Okazaki, and T.Kishi, Chem. Pharm. Bull., 1982, 32, 4350.
18 A.Nunata, K.Hokimoto, T.Takemura, T.Katsuno, and K.Yamamoto, Chem. Pharm. Bull., 1984, 32, 2815.
19 S.-Y.Chen and M.M.Joullie, J. Org. Chem., 1984, 49, 1769.
20 A.Calvo-Mateo, M.J.Camarasa, and F.G.De las Heras, J. Carbohydr. Chem., 1984, 3, 461.
21 P.J.Garegg, R.Johansson, and B.Samuelsson, J. Carbohydr. Chem., 1984, 3, 189.
22 R.J.Ferrier and S.R.Haines, J. Chem. Soc., Perkin Trans. 1, 1984, 1689.
23 B.Aebischer, R.Meuwly, and A.Vasella, Helv. Chim. Acta, 1984, 67, 2236.
24 F.Nicotra, F.Ronchetti, G.Russo, and L.Toma, Tetrahedron Lett., 1984, 25, 5697.

14
Branched-chain Sugars

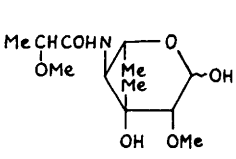
The synthesis of branched-chain sugars has been reviewed,[1] and another review on acyclic stereoselective synthesis of carbohydrates includes references to branched-chain sugars.

1 Characterization of Natural Products

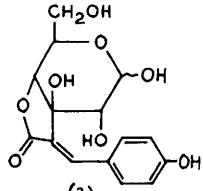
'Yersiniose', a component of an O-specific side-chain polysaccharide obtained from Yersinia pseudotuberculosis VI serovar, has been identified as 3,6-dideoxy-4-C-(1-hydroxyethyl)-D-xylo-hexose (1).[3]



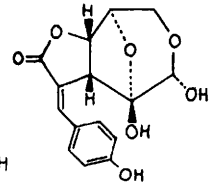
(1)



(2)



(3)

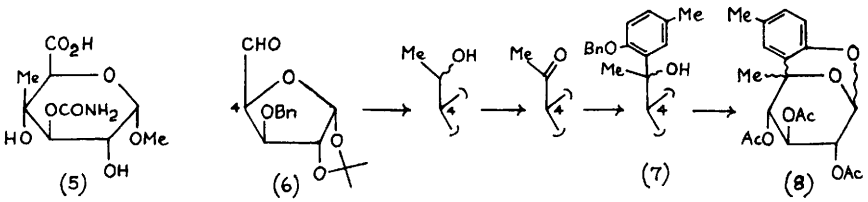


(4)

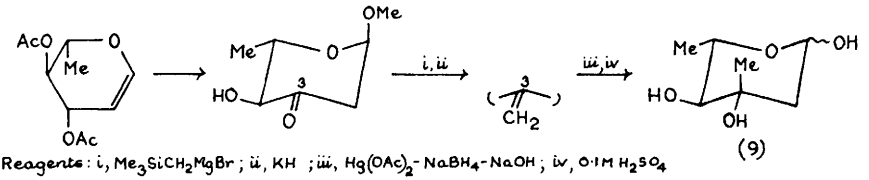
A novel amino-sugar, N-acyl-kansosamine, a component of antigenic trehalose-containing lipopolysaccharides from M. kansasii, has been proposed to be 4,6-dideoxy-2-O-methyl-3-C-methyl-4-(2'-methoxypropanamido)-L-mannopyranose (2).[4] A 3-C-branched D-glucose derivative plagiogyrin B (3) and a related hexos-2-ulose analogue plagiogyrin A (4) have been isolated from the fronds of Plagiogyria matsumureana; they are considered to be biosynthesized from 4-O-p-coumaroyl-D-glucose.[5] Six mono- to tetra-O-galloyl hamamelose derivatives have been isolated from Castanea crenata bark.[6]

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

A wide variety of established methods have been used to prepare naturally occurring branched-chain sugars and related analogues. As usual, glycosulose derivatives have been favoured starting materials. Methyl-lithium was used to introduce the branch methyl in the uronic acid (5), which served as a reference compound to establish the D-configuration of moenuronic acid in moenomycin.[7] Sequential use of methyl and aryl Grignard reagents allowed the



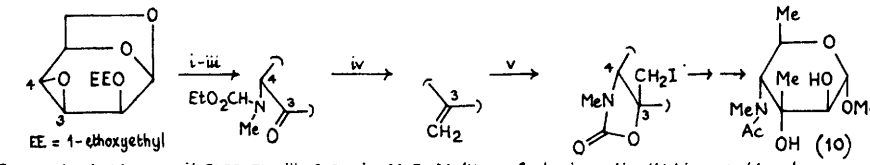
conversion of the xylo-dialdose derivative (6) to the corresponding branched-chain sugars (7) and hence to the acetylated sugars (8) required for studies on the antibiotic nogalamycin.[8] A new synthesis of L-olivomycose (9) utilizes an organosilicon reagent, as shown in Scheme 1.[9] An alternative route to exocyclic methylene was employed in a synthesis of the 3-epimer of methyl N-acetyl-



Reagents: i, Me_3SiCH_2MgBr; ii, KH; iii, $Hg(OAc)_2$-$NaBH_4$-NaOH; iv, 0·1M H_2SO_4

Scheme 1

sibirosaminide (10) outlined in Scheme 2,[10] whereas a standard Wittig procedure was used in a synthesis of methyl garosaminide (11)



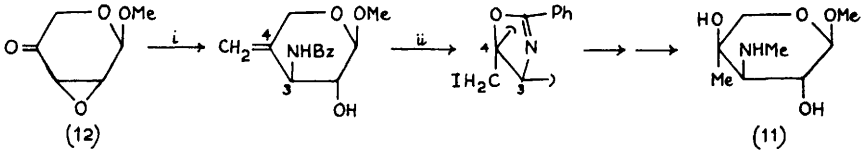
EE = 1-ethoxyethyl

Reagents: i, $MeNH_2$; ii $ClCO_2Et$; iii, CrO_3; iv, MeI-Mg/Hg; v, Iodonium dicollidine perchlorate

Scheme 2

from the epoxy-glycosidulose (12) shown in Scheme 3.[11] A cyanhydrin intermediate has been used to prepare the chloro derivative (13) of a branched-chain amino-sugar (Scheme 4), whose crystal structure was also determined.[12] Enolization (LDA) and C-methylation (MeI-HMPA) of the glycosidulose (14) furnished the branched-chain glycosidulose (15).[13]

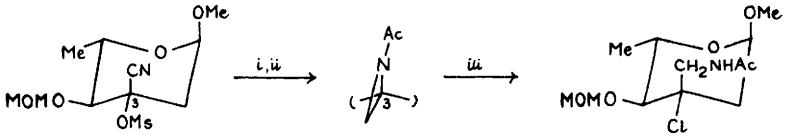
A sequence of standard reactions from the readily available oxiran (16) has been used to prepare 4-amino-3-C-methyl-altroside (17); attempts to prepare D-sibirosamine from (17) by boron-trihalide-catalysed de-O-methylation were unsuccessful.[14]



Reagents: i, $Ph_3P{=}CH_2$; ii, RNH_2 ; iii, Iodonium dicollidine perchlorate

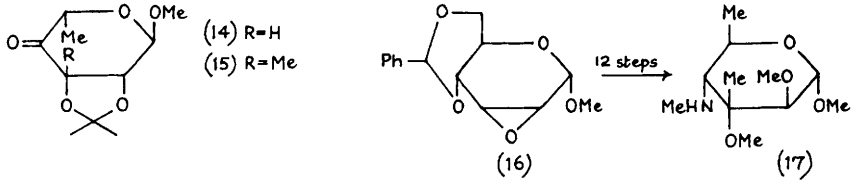
Scheme 3

Another route to the branched-chain sugar in nogalamycin and its analogues mentioned above has utilized a phenethyl furan derivative, the pyranose ring being elaborated as outlined in Scheme 5.[15]



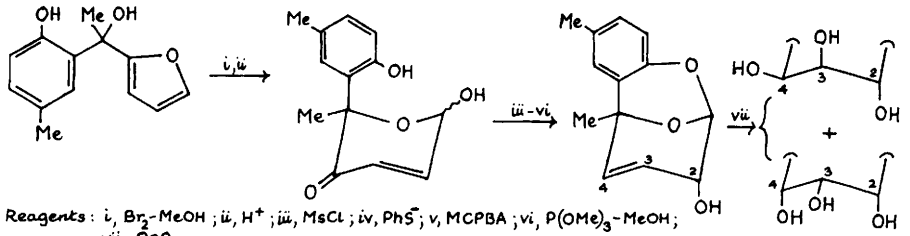
Reagents: i, LAH ; ii, Ac_2O-Py ; iii, HCl-aq.

Scheme 4



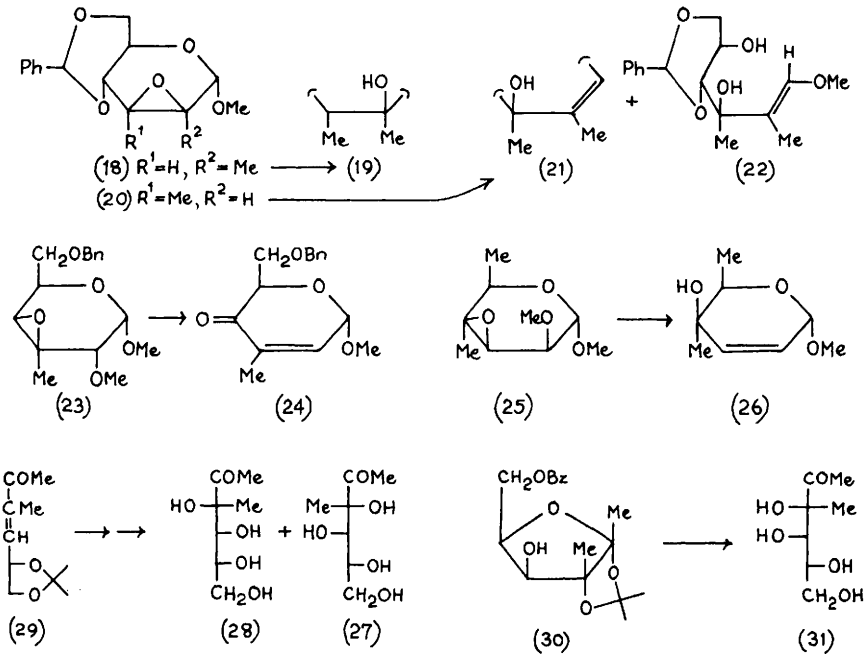
The reaction of lithium methyl cuprate reagents with 2,3- and 3,4-anhydro-hexopyranosides carrying methyl groups on either oxiran carbon has been studied; while the expected trans C-methyl substitution occurred in a majority of cases, e.g., (18)→(19), elimination to unsaturated compounds also occurred, e.g., (20)→(21)+(22), (23)→(24), and (25)→(26).[16]

1-Deoxy-3-C-methyl-D-fructose (27) and -D-sorbose (28) have been prepared by hydroxylation of the enone (29) (obtained from D-glyceraldehyde), the isomers being separated after acetonation.[17] The sorbose derivative (30) was then converted to 1-deoxy-3-C-methyl-D-psicose (31) by a standard oxidation-reduction inversion sequence at C-4.[18] 2-C-Hydroxymethyl-L-glycero-tetritol (3-C-hydroxymethyl-D-glycero-tetritol) and the corresponding 2-C-methyl analogue have been prepared by conventional reduction sequences from D-apiose (3-C-hydroxymethyl-D-glycero-tetrose).[19]



Reagents: i, Br_2-MeOH ; ii, H^+ ; iii, MsCl ; iv, PhS^- ; v, MCPBA ; vi, $P(OMe)_3$-MeOH ; vii, OsO_4

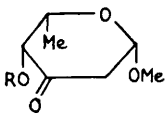
Scheme 5



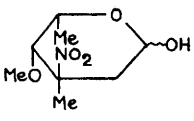
3 Compounds with an R-C-N Branch

Glycosidulose derivatives (32) have been converted to L-rubranitrose (33)[20] and the related amino-sugar (34)[21] using the cyanhydrin → spiro-aziridine route. A novel approach to α-amino-acidic sugar derivatives has been described, utilizing a dihydropyrazine carbanion with glyceraldehyde, illustrated in Scheme 6.[22]

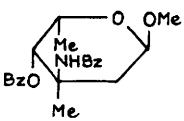
A stereoselective synthesis of L-vancosamine derivatives by an enolate alkylation procedure is referred to in Chapter 9.



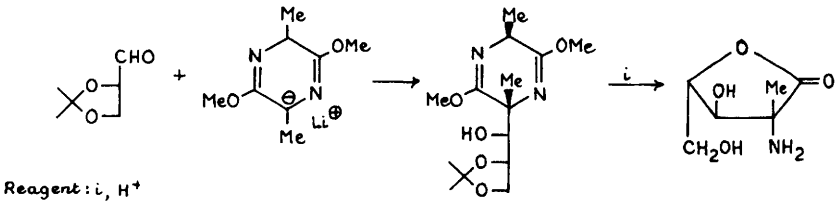
(32) R = Me or Bn



(33)



(34)

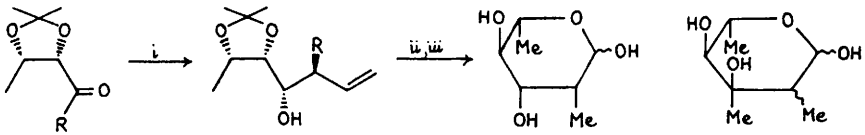


Reagent: i, H^+

Scheme 6

4 Compounds with an R-C-H or R-C-R Branch

Reaction of crotyl chromium with the 4-deoxy-L-threose derivative (35) proceeds stereoselectively according to Cram's rule to give the isomer (36), which could be ozonolysed to give 2,6-dideoxy-2-C-methyl-L-mannose (37) (Scheme 7); analogous reaction of the corresponding Grignard reagent, or of the chromium reagent with the corresponding ketose (38), was not stereospecific, giving mixtures of C-2 epimers in the product sugars, although the chromium reagent now showed anti-Cram selectivity at C-3, leading to the isomers (39).[23]



(35) R = H
(38) R = Me

(36) R = H

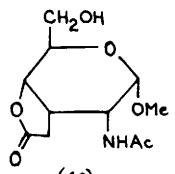
(37)

(39)

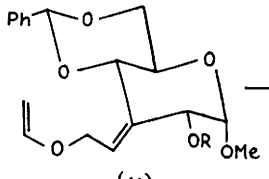
Reagents: i, CH_2Br - $CrCl_2$; ii, H_3O^+; iii, O_3

Scheme 7

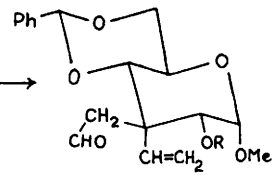
Wittig reactions of glycosidulose derivatives have been used in the synthesis of the branched-chain amino-sugar (40) from the corresponding amino-glycosidulose[24] and in syntheses of allyl vinyl ethers used in a study of the stereochemistry of the Claisen rearrangement route to gem dialkyl branched-chain sugars, e.g.,



(40)



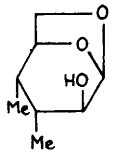
(41)



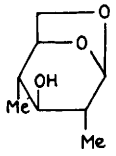
R = $SiMe_2Bu^t$ (42)

(41)→(42); these studies suggest that the stereochemistry is controlled by oxygen lone-pair interactions with the developing electron-deficient centre at the spiro carbon.[25,26] Such Claisen rearrangements to gem dialkyl sugars have also been used in syntheses directed towards verrucarol referred to in Chapter 24, which also mentions other Wittig-glycosidulose products, and some C-phosphonylmethyl branched-chain sugar nucleosides prepared using such Wittig reactions are covered in Chapter 20.

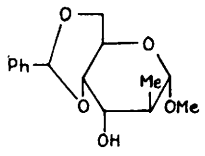
Several papers report on reaction of oxiran sugars with organometallic reagents. 1,5;2,3-Dianhydro-4,6-O-benzylidene-D-allitol with organocuprates undergoes oxiran ring opening at C-2, with inversion, whereas use of vinyl magnesium bromide with catalytic amounts of cuprous iodide led to a mixture of C-2 substituted epimers; the allo isomer was considered to be formed by initial oxiran opening by bromide ion with subsequent vinyl displacement.[27] Methyl 2,3-anhydro-5-deoxy-α-D-ribofuranoside with lithium methyl cuprate gave mainly C-2 substitution, leading to a series of derivatives of 2,5-dideoxy-2-C-methyl-D-arabinose.[28] Reaction of 1,6;2,3-dianhydro-4-deoxy-4-C-methyl-β-D-mannopyranose with dimethyl magnesium gave a 68:12 mixture of the di-C-methyl branched-chain sugars (43) and (44), the latter of interest for macrolide synthesis.[29]



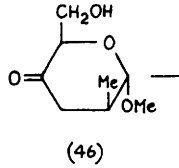
(43)



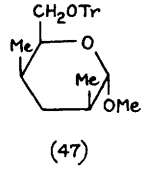
(44)



(45)



(46)

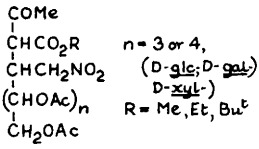


(47)

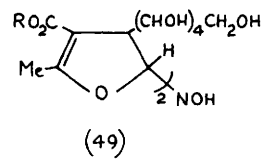
The readily prepared 2-deoxy-2-C-methyl-altroside (45) has been converted to the 4-ulose (46) and hence via Wittig methylenation to the 2,3,4-trideoxy-2,4-di-C-methyl pyranoside (47), another useful chiral intermediate for macrolide synthesis.[30] The same altroside

(45) has been used to make other deoxy-C-methyl branched-chain sugars, whose use in rifamycin synthesis is mentioned in Chapter 24. The preparation of a 4-C-aminocarbonyl branched-chain sugar from an oxiran sugar as an intermediate in carbapenem synthesis is also referred to in Chapter 24.

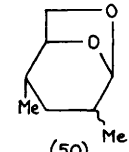
Michael additions to unsaturated sugars have been utilized for synthesizing the branched-chain sugars (48),[31] and hence, using excess methoxide, to the dimeric derivative (49).[32] Levoglucos-



(48)



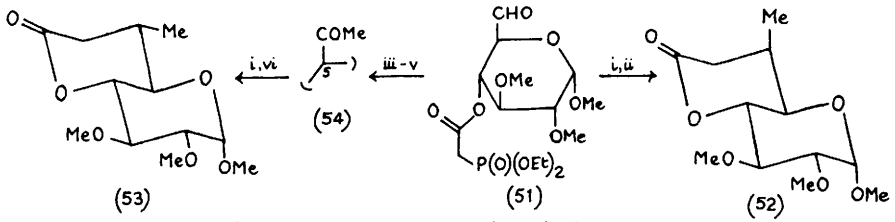
(49)



(50)

enone, by sequential methyl-cuprate Michael reaction and Wittig methylenation, provides a convenient source of the 2,4-di-C-methyl sugars (50) used in syntheses of (-)-δ-multistriatin and (+) Prelog-Djerami lactonic acid (see also Chapter 24).[33] An intramolecular Wadsworth-Emmons condensation followed by methyl cuprate Michael addition allowed the conversion of the dialdose (51) to the hepturonolactone (52), while the C-6 epimeric lactone (53) was obtained from the corresponding keto-aldose (54) (Scheme 8).[34]

The glycosidulose (55) derived from the corresponding 2,3;4,6-di-O-benzylidene-α-D-mannose C-glycoside underwent C-enolate alkyl-



(53) (54) (51) (52)

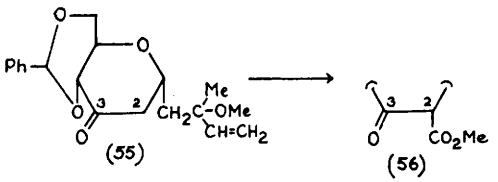
Reagents: i, NaH; ii, $Me_2Cu(CN)Li_2$; iii, $TiCl_4$-CH_2Br_2-Zn; iv, $Hg(OAc)_2$-H_2O; v, H_2CrO_4; vi, H_2-PtO_2

Scheme 8

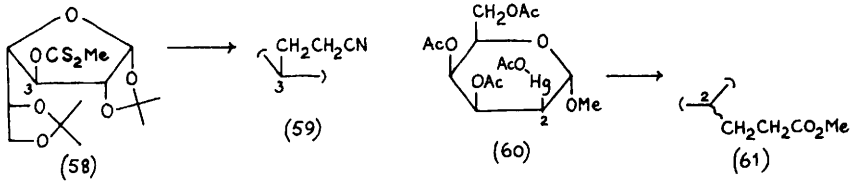
ation on treatment with methyl magnesium carbonate to yield the 2-C-methoxycarbonyl derivative (56); under other conditions O-alkylation occurred.[35]

Periodate-oxidized gluco- and manno-pyranosides can be condensed with β-dicarbonyl compounds to give 3-C-acylated branched-chain sugars (57).[36]

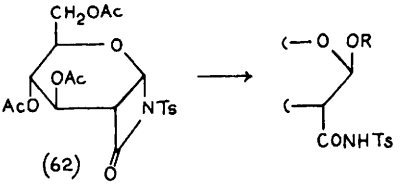
Newer methods of preparing branched-chain sugars have



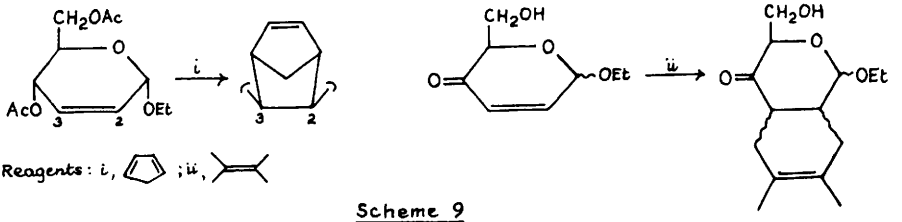
utilized tri-n-butyl stannane; it catalyses the condensation of the xanthate (58) with acrylonitrile to give the cyanoethyl branched-chain sugar (59) [37] and the condensation of the mercuriacetate glycal adduct (60) with methyl acrylate to give the C-2 epimeric mixture (61), with mainly equatorial (71:29) addition.[38]



[2+2] Cycloaddition of p-toluene sulphonyl isocyanate with acetylated glycals under high pressure gives β-lactam products stereoselectively such that bonding occurs trans to the 3-O-acetate group; thus, triacetyl-D-glucal yielded the gluco adduct (62), which gave the corresponding β-glycoside on alcoholysis.[39]

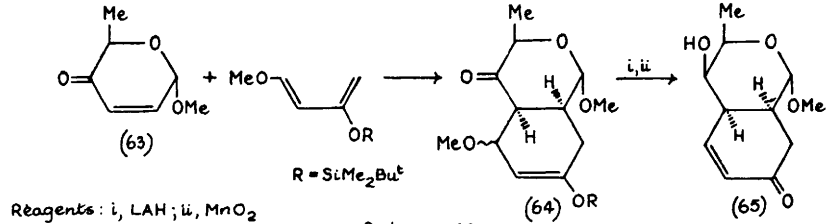


Futher examples of Diels-Alder addition products giving polycyclic derivatives have been reported, illustrated in Scheme 9; the glycosenone gave all the 4 possible addition stereoisomers, the



Scheme 9

trans isomers arising by epimerization of the initially formed cis compounds.[40] The related glycosenone (63) yielded the bicyclic sugar adduct (64) with the bis-enol ether of 3-oxo-butanal, which was converted to further derivatives, e.g., (65) (Scheme 10), lithium aluminium hydride desilylating (64) with concurrent loss of



Scheme 10

the methoxy group.[41] An attempt to add propenal to triacetylglucal, by analogy with its reaction with vinyl ethyl ether under ytterbium (fod)$_3$ catalysis failed, perhaps because of the C-3 acetoxy substituent.[42] Further studies have been made on the oxidation of the polycyclic adducts of levoglucosenone with cyclopentadiene (see Vol. 17, p.138)
carbonyl units, governed by their relative stereochemistry, with neighbouring-group participation where possible.[43]

A fused cyclopropyl derivative of methyl mannopyranoside is mentioned in Chapter 24 as an intermediate for a chiral synthesis of chrysanthemic acids, and the formation of a branched chain by ring contraction in an amino-sugar triflate is referred to in Chapter 9.

References

1 J.Yoshimura, Advan. Carbohydr. Chem. Biochem., 1984, 42, 69.
2 C.J.McGarvey, M.Kimura, T.Oh, and J.M.Williams, J. Carbohydr. Chem., 1984, 3, 125.
3 R.P.Gorskova, V.A.Zubkov, V.V.Isakov, and Y.S.Ovodov, Carbohyr. Res., 1984, 126, 308.
4 S.W.Hunter, T.Fujiwara, R.C.Murphy, and P.J.Brennan, J. Biol. Chem., 1984, 259, 9729.
5 T.Murakami, N.Tanaka, T.Noguchi, Y.Saiki, and C.-M.Chen, Chem. Pharm. Bull., 1984, 32, 1815.
6 G.Nonaka, K.Ishimaru, T.Tanaka, and I.Nishioka, Chem. Pharm. Bull., 1984, 32, 483.
7 P.Welzel, H.-P.Bulian, A.Maulshagen, D.Müller, and G.Snatzke, Tetrahedron, 1984, 40, 3657.
8 F.M.Hauser and T.C.Adams, J. Org. Chem., 1984, 49, 2296.
9 R.M.Giuliano, Carbohydr. Res., 1984, 131, 341.
10 M.Georges, D.MacKay, and B.Fraser-Reid, Carbohydr. Res., 1984, 130, 115.
11 H.W.Pauls and B.Fraser-Reid, Can. J. Chem., 1984, 62, 1532.
12 J.S.Brimacombe and T.J.R.Weakley, Carbohydr. Res., 1984, 126, 303.

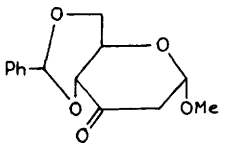
13 A.Klemer and H.Beermann, J. Carbohydr. Chem., 1983, 2, 457.
14 Atta-Ur-Rahman, N.Hong, and J.Yoshimura, J. Chem. Soc. Pak., 1983, 5, 253.
15 F.M.Hauser, W.P.Ellenberger, and T.C.Adams, J. Org. Chem., 1984, 49, 1169.
16 J.Yoshimura, N.Kawauchi, T.Yasumori, K.Sato, and H.Hashimoto, Carbohydr. Res., 1984, 133, 255.
17 F.J.Lopez Aparicio, I.Izquierdo Cubero, and M.D.Portal Olea, Carbohydr. Res., 1984, 134, 39.
18 I.Izquierdo Cubero, M.D.Portal Olea, and D.Garcia Poza, Carbohydr. Res., 1984, 134, 327.
19 Z.J.Witczak, R.L.Whistler, and J.R.Daniel, Carbohydr. Res., 1984, 133, 235.
20 J.Yoshimura, T.Yasumori, T.Kondo, and K.-i. Sato, Bull. Chem. Soc. Jpn., 1984, 57, 2535.
21 T.Yasumori, K.-i.Sato, H.Hashimoto, and J.Yoshimura, Bull. Chem. Soc. Jpn., 1984, 57, 2538.
22 J.-C.Depezay and A.Dureault, Tetrahedron Lett., 1984, 25, 1459.
23 G.Fronza, C.Fuganti, P.Grasselli, G.Pedrocchi-Fantoni, and C.Zirotti, Chem. Lett., 1984, 335.
24 A.Calvo-Mateo, M.J.Camarasa, and F.G.De las Heras, J. Carbohydr. Chem., 1984, 3, 475.
25 D.B.Tulshian, R.Tsang, and B.Fraser-Reid, J. Org. Chem., 1984, 49, 2347.
26 B.Fraser-Reid, D.B.Tulshian, R.Tsang, D.Lowe, and V.G.S.Box, Tetrahedron Lett., 1984, 25, 4579.
27 C.Brockway, P.Kocienski, and C.Pant, J. Chem. Soc., Perkin Trans. I, 1984, 875.
28 H.Yamamoto, H.Sasaki, and S.Inokawa, Carbohydr. Res., 1984, 132, 287.
29 A.F.Sviridov, D.V.Yashunskii, M.S.Ermolenko, and N.K.Kochetkov, Izv. Akad. Nauk SSSR, Ser. Khim., 1984, 723 (Chem. Abstr., 1984, 101, 171 598).
30 Y.Chapleur, F.Germain, A.Aubry, and D.Bayeul, J. Carbohydr. Chem., 1984, 3, 443.
31 A.Gomez Sanchez, M.Mancera, F.Rosado, and J.Bellanato, Carbohydr. Res., 1984, 134, 63.
32 A.Gomez Sanchez, M.Mancera, F.Rosado, and M.Rico, Carbohydr. Res., 1984, 134, 75.
33 M.Mori, T.Chuman, and K.Kato, Carbohydr. Res., 1984, 129, 73.
34 D.Nicoll-Griffith and L.Weiler, J. Chem. Soc., Chem. Commun., 1984, 659.
35 R.Tsang and B.Fraser-Reid, J. Chem. Soc., Chem. Commun., 1984, 60.
36 Yu.V.Nesal'tsev, V.A.Afanas'ev, and A.S.Shashkov, Bioorg. Khim., 1984, 10, 702 (Chem. Abstr., 1984, 101, 171 607).
37 B.Giese, J.A.Gonsalez-Gomez, and T.Witzel, Angew. Chem. Int. Ed. Engl., 1984, 23, 69.
38 B.Giese and K.Gröninger, Tetrahedron Lett., 1984, 25, 2743.
39 M.Chmielewski, Z.Kaluza, C.Belzecki, P.Salanski, and J.Jurczak, Tetrahedron Lett., 1984, 25, 4797.
40 H.Gnichtel, C.Gumprecht, and P.Luger, Justus Liebigs Ann. Chem., 1984, 1531.
41 B.Fraser-Reid, A.Rahman, D.R.Kelly, and R.M.Srivastava, J. Org. Chem., 1984, 49, 1835.
42 S.Danishefsky and M.Bednarski, Tetrahedron Lett., 1984, 25, 721.
43 M.G.Essig and F.Shafizadeh, Carbohydr. Res., 1984, 127, 235.

15
Aldosuloses and Dialdoses

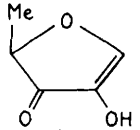
Pyridinium dichromate-acetic anhydride is very simple and efficient for use in the oxidation of carbohydrate alcohols. Examples illustrating the oxidation of secondary alcohols in pyranoid and furanoid compounds in almost quantitative yield were provided.[1]

In the field of 2-uloses, dimers of D-arabino-, D-lyxo- and L-xylo-hexosuloses were characterized by the m.s. of acetals and TMS ethers as 1,2':2,1'-dianhydrides of the 2,5-furanose forms,[2] and m.s.-g.c. examinations of the monomer TMS ethers, acetates, isopropylidene acetals, methyl glycosides and 1,1-dimethylacetals have been reported.[3] Kinetics of the degradation of D-arabino-hexos-2-ulose with hydrogen peroxide have been measured,[4] and the conversions of ribo- to arabino-nucleosides by way of 2-keto derivatives and to xylo-nucleosides by way of 3-keto derivatives have been reported.[5] A naturally occurring branched-chain hexos-2-ulose derivative is referred to in Chapter 14.

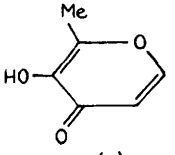
Reaction of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside with magnesium iodide in ether gives the 2-deoxy-2-iodo-altroside in almost quantitative yield which, with tributyltin chloride and sodium borohydride, gave the 2-deoxy compound which



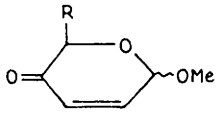
(1)



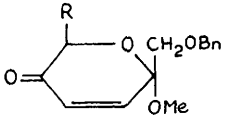
(2)



(3)

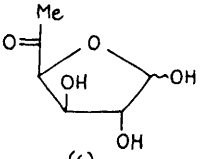


(4)

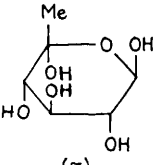


(5)

R = H, Me, Et, Pr^i, Bu^t, CH_2OBn



(6)

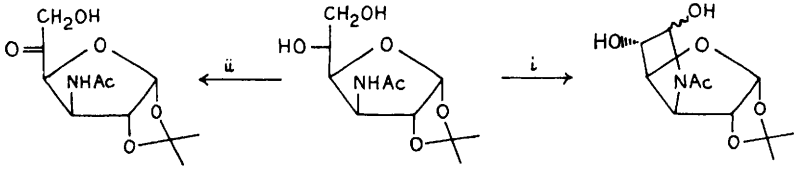


(7)

oxidized readily (PDC) to the 3-uloside (1), an important starting material for L-daunosamine.[6] The food flavours (2) and (3) (maltol) have been made via 5-deoxy-1,2-O-isopropylidene-D-erythro-pentos-3-ulose and methyl 6-deoxy-2,3-di-O-methyl-α-D-xylo-hexosid-4-ulose, respectively.[7] The racemic glycosides (4) and (5) give mainly erythro-products on LAH reduction, α-anomers showing greater selectivity.[8]

Hydrolysis of 6-deoxy-1,2-O-isopropylidene-α-D-xylo-hexofuranos-5-ulose gives the osulose which was shown by ^{1}H and ^{13}C n.m.r. spectroscopy to be a mixture of furanose and hydrated pyranose forms (6) and (7).[9]

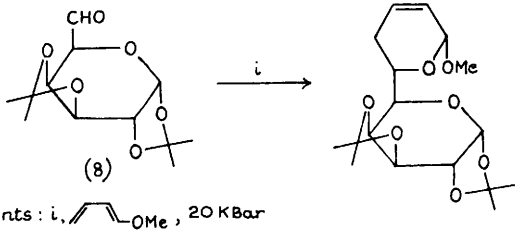
Whereas di-isopropyl sulphide-N-chlorosuccinimide oxidizes primary hydroxyl groups preferentially at 0°, at -78° secondary groups are oxidized selectively, which is illustrated in Scheme 1.[10]



Reagents: i, $Pr^{i}_{2}S$-NCS, 0°; ii, $Pr^{i}_{2}S$-NCS, -78°

Scheme 1

Titanium tetrachloride-catalysed photo-oxidation of D-glucose and D-galactose affords the corresponding pentodialdoses.[11] The hexodialdose derivative (8) takes part in the hetero-Diels-Alder reaction indicated in Scheme 2.[12]



Reagents: i, , 20 KBar

Scheme 2

References

1 F.Andersson and B.Samuelsson, Carbohydr. Res., 1984, 129, C1.
2 P.A.G.Ruiz, I.C.Travesedo, and A.S.Martinez, Can. J. Chem., 1984, 62, 561.
3 P.A.G.Ruiz, I.C.Travesedo, and A.S.Martinez, Can. J. Chem., 1984, 62, 870.

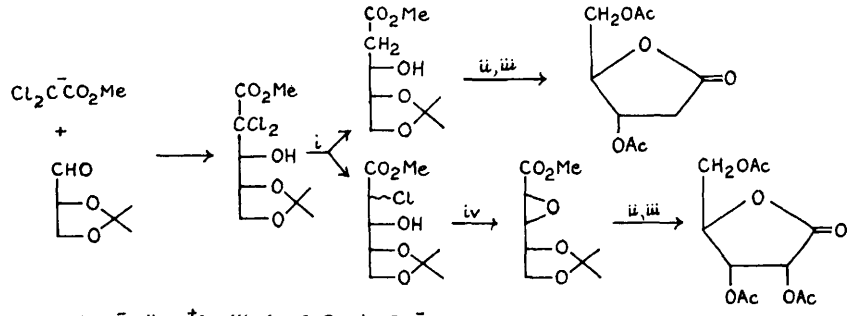
4 T.Vuorinen, Carbohydr. Res., 1984, 127, 319.
5 F.Hannsske, D.Madej, and M.J.Robins, Tetrahedron, 1984, 40, 125.
6 M.K.Gurjar, J.S.Yadav and A.V.R.Rao, Indian J. Chem., Sect. B, 1983, 22B, 1139 (Chem. Abstr., 1984, 101, 91 377).
7 T.Shono, Y.Matsumura, H.Hamaguchi and S.Naitoh, J. Org. Chem., 1983, 48, 5126.
8 O.Achmatowicz, Jr. and M.H.Burzynska, Pol. J. Chem., 1983, 57, 1275.
9 D.E.Kiely, J.W.Talhouk, J.M.Riordan, and K.Gray, J. Carbohydr. Chem., 1983, 2, 427.
10 K.S.Kim, I.H.Cho, B.K.Yoo, Y.H.Song, and C.S.Hahn, J. Chem. Soc., Chem. Commun., 1984, 762.
11 T.Sato, K.Takahashi, and S.Ichikawa, Nippon Kagaku Kaishi, 1984, 119 (Chem. Abstr., 1984, 100, 210 275).
12 J.Jurczak, T.Bauer, and S.Jarosz, Tetrahedron Lett., 1984, 25, 4809.

16
Sugar Acids and Lactones

1 Aldonic Acids

The kinetics and mechanism of the electrochemical oxidation of D-glucose to D-gluconic acid at a platinum electrode have been reported.[1]

In the area of aldonic acid derivatives, 6-amino-6-deoxy-2,3,4,5-tetra-O-methyl-D-gluconic acid and related compounds have been made from 6-azido-6-deoxy-1,2-O-isopropylidene-α-D-gluco-furanose,[2] and several members of the series have been reported following the reaction between 1,2-O-isopropylidene-D-glycer-aldehyde and an anion derived electrochemically from methyl tri-chloroacetete (Scheme 1). The products were formed with good selectivity, and several related compounds, e.g., 3,5,6,7-tetra-O-acetyl-2,2-dichloro-2-deoxy-D-manno-heptono-γ-lactone, were described.[3]

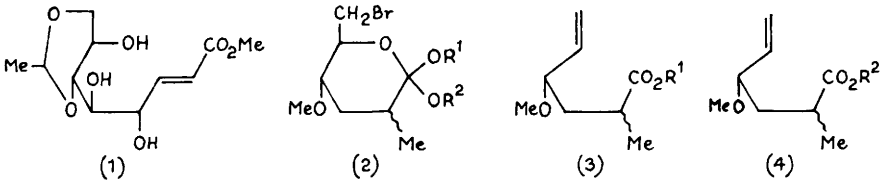


Reagents: i, e^-; ii, H_3^+O; iii, Ac_2O-Py; iv, OH^-

Scheme 1

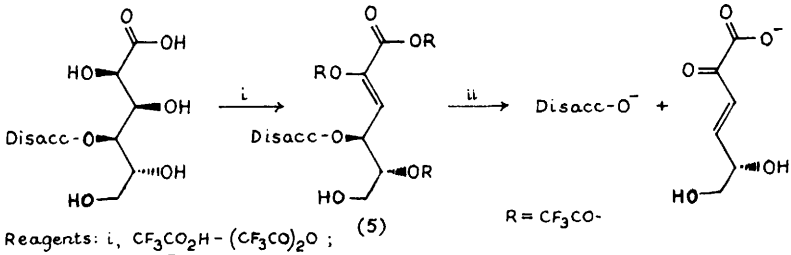
4,6-O-Ethylidene-D-glucose reacts with neutral Wittig reagent to give mainly the (E) methyl 2,3-dideoxyoct-2-enoate derivative (1).[4] The 6-bromo-mixed orthoesters (2, R^1,R^2 = CH_3,CD_3,CH_2CH_3,CH_2CD_3) on treatment with zinc undergo ring-opening to give mixed unsaturated aldonates (3) and/or (4), analysis of which allowed an understanding

of details of this reaction.[5]



Alkaline treatment of 3-deoxy-D-erythro-hexos-2-ulose gives 3-deoxyhexonic acids by a mechanism analogous to benzilic acid rearrangement.[6]

4-Substituted aldonic acids which cannot form γ-lactones (and likewise 3-substituted hexuronic acids) are sensitized towards loss of the substituent on trifluoroacetolysis (anhydride:acid, 50:1, 100°), and therefore 4-linked oligosaccharides are selectively cleaved. The aldonic acids derived from isomaltotriose (1→6 link) and laminaritriose (1→3 link) are therefore stable on such treatment, whereas maltotriose aldonic acid is converted into the substituted trifluoroacetylated enol of 3-deoxy-2-hexulosonic acid (5) and hence, with mild base, into maltose (Scheme 2).[7]

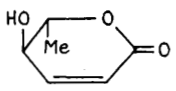


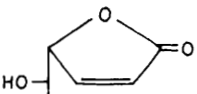
Scheme 2

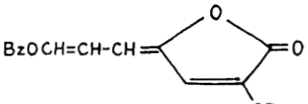
D-Gluconylhydrazide reacts with aldehydes, e.g., 5-nitrofurfural, to give D-gluconylhydrazones.[8]

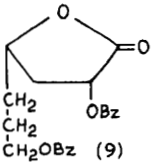
80 MHz proton and 20 MHz proton coupled ^{13}C n.m.r. examinations of D-arabinono-1,4-lactone have been reported with ^{2}J and ^{3}J values derived by computer simulation methods.[9] The unsaturated lactones (6) and (7) have been identified in Osmunda japonica and are butterfly antifeedants.[10] Triethylamine treatment of 2,3,5,6,7-penta-O-benzoyl-D-glycero-D-gulo-heptono-1,4-lactone yields the 2,7-dibenzoate (8) rather than the 2,6-diester as previously claimed. Reduction with hydrogen on palladium-charcoal gave the DL-lactone derivative (9).[11]

Two papers have illustrated some specific reactions of aldono-γ-lactone derivatives. 2-Deoxy compounds, including L-digitoxose

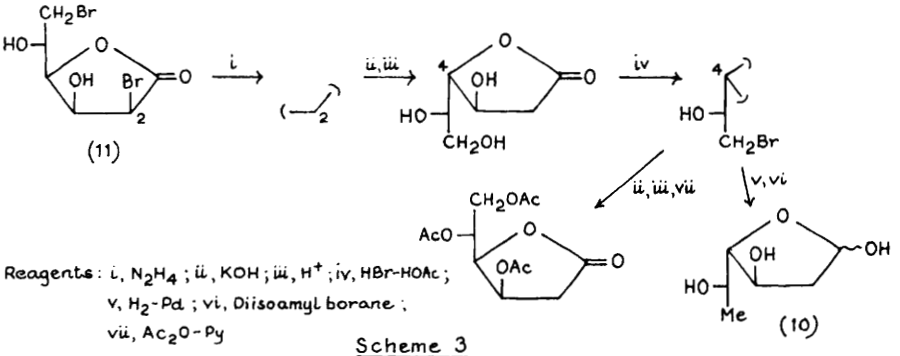

(6)


(7)


(8)

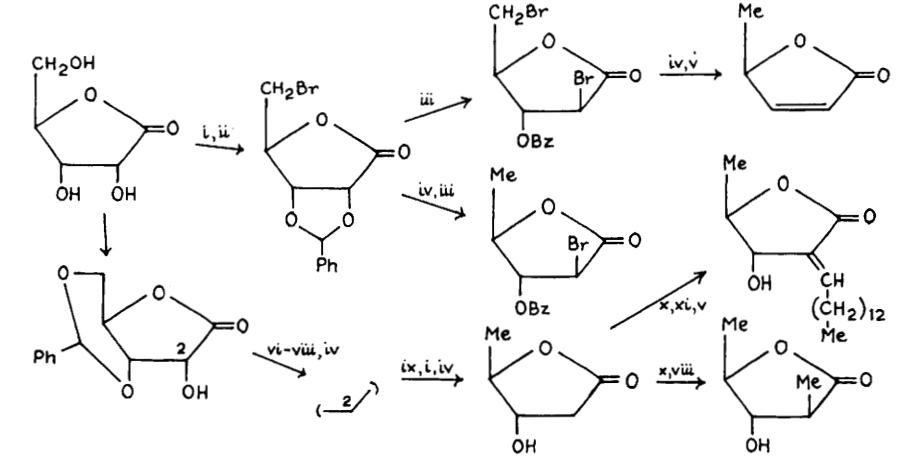

(9)

(10), are accessible from the 2,6-dibromo-lactone (11), which is easily made from calcium D-gluconate (Scheme 3). Mechanisms for



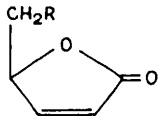
Scheme 3

the inversions at C-4 and C-5 in both the alkali-catalysed steps are discussed in terms of epoxide intermediates.[12] In related work D-ribono-γ-lactone has been used as the base material for

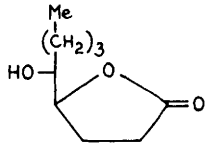


Scheme 4

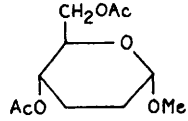
several lactone derivatives including natural products (Scheme 4),[13] and the same initial lactone has been used to produce lactones of the type (12, R = Me,Bu) and 2,3-saturated analogues which are related to pheromones and aroma compounds.[13a] The lactone (13), prepared from the pyranoside (14), was shown not to be "L-factor" associated with autoregulation of cytodifferentiation in Streptomyces growth and antibiotic production.[14]



(12)



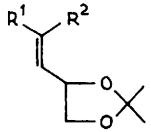
(13)



(14)

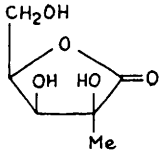
2 Saccharinic Acids

Hydroxylation of the unsaturated esters (15) and (16) with osmium tetraoxide led to routes to the saccharinic acid lactones (17) and (18).[15]

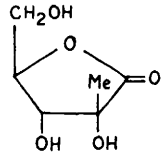


(15) $R^1 = Me$, $R^2 = CO_2Et$

(16) $R^1 = CO_2Et$, $R^2 = Me$



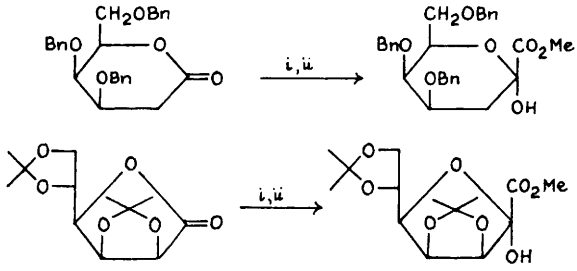
(17)



(18)

3 Ulosonic Acids

A new, general synthesis of ulosonic acid derivatives involves the

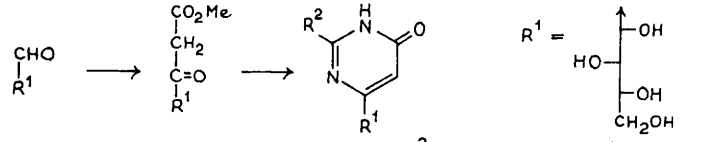


Reagents: i, $LiC(SMe)_3$; ii, MeOH-H_2O-HgO-$HgCl_2$

Scheme 5

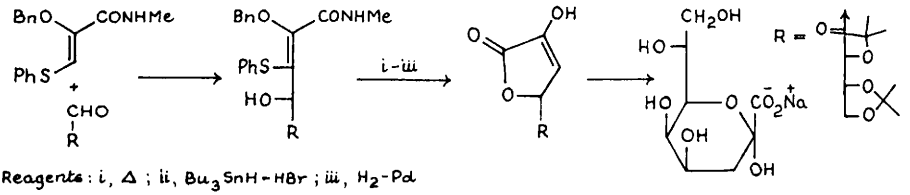
use of tris(methylthio)methyl lithium as an ester anion equivalent - see Scheme 5.[16] A related chemical synthesis of 3-deoxy-D-arabino-heptulosonic acid as the methyl glycoside methyl ester uses 2-deoxy-D-arabino-hexose as the 3,4:5,6-di-O-isopropylidene propylene dithioacetal anion and methyl chloroformate whereas a less efficient but easier biosynthetic procedure starts from D-glucose.[17] The 7-phosphate of this ulosonic acid has been structurally analysed by ^{1}H and ^{13}C n.m.r. spectroscopy.[18]

Reaction of 2,3:4,5-di-O-isopropylidene-D-xylose with methyl diazoacetate gave the 4,5:6,7-diacetal of methyl 2-deoxy-D-xylo-hept-3-ulosonate from which polyhydroxyalkyl heterocycles, e.g., compounds (19), can be made.[19]



(19) R^2 = SH, SMe, NH_2 (or as a diacetal)

A new biomimetic synthesis of 3-deoxy-D-manno-2-octulosonic acid is illustrated in Scheme 6.[20] Spectroscopic studies of the



Reagents: i, Δ ; ii, Bu_3SnH-HBr ; iii, H_2-Pd

Scheme 6

glycosidically linked dimer of the acid derived from a Salmonella lipopolysaccharide showed that it was α-2',4-linked.[21]

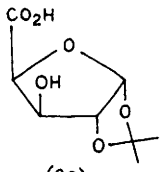
A synthesis of N-acetyl neuraminic acid from a 2-N-acetylamino-2-deoxy-D-glucose and -D-mannose mixture together with pyruvic acid and an immobilised enzyme has been described [22] and its 5-epimer prepared via a 4,5-oxazoline intermediate in a standard sequence. 7,8-Epoxides were made and treated with trimethylsilyl iodide to give 8-deoxy-8-iodo products.[23]

The ^{1}H n.m.r. spectrum of the α-anomer of N-acetyl-D-neuraminic acid was obtained by enzymic cleavage of the glycosyl azide in the n.m.r. probe, and then compared with that of the β-anomer.[24] The kinetics of C-3 deuteration under basic conditions have been determined. At high pH values the axial proton is exchanged 25 times faster than is the equatorial.[25] The hydrolysis of cytidine

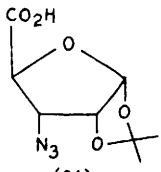
5'-phosphate-N-acetyl-β-D-neuraminic acid gives cytidine phosphate and N-acetylneuraminic acid except at pH >7 when the 2,3-unsaturated acid and N-acetylneuraminic acid 2-phosphate are produced.[26]

4 Uronic Acids

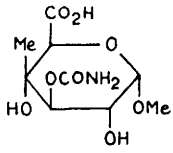
Compounds (20) and (21) have been produced from 1,2-O-isopropylidene-α-D-glucofuranose,[27] and the following methyl ethers of methyl (methyl α-D-mannopyranosid)uronate have been specifically prepared: the 2-,[28] 4-[28] and 3-[29] monoethers and the 2,3-[29] and 3,4-[29] di- and 2,3,4-[29] triethers. The ^{13}C n.m.r. spectra of ethers of this series[30] have been reported, as have those of 1,2-O-isopropylidene- and 1,2-O-benzylidene-α-D-gluco- and β-L-ido-furanurono-3,6-lactones, these last being assigned using 2D-^{1}H-^{13}C-correlated spectra.[31] The intramolecular coordination of the cations of sodium, potassium and rubidium with D-glucuronate have been examined by infrared methods.[32]



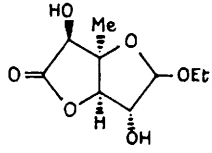
(20)



(21)



(22)



(23)

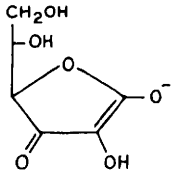
Reaction of D-glucuronic and D-galacturonic acid with hydroxy radicals gives radicals derived by hydrogen abstraction from all possible carbon atoms; for α-D-galacturonic acid and α-D-galacturonic acid polymer, C-5 abstraction predominates.[33] The anomers of D-mannuronolactone triacetates were found to react differently under different conditions: the β-form decomposed exclusively with triethylamine in benzene, the lactone ring of the α-form cleaved selectively on a chromatographic column and trifluoroacetic anhydride-acetic acid caused the α-form to be converted to 2,5-di-O-acetyl-1-O-trifluoroacetyl-β-D-mannuronolactone.[34]

The branched-chain uronic acid (22) has been synthesized from D-galactose via a 4-uloside; on ethanolysis it gave the lactone (23) which was identical with a compound obtained from the antibiotic *moenomycin*. Both the configurational and conformational features of compounds such as (23) determine the observed chiroptical properties.[35] Oxidation at C-6 of the iridoid glycoside loganin gave a uronic glycoside which was coupled to

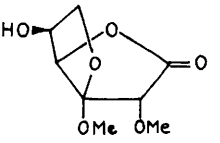
bovine serum albumin for radioimmunoassay of the glycoside.[36]

5 Ascorbic Acids

Ascorbate anion is a much more reactive nucleophile than expected from its pK_a, which has been attributed to the acidity of the C-2 hydroxy group. The observation was made by comparing the rates of reactions of many oxyanion nucleophiles with electrophiles such as *p*-nitrophenyl acetate, and suggests that the ascorbate anion may be involved in biological acyl transfer reactions.[37] A related report notes the pH dependence of ^{13}C-^{13}C spin-spin coupling constants of ascorbic acid and concludes that structure (24) best describes the monoanion, while the dianion is best represented by equal contributions from the two possible mesomeric forms.[38] However, reaction of L-ascorbic acid with dimethyl sulphate at



(24)



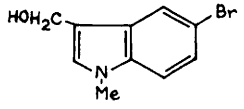
(25)

pH 10.5 gives 76% of the 2-ether rather than the 1-ether, together with 15% of a by-product believed to be the bicyclic acetal (25), which could be converted to the main product with methanolic hydrogen chloride. The 1-, 2- and 3-ethers were examined by ^{13}C n.m.r. and u.v. spectroscopy.[39] 5,6-Anhydro-L-ascorbic acid prepared from the 6-bromo-derivative reacts with common nucleophiles (*e.g.*, PhO^-, PhS^-, N_3^-) to give 6-substituted compounds.[40]

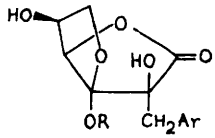
Photochemical reaction of L-ascorbic acid with tris(2,2'-bipyridyl)ruthenium(II) and hydridotris(triethylphosphine)-palladium(II) produces hydrogen. Electron transfer occurs from photo-produced $[Ru(bpy)_3]^+$ to $[PdH(PEt_3)_3]^+$ to give a Pd(I) radical from which hydrogen is produced.[41] L-Ascorbic acid scavenges phosphonyl radicals to yield a persistent complex radical, the structure of which was elucidated by e.s.r. spectrocopy.[42] L-Ascorbic acid reacts with amines in organic solvents and is thus solubilized by way of the ascorbate radical anion. This redox reaction can be induced photochemically and examined by e.s.r. methods.[43]

Reaction of L-ascorbic acid with 3-(hydroxymethyl)indole

derivatives, e.g., (26), gives ascorbigin, compounds (27) which with acetic anhydride, methanolic hydrogen chloride and ammonia in methanol give (28), (29) and (30), respectively.[44] The 2-m-chlorophenylhydrazone of dehydroascorbic acid has been prepared, as well as the 2,3-bis compound, which with base gave the pyrazole derivative (31).[45]

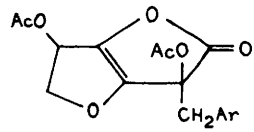


(26)

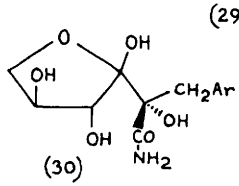


(27) R = H

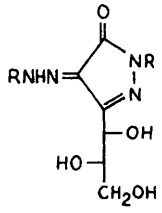
(29) R = Me

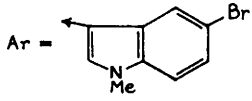


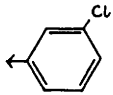
(28)



(30)





(31) R = 

Further reports on ascorbic acid describe the laser-induced mass spectra of the acid and its sodium salt and that of potassium isoascorbate,[46] the ascorbic acid content of 41 species of "woody" shrubs and trees,[47] and a method for its quantitative determination using a molybdenum(VI) peroxoborate, iodide and H^+ in a fluorimetric determination.[48]

References

1 N.N. Nikolaeva, O.A.Khazova and Yu.B.Vasil'ev, Elektrokhimiya, 1983, 19, 1476 (Chem. Abstr., 1984, 100, 139 491).

2 K.Kefurt, Z.Kefurtova, and J.Jary, Collect. Czech. Chem. Commun., 1984, 49, 2665.

3 T.Shono, N.Kise, and T.Suzumoto, J. Am. Chem. Soc., 1984, 106, 259.

4 R.D.Dawe and B.Fraser-Reid, J. Org. Chem., 1984, 49, 522.

5 B.Bernet and A.Vasella, Helv. Chim. Acta, 1984, 67, 1328.

6 T.Vuorinen, Carbohydr. Res., 1984, 127, 327.

7 A.Gunnarsson and S.Svensson, Carbohydr. Res., 1984, 132, 45.

8 V.I.Veksler, Zh. Obshch. Khim., 1983, 53, 2799 (Chem. Abstr., 1984, 100, 156 916).

9 H.Wong, Aust. J. Chem., 1984, 37, 327.

10 A.Nunata, K.Hokimoto, T.Takemura, T.Katsuno, and K.Yamamoto, Chem. Pharm. Bull., 1984, 32, 2815.

11 L.O.Jeronic, O.J.Varela, A.Fernández Cirelli, and R.M.de Lederkremer, Tetrahedron, 1984, 40, 1425.

12 K.Bock, I.Lundt, and C.Pedersen, Acta Chem. Scand., Ser. B, 1984, 38, 555.

13 S.-Y.Chen and M.M.Joullié, J. Org. Chem., 1984, 49, 2168.

13a J.Cardellach, J.Font, and R.M.Ortuno, J.Heterocycl. Chem., 1984, 21, 327.

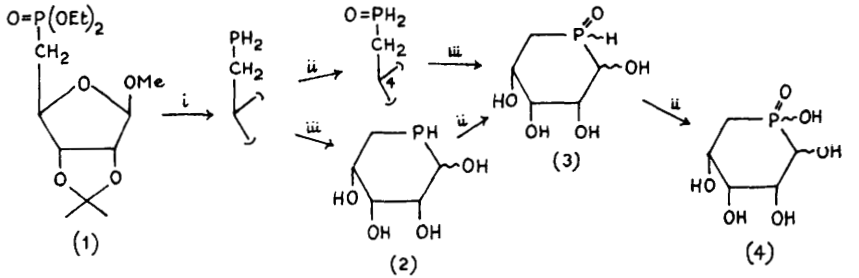
14 L.Stamatatos, P.Sinäy, and J.-R.Pougny, Tetrahedron, 1984, 40, 1713.

15 F.J.Lopez Aparicio, I.Izquierdo Cubero, and M.D.Portal Olea, Carbohydr. Res., 1984, 129, 99.
16 J.E.Hengeveld, V.Grief, J.Tadanier, C.-M.Lee, D.Riley, and P.A.Lartey, Tetrahedron Lett., 1984, 25, 4075.
17 J.W.Frost and J.R.Knowles, Biochemistry, 1984, 23, 4465 (Chem. Abstr., 1984, 101, 111 323).
18 C.C.Garner and K.M.Herrman, Carbohydr. Res., 1984, 132, 317.
19 C.Gomez Perez, M.Valpuesta Fernandez, and F.J.Lopez Herrera, An. Quim., Ser. C., 1984, 80, 45 (Chem. Abstr., 1984, 101, 230 919).
20 R.R.Schmidt and R.Betz, Angew. Chem. Int. Ed. Engl., 1984, 23, 430.
21 H.Brade, U.Zähringer, E.T.Rietschel, R.Christian, G.Schulz, and F.M.Unger, Carbohydr. Res., 1984, 134, 157.
22 C.Auge, S.David, and C.Gautheron, Tetrahedron Lett., 1984, 25, 4663.
23 H.H.Brandstetter and E.Zbiral, Justus Liebigs Ann. Chem., 1983, 2055.
24 R.Rensch, W.Baumann, and H.Friebolin, J. Carbohydr. Chem., 1983, 2, 415.
25 H.Schmidt and H.Friebolin, J. Carbohydr. Chem., 1983, 2, 405.
26 J.M.Beau, R.Schauer, J.Haverkamp, J.P.Kamerling, L.Dorland, and J.F.G.Vliegenthart, Eur. J. Biochem., 1984, 140, 203 (Chem. Abstr., 1984, 100, 134 659).
27 L.N.Kulinkovich and V.A.Timoshchuk, Zh. Obshch. Khim., 1983, 53, 2126 (Chem. Abstr., 1984, 100, 51 927).
28 V.I.Grishkovets, A.E.Zemlyakov, and V.Ya.Chirva, Khim. Prir. Soedin., 1983, 429 (Chem. Abstr., 1984, 100, 7025).
29 V.I.Grishkovets, A.E.Zemlyakov, and V.Ya.Chirva, Khim. Prir. Soedin., 1983, 555 (Chem. Abstr., 1984, 100, 139 534).
30 A.S.Shashkov, V.I.Grishkovets, A.E.Zemlyakov, and V.Ya.Chirva, Bioorg. Khim., 1984, 10, 88 (Chem. Abstr., 1984, 100, 175 185).
31 R.Csuk, N.Mueller, and H.Weidmann, Monatsh. Chem., 1984, 115, 93 (Chem. Abstr., 1984, 100, 192 198).
32 H.-A. Tajmir-Riahi, Carbohydr. Res., 1984, 125, 13.
33 B.C.Gilbert, D.M.King, and C.B.Thomas, Carbohydr. Res., 1984, 125, 217.
34 K.Tajima, Noguchi Kenkyusho Jiho, 1983, 39 (Chem. Abstr., 1984, 101, 387 611).
35 P.Welzel, H.-P.Bulian, A.Maulshagen, D.Müller, and G.Snatzke, Tetrahedron, 1984, 40, 3657.
36 T.Tanahashi, N.Nagakura, H.Inouye, and M.H.Zenk, Phytochemistry, 1984, 23, 1917.
37 J.Shaskus and P.Haake, J. Org. Chem., 1984, 49, 197.
38 S.Berger, J. Chem. Soc., Chem. Commun., 1984, 1252.
39 P.W.Lu, D.W.Lillard, P.A.Seib, K.J.Kramer, and Y.-T.Liang, J. Agric. Food Chem., 1984, 32, 21 (Chem. Abstr., 1984, 100, 51 926).
40 G.C.Andrews, Carbohydr. Res., 1984, 134, 321.
41 J.R.Fisher and D.J.Cole-Hamilton, J. Chem. Soc., Dalton Trans., 1984, 809.
42 W.G.McGimpsey, G.F.Pedulli, M.C.Depew, and J.K.S.Wan, Phosphorus Sulfur, 1983, 17, 253 (Chem. Abstr., 1984, 100, 139 533).
43 M.C.Depew, M.Chan, and J.K.S.Wan, J. Magn. Reson., 1984, 57, 297 (Chem. Abstr., 1984, 101, 23 859).
44 V.I.Mukhanov, I.V.Yartseeva, B.S.Kikot, Yu.Yu.Volodin, I.L.Kustova, N.A.Lesnaya, Z.P.Sof'ina, N.P.Ermakova, and M.N.Preobrazhenskaya, Bioorg. Khim., 1984, 10, 544 (Chem. Abstr., 1984, 101, 192 372).
45 Y.El Kilany, H.A.Hamid, and E.S.H.El Ashry, Carbohydr. Res., 1984, 125, 77.
46 W.Lohmann, F.Hillenkamp, J.Rosmarinowsky, D.Bachmann, and M.Karas, Fresenius' Z. Anal. Chem., 1984, 317, 129 (Chem. Abstr., 1984, 100, 175 186).
47 E.Jones and R.E.Hughes, Phytochemistry, 1985, 23, 2366.
48 M.Kataoka, H.Hemmi, and T.Kambara, Bull. Chem. Soc. Jpn., 1984, 57, 1083.

17
Inorganic Derivatives

1 Carbon-bonded Phosphorus Derivatives

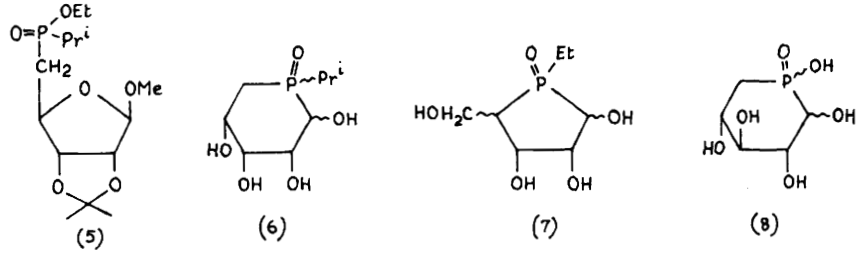
Two reviews have appeared on the chemistry of carbohydrate derivatives having phosphorus as the hetero ring atom.[1,2]



Reagents: i, $NaAlH_2(OCH_2CH_2OMe)_2$; ii, H_2O_2; iii, H^+

Scheme 1

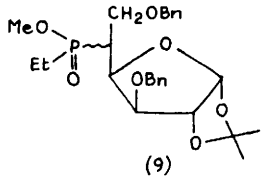
Compound (1) has been used to make the series of D-ribose compounds (2)-(4) (Scheme 1),[3] and from the analogue (5) the phosphinoxy derivative (6) has been prepared and yielded four diastereoisomers on acetylation that were separated chromatographically and characterized.[4] Starting from methyl 2,3-O-



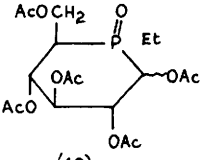
isopropylidene-α-L-lyxopyranoside, the L-lyxo- and D-ribo-furanose compounds (7) were obtained,[5] and a similar sequence yielded the D-xylopyranose analogue (8) from 3-O-acetyl-5-deoxy-5-iodo-1,2-O-isopropylidene-α-D-xylofuranose via the 5-phosphinyl derivative. Again, four derived tetra-acetates were characterized by n.m.r.

methods.[6]

Two related routes from 5-deoxy-5-C-[ethyl(methoxy)phosphinyl] compounds, e.g., (9), have been used to prepare the epimeric D-glucose penta-acetate analogues (10).[7,8]

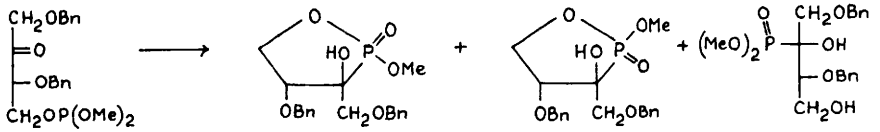


(9)



(10)

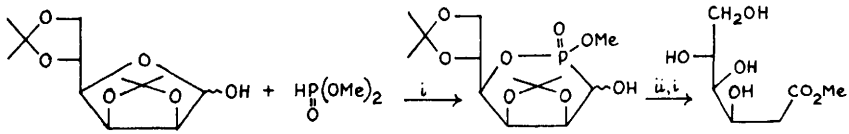
Two reports describe the first analogues to cyclic carbohydrates having phosphorus at the anomeric centre ("phostones"). Furanoid analogues (11) and (12) were obtained by hydrolysis of the phosphite (13) together with the acyclic product (14) (Scheme 2), the latter undergoing ring closure to (11) and (12) on treatment



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

Scheme 2

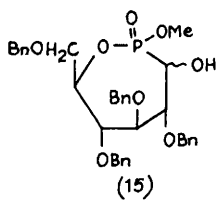
with triethylamine. Related compounds analogous to methyl 3,5-O-benzylidene-α- and β-D-lyxofuranoside are also described.[9] Application of the Abramov reaction with 2,3:5,6-di-O-isopropylidene-D-mannose led to a pyranose analogue (Scheme 3); 2,3,4,6-tetra-O-



Reagents: i, Base ; ii, TsCl-Py

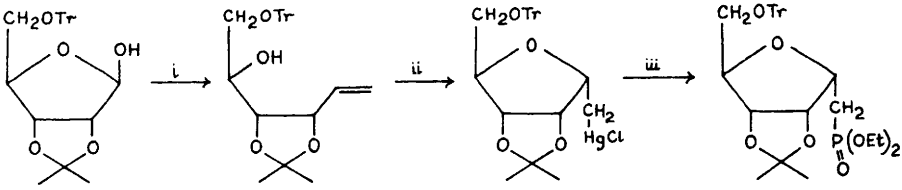
Scheme 3

benzyl-D-glucose, under these conditions, gave the novel 7-membered ε-phostones (15).[10]



(15)

Alkenes produced from aldoses with free anomeric groups can be converted to methylene alkenes and then cyclized to give C-glycosides having mercuriated methyl "aglycones". From these, phosphonates which are analogues of aldose 1-phosphates can be produced. The method has been used to obtain the α-D-ribofuranose 1-phosphate (16) (Scheme 4)[11] and also β-D-mannopyranose 1-phosphate analogues.[12] The dimethyl ester analogue of compound

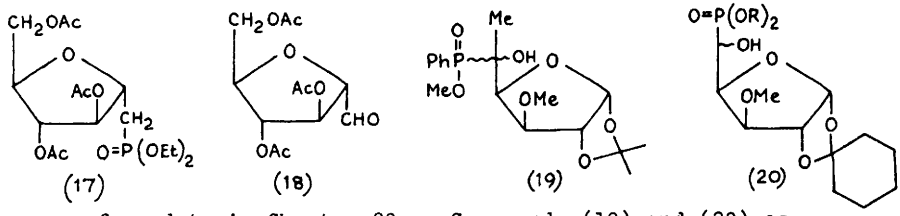


Reagents: i, $Ph_3P{=}CH_2$; ii, $Hg(OAc)_2$; iii, I_2-CCl_4 ; iv, $P(OEt)_3$

(16)

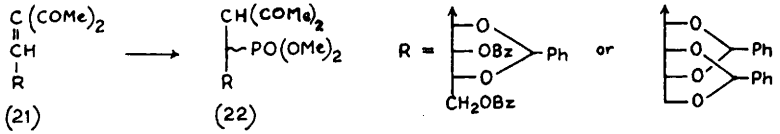
Scheme 4

(16) can also be made, together with its β-anomer, by direct treatment of 2,3-O-isopropylidene-6-O-trityl-D-ribose with $(MeO)_2POCH_2PO(OMe)_2$,[13] and the α-D-arabinofuranose diethyl compound (17) from the 2,5-anhydride (18) via the bromomethyl intermediate.[14] Nucleosides containing phosphonomethyl groups at C-3'



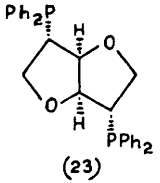
(17) (18) (19) (20)

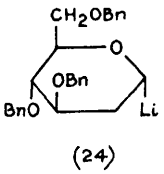
are referred to in Chapter 20. Compounds (19) and (20) as epimeric pairs have been synthesized by nucleophilic additions to appropriate carbonyl derivatives,[15,16] and Michael addition reactions applied to the enones (21) have afforded the corresponding 2-C-phosphonate sugars (22).[17]

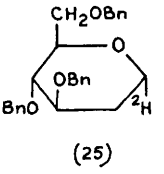


(21) (22)

The diphosphine (23), derived from D-mannitol, affords rhodium complexes which are asymmetric, homogeneous hydrogenation catalysts which have been used to produce (S)-amino acids from dehydroamino acids in 21-58% optical yields.[18]


(23)


(24)

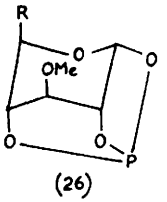

(25)

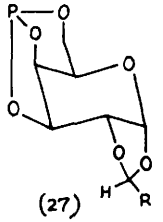
2 Other Carbon-bonded Derivatives

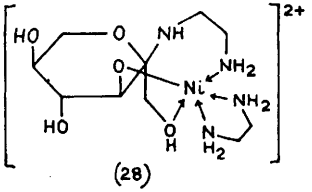
A review has been published on the synthesis and antitumour activities of selenium derivatives of nucleosides.[19] The glycopyranosyl lithium (24) has been generated from both tri-O-benzyl-D-glucal by reductive lithiation and from phenyl 3,4,6-tri-O-benzyl-2-deoxy-1-thio-D-arabino-hexopyranoside by the same process. Reaction with aldehydes converts (24) into diastereoisomeric C-glycosidic pairs, and with D_2O into the α-^{2}H-labelled 1,5-anhydro glycitol derivative (25).[20]

3 Oxygen-bonded Derivatives

Cyclic phosphites (26, R=H, Me, CH_2OH) have been made from the corresponding 3-O-methyl sugars[21] and likewise the D-galactose esters (27, R = Me, Ph), which were oxidized to the analogous phosphates.[22] A series of 3,5-cyclic phosphite compounds were also prepared from 6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose.[23]


(26)


(27)


(28)

Associations between D-glucose, D-fructose and sodium hydroxide in ethanol, acetone and dioxan have been examined in detail,[24] and a potassium ion lactose complex has been postulated.[25] The interactions between calcium ions and a range of monosaccharides have been studied using OH-^{1}H n.m.r. spectra, and different strengths of bindings have been recognised.[26] The infrared spectra of α-L-arabinose $CaCl_2$ and $CaBr_2$ complexes have been examined

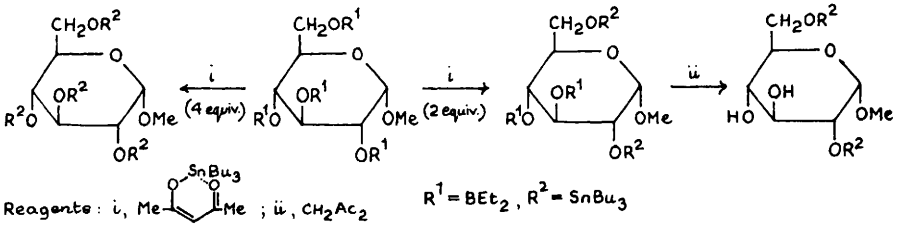
in detail.[27]

Photochemical reactions of monosaccharides with iron(III) chloride have been reported in Chapter 2. L-Sorbose and tris-(ethylenediamine)nickel(II) chloride give a crystalline cationic adduct.[28]

Electron-nuclear relaxation rates have been used to determine interactions between methyl galactopyranoside and Mn^{2+}; associations are strongest with O-6 and weaker with O-2 and O-3.[29] Polarimetric studies suggest a 1:1 complex forms between fructose and basic lead acetate.[30]

Molybdate complexes with tetroses and 5-deoxypentoses in tridentate fashion[31] and the absolute configurations of glycols have been determined by examination of the c.d. spectra of their molybdenum tetra-acetate complexes.[32]

O-Stannyl derivatives of carbohydrates can be made by way of borinate esters by use of the tributylstannyl enolate of acetylacetone (Scheme 5); the reaction can be carried out selectively.[33]



Scheme 5

A detailed ^{13}C and ^{119}Sn n.m.r. study has examined the natures of the interactions between tin(II) chloride and vicinal diols in polar organic solvents. A mechanism for the monoalkylation of vicinal diols by diazomethane in the presence of tin(II) chloride was established.[34]

Complexing of 1,4:3,6-dianhydro-D-glucitol, -iditol and -mannitol with lanthanide chelates has been examined by ^{1}H and ^{13}C n.m.r. methods. $Gd(dpm)_3$ complexes with the first of these at the O-C-6–C-5-OH site. $Eu(fod)_3$-induced ^{1}H shifts showed that mannitol complexes in the same way, but iditol associates only poorly.[35]

References

1 H.Yamamoto and S.Inokawa, Advan. Carbohydr. Chem. Biochem., 1984, 42, 135.
2 Z.J.Witczak and R.L.Whistler, J. Carbohydr. Chem., 1983, 2, 351.
3 H.Yamamoto, M.Harada, S.Inokawa, K.Seo, M.-A.Armour, and T.T.Nakashima, Carbohydr. Res., 1984, 127, 35.

4 K.Seo, Carbohydr. Res., 1984, 125, 172.
5 H.Yamamoto, Y.Nakamura, S.Inokawa, M.Yamashita, M-A.Armour, and T.T.Nakashima, J. Org. Chem., 1984, 49, 1364.
6 H.Yamamoto, T.Hanaya, S.Inokawa, M.Yamashita, M.-A.Armour, and T.T. Nakashima, Carbohydr. Res., 1984, 128, C5.
7 H.Yamomoto, H.Murata, S.Inokawa, M.Yamashita, M.-A.Armour, and T.T.Nakashima, Carbohydr. Res., 1984, 133, 45.
8 H.Yamamoto, K.Yamamoto, S.Inokawa, M.Yamashita, M.-A.Armour, and T.T. Nakashima, J. Org. Chem., 1983, 48, 435.
9 A.E.Wroblewski, Carbohydr. Res., 1984, 125, C1.
10 J.Thiem and M.Guenther, Phosphorus Sulphur, 1984, 20, 67 (Chem. Abstr., 1984, 101, 230 851).
11 F.Nicotra, L.Panza, F.Ronchetti, and L.Toma, Tetrahedron Lett., 1984, 25, 5937.
12 F.Nicotra, R.Perego, F.Ronchetti, G.Russo, and L.Toma, Carbohydr. Res., 1984, 131, 180.
13 R.B.Meyer, Jr., T.E.Stone, and P.K.Jesthi, J. Med. Chem., 1984, 27, 1095.
14 Yu.A.Zhdanov, Z.I.Glebova, L.A.Uzlova, and N.I.Vikrishchuk, Zh. Obshch. Khim., 1983, 53, 2616 (Chem. Abstr., 1984, 100, 175 136).
15 M.Yamashita and L.P.Thanh, Shiznoka Daigaku Kogakubu Kenkyu Hokoku, 1982, 33, 47 (Chem. Abstr., 1984, 100, 6 981).
16 Yu.A.Zhdanov, G.K.Kist'yan, L.A.Uzlova, V.A.Polenov, and N.V.Yakshina, Zh. Obshch. Khim., 1983, 53, 1414 (Chem. Abstr., 1984, 100, 1 414).
17 E.Breuer, D.Melumad, S.Sarel, and E.Katz, Eur. J. Med. Chem. - Chim. Ther., 1983, 18, 487 (Chem. Abstr., 1984, 100, 156 884).
18 J.Bakos, B.Heil, and L.Marko, J. Organomet. Chem., 1983, 253, 249 (Chem. Abstr., 1984, 100, 7 002).
19 Z.J.Witczak, Nucleosides Nucleotides, 1983, 2, 295 (Chem. Abstr., 1984, 100, 51 900).
20 J.-M.Lancelin, L.Morin-Allory, and P.Sinaÿ, J. Chem. Soc., Chem. Commun., 1984, 355.
21 E.E.Nifant'ev, M.P.Koroteev, and A.A.Zharkov, Zh. Obshch. Khim., 1984, 54, 1663 (Chem. Abstr., 1984, 101, 211 578).
22 E.E.Nifant'ev, S.A.Rumyantseva, M.P.Koroteev, O.N.Grigor'eva, and A.I.Lutsenko, Zh. Obshch. Khim., 1984, 54, 1410 (Chem. Abstr., 1984, 101, 211 574).
23 M.P.Koroteev, A.V.Vasil'ev, A.A.Borisenko, E.M.Abbasov, and E.E.Nifant'ev, Zh. Obshch. Khim., 1984, 54, 1402 (Chem. Abstr., 1984, 101, 211 573).
24 S.P.Movlik and D.Basu, Carbohydr. Res., 1984, 132, 201.
25 R.A.Munavu, B.Nasseri-Noori, and H.H.Szmant, Carbohydr. Res., 1984, 125, 253.
26 M.C.R.Symons, J.A.Benbow, and H.Pelmore, J. Chem. Soc., Faraday Trans. 1, 1984, 80, 1999.
27 H.-A.Tajmir-Riahi, Carbohydr. Res., 1984, 127, 1.
28 T.Tsubomura, S.Yano, K.Toriumi, T.Ito and S.Yoshikawa, Bull. Chem. Soc. Jpn., 1984, 57, 1833.
29 M.E.Daman and K.Dill, Carbohydr. Res., 1984, 132, 335.
30 A.Rodriguez, A.Perdomo, F.Fernandez, and J.Fernandez Bertran, Int. Sugar. J., 1984, 86, 179 (Chem. Abstr., 1984, 101, 171 605).
31 V.Bilik, J.Alfoldi, and E.Sookyova, Chem. Zvesti, 1984, 38, 499.
32 J.Frelek and G.Snatzke, Fresenius' Z. Anal. Chem., 1983, 316, 261 (Chem. Abstr., 1984, 100, 121 490).
33 K.M.Taba, R.Koster, and W.V.Dahlhoff, Synthesis, 1984, 399.
34 S.J.Blunden, P.A.Cusack, P.J.Smith, and D.G.Gillies, Inorg. Chim. Acta, 1984, 84, 35 (Chem. Abstr., 1984, 101, 71 965).
35 J.A.Peters, W.M.M.J.Bovée, and A.P.G.Kieboom, Tetrahedron, 1984, 40, 2885.

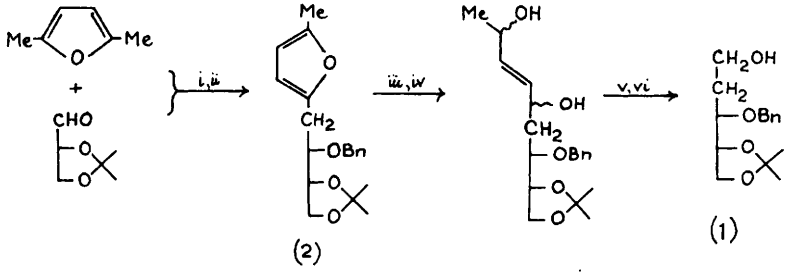
18
Alditols and Cyclitols

1 Alditols

Altritol (identical to talitol) has been isolated for the first time from a biological source as a major constituent of the brown alga Himanthalia elongata.[1] 6-Deoxyallitol and 6-deoxygulitol have been identified as normal components of human urine.[2] The per(4-hydroxybenzoyl)ated derivatives of erythritol and 2-deoxy-D-erythro-pentitol have been isolated from a marine mollusc.[3]

The ^{13}C-n.m.r. spectra and conformations of heptitols in solution have been reported, spectral assignments being obtained using specifically deuterated compounds.[4] Other n.m.r. studies on alditols are covered in Chapter 21. A 3:1 mixture of D-mannitol and D-glucitol has been obtained by hydrogenation of D-arabino-hexosulose (i.e., D-glucosone) over Raney nickel; since D-glucosone can be produced by enzymic oxidation of D-glucose (Vol.17, p.141), this constitutes an efficient method for the preparation of D-mannitol.[5] A kinetic study of the hydrogenolysis of sorbitol over Raney nickel, for glycerol production, has been reported.[6]

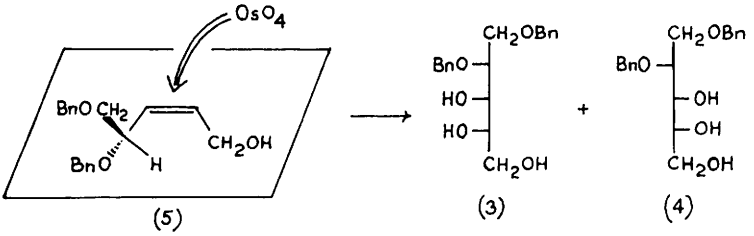
Alditol examples have been included in an extensive review on the acyclic stereoselective synthesis of carbohydrates from non-carbohydrate starting materials.[7] The 2-deoxy-D-ribitol derivative (1) has been synthesized as shown in Scheme 1, a high-



Reagents: i, 20 Kbar, 55°; ii, NaH-BnBr; iii, PCC-NaOAc; iv, Bu^i_2AlH; v, OsO_4-$NaIO_4$; vi, $NaBH_4$

Scheme 1

pressure coupling reaction providing a 4:1 mixture of epimers from which adduct (2) was isolated as the major product.[8] From a study of this cis-hydroxylation by osmium tetraoxide of 16 acyclic allylic alcohol systems, and a survey of published reports, Kishi and co-workers have derived an empirical rule that predicts that the major product will result from attack of the reagent onto the face of the olefinic bond opposite to that containing the allylic hydroxy- or alkoxy-group. This is exemplified by the production of L-ribitol and D-arabinitol derivatives (3) and (4) in an 8:1 ratio on cis-hydroxylation of alkene (5) (Scheme 2), the reagent

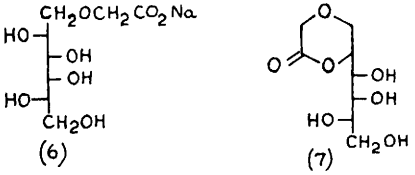


(5) (3) (4)

Scheme 2

having approached from the side opposite to the allylic benzyloxy substituent in the assumed eclipsed conformation shown.[9]

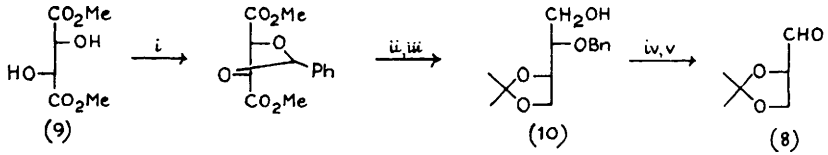
1-O-(Carboxymethyl)-L-galactitol sodium salt (6) has been synthesized by carboxymethylation of 1,2:3,4-di-O-isopropylidene-D-galactopyranose followed by hydrolysis and reduction, and has been



(6) (7)

shown to complex Fe^{2+}, Co^{2+}, Ni^{2+}, Mn^{2+}, Cu^{2+}, and Al^{3+} at concentrations down to 2.5-25 x 10^{-5} mmol. Acidic treatment of compound (6) provided the lactone (7).[10]

A practical synthesis of 1,2-O-isopropylidene-L-glyceraldehyde (8) from L-tartaric acid (9) (Scheme 3) has been described, and involves the intermediacy of the L-threitol derivative (10).[11]



(9) (10) (8)

Reagents: i, PhCHO-TsOH; ii, LAH-$AlCl_3$; iii, Me_2CO-TsOH; iv, H_2-Pd; v, $NaIO_4$

Three alternative procedures for the synthesis of 1,2:5,6-di-O-isopropylidene-D-mannitol by acetonation of D-mannitol have been monitored by acetylation-capillary g.c. analysis. The use of acetone and zinc chloride gave the best yield (63%), whereas other reagent systems [$Me_2C(OMe)_2$-$SnCl_2$ or $MeCH(OMe)=CH_2$-TsOH] gave more complex mixtures than claimed in recent literature (c.f. Vol.14, p.44; Vol.17, p.161). A new triacetal, 1,2:3,6:4,5-tri-O-isopropylidene-D-mannitol, has also been isolated, and the graded hydrolysis of it and the isomeric 1,2:3,4:5,6-triacetal compared.[12] The synthesis of 1,2:5,6-di-O-cyclohexylidene-D-mannitol and its conversion to 2,3-O-cyclohexylidene-D-glyceraldehyde are covered in Chapter 6.

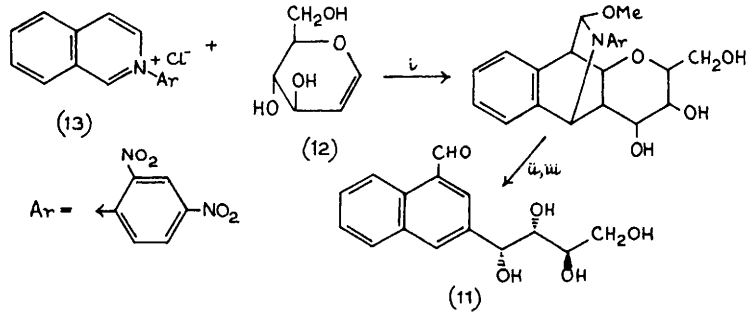
N-(1-Deoxy-D-mannitol- and -D-glucitol-1-yl) derivatives of L-valine, L-alanine, L-threonine, and L-leucine have been isolated (51-55% yield) following reductive amination ($NaBH_3CN$) of the appropriate hexose and amino acid. Related N^{ε}-substituted lysine derivatives were prepared using the N^{α}-tert-butoxy- or benzyloxy-carbonyl-protected amino acid. These compounds were required as standards in the analysis of non-enzymically glycosylated proteins and could be determined by O-trimethylsilylation-g.c.-m.s.[13] The salt of 1,6-bis(2-chloroethylamino)-1,6-dideoxy-D-mannitol with adenosine 5'-triphosphate has been prepared and shown to have antitumour activity.[14]

2-Amino-1,2-dideoxy-1-nitroheptitol derivatives have been obtained on addition of ethylamine or propylamine to the corresponding nitro-olefins obtained by condensing nitromethane with D-glucose, D-mannose, or D-galactose.[15] Model studies relating to the hydrazinolysis of glycoproteins and glycopeptides have been reported. Preparatively useful quantitites of 1,2-dideoxy-alditols have been isolated following hydrogenation of the mixture containing them, their corresponding 1-alkenes (i.e., 1,2-dideoxy-1-hex- or pent-enitols), and 1-deoxyalditols obtained on reaction of D-glucose, L-arabinose, D-mannose, or D-xylose in anhydrous hydrazine under reflux. Under such conditions, diimide (HN=NH) is the reducing species. In a sealed tube in the absence of air, however, this species is not present, and D-galactose then gave its hydrazone, 1-deoxy-D-galactitol, and the 1-alkene, but no 1,2-dideoxy-alditol; in the presence of hydrazinium sulphate (105°, 10 h) 1-deoxy-D-tagatose hydrazone was formed in ca. 24% yield.[16]

The mechanism of the autocatalytic primary reaction step in the formose reaction has been examined, and the activation of

formaldehyde by calcium endiolate complexes in an autocatalytic cycle proposed, with competition between Cannizzaro and oligomerization reactions.[17]

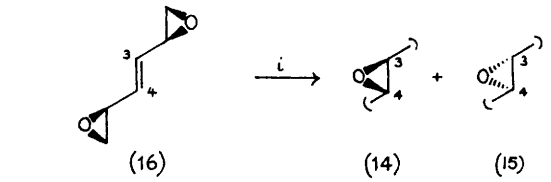
Substituted naphthaldehydes, e.g., (11) (inaccurately described as a model C-naphthyl glycosides), have been obtained via cycloaddition between sugar enol ethers such as glucal (12) and 2-(2,4-dinitrophenyl)isoquinolinium chloride (13) (Scheme 4).[18] Several N-heterocycles bearing alditol chains are covered in



Scheme 4

Chapter 10.

1,2:3,4:5,6-Trianhydro-D-iditol and -D-mannitol, (14) and (15), respectively, have been synthesized from D-mannitol via the diepoxide (16) (Scheme 5). The corresponding glucitol triepoxide was obtained similarly, as a racemate, from D-glucitol.[19]

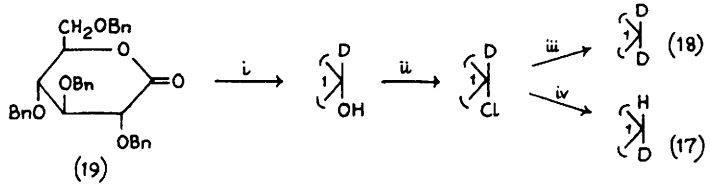


Scheme 5

The formation of anhydro-derivatives from alditols under methanolysis conditions has been investigated, and xylitol, D-arabinitol, L-fucitol, D-glucitol, galactitol, 2-acetamido-2-deoxy-D-galactitol, and the alditol of N-acetyl-neuraminic acid were prone to anhydride formation, whereas 2-amino-2-deoxy-D-galactitol and -glucitol, 2-acetamido-2-deoxy-D-glucitol, and D-mannitol were not.[20] A convenient preparation of 1,4-anhydro-D-mannitol from 2,3:5,6-di-O-isopropylidene-D-mannose in 55-65% overall yield has been described involving borohydride reduction and cyclization

via tosylation.[21]

(1S)-[1-$^{2}H_{1}$]-1,5-Anhydro-D-glucitol, with a β-deuterium, has been synthesized by reduction of α-acetobromoglucose with lithium aluminium deuteride, while its (1R)-epimer (17) and the 1,1-dideuterated analogue (18) have been prepared from the glucono-1,5-lactone derivative (19) (Scheme 6).[22] The 2-deoxy-analogue of

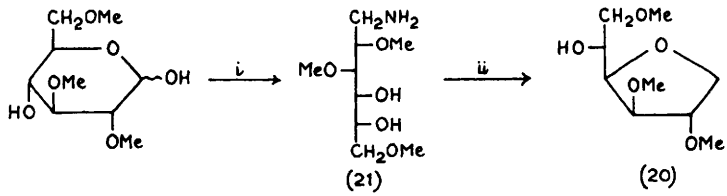


Reagents: i, $LiAlD_4$ - $BF_3.Et_2O$; ii, MsCl-collidine; iii, $LiAlD_4$; iv, $LiAlH_4$

Scheme 6

compound (17) has been obtained by reaction of 3,4,6-tri-O-benzyl-2-deoxy-α-D-arabino-hexopyranosyl lithium (see Chapter 13) with deuterium oxide.[23]

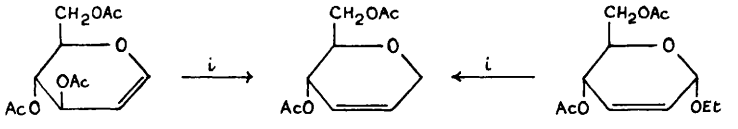
Gray and co-workers have continued to develop reductive glycosidic cleavage with triethylsilane ("ionic hydrogenation") as a general procedure for the analysis of polysaccharides following permethylation (Vol.16, p.38). Trimethylsilyl triflate was found to be a more effective catalyst for this reaction than boron trifluoride diethyl etherate. Reductive cleavage (using Et_3SiD) of permethylated methyl α- and β-D-glucopyranoside, cyclohexaamylose, and cellulose provided methylated 1-deuterio-1,5-anhydro-D-glucitol derivatives with an α-D:β-D ratio of ~95:5, and this was taken as evidence for the intermediacy of free oxonium ions in the reduction.[24] In the presence of adventitious or deliberately added water, 1,4-anhydro-2,3,6-tri-O-methyl-D-glucitol (20) was formed from permethylated 4-linked glucopyranosyl residues in up to 45% yield, in addition to the expected 1,5-anhydride, but the formation of this secondary product could be reduced to ca. 2% by addition of calcium hydride to the reaction mixture. The synthesis of 1,4-anhydride (20) was effected through kinetically



Reagents: i, NH_4OAc-$NaBH_3CN$; ii, HNO_2

Scheme 7

controlled ring closure on deamination of compound (21) (Scheme 7).[25] All the partially methylated and ethylated 1,5-anhydro-D-mannitol acetates expected from reductive cleavage-acetylation of permethylated or perethylated D-mannans have been synthesized by standard procedures and their mass spectra recorded.[26] Application of the method to fructans revealed that 1,2-linked D-fructofuranosyl units gave mainly a 2,5-anhydro-D-mannitol derivative, while 2,6- and 1,2,6-linked units gave mainly 2,5-anhydro-D-glucitol derivatives all of which were independently synthesized. The fructose moiety in permethylated sucrose gave 2,5-anhydro-1,3,4,6-tetra-O-methyl-D-mannitol and -glucitol in a 5:1 ratio.[27] Ionic hydrogenation of the glucal (22) or the hex-2-enopyranoside (23) provided the same reduction product, 4,6-di-O-acetyl-1,5-anhydro-2,3-dideoxy-D-*erythro*-hex-2-enitol (24) in 95% yield (Scheme 8).[28]

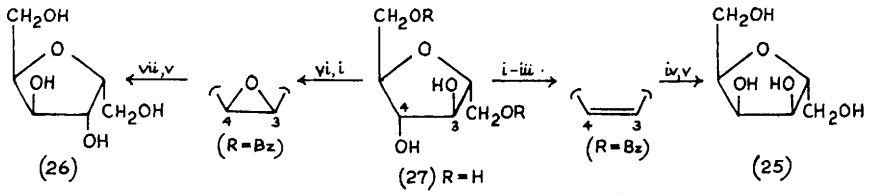


Reagents: i, Et_3SiH-$BF_3.Et_2O$

Scheme 8

A review (in French) on the preparation and application of isosorbide (1,4:3,6-dianhydro-D-glucitol) has appeared.[29]

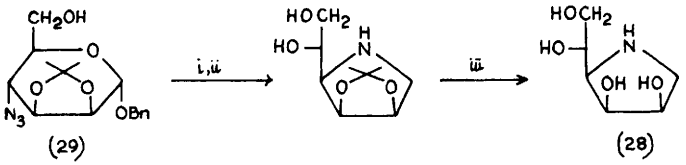
A new synthesis of 2,5-anhydro-D-altritol (25) and the first synthesis of 2,5-anhydro-D-iditol (26) have been reported, both from 2,5-anhydro-D-mannitol (27), by conventional routes outlined in Scheme 9 [30]



Reagents: i, BzCl-Py; ii, MsCl-Et_3N; iii, Zn/Cu-KI-DMF; iv, OsO_4-; v, MeONa-MeOH; vi, DEAD-TPP; vii, H^+-EtOH

Scheme 9

1,4-Dideoxy-1,4-imino-D-mannitol (28), a potent α-mannosidase inhibitor, has been synthesized from benzyl α-D-mannopyranoside *via* the 4-azido-derivative (29) (Scheme 10). The presence of the isopropylidene ring assisted formation of the second five-membered ring during reductive amination.[31] A related synthesis of 1,5-dideoxy-1,5-imino-D-mannitol is covered in Chapter 9.



(29) (28)

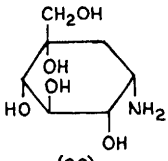
Reagents: i, H_2-Pd-MeOH; ii, H_2-Pd-$MeCO_2H$; iii, H_3O^+

Scheme 10

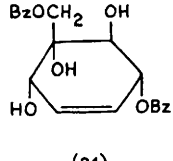
2 Cyclitols

D-Pinitol has been shown to be biosynthesized in jojoba leaves by epimerization of D-ononitol, whereas in gymnosperms and other plants it results from epimerization of sequoyitol.[32] The accumulation of O-methyl-inositols in tropical legumes subjected to water stress has been further investigated.[33] 1L-1-O-Methyl-*myo*-inositol and *neo*-inositol have been identified as components of *Croton celtidifolius*, the latter compound for the first time in plants.[34] O-Methyl-inositols in clover and peanut have been identified by trimethylsilylation-g.c.-m.s. analysis, and several have been synthesized (*e.g.* the 2-O-methyl ether by partial methylation) or isolated from plant sources (e.g. 1L-1-O-methyl-*chiro*-inositol).[35]

Eight new di- to penta-O-galloyl derivatives of proto-quercitol (a deoxyinositol) and two related ellagitannins have been isolated from *Quercus stenophylla* bark.[36] Valiolamine (30), a new α-glucosidase inhibitor from *Streptomyces hygroscopicus*, has been found to be more potent than valienamine, validamine and 6-hydroxy-



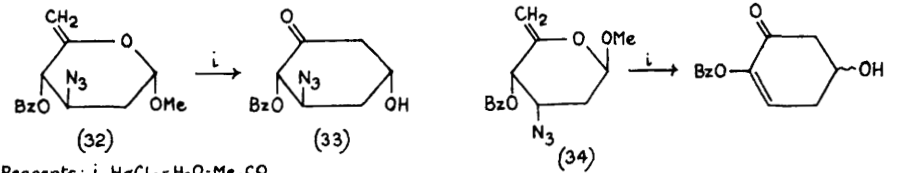
(30)



(31)

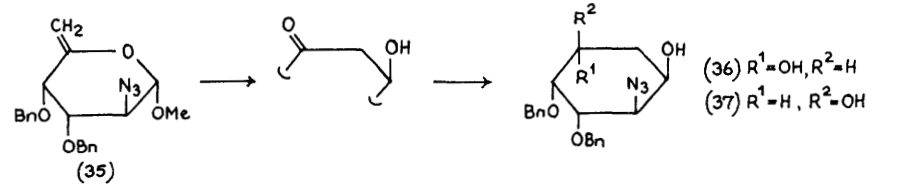
validamine analogues isolated from the same fermentation broth.[37] 1-Epizeylenol (31) has been isolated from *Ulvaria zeylanica* roots; the C-1 epimer zeylenol had been isolated previously.[38]

Several syntheses of cyclitols from aldoses have appeared. Ferrier's carbocyclization of hex-5-enopyranosides has been further extended. The 5,6-ene (32) provided the cyclohexanone (33) as expected, but its C-3 epimer (34) underwent concomitant elimination

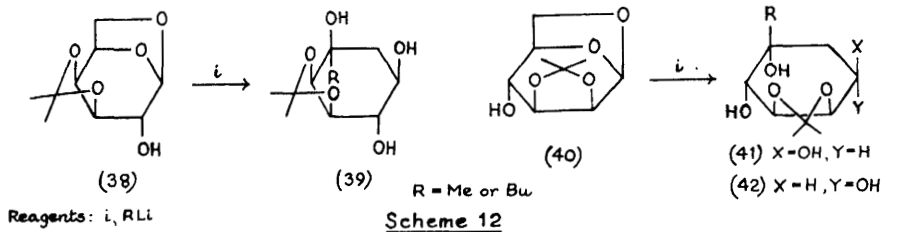


Scheme 11

of hydrazoic acid (Scheme 11).[39] Mercury(II) trifluoroacetate proved to be effective for converting the D-arabino-5,6-ene (35) into the corresponding cyclohexanone, reduction of which provided the epimeric azidocyclitols (36) and (37) in a 9:1 ratio.[40]

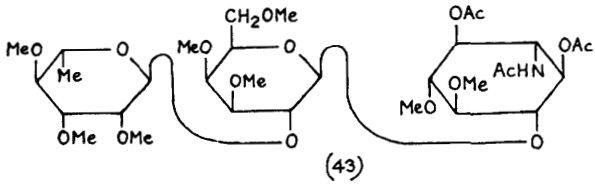


Klemer and Kohla have reported further remarkable transformations of sugar acetals on treatment with alkyl lithium reagents. 1,6-Anhydro-D-galactose derivative (38) gave the cyclitol (39), in 85% yield for R=Bu, while the 1,6-anhydro-D-mannose derivative (40) gave mixtures of the epimers (41) and (42), in 52 and 12% yield respectively for R=Bu (Scheme 12).[41]



Scheme 12

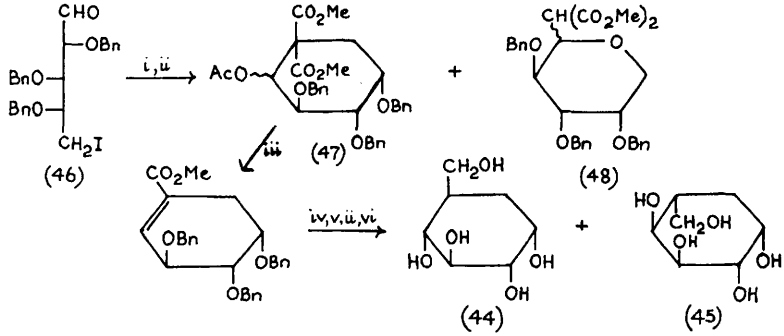
Per-O-methylated scyllo-aminocyclitol-oligoglycosides such as the L-rhamnosyl-D-galactosyl-aminocyclitol (43) have been synthesized from per-O-methylated glucuronide saponins by sequential



decarboxylative acetoxylation [$Pb(OAc)_4$] of the uronic acid moiety, nitromethane cyclization, and reduction [H_2-Raney Ni].[42] The

synthesis of ribostamycin by a related procedure is mentioned in Chapter 19 (ref.13).

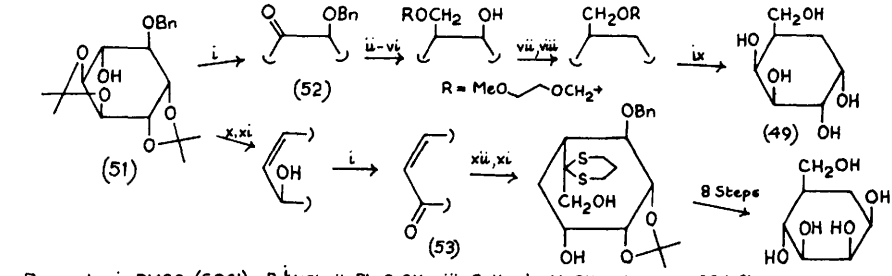
Several pseudo-sugars have been synthesized. Pseudo-α-D-glucose (44) and pseudo-β-L-altrose (45) have been obtained from the L-arabinose-derived 6-iodo-pentose (46) (Scheme 13), the isomers being obtained in a 1:1 ratio; the initial condensation



Reagents: i, $(MeO_2C)_2CH^-$; ii, Ac_2O-Py; iii, NaCl-DMSO; iv, LAH; v, B_2H_6, then H_2O_2; vi, Na-NH_3

Scheme 13

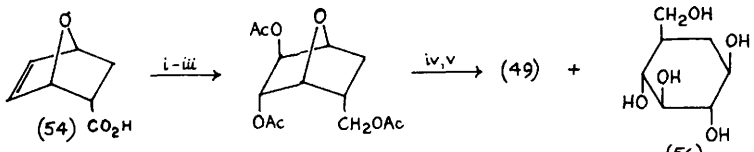
with dimethyl malonate produced both the required cyclohexane (47) and the tetrahydropyran (48), in 43 and 33% yields respectively.[43] Pseudo-α-D-galactose (49) and pseudo-β-D-mannose (50) have been synthesized separately from quebrachitol via the L-chiro-inositol derivative (51), the required hydroxymethyl substituents being introduced by either a Wittig olefination-hydroboration sequence on ketone (52) or a Michael addition to enone (53) (Scheme 14).[44]



Reagents: i, DMSO-$(COCl)_2$-Pr^i_2NEt; ii, $Ph_3P{=}CH_2$; iii, B_2H_6; iv, NaOH; v, MeO⌒OCH$_2$Cl; vi, H_2-Pd; vii, NaH-CS_2-MeI; viii, Bu_3SnH; ix, H^+; x, I_2-PPh_3-imidazole; xi, LAH; xii,

Scheme 14

Ogawa and co-workers have resolved the (-)-isomer (54), as its α-methylbenzylammonium salt, from a racemic Diels-Alder furan-methyl acrylate adduct (55, see Scheme 16), and converted it into a mixture of pseudo-α-D-galactose (49) and pseudo-β-D-glucose (56) (Scheme 15), using methodology previously developed for the racemic

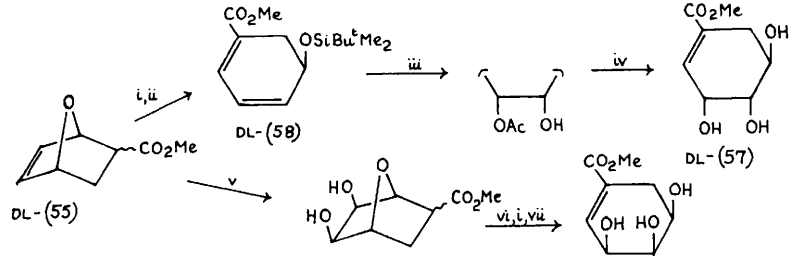


Reagents: i, H_2O_2-HCO_2H; ii, LAH; iii, Ac_2O-Py; iv, Ac_2O-AcOH-H_2SO_4; v, NaOMe-MeOH

Scheme 15

analogues (Vol.11, p.150).[45]

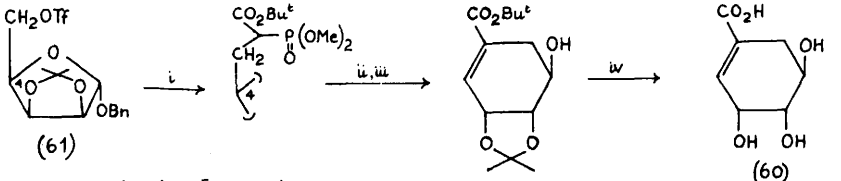
The racemic 7-oxabicyclo[2.2.1] heptene (55) has been employed in the synthesis of racemic methyl shikimate (57), selective cis-hydroxylation of the disubstituted double bond in diene (58) being effected with either osmium tetraoxide [46] or more effectively a Prévost-type reaction under "wet" conditions,[47] as shown in Scheme 16. Methyl epishikimate (59) was also prepared by cis-



Reagents: i, BuLi-$(Me_3Si)_2NH$; ii, Bu^tMe_2SiTf-2,6-lutidine; iii, I_2-AgOAc-HOAc-H_2O(1 eq.); iv, deprotection; v, OsO_4; vi, $Me_2C(OMe)_2$-H^+; vii, H_3O^+

Scheme 16

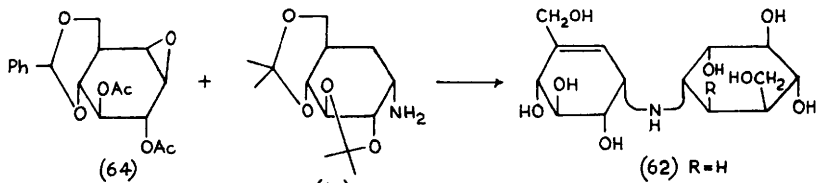
hydroxylation of the bicyclic derivative prior to ring cleavage.[46] (-)-Shikimic acid (60) has been synthesized from D-mannose via the derivative (61) using an intramolecular Horner-Wittig reaction to produce the cyclohexane structure (Scheme 17).[48]



Reagents: i, $(MeO)_2POCHCO_2Bu^t$; ii, H_2-Pd/C; iii, NaH; iv, CF_3CO_2H

Scheme 17

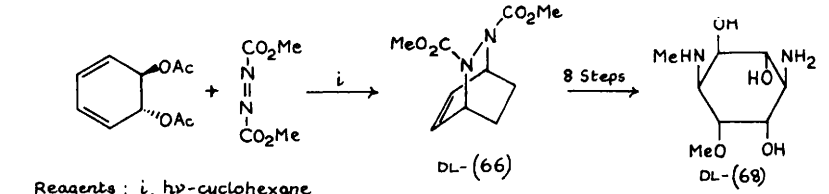
Ogawa and co-workers have also synthesized racemic validoxylamine A (62) and B (63) by coupling the cyclitol epoxide (64) and validamine derivative (65) (Scheme 18), both of which had been derived from the Diels-Alder adduct (55).[49] Work on their



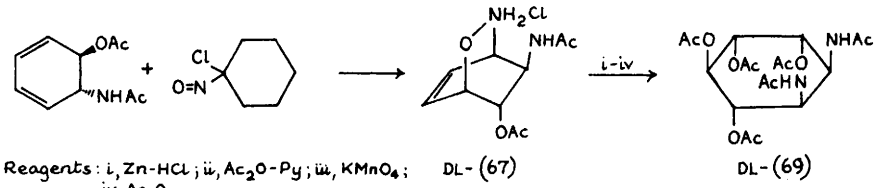
Scheme 18

syntheses of the racemic aminocyclitols validamine, hydroxy-validamine, and valienamine has been reviewed (in Japanese).[50]

Hetero-Diels-Alder adducts (66) and (67) have been converted into racemic fortamine (68) (Scheme 19),[51] DL-chiro-inosadiamine derivative (69) (Scheme 20), and various amino-deoxy-conduritols and streptamines.[52]

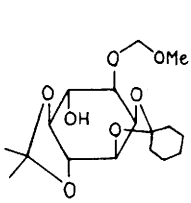


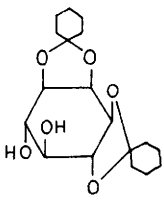
Scheme 19

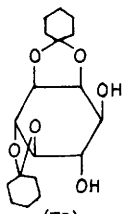


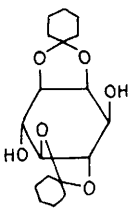
Scheme 20

Attempts to phosphorylate myo-inositol with various polyphosphates or urea-phosphate under aqueous conditions according to published procedures proved unsuccessful, but an easy method for complete phosphorylation was to heat (150°, 6 h) myo-inositol with phosphoric acid under reduced pressure.[53] Racemic surugatoxin, an esterified myo-inositol, has been synthesized using the racemic myo-inositol derivative (70).[54] Cyclohexylidenation of myo-inositol has provided a mixture of the three diacetalated derivatives (71)-(73), isolated in 19, 38, and 26% yield, respectively. By phase-transfer catalyzed monobenzylation of these derivatives, mono-O-benzyl-myo-inositols and penta-O-methyl-myo-inositols could be obtained.[55] Hexa-O-n-pentanoyl, n-heptanoyl, and n-nonanoyl derivatives of scyllo-inositol have been


DL-(70)


(71)


(72)


(73)

claimed as the first alicyclic, saturated, discotic liquid crystals.[56]

References

1 J.A.Chudek, R.Foster, I.R.Davison, and R.H.Reed, Phytochemistry, 1984, 23, 1081.
2 T.Niwa, K.Yamada, T.Ohki, A.Saito, and M.Mori, J. Chromatogr., 1984, 336, 345.
3 A.A.Tymiak and K.L.Rinehart, J. Am. Chem. Soc., 1983, 105, 7396.
4 S.J.Angyal and R.Le Fur, Carbohydr. Res., 1984, 126, 15.
5 M.Moreland, J.Wadsworth, J.Geigert, and S.L.Neidleman, Carbohdr. Res., 1984, 127, 154.
6 F.W.Chang, K.T.Kuo, and C.N.Lee, Proc.-Pac. Chem. Eng. Congr., 3rd, 1983, 2, 179 (Chem. Abstr., 1984, 101, 192 354).
7 G.J.McGarvey, M.Kimura, T.Oh, and J.M.Williams, J. Carbohydr. Chem., 1984, 3, 125.
8 J.Jurczak and S.Pikul, Tetrahedron Lett., 1984, 25, 3107.
9 J.K.Cha, W.J.Christ, and Y.Kishi, Tetrahedron, 1984, 40, 2247.
10 M.I.Goguadze, N.S.Melua, and M.E.Shishniashvili, Izv. Akad. Nauk Gruz. SSR, Ser. Khim., 1983, 9, 124 (Chem. Abstr., 1984, 100, 22940).
11 A.Tanaka, S.Otsuka, and K.Yamashita, Agric. Biol. Chem., 1984, 48, 2135.
12 J.Kuszmann, E.Tomori, and I.Meerwald, Carbohydr. Res., 1984, 128, 87.
13 D.J.Walton, E.R.Ison, and W.A.Szarek, Carbohydr. Res., 1984, 128, 37.
14 I.Isakov, I.Mircheva, and T.Panter, Khim.-Farm. Zh., 1983, 17, 1446 (Chem. Abstr., 1984, 100, 139 544).
15 J.A.Galbis Perez and J.A.Serrano Blazquez, An. Quim., Ser. C., 1983, 79, 33 (Chem. Abstr., 1984, 100, 7 011).
16 J.M.Williams, Carbohydr. Res., 1984, 128, 73.
17 G.Harsch, M.Harsch, and W.Voelter, Z. Naturforsch., B: Anorg. Chem., Org. Chem., 1983, 38B, 1257 (Chem. Abstr., 1984, 100, 121 456).
18 R.W.Franck and R.B.Gupta, J. Chem. Soc., Chem. Commun., 1984, 761.
19 P.Köll, M.Oelting, and J.Kopf, Angew. Chem. Int. Ed. Engl., 1984, 23, 242.
20 G.J.Gerwig, J.P.Kamerling, and J.F.G.Vliegenthart, Carbohydr. Res., 1984, 129, 149.
21 H.B.Sinclair, Carbohydr. Res., 1984, 127, 146.
22 M.Funabashi and S.Yoshioka, Chem. Lett., 1984, 677.
23 J.-M.Lancelin, L.Morin-Allory, and P.Sinaÿ, J. Chem. Soc., Chem. Commun., 1984, 355.
24 D.Rolf, J.A.Bennek, and G.R.Gray, J. Carbohydr. Chem., 1983, 2, 373.
25 J.A.Bennek, D.Rolf, and G.R.Gray, J. Carbohydr. Chem., 1983, 2, 385.
26 J.U.Bowie and G.R.Gray, Carbohydr. Res., 1984, 129, 87.
27 D.Rolf and G.R.Gray, Carbohydr. Res., 1984, 131, 17.
28 G.Grynkiewicz, Carbohydr. Res., 1984, 128, C9.
29 F.Jacquet, A.Gaset, and J.P.Gorrichon, Inf. Chim., 1984, 246, 155 (Chem. Abstr., 1984, 101, 73 012).
30 D.A.Otero and R.Simpson, Carbohydr. Res., 1984, 128, 79.
31 G.W.J.Fleet, P.W.Smith, S.V.Evans, and L.E.Fellows, J. Chem. Soc., Chem. Commun., 1984, 1240.

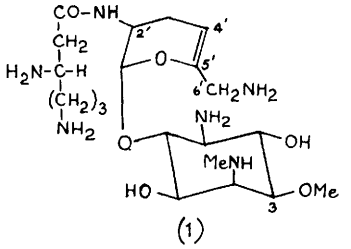
32 P.Dittrich and A.Korak, Phytochemistry, 1984, 23, 65.
33 C.W.Ford, Phytochemistry, 1984, 23, 1007.
34 R.Mukherjee and E.M.Axt, Phytochemistry, 1984, 23, 2682.
35 R.G.Binder and W.F.Haddon, Carbohydr. Res., 1984, 129, 21.
36 H.Nishimura, G.Nonaka, and I.Nishioka, Chem. Pharm. Bull., 1984, 32, 1741 and 1750.
37 Y.Kameda, N.Asano, M.Yoshikawa, M.Takeuchi, T.Yamaguchi, K.Matsui, S.Horii, and H.Fukase, J. Antibiot., 1984, 37, 1301.
38 S.D.Jolad, J.J.Hoffmann, J.R.Cole, M.S.Tempesta, and R.B.Bates, Phytochemistry, 1984, 23, 935.
39 I.Pelyvás, F.Sztaricskai, and R.Bognár, J. Chem. Soc., Chem. Commun., 1984, 104.
40 F.Chretien and Y.Chapleur, J. Chem. Soc., Chem. Commun., 1984, 1268.
41 A.Klemer, M.Kohla, Justus Liebigs Ann. Chem., 1984, 1662.
42 I.Kitagawa, T.Kamigauchi, Y.Ikeda, and M.Yoshikawa, Chem. Pharm. Bull., 1984, 32, 4858.
43 T.Suami, K.Tadano, Y.Kameda, and Y.Iimura, Chem. Lett., 1984, 1919.
44 H.Paulsen, W.von Deyn, and W.Röben, Justus Liebigs Ann. Chem., 1984, 49, 433.
45 S.Ogawa, Y.Iwasawa, and T.Suami, Chem. Lett., 1984, 355.
46 M.M.Campbell, A.D.Kaye, M.Sainsbury, and R.Yavarzadeh, Tetrahedron, 1984, 40, 2461.
47 M.M.Campbell, M.Sainsbury, and R.Yavarzadeh, Tetrahedron, 1984, 40, 5063.
48 G.W.J.Fleet, T.K.M.Shing, and S.M.Warr, J. Chem. Soc., Perkin Trans. 1, 1984, 905.
49 S.Ogawa, T.Ogawa, Y.Iwasawa, T.Toyokuni, N.Chida, and T.Suami, J. Org. Chem., 1984, 49, 2594.
50 S.Ogawa, T.Toyokuni, N.Chida, and T.Suami, Kenkyu Hokoku-Asahi Garasu Kogyo Gijutsu Shoreikai, 1983, 43, 127 (Chem. Abstr., 1984, 100, 192 193).
51 C.H.Kuo and N.L.Wender, Tetrahedron Lett., 1984, 25, 2291.
52 G.Kresze, M.M.Weiss, and W.Dittel, Justus Liebigs Ann. Chem., 1984, 203.
53 J.Emsley and S.B.Niazi, Soil Biol. Biochem., 1984, 16, 73 (Chem. Abstr., 1984, 101, 38 749).
54 S.Inoue, K.Okada, and H.Tanino, Tetrahedron Lett., 1984, 25, 4407.
55 P.J.Garegg, T.Iversen, R.Johansson, and B.Lindberg, Carbohydr. Res., 1984, 130, 322.
56 B.Kohne and K.Praefcke, Angew. Chem. Int. Ed. Engl., 1984, 23, 82.

19
Antibiotics

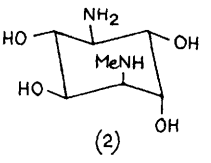
1 Aminoglycoside and Aminocyclitol Antibiotics

Newer synthetic methods for aminoglycoside antibiotics have been reviewed.[1]

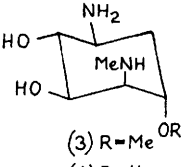
The new aminoglycoside antibiotic lysinomycin (previously AX-127B-1) has been characterized as 3-epi-2'-N-(L-β-lysyl)-4',5'-didehydro-6'-de-C-methyl-fortimicin B (1).[2] The degradation of



(1)

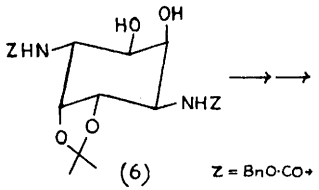


(2)

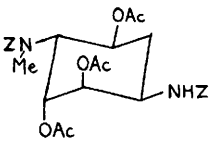


(3) R=Me
(4) R=H

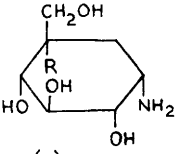
validamycin A by Flavobacterium saccharophilum has been studied using N-p-nitrophenyl derivatives of validamine and valienamine as model compounds; a pathway was proposed involving oxidation of either ring in the validoxylamine unit with consequent cleavage of the N linkage between them.[3] Syntheses have been reported for 3-de-O-methylfortamine (2) from 1,2:4,5-dianhydro-epi-inositol[4] and of (-)-2-deoxyfortamine (3) and its 3-de-O-methyl derivative (4) from a racemic 1,2:4,5-dianhydro-6-deoxy-inositol derived from benzene, involving classical resolution of the enantiomers.[5] The derivative (5) of the aminocyclitol unit in 5-de-O-methyl-sporaricin A has also been prepared from the diaminocyclitol precursor (6).[6]



(6) Z = BnO·CO→



DL-(5)

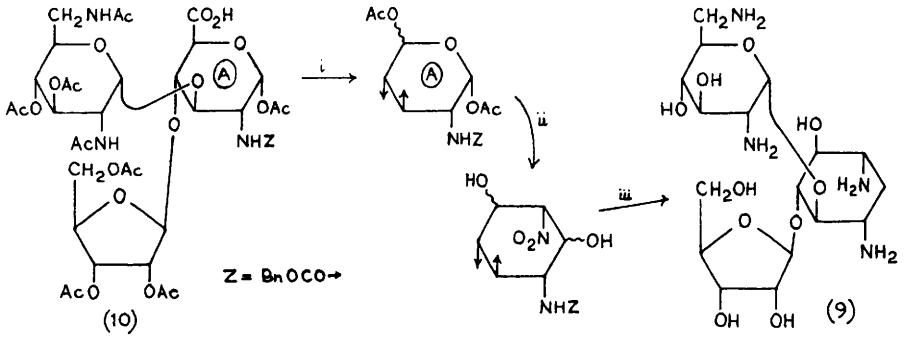


(7) R=OH
(8) R=H

Valiolamine, a new α-glucosidase inhibiting aminocyclitol produced by S. hygroscopicus, has the structure (7), being a more potent analogue of validamine (8) and its relatives which occur in the same fermentation broth.[7] Syntheses of validoxylamine and validamine (ref. 49) and fortamine (ref. 51) are referred to in Chapter 18. The valienamine-containing trestatins are referred to below (ref. 83).

Standard transformations have been used to convert kanamycin A to 2'-deoxykanamycin A, 2'-epi-kanamycin A and 2'-epi-kanamycin B, making use of selective 2'-de-O-benzoylation using hydrazine-pyridine to allow 2'-triflylation, thereby providing an efficient route to 2'-substituted kanamycins,[8] and double inversion at C-4" via triflates has allowed access to 4"-amino-,4"-bromo-, and 4"-fluoro-kanamycins.[9] A 4",6"-di-triflate derivative of kanamycin A has been employed to furnish 4",6"-dideoxy-4",6"-difluoro-, 4",6"-dideoxy-4"-fluoro-, 6"-deoxy-6"-fluoro-, and 6"-deoxy-derivatives of 4"-epi-kanamycin A.[10] 6'-N-formimidoyl and 6'-N-acetimidoyl derivatives of amikacin and the 6'-N-formimidoyl derivative of dibekacin have been prepared and shown to be more active against resistant organisms than the parent antibiotics.[11] Likewise N-guanyl derivatives of kanamycin A and gentamicins C_1, C_{1a} and C_2 (N-6',2' and 3'-substitutions) have been synthesized and tested.[12]

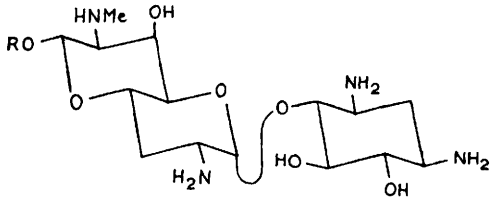
A synthesis of ribostamycin (9) has been described in which the uronic acid in the trisaccharide (10) was converted to the required deoxystreptamine unit (Scheme 1)[13] (c.f., Vol. 16, p. 189, ref. 35). Other pseudotrisaccharides related to ribostamycin have been prepared from sisamine derivatives with an unsubstituted 5-hydroxy group by glycosylation with the pentofuranoses 3-C-methyl-β-D-



Reagents: i, $Pb(OAc)_4$-C_6H_6-Py ; ii, $MeNO_2$-NaOMe ; iii, $NaBH_4$-EtOH

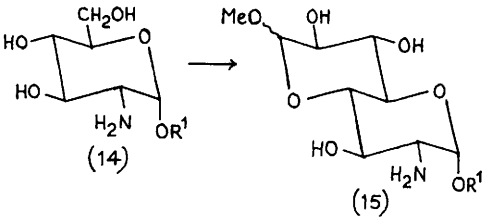
Scheme 1

ribose, 3-deoxy-3-C-methyl-β-D-xylose, and α-D- and α-L-arabinose, but these only showed weak antibiotic activity.[14] A synthesis of apramycin (11) and saccharosin (KA 5685) (12) has been described, in which neamine was converted to the aminooctadiose aprosamine (13) and then glycosylated with 4-amino-4-deoxy-D-glucose or D-glucose, respectively.[15] A conversion of sisomycin to its 1-N-ethyl



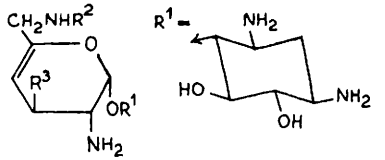
(11) R = β-D-Glc·p(4-NH_2)
(12) R = β-D-Glc·p
(13) R = H

derivative (netilmicin) has been described.[16] A route from paromamine (14) to the octodiose-containing pseudodisaccharide (15) present in (oxy)apramycin has been investigated; chain extension



(14)

(15)



(16) R^2 = H or Me
R^3 = H or OH

was by Wittig reaction of a dialdose derivative with subsequent osmium tetraoxide hydroxylation.[17] Paromamine has also been converted to the corresponding ethenic 6'-aldehyde and hence to sisamine and its analogues (16); lividamine (3'-deoxyparomamine) was similarly manipulated.[18] Whereas neamine is a direct precursor for neomycin, paromamine is not, contrasting with evidence from studies on other amino-cyclitols; the authors speculate that deoxystreptamine is glycosylated with preformed 2,6-diamino-2,6-deoxy-glucose to give neamine.[19]

Underivatized aminoglycosides can be characterized by glycerol matrix-assisted molecular SIMS.[20]

2 Macrolide Antibiotics

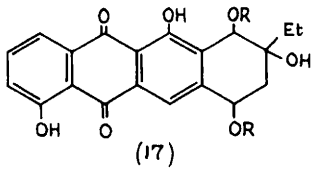
A method has been described for the semi-automated synthesis of radiolabelled erythromycin A using [^{11}C]formaldehyde to remethylate the amino sugar in N-demethyl-erythromycin A.[21] The mycarose unit

in spiramycin I has been substituted to give 4"-sulphonates and 4"-alkyl ethers[22] and 3",4"-diacylates and 3,3",4"-triacylates of spiramycin I,[23] some of which are more active than the parent antibiotic. Neospiramycin has been converted to its 4'-deoxy analogue by a procedure involving reductive dechlorination using tributylstannane,[24] and reductive amination of a 4"-keto derivative has been used to prepare 4'-aminooleandomycin from oleandomycin, and hence a number of sulphonamido-oleandomycins.[25]

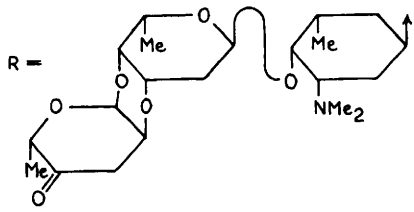
Kijanimicin has been studied using special techniques of fast atom bombardment m.s.; the method was particularly useful for characterizing the nitro-sugar component.[26]

3 Anthracycline Antibiotics

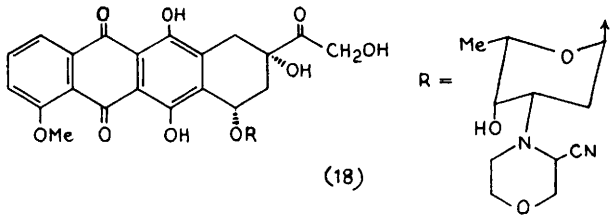
Further details of the structural analysis of arugomycin[27] and the related antibiotic decilorubicin[28] have been published (see Vol. 17, p.176, refs. 59,60). The macrolide-containing sporaviridin complex is mentioned below (ref. 82). Akrobomycin, produced by Actinomadura roseoviolacea, contains daunosamine attached to 9,10-anhydro-13-deoxocarminomycin,[29] and cosmocarcin A (17), obtained from S. cosmosus, has two chains of the trisaccharide α-cinerulose B + 2-deoxy-fucose + rhodosamine (also present in ditrisarubicin B (Vol. 17, p.176) and the aclacinomycin B group of antibiotics (see Vol. 16, p. 194)) attached at O-4 and O-7 of the aglycone α-citromycinone.[30]



(17)



The synthesis of the anthracycline antibiotics adriamycin, daunorubicin, and carminomycin has been reviewed (in Korean).[31] A series of highly potent cytotoxic morpholinyl anthracyclines have been synthesized from daunorubicin or doxorubicin by N-condensation with 2,2'-oxy - bis-ethanal derivatives in presence of sodium cyanoborohydride; the most potent antileukemic agent yet known is the 2-cyanomorpholinyl derivative of doxorubicin (18).[32] The preparation of (+)-4-demethoxy-daunorubicin[33] and (+)-4-demethoxy-adriamycin has been reported,[34] using trimethylsilyl triflate as a



(18)

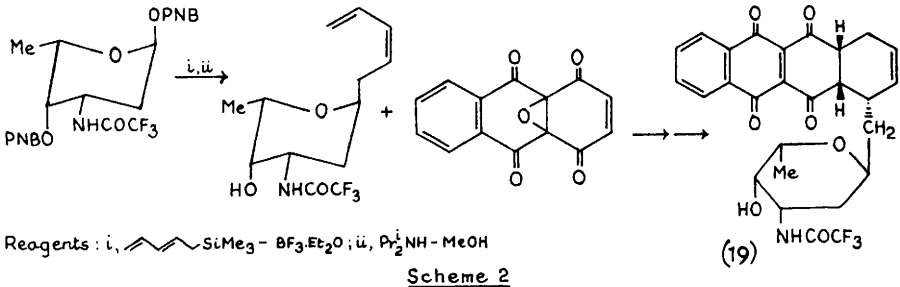
glycosidation reagent for the aglycone in conjunction with a daunosamine 1-O-p-nitrobenzoate derivative, which gave high yields of the required α-form (a previously claimed synthesis of the latter compound is now shown to give its formate ester instead). Other syntheses have included 3'-deamino-3'-hydroxy-doxorubicin, which showed high anti-tumour activity,[35] a total synthesis of 4-demethoxy-10,10-dimethyldaunomycin from 5,8-dimethoxy-2-tetralone, which proved to be inactive as an anti-leukemic agent,[36] and daunosaminyl and rhodosaminyl derivatives of 4,11-dideoxy-10-oxy-rhodomycinone.[37] The synthesis of 4-demethoxy-anthracyclinone using a saccharino-lactone as chiral source is referred to in Chapter 24.

N-Glycosyl derivatives of daunorubicin have been prepared by direct condensation of the free sugar with the antibiotic; these are less effective antileukemic agents than daunorubicin itself.[38]

In an alternative approach, a wide range of aglycones,[39] and rhodomycinone in particular,[40] have been used to prepare known anthracycline antibiotics together with synthetic analogues by microbial conversion using a strain of S. galilaeus; the cinerulosyl → 2-deoxy-fucosyl → rhodosaminyl derivatives of rhodomycinone and isorhodomycinone showed potent antileukemic activity.[40] Umezawa's group have also reported new anthracycline derivatives prepared from betaclamycin A by mutant biosynthesis from β-rhodomycinone; the compounds produced contained varying ratios of 2-deoxy-fucose, cinerulose, amicetose, and rhodinose attached in oligosaccharide chains to rhodosamine, and derivatives lacking rhodosamine were also prepared.[41]

A penta-2-4-dienyl C-glycoside of daunosamine has been prepared which underwent Diels-Alder condensation with a quinone, which led to the anthracycline analogue (19) (Scheme 2).[42]

N-3',O-4'-Isopropylidene derivatives of daunorubicin-doxorubicin have been prepared, using dry acetone with molecular sieves, allowing subsequent selective N-3' acylation.[43]



Scheme 2

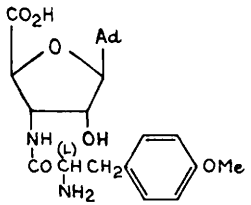
The absolute configuration of rubeomycins A, A_1, B, and B_1, which are the stereoisomers in the hydroxy-butanal sidechain, has been determined from optical rotation and other spectral data comparison with daunomycin and L(+)lactic acid.[44] The absolute structure of 4'-O-tetrahydropyranyl-adriamycin has been determined from an X-ray crystal study.[45]

The synthesis of the branched-chain sugar of nogalamycin is referred to in Chapter 14 (refs. 8, 15).

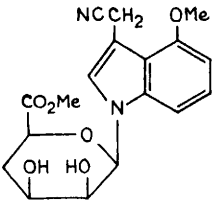
4 Nucleoside Antibiotics

An extensive review on the C-nucleoside antibiotics has been published,[46] and the synthesis of antibiotic nucleosides by enzymic reactions coupled with chemical methods has been discussed (in Japanese).[47]

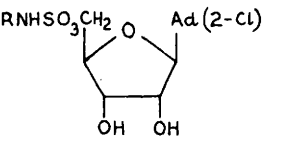
The structure and synthesis of the new peptidyl nucleoside antibiotic chryscandin (20), produced by *Chrysosporium pannorum*, have been reported; it contains 3-amino-β-D-arabinofuranuronic acid N-linked to O-methyltyrosine.[48] A new antibiotic elaborated by a



(20)



(21)

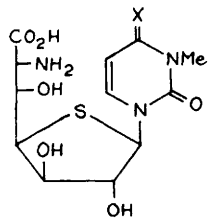


(22) R = ←COCHNH2 (Me)

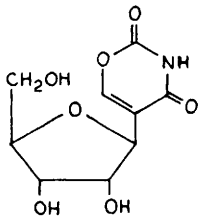
(23) R = H

strain of *Actinomadura* has the structure (21), containing a *lyxo*-hexuronic acid linked to an indole.[49] Ascamycin (22) and dealanyl-ascamycin (23), antibiotics obtained from *S. sp.*, have been shown by spectral analysis (principally FAB m.s.) to be 2-chloro-

adenosine sulphonamide derivatives;[50] the latter compound is identical with antibiotic AT 265 (E. Takahashi and T. Beppu, J. Antibiot., 1982, 35, 939). Some new nikkomycins, peptidyl-nucleoside antibiotics, have been obtained by mutasynthesis and directed fermentation; the new compounds contain thymine or 5-hydroxymethyluracil in place of uracil.[51] Enzymic cleavage of albomycin δ_1 and δ_2 has yielded the thio-nucleosides (24),[52] some reactions of which were studied and a crystalline derivative characterized by X-ray analysis. A minor component of the mildiomycin complex mildiomycin D has been identified as the 8'-deoxy analogue of mildio-



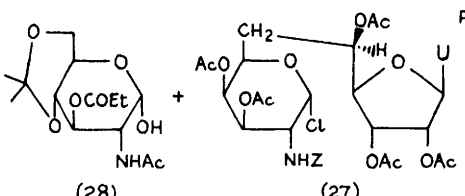
(24) X = O or $NCONH_2$



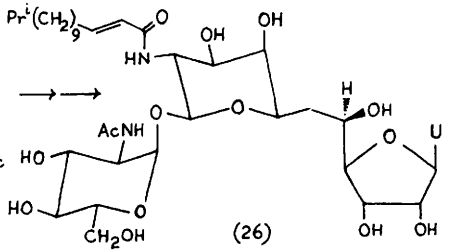
(25)

mycin (see Vol. 12, p. 151).[53] Further studies have been reported on dapiramicins A and B, disaccharide pseudo-nucleosides (see Vol. 17, p.180, ref. 83); dapiramicin A undergoes acid-catalysed anomerization to epidapiramicin. Oxazinomycin (25) has been isolated from a bacterial culture for the first time (previously from Streptomyces strains).[55]

Tunicamycin V (formerly "A") (26) has been prepared, together with 3 minor components of the complex and other analogues; in the key step, the glycosyl chloride (27) was condensed with the reducing amino-sugar derivative (28), which was then conventionally converted to (26).[56] Another communication reports a 'total' synthesis of polyoxin J (29), converting 4-O-benzyl-2,3-O-isopropylidene-L-threose to deoxypolyoxin C (30) on the one hand and to the 5-O-carbamoyl-polyoxamic acid derivative (31) on the other, these

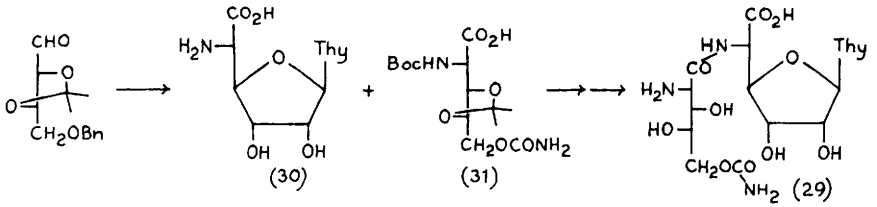


(28) (27)



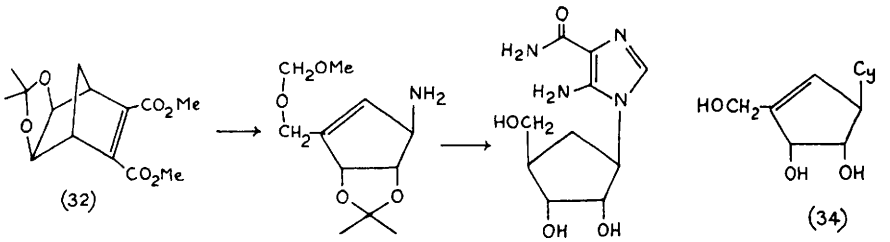
(26)

leading to (29) on condensation.[57] A readily obtainable Diels-Alder adduct (32) has been employed in syntheses of analogues of



(30) (31) (29)

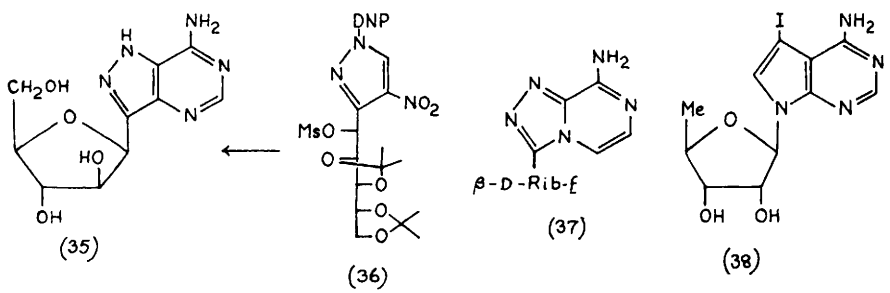
aristeromycin and neplanocin A, e.g., (33) and (34).[58] Coformycin and 3'-deoxy-coformycin have been conventionally synthesized using



(32) (33) (34)

the corresponding sugars and base with Lewis acid catalyst. Reduction of the 8-keto group to the (8R)-hydroxy analogue gave a product which was a potent inhibitor of adenosine deaminase.[59]

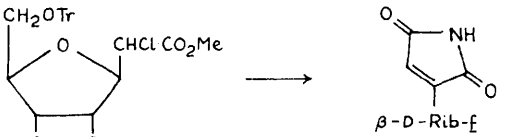
The arabino-analogue (35) of formycin has been prepared from D-mannose via the D-manno-pentahydroxypentyl pyrazole derivative (36), which was made by an improved procedure.[60] The synthesis of the triazolo-pyrazine isomer (37) of formycin has also been improved.[61]



(35) (36) (37) (38)

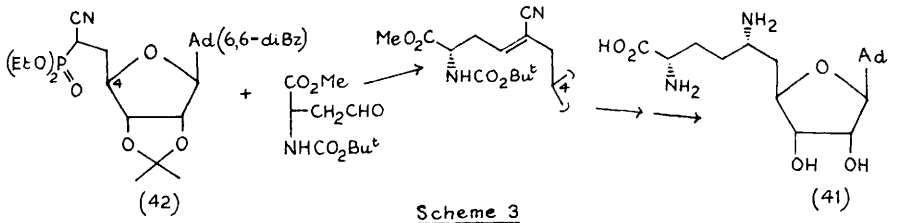
Tubercidin has been converted to its 5'-deoxy-5-iodo analogue (38) which has recently been isolated from a marine alga; it is a powerful inhibitor of adenosine kinase.[62] A simple synthesis of showdomycin (39) follows from the condensation of 2,3-O-isopropylidene-

5-O-trityl-D-ribose with a Wittig reagent ($Ph_3P{=}CClCO_2Me$) to give the C-glycoside (40).[63] Tracer evidence (^{13}C, ^{2}H, ^{15}N) on the



(40) (39)

biosynthesis of showdomycin by S. showdoensis indicates that D-ribose and L-glutamic acid are incorporated, the latter providing the entire maleimide ring.[64,65] 5-Alkenyl-1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl) uracils have been synthesized (glycosyl bromide + trisilylated base without catalyst); some showed good antiviral activity with little cytotoxicity.[66] Standard methods have been employed to prepare a number of 3-deaza-guanine nucleosides, some showing moderate antiviral or antitumour activity.[67] 2'-Deoxy-oxanosine has been prepared from oxanosine by tributylstannane reduction of a 2'-thionocarbonate intermediate; the product was a more potent antibiotic than its parent.[68] A synthesis of sinefungin (41) utilized the Wadsworth Emmons reagent (42) as outlined in Scheme 3.[69]



Scheme 3

A series of 2'-O-acyl derivatives ($C_1 \rightarrow C_4$ acids) of ara-adenosine have been prepared and evaluated as antiherpes agents.[70] References to antibiotic nucleosides are also made in Chapter 20.

5 Glyco-Peptide Antibiotics

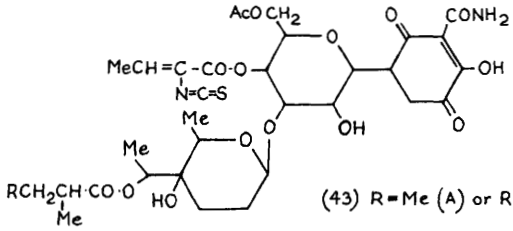
Actaplanin, a new glycopeptide antibiotic from Actinoplanes missouriensis, is a complex of at least six components, all containing the same peptide core, the amino-sugar L-ristosamine (3-amino-2,3,6-trideoxy-L-ribo-hexose), and varying amounts of glucose, mannose, and rhamnose.[71] Muraceins A, B, and C, three

new enzyme inhibitors isolated from fermentations of Nocardia orientalis, contain muramic acid glycosidically linked by peptide bond to a tri- or penta-peptide.[72] The structure and conformation of epimers derived by isomerization in the cyclic peptide core of teichoplanin (which contains glucosamine and mannose) have been characterized.[73] Controlled hydrolysis of teichoplanin has yielded derivatives arising by consecutive removal of three sugar units; all components carried one N-acyl-D-glucosamine unit, and at least two carry N-decanoyl and N-undecanoyl groups on this sugar.[74]

A combined TLC/FAB m.s. technique has been developed for identifying the components of the bleomycin complex (these contain an attached disaccharide); rapid analysis is possible for such polar, high molecular weight and thermally unstable compounds.[75]

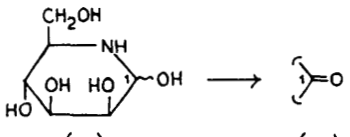
6 Miscellaneous Antibiotics

New antibacterial agents, paulomycins A and B, have been characterized as disaccharide C-glycosides (43), containing a branched-chain sugar related to quinocyclinose; configurations were not established.[76]

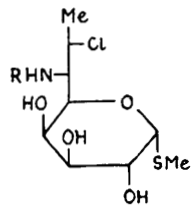


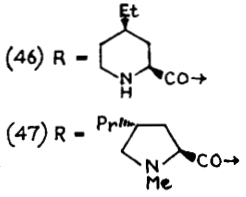
(43) R = Me (A) or R = H (B)

Norjirimycin B (5-amino-5-deoxy-D-mannopyranose) (44), the 2-epimer of norjirimycin with which it can be isolated from S. lavendulae, can be oxidized microbiologically (Gluconobacter suboxydans) to the corresponding D-mannono-δ-lactam (45); both of these compounds, characterized by n.m.r. and X-ray analysis, are powerful glycosidase inhibitors.[77] The synthesis of norjirimycin is also mentioned in Chapter 24. The introduction of 7S-alkylthio-



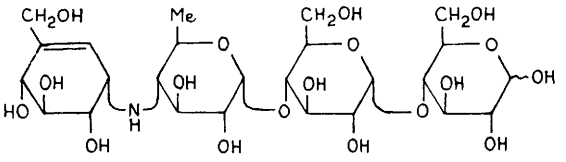
(44) (45)



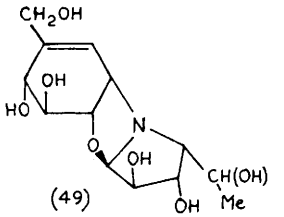


substituents into the lincomycin structure has been reviewed; most syntheses involved sulphur nucleophiles reacting with a 6,7-N-acetyl epimine derivative.[78] A synthetic clindamycin analogue, pirlimycin (46), is a more potent antibacterial agent than clindamycin (47) itself.[79]

Moenomycin A (see Vol. 15, p. 191) has been degraded by stepwise removal of successive sugar units.[80] Hydrolysis of acarbose (48), a potent inhibitor of intestinal α-D-glucosidases, yielded glucose and the tricyclic pseudo-disaccharide (49); methanolysis yielded an equivalent disaccharide methyl glycoside.[81] Further studies



(48)



(49)

reported on the sporaviridin complex (see Vol. 16, p. 198; Vol. 17, p. 181) including the isolation and characterization of six components of N-acetyl-sporaviridins, containing seven monosaccharide units and a macrolide aglycone, the carbohydrate portion comprising a viridopentaose with D-glucose and N-acetyl-L-vancosamine.[82] Further work on the structure of trestatins (see Vol. 17, p. 181) reports some new components of the complex; these contain maltose as an additional unit attached to the valienamine endgroup in trestatins A-C.[83]

Antibiotics 1072A and 1072B have been identified as gilvocarcin M and toromycin (gilvocarcin V), respectively (see Vol. 15, p. 45; Vol. 17, p. 182)[84].

The biosynthesis of the trisaccharide antibiotic complex cinodine (see Vol. 12, p. 153, ref. 63) has been investigated; ^{14}C- and ^{13}C-studies indicate that tyrosine is efficiently incorporated into the aglycone, and that D-glucosamine is the source of all three sugar units.[85]

References

1 I.Kitagawa, Farumashia, 1983, 19, 1247 (Chem. Abstr., 1984, 100, 85999).
2 P.Kurath, W.Rosenbrook,Jr., D.A.Dunnigan, J.B.McAlpine, R.S.Egan, R.S. Stanaszek, M.Cirovic, S.L.Mueller, and W.H.Washburn, J. Antibiot., 1984, 37, 1130.
3 N.Asano, M.Takeuchi, K.Ninomiya, Y.Kameda, and K.Matsui, J. Antibiot., 1984, 37, 859.

4 J.Schubert, R.Schwesinger, and H.Prinzback, Angew. Chem. Int. Ed. Engl. 1984, 23, 167.
5 R.Kühlmeyer, R.Schwesinger, and H.Prinzback, Tetrahedron Lett., 1984, 25, 3429.
6 N.Yasuda, K.Matsuda, H.Tsutsumi, and T.Takaya, Chem. Lett., 1984, 1665.
7 Y.Kameda, N.Asano, M.Yoshikawa, M.Takeuchi, T.Yamaguchi, K.Matsui, S.Horii, and H.Fukase, J. Antibiot., 1984, 37, 1301.
8 N.Sakairi, T.Yoneta, Md.D.Rahman, and Y.Ishido, J. Carbohydr. Chem., 1984, 3, 51.
9 R.Albert, K.Dax, and A.E.Stütz, Carbohydr. Res., 1984, 132, 162.
10 R.Albert, K.Dax, and A.E.Stütz, J. Carbohydr. Chem., 1984, 3, 267.
11 H.Iwasawa, D.Ikeda, S.Kondo, and H.Umezawa, J. Antibiot., 1984, 37, 428.
12 W.Streicher, H.Loibner, J.Hildebrandt, and F.Turnowsky, Drugs Exp. Clin. Res., 1983, 9, 591 (Chem. Abstr., 1984, 100, 103 788).
13 M.Yoshikawa, Y.Ikeda, K.Takenaka, M.Torihara, and I.Kitagawa, Chem. Lett., 1984, 2097.
14 J.-M.Girodeau, R.Pineau, M.Masson, and F.Le.Goffic, J. Antibiot., 1984, 37, 150.
15 K.Tatsuta, K.Akimoto, H.Takahashi, T.Hamatsu, M.Annaka, and M.Kinoshita, Bull. Chem. Soc. Jpn., 1984, 57, 529.
16 T.L.Nagabhushan, W.N.Turner, H.Tsai, R.S.Jaret, D.Schumacher, J.K.Jenkins, and J.S.Chiu, Carbohyr. Res., 1984, 130, 243.
17 O.R.Martin and W.A.Szarek, Carbohydr. Res., 1984, 130, 195.
18 J.-M.Girodeau, R.Pineau, M.Masson, and F.Le Goffic, J. Antibiot., 1984, 37, 143.
19 J.-R.Fang, C.J.Pearce, and K.L.Rinehart,Jr., J. Antibiot., 1984, 37, 77.
20 M.Suzuki and K.Harada, Spectrosc.:Int. J., 1983, 2, 267 (Chem. Abstr., 1984, 100, 156 914).
21 V.W.Pike, A.J.Palmer, P.L.Horlock, T.J.Perun, L.A.Freiberg, D.A.Dunnigan, and R.H.Liss, Int. J. Appl. Radiat. Isot., 1984, 35, 103 (Chem. Abstr., 1984, 101, 38751.
22 H.Sano, T.Sunazuka, H.Tanaka, K.Yamashita, R.Okachi, and S.Omura, J. Antibiot., 1984, 37, 750.
23 H.Sano, T.Sunazuka, H.Tanaka, K.Yamashita, R.Okachi, and S.Omura, J. Antibiot., 1984, 37, 760.
24 H.Sano, M.Inoue, and S.Omura, J. Antibiot., 1984, 37, 738.
25 G.M.Bright, A.R.English, A.A.Nagel, J.A.Retsema, and F.C.Sciavolino, Antimicrob. Agents Chemother.; 1984, 25, 113 (Chem. Abstr., 1984, 100, 175 174).
26 B.N.Pramanik, A.K.Mallams, P.L.Bartner, R.R.Rossman, J.B.Morton, and J.H.McGlotten, J. Antibiot., 1984, 37, 818.
27 H.Kawai, Y.Hayakawa, M.Nakagawa, K.Furihata, H.Seto, and N.Otake, Tetrahedron Lett., 1984, 25, 1941.
28 K.Ishii, Y.Nishimura, H.Naganawa, S.Kondo, and H.Umezawa, J. Antibiot., 1984, 37, 344.
29 K.Imamura, A.Odagawa, K.Tanabe, Y.Hayakawa, and N.Otake, J. Antibiot., 1984, 37, 83.
30 T.Tsuji, M.Takezawa, H.Morioka, T.Kida, I.Horino, Y.Eto, and H.Shibai, Agric. Biol. Chem., 1984, 48, 3181.
31 I.Jo and P.R.Lee, Hwahak Kwa Kongop Ui Chinbo, 1984, 24, 354 (Chem. Abstr., 1984, 101, 152 193).
32 E.M.Acton, G.L.Tong, C.W.Mosher, and R.L.Wolgemuth, J. Med. Chem., 1984, 27, 638.
33 Y.Kimura, M.Suzuki, T.Matsumoto, R.Abe, and S.Terashima, Chem. Lett., 1984, 501.
34 Y.Kimura, M.Suzuki, and S.Terashima, Chem. Lett., 1984, 2113.
35 D.Horton, W.Priebe, and O.Varela, J. Antibiot., 1984, 37, 853.
36 J.Alexander, I.Khanna, D.Lednicer, L.A.Mitscher, T.Veysoglu, Z.Wielogorski, and R.L.Wolgemuth, J. Med. Chem., 1984, 27, 1343.
37 H.Tanaka, T.Yoshioka, Y.Shimauchi, A.Yoshimoto, and T.Ishikura, Tetrahedron Lett., 1984, 25, 3355.

38 B.Stefanska, Z.Mazerska, L.Falkowski, and E.Borowski, J. Antibiot., 1984, 37, 1213.
39 T.Hoshino, Y.Setoguchi, and A.Fujiwara, J. Antibiot., 1984, 37, 1469.
40 A.Yoshimoto, O.Johdo, Y.Takatsuki, T.Ishikura, T.Sawa, T.Takeuchi, and H.Umezawa, J. Antibiot., 1984, 37, 935.
41 A.Yoshimoto, Y.Matsuzawa, T.Ishikura, T.Sawa, T.Takeuchi, and H.Umezawa, J. Antibiot., 1984, 37, 920.
42 E.M.Acton, K.J.Ryan, and M.Tracy, Tetrahedron Lett., 1984, 25, 5743.
43 R.Mondelli, A.Arpone, G.Fronza, G.Cassinelli, B.Gioia, and A.Vigevani, J. Chem. Res., Synop., 1984, 180.
44 Y.Ogawa, H.Mori, N.Yamada, and K.Kon, J. Antibiot., 1984, 37, 44.
45 H.Umezawa, Y.Takahashi, T.Takeuchi, H.Nakamura, Y.Iitaka, and K.Tatsuta, J. Antibiot., 1984, 37, 1094.
46 J.G.Buchanan, Prog. Chem. Org. Nat. Prod., 1983, 44, 243.
47 T.Utagawa and Y.Hirose, Yuki Gosei Kagaku Kyokaishi, 1983, 41, 1076 (Chem. Abstr., 1984, 100, 68609).
48 M.Yamashita, Y.Kawai, I.Uchida, T.Komori, M.Kohsaka, H.Imanaka, K.Sakane, M.Setoi, and T.Teraji, J. Antibiot., 1984, 37, 1284; Tetrahedron Lett., 1984, 25, 4689.
49 T.Ito, K.Ohba, M.Koyama, M.Sezaki, H.Tohyama, T.Shomura, H.Fukuyasu, Y.Kazuno, T.Niwa, M.Kojima, and T.Niida, J. Antibiot., 1984, 37, 931.
50 K.Isono, M.Uramoto, H.Kusakabe, N.Miyata, T.Koyama, M.Ubukata, S.K.Sethi, and J.A.McCloskey, J. Antibiot., 1984, 37, 670.
51 J.Delzer, H.-P.Fiedler, H.Müller, H.Zähner, R.Rathmann, K.Ernst, and W.A.König, J. Antibiot., 1984, 37, 80.
52 G.Benz, Liebigs Ann. Chem., 1984, 1399 and 1408.
53 S.Tashiro, N.Sugita, T.Iwasa, and H.Sawada, Agric. Biol. Chem., 1984, 48, 881.
54 N.Nishizawa, Y.Kondo, M.Koyama, S.Omoto, M.Iwata, T.Tsuruoka, and S.Inouye, J. Antibiot., 1984, 37, 1.
55 A.A.Tymiak, C.A.Culver, J.F.Goodman, V.S.Seiner, and R.B.Sykes, J. Antibiot., 1984, 37, 416.
56 T.Suami, H.Sasai, K.Matsuno, N.Suzuki, Y.Fukuda, and O.Sakanaka, Tetrahedron Lett., 1984, 25, 4533.
57 F.Tabusa, T.Yamada, K.Suzuki, and T.Mukaiyama, Chem. Lett., 1984, 405.
58 M.Arita, K.Adachi, H.Sawai, and M.Ohno, Nucleic Acids Symp. Ser., 1983, 12 (Symp. Nucleic Acids Chem., 11th) 25 (Chem. Abstr., 1984, 101, 38767).
59 L.D.Hawkins, C.J.Hanvey, F.L.Boyd, Jr., and H.D.H.Showalter, Nucleosides, Nucleotides, 1983, 2, 479 (Chem. Abstr., 1984, 101, 23863).
60 J.G.Buchanan, D.Smith, and R.H.Wightman, Tetrahedron, 1984, 40, 119.
61 S.W.Schneller, R.D.Thompson, J.G.Cory, R.A.Olsson, E.de Clercq, I.-K.Kim, and P.K.Chiang, J. Med. Chem., 1984, 27, 924.
62 A.F.Cook and M.J.Holman, Nucleosides, Nucleotides, 1984, 3, 401.
63 N.Katagiri, T.Haneda, and N.Takahashi, Heterocycles, 1984, 22, 2195.
64 J.G.Buchanan, M.R.Hamblin, A.Kumar, and R.H.Wightman, J. Chem. Soc., Chem. Commun., 1984, 1515.
65 J.G.Buchanan, A.Kumar, R.H.Wightman, S.J.Field, and D.W.Young, J. Chem. Soc., Chem. Commun., 1984, 1517.
66 K.A.Watanabe, T.-L.Su, U.Reichman, N.Greenberg, C.Lopez, and J.J.Fox, J. Med. Chem., 1984, 27, 91.
67 G.R.Revankar, P.K.Gupta, A.D.Adams, N.K.Dalley, P.A.McKernan, P.D.Cook, P.G.Canonico, and R.K.Robins, J. Med. Chem., 1984, 27, 1389.
68 K.Kato, N.Yagisawa, N.Shimada, M.Hamada, T.Takita, K.Maeda, and H. Umezawa, J. Antibiot.,1984, 37, 941.
69 M.Geze, P.Blanchard, J.L.Fourray, and M.Robert-Gero, J. Am. Chem. Soc., 1983, 105, 7638.
70 D.C.Baker, S.D.Kumar, W.J.Waites, G.Arnett, W.M.Shannon, W.I.Higuchi, and W.J.Lambert, J. Med. Chem., 1984, 27, 270.
71 M.Debono, K.E.Merkel, R.M.Molloy, M.Barnhart, E.Presti, A.H.Hunt, and R.L.Hamill, J. Antibiot., 1984, 37, 85.
72 P.D.Singh and J.H.Johnson, J. Antibiot., 1984, 37, 336.

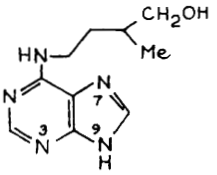
73 J.C.J.Barna, D.H.Williams, P.Strazzolini, A.Malabarba, and T.-W.C.Leung, J. Antibiot., 1984, 37, 1204.
74 A.Malabarba, P.Strazzolini, A.de Paoli, M.Landi, M.Berti, and B.Cavalleri, J. Antibiot., 1984, 37, 988.
75 T.D.Chang, T.M.Lee, and D.B.Borders, J. Antibiot., 1984, 37, 1098.
76 P.F.Wiley, S.A.Mizsak, L.Baczynskyj, and A.D.Argoudelis, J. Antibiot., 1984, 37, 1273.
77 T.Niwa, T.Tsuruoka, H.Goi, Y.Kodama, J.Itoh, S.Inouye, Y.Yamada, T.Niida, M.Nobe, and Y.Ogawa, J. Antibiot., 1984, 37, 1579.
78 B.Bannister, Tetrahedron, 1984, 40, 1633.
79 R.D.Birkenmeyer, S.J.Kroll, C.Lewis, K.F.Stern, and G.E.Zurenko, J. Med. Chem., 1984, 27, 216.
80 P.Welzel, F.Kunisch, F.Kruggel, H.Stein, A.Ponty, and H.Duddeck, Carbohydr. Res., 1984, 126, C1.
81 B.Junge, F.-R.Heiker, J.Kurz, L.Müller, D.D.Schmidt, and C.Wünsche, Carbohydr. Res., 1984, 128, 235.
82 K.-I.Harada, I.Kimura, E.Takami, and M.Susuki, J. Antibiot., 1984, 37, 976.
83 K.Yokose, M.Ogawa, and K.Ogawa, J. Antibiot., 1984, 37, 182.
84 V.I.Frolova, A.D.Kuzovkov, and A.I.Chernyshev, Antibiotiki (Moscow), 1984, 29, 329 (Chem. Abstr., 1984, 101, 230 867).
85 S.H.L.Chiu, R.Fiala, R.Kennett, L.Wozniak, and M.W.Bullock, J. Antibiot., 1984, 37, 1000.

20
Nucleosides

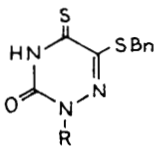
1 General

The cytokinin metabolites isolated from derooted radish seedlings to which had been administered (±)[8-^{14}C]-dihydrozeatine (1) have been isolated and shown to be the known 7-D-glucopyranoside and also unexpectedly the 3- and 9- substituted isomers.[1]

The use of cyano compounds in the synthesis of nucleosides has been discussed in a review on hydrogen cyanide and chemical evolution.[2] Reviews have also appeared on selenium-containing nucleosides, including the use of selenium-containing intermediates in the synthesis of unsaturated and deoxynucleosides,[3] on the synthesis of antibiotic nucleosides by combined chemical and enzymic methods,[4] and, in Chinese, on the preparation of nucleosides by chemical degradation of polynucleosides.[5]

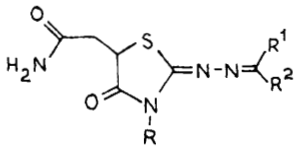


(1)



(2)

R = β-D-Rib·f

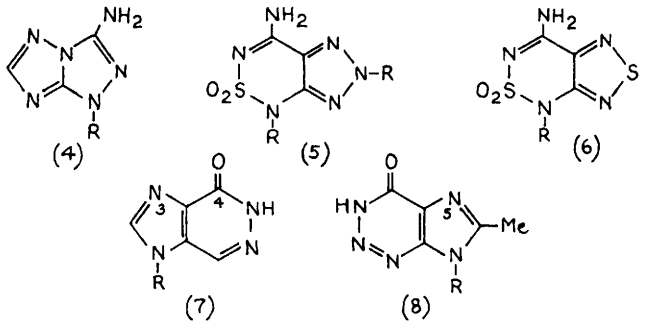


(3)

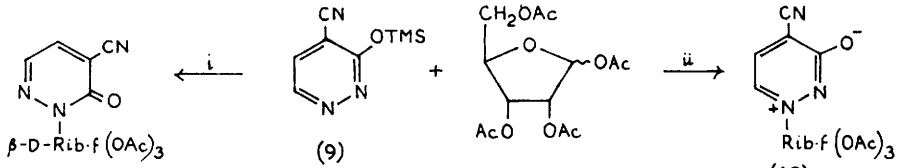
2 Synthesis

Standard procedures have been employed to synthesize β-D-ribofuranosyl derivatives of the triazine (2),[6] thiazolidinones (3),[7] 3-hydroxy-2- and 4-pyridones,[8] 2-methyl and -bromomethylimidazoles,[9] the triazolotriazole (4),[10] imidazo [1,2-b] pyrazoles,[11] the triazolothiadiazine dioxide (5) and thiadiazolothiadiazine (6) together with their β-D-glucosides,[12] pyrazolo [3,4-d] pyrimidines,[13,14,15] pyrazolo [4,3-d] pyrimidin-7-ones,[16] 2-alkylthio-8-azaadenine (and the corresponding rhamnoside),[17] imidazo [4,5-d] pyridazine (7), its 4-thio- and 4-amino-derivatives and the corresponding N-3 ribosylated compounds.[18] The imidazotriazinone (8) was prepared by nitrous acid cyclization of the aminoimidazolecarboxamido-

nucleoside, whilst glycosylation of the preformed bicycle gave the N-5 regioisomer.[19]



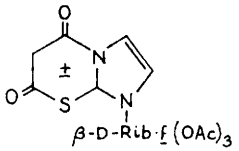
Ribofuranosylation of silylated pyridazinone (9) gave either a normal nucleoside or the mesoionic system (10), depending on the reaction conditions (Scheme 1). The nucleoside formed on deacetylation of (10) had pronounced antibiotic activity.[20,21] A number



Scheme 1

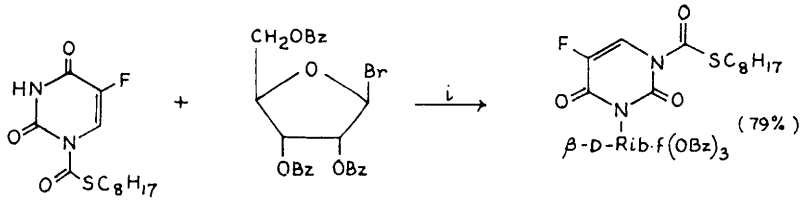
of related 4-substituted 3-oxidopyridazinium ribosides were prepared,[21] and four other 4-cyanopyridine and -pyrimidine nucleosides have been reported.[22]

A number of 2- and 6-mono- and 2,6-disubstituted derivatives of tubercidin have been prepared using the direct glycosylation of the sodium salt of the base with tri-O-benzoyl ribofuranosyl bromide, this method being superior to other procedures.[23] 2,7-Dichloro-9-β-D-ribofuranosyl-1-deazapurine has been prepared in a new way involving 'deoxygenative chlorination' of N-oxides to introduce both chlorine atoms, followed by transglycosylation; the product was converted to 2-chloro-1-deazadenosine, and 2-chloro-1-deazainosine by nucleophilic substitution.[24] The mesoionic system (11) has been prepared by reaction of tri-O-acetylribofuranosyl imidazole 2-thione with carbon suboxide.[25]



(11)

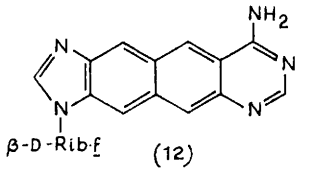
A study has been made of a 'one-pot' procedure for the synthesis of 6-oxopurine ribonucleosides.[26] Octylthiocarbonyl derivatives of pyrimidines have been used to form nucleosides in the presence of tertiary amines, exemplified in Scheme 2; isopropylamine selectively cleaves the octylthio group, whilst ammonia in methanol gives fully deprotected systems.[27]



Reagents : i, Pr^iNEt_2 - DMF (r.t., 18hr)

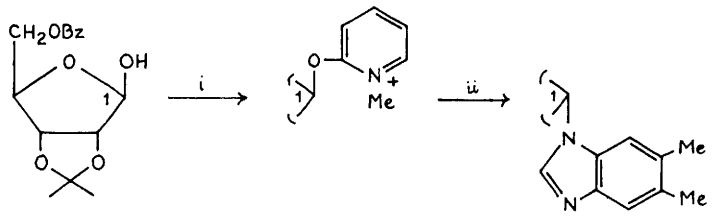
Scheme 2

Two reduced pyrimidine-2-thione derivatives were obtained in low yield by reaction of 2,3-O-isopropylidene-β-D-ribofuranosylamine with 4-methyl-4-isothiocyanato-2-pentanone.[28] Leonard's group has reported the synthesis of the lin-naphthoadenosine (12); this was not a substrate for adenosine deaminase, unlike the benzo analogue.[29]



(12)

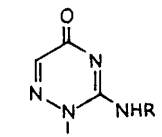
α-Ribazole (1-α-D-ribofuranosyl-5,6-dimethylbenzimidazole) has been prepared by cerous hydroxide-catalysed hydrolysis of cyanocobalamin and its acid-base properties studied.[30] A derivative of α-ribazole has been synthesized as in Scheme 3, in a procedure that was applied to a number of other silylated bases.[31]



Reagents: i, 1-Methyl-2-fluoropyridium tosylate – Pr^i_2NEt – CH_2Cl_2; ii, TMS·dimethylbenzimidazole

Scheme 3

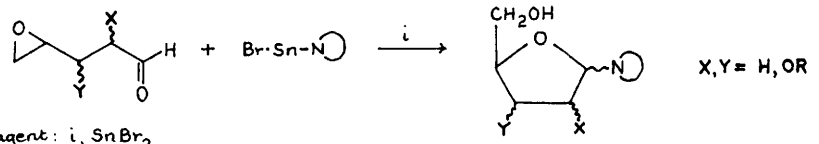
1-β-D-Arabinofuranosyl-5-mercaptocytosine has been synthesized via the corresponding uracil derivative,[32] and phase-transfer glycosylation has been used to prepare ara-7-desazaxanthosine[33] and its 2,4-dichloro-derivative.[34] Ribonucleosides have been converted to their arabino-analogues by oxidation of suitably 3', 5'-protected derivatives and subsequent borohydride reduction;[35,36] similar operations on 2',5'-diprotected ribonucleosides and on 5'-protected 2'- or 3'-deoxy-β-D-erythropentofuranosyl nucleosides gave inverted xylo or deoxy-threo-isomers as major products.[35] Oxidation of 3',5'-di-O-benzoyl-β-D-xylofuranosyl nucleosides, followed by borohydride reduction, also gave arabino-systems; in these cases, base-catalysed epimerization at C-3' in the intermediate 2'-oxo- system is presumably occurring.[37] As a model for its interaction with proteins, 2,2'-anhydro-1-(β-D-arabinofuranosyl)-6-azauracil reacted with aminoacids to give systems of type (13).[38]



β-D-Ara-f

(13)

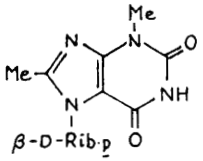
A new approach to nucleoside synthesis, illustrated generally in Scheme 4, has been applied to the synthesis of α-L-lyxonucleosides and 2-deoxy-α-DL-ribofuranosyl nucleosides.[39]



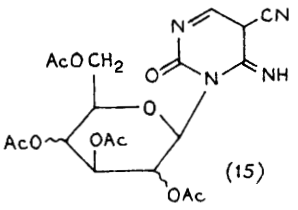
Reagent: i, $SnBr_2$

Scheme 4

A variety of O-benzoyl N-glycosylimidazoles and -pyrazoles have been prepared,[40] and 1-β-D-glucopyranosyl-3- and 5-nitrotriazoles, with the 5-nitro-isomer predominating, were synthesized conventionally.[41] 1-β-D-Allofuranosyluracil, its 6'-deoxy-derivative, and 1-β-D-altrofuranosyluracil have been reported.[42] The ribopyranosyl nucleoside (14), and its arabino counterpart, have been prepared by cyclization of acyclic precursors,[43] and pyrimidine nucleosides of type (15), with gluco, manno- and galacto-configurations, were prepared from the corresponding D-glycosyl ureas;[44] an α-D-arabinopyranosyl analogue of (15) was also reported and its conformation discussed.[45]

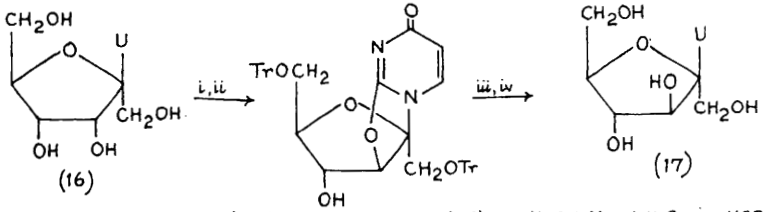


(14)



(15)

High-yielding stereoselective syntheses have been reported for psicofuranine and 9-α-D-fructofuranosyladenine; 1-β-D-psicofuranosyluracil (16) was also prepared in an improved procedure, and converted, via a cyclonucleoside, to the fructofuranosyl nucleoside (17) as in Scheme 5.[46]



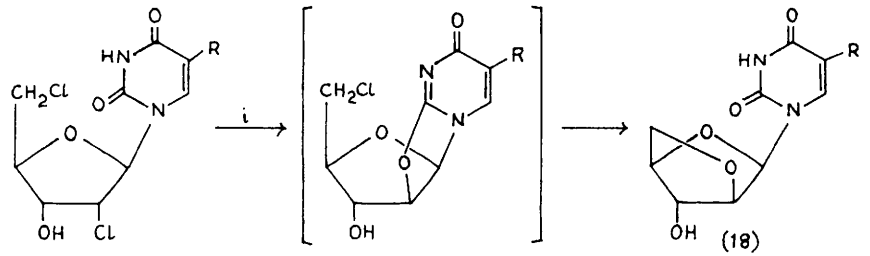
Reagents: i, TrCl-Py ; ii, $(PhO)_2CO$-$NaHCO_3$-DMF (80°) ; iii, NaOH-MeOH-H_2O ; iv, HCO_2H-H_2O

Scheme 5

3 Anhydro- and Cyclonucleosides

Various 5-substituted 2',5'-anhydro-1-β-D-arabinofuranosyluracils (18,R=H,F,Br,Me) were obtained in high yield from the dichlorides (Scheme 6), presumably by way of the 2,2'-cyclonucleosides.[47] Treatment of uridine with either diiminosuccinonitrile or cyanogen bromide gave as major product 2,2'-anhydrouridine-3'O-carbamate, probably via the 2',3'-cyclic imidocarbonate.[48] An imidazole

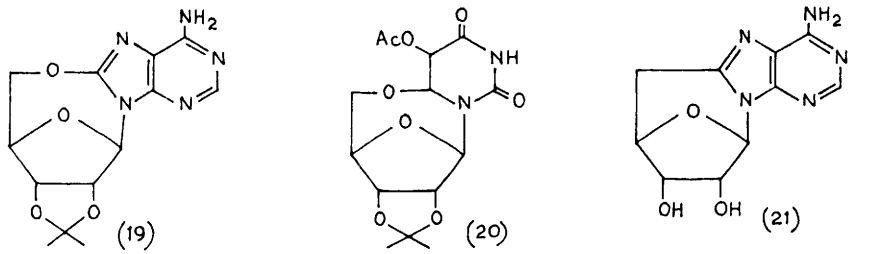
2,2'-cyclonucleoside has been reported.[49]



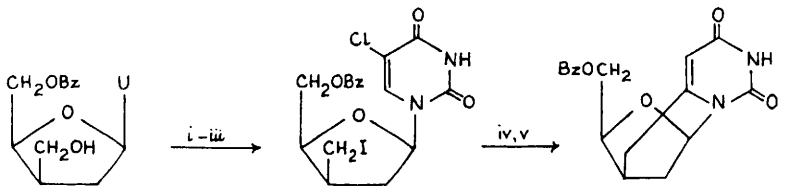
Reagent: i, NaOH-MeOH

Scheme 6

Lead tetracetate oxidation of 2',3'-O-isopropylidene adenosine gave the 5'-O,8-cyclonucleoside (19), and an N^2-benzoylguanosine analogue was prepared similarly. Isopropylidene uridine gave the cyclic derivative (20) as a single isomer of unknown stereochemistry, whilst oxidation of the N^4-benzoyl cytidine derivative gave (20) as major product, plus some 5'-O, 6-cyclocytidine derivative.[50] Improved procedures for the synthesis of 5'-O,



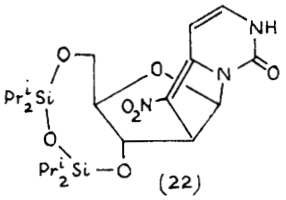
8-cycloadenosine and its N- and S- bridged analogues have been given, along with a preparation of 8,5'-anhydroadenosine (21) involving photochemical cyclization.[51] A full account has been given of earlier reports (Vol. 16, p.207) on the synthesis of 6,5'-cyclo-5'-deoxyuridine; the 2',3'-cyclic phosphate of this system was hydrolysed by pancreatic ribonuclease, thereby establishing the requirement for an anti conformation.[52]



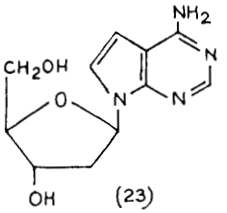
Reagents: i, Cl_2 ; ii, TsCl-Py ; iii, LiI ; iv, Bu_3SnH ; v, DBU

Scheme 7

Free-radical cyclization has been used to prepare a 6,3'-methanocyclouridine (Scheme 7),[53] and the unusual 6,2'-metheno-bridged compound (22) was synthesized by a sequence involving intramolecular Michael addition of a 2'-C-methylnitronate anion to a 5-bromouracil ring.[54]



(22)

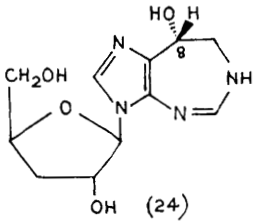


(23)

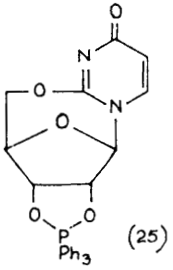
4 Deoxynucleosides

Chloro- and methylthio-substituted purines and deazapurines can, after conversion to their sodium salts, be condensed with 2-deoxy-3,5-di-O-p-toluoyl-α-D-ribofuranosyl chloride to give good yields of protected β-D-nucleosides, e.g., 2'-deoxytubercidin (23).[55] Alternatively, phase transfer glycosylation has been employed for various pyrrolo[4,3-d] pyrimidines,[56,57] a method which has also been used to prepare 2'-deoxyribonucleosides of allopurinol, with the β-D-isomer predominating.[58]

Syntheses of coformycin and its 3'-deoxyderivative have been described; the 8R-isomer (24) of 3'deoxycoformycin is a powerful inhibitor of adenosine deaminase.[59] Reduction of the triphenyl-phosphoranediyl cyclonucleoside (25) with tributylstannane gives 5'-deoxyuridine in high yield.[60]



(24)

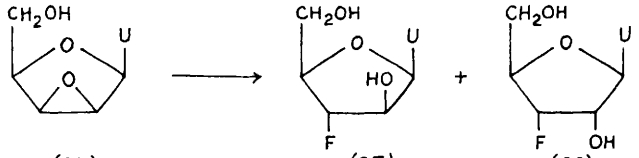


(25)

A number of 2'-deoxy-α-D-ribofuranosyl nucleosides have been prepared either by anomerization or transglycosylation of peracylated derivatives, catalysed by trimethylsilyl triflate, followed by separation of anomers.[61]

5 Halogenosugar and Aminosugar Nucleosides

An improved procedure has been developed for the synthesis of 2'-fluoro-2'-deoxyadenosine, which was converted to its 5'-phosphate and 3',5'-cyclic phosphate.[62] The synthesis of 2'-fluoro-5-iodo-1-β-D-arabinofuranosylcytosine has been described more fully (see Vol. 16, p.210); this compound has anti-herpetic activity and it appears to be phosphorylated by the virus-specified pyrimidine nucleoside kinase.[63] The corresponding 5-ethynyl analogue has also been prepared, and it too is active against herpes viruses.[64] Reaction of the D-lyxo epoxide (26) with HF in dioxan gave in low (13%) yield the expected product (27) together with ribo-product (28) (Scheme 8). It appeared that (28) was formed from (27) by an unknown mechanism, structure (28) being confirmed by an unambiguous synthesis via a 2,3'-anhydrouridine.[65] Similar openings of 2,3'-anhydro systems were used to prepare

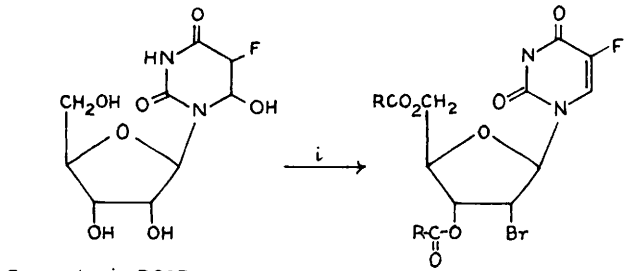


(26) (27) (28)

Scheme 8

2',3'-dideoxy-3',5-difluorouridine[66] and the 5'-O-mesylate of 3'-deoxy-3'-fluorothymidine.[67]

A series of di-O-acyl-2'-deoxy-2'-bromo-5-fluorouridines has been synthesized as in Scheme 9. This conversion can be used to give a route from uridine to 2'-deoxy-5-fluorouridine in four



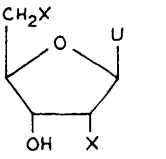
Reagent: i, RCOBr

Scheme 9

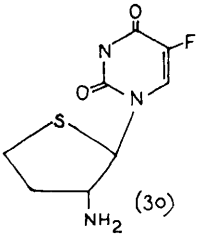
steps.[68] Similarly, 3',5'-di-O-acetyl-2'-deoxy-2'-halouridines can be prepared by treatment of uridine with o-acetoxybenzoyl halides; known chemistry then gives a route to 2'-deoxyuridine.[69]

A number of anhydro- and cyclouridines give halogenated cleavage products with Vilsmeier reagents, as for example in the formation of (29) from 2,2'-anhydrouridine.[70]

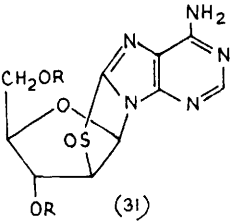
When the 5'-O-benzoate of (26) was treated with ammonium azide in refluxing ethanol, the D-arabino-product of ring opening predominated over the D-xylo isomer by a factor of 3:1; hydrolysis and reduction gave 3'-amino-3'-deoxyarabinouridine.[71] A number of 3'-amino-2',3'-dideoxynucleoside 5'-mono- and triphosphates have been prepared by a sequence involving azide ion opening of 2,3'-anhydro-2'-deoxynucleosides.[72]



(29) X = Cl, Br



(30)



(31)

6 Thionucleosides

The racemic thionucleoside (30) and a range of related compounds have been reported.[73] Either of the two diastereomers of the sulphoxide (31) can be prepared preferentially, depending on the nature of the oxidant and the group R (H or Ac); Pummerer-type rearrangements of these compounds were unsuccessful.[74]

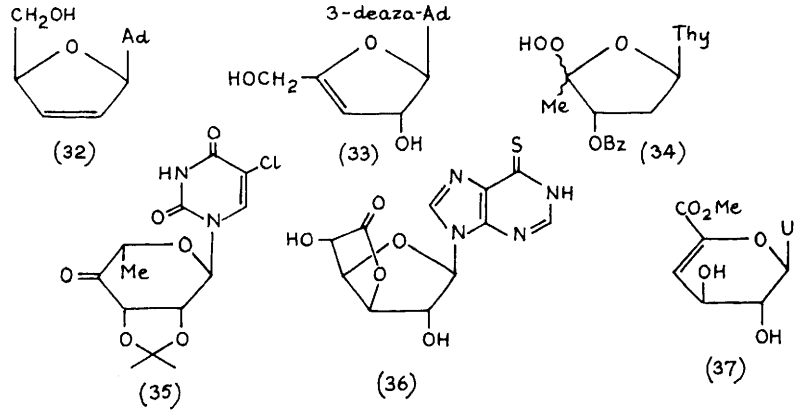
An improved procedure is recommended for the synthesis of S-adenosylhomocysteine (SAH) and base-modified analogues, involving reaction of the 5'-chloro-5'-deoxynucleoside with the sodium salt of homocysteine in aqueous medium.[75] Reaction of formycin and N^6-methyladenosine with homocysteine in the presence of SAH-hydrolase gave the appropriate SAH analogues. These were methylated to sulphonium salts which at pH 4.5 were hydrolysed to give 5'-deoxy-5'-thiomethyl nucleosides, the formycin analogue being an effective inhibitor of rat liver 5'-methythioadenosine phosphorylase.[76] 5'-Deoxy-5'-methylthioadenosine sulphoxide has been isolated from human urine; elevated levels are present in children with severe combined immunodeficiency.[77] Some other references to thionucleosides can be found in Chapter 11.

7 Nucleosides of Unsaturated Sugars, Ketosugars and Uronic Acids

Treatment of adenosine with α-acetoxyisobutyryl bromide in moist

acetonitrile gave a mixture of trans -3'(2')-bromo-2'(3')-acetates, which on acetylation, treatment with zinc-copper couple and deacetylation gave the 2'-ene (32) in 81% overall yield.[78] The unsaturated derivative (33) of 3-deazaadenosine has been prepared, as has the isomeric 4',5'-dehydrosystem and 9-β-D-xylofuranosyl-3-deazaadenosine.[79] As a model for the oxidative degradation of DNA by bleomycins, treatment of 3'-benzoyl-4',5'-dehydro-5'-deoxy-thymidine with hydrogen peroxide-TFA gave the isomeric hydroperoxides (34).[80]

A review on ketonucleosides has appeared.[81] Adenosine can be converted to a mixture of 2',5'- and 3',5'-di(monomethoxytrityl)



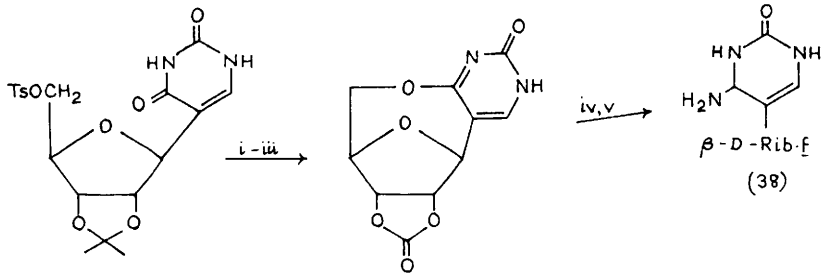
ethers; these on oxidation and deblocking with anhydrous acid in chloroform gave the 2'- and 3'-ketoanalogues of adenosine, which had half-lives of 11 and 84 hours, respectively, at 25° and pH 6.86.[82] The ketorhamnopyranosyl nucleoside (35) has been prepared.[83]

The D-glucofuranuronoside (36) and its S-methyl derivative[84] and 1-β-D-glucopyranosiduronamidocytosine[85] have been prepared by standard procedures, and the unsaturated uronic ester nucleoside (37) was synthesized by coupling silylated uracil with a derivative of D-galacturonic acid, followed by β-elimination.[86]

8 C-Nucleosides

A review has appeared on n.m.r. methods for the determination of the anomeric configuration of C-nucleosides and their protected derivatives.[87] Pseudouridine and two related nucleotides have been found in the free state in the seeds of Cicer arietinum.[88]

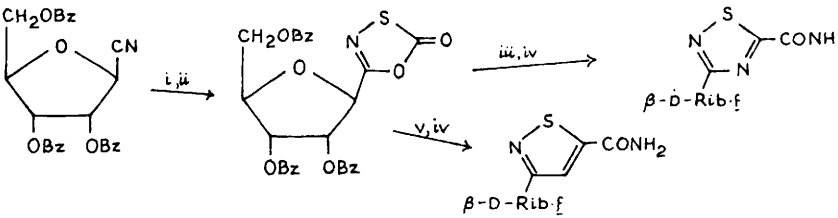
Details have been published of the enantioselective synthesis of showdomycin (see Vol. 15, p.44), 6-azapseudouridine, and cordycepin, by a chemicoenzymatic approach from the furan-dimethyl-acetylenedicarboxylate adduct.[89] A good synthesis of ψ-cytidine (38) from ψ-uridine proceeds in its later stages as indicated in Scheme 10.[90] The 1-N-, 3-N-, and 4-O-methyl-ψ-isocytidines and their 2'-deoxyderivatives have been prepared.[91]



Reagents: i, $HOAc-H_2O$; ii, $(N{=}CH{-}N)_2CO$; iii, DBU-DMF ; iv, $Py-H_2O$; v, NH_3-MeOH

Scheme 10

An intermediate nitrile sulphide is presumed to be implicated in the synthesis of the thiadiazole and thiazole C-nucleosides outlined in Scheme 11; these compounds are related structurally to ribavirin, but they did not show antiviral activity.[92]

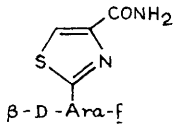


Reagents: i, HCO_2H-HCl ; ii, $ClS-COCl-C_6H_6-\Delta$; iii, $NC-CO_2Et-220°$; iv, NH_3-MeOH ; v, $HC{\equiv}CCO_2Et-220°$

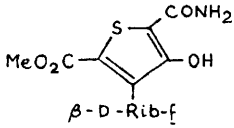
Scheme 11

The antitumour activity of tiazofurin has led to the preparation of analogues with modified sugars; the D-arabino analogue (39) and D-xylo compound were prepared from the ribofuranosyl compound by specific displacements,[93] and both α- and β-D-arabino analogues were synthesized from protected arabinofuranosyl nitriles.[94] The 3'-deoxyanalogue was also made from tiazofurin itself.[95] The thiophene (40) and the corresponding diamide, analogues of pyrazofurin, have been reported.[96] A number of C-glycosyl tetrazoles have been converted into 2-β-D-glycosyl-5-halogenomethyl-1,3,4-oxadiazoles by reaction with chloroacetyl chloride.[97]

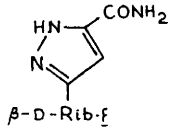
A number of compounds have been described which contain the ring systems of the C-nucleoside antibiotics pyrazofurin and formycin; these include the 4-deoxyderivative of pyrazofurin (41),[98] the thioguanosine-type analogue of formycin (42) and the corresponding β-D-arabinofuranosyl- and 2'-deoxycompounds,[99] and the strongly fluorescent isoguanosine analogue (43) made from formycin



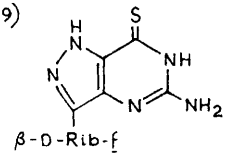
(39)



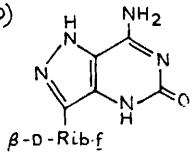
(40)



(41)



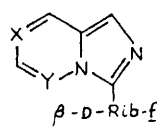
(42)



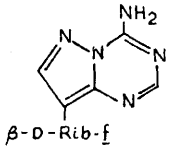
(43)

via the photochemical ring opening of its N-6 oxide.[100]

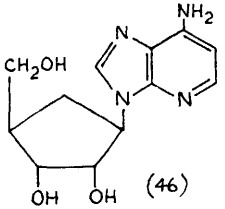
A range of imidazo-fused C-nucleosides with bridgehead nitrogen of the general type (44,X,Y=CH or N) have been prepared,[101] and the somewhat similar pyrazolotriazine (45) shows good antileukaemic activity;[102] the corresponding 4-thiocompound has also been reported.[103] Cycloaddition of maleimide to 2-(tri-O-benzoyl-β-D-ribofuranosyl)furan and deprotection give rise to 3-(β-D-ribofuranosyl)phthalimide.[104] Some pyrazolo [3,4-b]quinoxaline C-nucleoside analogues have been synthesized,[105] and a correlation has been noted between circular dichroism and anomeric configuration for C-nucleoside 1,2,3-ozotriazoles.[106]



(44)



(45)



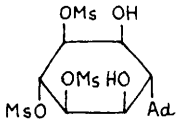
(46)

9 Carbocyclic Nucleoside Analogues

The 1-deaza analogue (46) of aristeromycin is a potent irreversible inhibitor of SAH-hydrolase.[107] A number of carbocyclic analogues of 2-amino-6-substituted-purine and 2-amino-6-substituted-8-aza-purine ribonucleosides had significant activity against type 1 herpes and vaccinia viruses,[108] and analogous 2'-deoxyribonucleo-

sides also had activity against herpes virus.[109] The carbocyclic analogues of xylo-adenosine and xylo-8-azaadenosine were resistant to deamination by adenosine deaminase, and the 8-aza-derivative showed significant in vivo antitumour activity.[110]

The adeninyl inositol (47) has been prepared via an epoxide intermediate.[111] Conformational studies on carbocyclic nucleoside analogues are mentioned in Chapter 21.



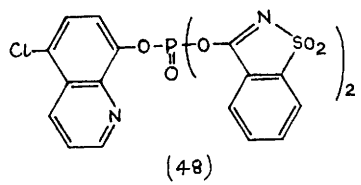
(47)

10 Nucleoside phosphates and phosphonates

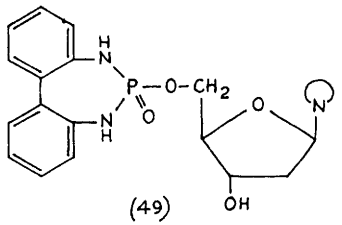
As in previous years, standard syntheses of nucleotides are not included here. Phosphorylation in the synthesis of both mono- and oligonucleotides has been reviewed.[112] The β-L-enantiomer of guanosine monophosphate has been prepared as a substrate for studying chiral selection in non-enzymic RNA synthesis; experiments indicated that the D-nucleotide was selected from a mixture of enantiomers in template-directed oligomerization.[113]

Bis-(pyrrolidino)methoxyphosphine, activated by 4,5-dichloroimidazole, has been developed for the preparation of deoxynucleoside 3'-phosphoramidites.[114] Four new trivalent phosphorus reagents have been described, two of which react selectively with ribonucleosides at the primary hydroxy group and two of which react preferentially at the cis-glycol.[115] The new phosphorylating agent (48) was used to prepare nucleoside 3'-phosphodiester intermediates,[116] whilst the p-nitrophenylethyl protecting group has been introduced in phosphotriester syntheses, where it can also be used for protection of aglycones.[117,118] Cyclic phosphorodianilidates of type (49) have been introduced for the protection of 5'-phosphates for coupling to oligodeoxyribonucleosides.[119] 5-Aminoimidazole nucleosides can be converted to their 5'-phosphates using a phosphotransferase from wheat.[120]

Phosphoryl tris(triazole) has been employed for the formation of nucleoside 2',3'-cyclic phosphates, but was unsuccessful for forming the 3',5'-isomers.[121] Both stereoisomers at phosphorus of ribonucleoside 3',5'-cyclic N,N-dimethylphosphoramidates can be made from the cyclic phosphate using TPS chloride activation; the

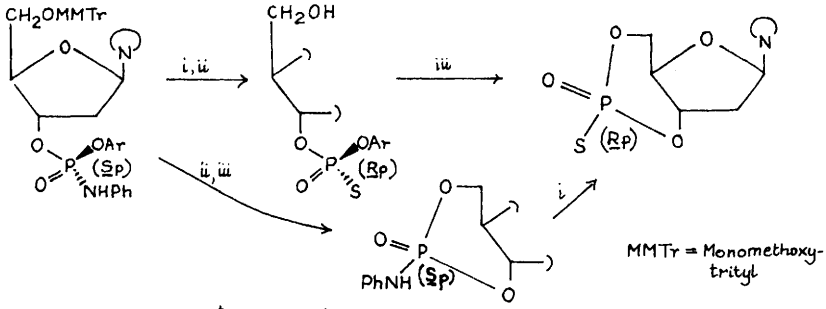


(48)



(49)

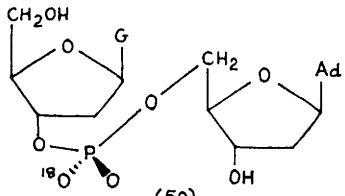
S_p isomers predominate.[122] The 3'-aryl phosphoranilidates of 5'-O-monomethoxytrityl-2'-deoxyribonucleosides can be separated into their diastereoisomers, and these can be used for the stereospecific synthesis of cyclic 3'-5'-phosphorothioates, as outlined in Scheme 12 for the S_p-isomer.[123] The chiral ^{18}O-labelled dinucleoside phosphate (50) was prepared by oxidation of a phosphite triester in the presence of $H_2{}^{18}O$, separation of diastereomers and deprotection.[124]



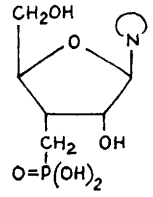
Reagents: i, NaH-CS_2; ii, H^+; iii, $KOBu^t$

Scheme 12

Deoxynucleoside 3'-methylphosphonamidites have been used to produce dideoxynucleoside methylphosphonates.[125] A full account has been given of the preparation of isosteric phosphonate analogues of ribonucleoside 3'-phosphates (51),[126] and the corresponding 2'-deoxyadenosine phosphonate has been reported.[127]



(50)



(51)

A number of phosphonate analogues of diadenosine tetraphosphate have been prepared.[128]

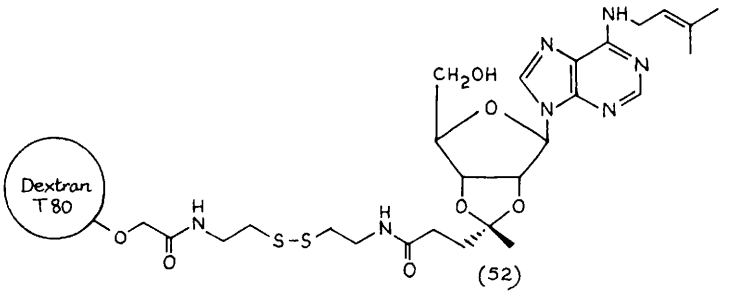
5'-Arsenates of adenosine, inosine and their deoxyanalogues have been shown to be produced by interaction of the nucleosides with inorganic arsenate.[129]

11 Ether, acetal and ester derivatives

Treatment of deoxynucleosides with dichlorosilanes in pyridine gave 3',5'-cyclic dimethylsilanediyl and tetramethyldisiloxanediyl derivatives, which were cleaved readily with water. These groupings can thus be used for protection of the 3'- and 5'-hydroxy functions when N-acylation of the base is required.[130]

2',3'-O-Ethoxymethylidene acetals of nucleosides were prepared by reaction with triethylorthoformate. Neither these acetals nor the products of methylating 2',3'-O-(dimethylamino)methylidene acetals gave 2',3'-unsaturated derivatives on pyrolysis.[131]

N^6-(2-Isopentenyl)adenosine, which shows strong antitumour activity, has been covalently linked to a dextran via a functionalized 2',3'-acetal, as in (52). This attachment was expected to increase circulatory lifetime of the drug and give increased antitumour activity. The disulphide link in (52) was slowly cleaved chemically by dithiothreitol, as a model for drug delivery by reducing enzymes.[132]

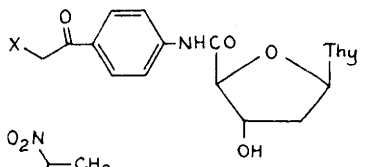


(52)

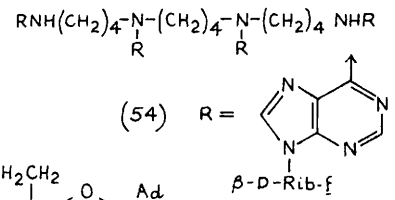
N,N'-Thiocarbonyldiimidazole has been employed as a condensing agent for the formation of 2'(3')-O-aminoacylnucleotides.[133] The antiviral agent 5-ethyl-2'-deoxyuridine was acylated at O-5' to give useful prodrugs.[134] The acetylation of nucleosides by aspirin has been investigated; in pyridine, fully acetylated products were formed, and this process may have relevance to the teratogenic behaviour of aspirin.[135]

12 Miscellaneous Nucleoside Analogues

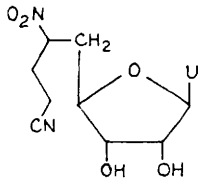
Halomethyl ketone derivatives of deoxypyrimidine nucleosides, e.g., (53, X=halogen), have been prepared and shown to be cytotoxic as predicted.[136] The oligonucleotide analogue (54) appears on UV and CD evidence to exist in conformations with significant base-stacking.[137] The homonucleoside analogue 5-deoxy-5-(1,3-dimethyl-7-xanthinyl)-D-xylose has been prepared.[138] A nitroaldol reaction of 2',3'-O-isopropylidene-5'-aldehydo-uridine was the key step in the formation of (55), the base residue of which could be exchanged by transglycosylation to give analogues of SAH and the antibiotic sinefungin.[139] 5'-Homologues of adenosine (56, R=-OH and $-CH_2OH$) have been reported,[140] as have a number of sulphonamide analogues of pyrimidine nucleoside 5'-triphosphates of general structure (57, A = p-C_6H_4NH- or $-(CH_2)_3$-).[141]



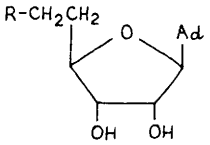
(53)



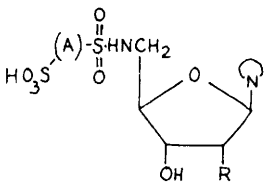
(54) R =



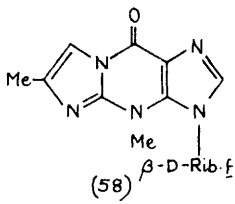
(55)



(56) R = OH or CH_2OH



(57) R=H or OH



(58)

13 Reactions

The triol produced by periodate cleavage- borohydride reduction of guanosine has been isolated for the first time as a pure species in good yield.[142] By the study of models such as the N^4-demethyl-compound, the unusually high susceptibility towards acid, base or nucleophilic cleavage of the N-ribosyl bond in 3-β-D-ribofuranosylwye (58) seems to be due to steric crowding between the N^3- and N^4-substituents.[143] The structure of an adduct formed from adenosine and the antitumour agent N-2-methyl-9-hydroxyelliptic-inium acetate in the presence of hydrogen peroxide and peroxidase

has been determined by n.m.r. methods.[144]

As a result of a study of the acid-catalysed hydrolysis of uridine, 6-hydroxy-5,6-dihydrouridine has been implicated as an intermediate.[145] In the hydrolysis of 9-β-D-ribofuranosylpurine in strongly acidic solution, the major reaction pathway involves rate-limiting formation of protonated purine and the oxocarbonium ion, whilst at higher pH the imidazole ring undergoes opening, and 4-amino-5-formamidopyrimidine is formed as a relatively stable intermediate.[146] The degradation of deoxynucleosides in aqueous KBr solution by γ-radiation has been investigated; the main degradation products were identified and proposals made as to the oxidizing species responsible.[147]

14 Spectroscopic and Conformational Studies

F.t.-i.r. and laser Raman spectra of adenine and adenosine[148] and of thymine and thymidine[149] have been reported.

The crystal structures of six isopropylidene nucleosides indicate that under external cyclic constraints the ribose ring can assume a variety of unusual conformations.[150]

In a series of pyrimidine cyclonucleosides, the magnitude of ^{1}J(C1',H1') varies quantitatively with glycosidic bond conformation. Measurement of this coupling constant in pyrimidine nucleosides can be used to determine the range of allowed *syn* and *anti* conformations.[151] In rigid cyclonucleosides of adenosine, it has been observed that the magnitude of $^{3}J_{C,H}$ in systems of the type ^{13}C-C-C(O)-H is much reduced if the oxygen atom is located *trans* to the observed carbon.[152] The conformational behaviour of some 2'-deoxy-2'-halo-D-xylofuranosyluracils and 2',3'-dideoxy-3'-halo-D-ribofuranosyl pyrimidines has been studied by n.m.r. methods,[153] and a detailed interpretation of the ^{13}C n.m.r. of 3',5'-di-*O*-acetyl-2'-deoxy-2'-fluorouridine has been given.[154] High-field n.m.r. studies have been carried out on the trinucleoside diphosphate 3'd(A2'-5'-A2'-5'A)[155] and on various oligoarabinonucleotides;[156] in addition CD was used to study base stacking.

A study has been made of the FAB mass spectra of a number of nucleosides and nucleotides.[157] Exhaustive methylation with CD_3-labelled trimethylanilinium hydroxide, followed by g.c.-m.s., has been developed as a way of distinguishing 'native' methyl groups in methylated nucleosides from those introduced during derivatiz-

ation.[158] Additional references to mass spectrometry of nucleosides can be found in Chapter 22.

References

1 B.A. McGaw, J.K. Heald, and R. Horgan, Phytochemistry, 1984, 23, 1373.
2 J.P. Ferris and W.J. Hagan Jr., Tetrahedron, 1984, 40, 1093.
3 Z.J. Witczak, Nucleosides Nucleotides, 1983, 2, 295.
4 T. Utagawa, and Y. Hirose, Yuki Gosei Kagaku Kyokaishi, 1983, 41, 1076 (Chem. Abstr., 1984, 100, 68609).
5 F. Gu, Zhongguo Niangzao, 1983, 2, 15 (Chem. Abstr., 1984, 100, 175131).
6 C. Cristescu, Rev. Roum. Chim., 1983, 28, 989 (Chem. Abstr., 1984, 100, 210 317).
7 J. Kobe, B. Rusjakovski, and B. Brdar, Croat. Chem. Acta, 1984, 57, 295 (Chem. Abstr., 1984, 101, 171 637).
8 D.T. Mao, J.S. Driscoll, and V.E. Marquez, J. Med. Chem., 1984, 27, 160.
9 T. Garcia-Lopez, R. Herranz, and J. Ignacio Andres, Eur. J. Med. Chem. - Chim. Ther., 1984, 19, 187 (Chem. Abstr., 1984, 101, 152 242).
10 S.G. Wood, N.K. Dalley, R.D. George, R.K. Robins, and G.R. Revankar, Nucleosides Nucleotides, 1984, 3, 187.
11 S.G. Wood, N.K. Dalley, R.D. George, R.K. Robins, and G.R. Revankar, J. Org. Chem., 1984, 49, 3534.
12 B. Azmy, P. Fernández-Resa, P. Goya, R. Nieves, C. Ochoa, M. Stud, and M.L. Jimeno, Nucleosides Nucleotides, 1984, 3, 325.
13 H.B. Cottam, C.R. Petrie, P.A. McKernan, R.J. Goebel, N.K. Dalley, R.B. Davidson, R.K. Robins, and G.R. Revankar, J. Med. Chem., 1984, 27, 1119.
14 Yu. N. Bulychev, I.A. Korbukh, and M.N. Preobrazhenskaya, Khim. Geterotsikl. Soedin., 1984, 253 (Chem. Abstr., 1984, 100, 210 333).
15 P. Finlander, and E.B. Pedersen, Chem. Scr., 1984, 23, 23 (Chem. Abstr., 1984, 101, 7576).
16 P.G. Baraldi, D. Simoni, V. Periotto, S. Manfredini, M. Guarneri, R. Manservigi, E. Cassai, and V. Bertolasi, J. Med. Chem., 1984, 27, 986.
17 D.S. Bhakuni, S. Roy, P.K.Gupta, and B.L. Chowdhury, Indian J. Chem., Sect. B, 1984, 23B, 369 (Chem. Abstr., 1984, 101, 211 628).
18 R.P. Gagnier, M.J. Halat, and B.A. Otter, J. Heterocycl. Chem., 1984, 21, 481.
19 J. Ignacio Andres, R. Herranz, and M. Teresa Garcia Lopez, J. Heterocycl. Chem., 1984, 21, 1221.
20 R.E. Bambury, D.T. Feeley, G.C. Lawton, J.M. Weaver, and J. Wemple, J. Chem. Soc., Chem. Commun., 1984, 422.
21 R.E. Bambury, D.T. Feeley, G.C. Lawton, J.M. Weaver, and J. Wemple, J. Med. Chem., 1984, 27, 1613.
22 C.A. Schleiper and J. Wemple, Nucleosides Nucleotides, 1984, 3, 369.
23 Z. Kazimierczuk, G.R. Revankar, and R.K. Robins, Nucleic Acids Res., 1984, 12, 1179 (Chem. Abstr., 1984, 101, 23860).
24 T. Itoh, T. Sugawara, A. Nomura, and Y. Mizuno, Nucleosides Nucleotides, 1983, 2, 387 (Chem. Abstr., 1984, 100, 139 543).
25 R.A. Glennon and S.M. Tejani, Nucleosides Nucleotides, 1984, 3, 389.
26 L.W. Dudyez and G.E. Wright, Nucleosides Nucleotides, 1984, 3, 33.
27 S. Ozaki, Y. Watanabe, T. Hoshiko, H. Fujisawa, A. Vemura, and K. Ohrai, Tetrahedron Lett., 1984, 25, 5061.
28 A.D. Shutalev, L.A. Ignatov, and B.V. Unkovskii, Khim. Geterotsikl. Soedin., 1984, 244 (Chem. Abstr., 1984, 100, 210 332).
29 T.M. Stevenson and N.J. Leonard, J. Org. Chem., 1984, 49, 2158.
30 K.L. Brown, J.M. Hakimi, D.M. Nuss, Y.D. Montejano, and D.W. Jacobsen, Inorg. Chem., 1984, 23, 1463 (Chem. Abstr., 1984, 100, 175 197).
31 T. Mukaiyama, J. Hashimoto, Y. Hayashi, and S. Shoda, Chem. Lett., 1984, 557.

32 V.C. Solan, G.L. Szekeres, E.K. Rya, H. Kung, Y.K. Ho, and T.J. Bardos, Nucleosides Nucleotides, 1983, 2, 419.
33 F. Seela and U. Liman, Justus Liebigs Ann. Chem., 1984, 273.
34 F. Seela and H. Driller, Justus Liebigs Ann. Chem., 1984, 722.
35 F. Hansske, D. Madej, and M.J. Robins, Tetrahedron, 1984, 40, 125.
36 N. Sakairi, I. Hirao, Y. Zama, and Y. Ishido, Nucleosides Nucleotides, 1983, 2, 221 (Chem. Abstr., 1984, 100, 34774).
37 G. Gosselin, M.-C. Bergogne, and J.L. Imbach, Nucleosides Nucleotides, 1984, 3, 265.
38 H. Hrebabecky, and J. Beranek, Collect. Czech. Chem. Commun., 1984, 49, 2689.
39 T. Miwa, K. Narasaka, and T. Mukaiyama, Chem. Lett., 1984, 1093.
40 D. Mackiewiczowa, J. Jasinska, and J. Sokolowski, Pol. J. Chem., 1983, 57, 745.
41 F.G. De Las Heras, M.J. Camarasa, A.R. Martinez-Fernandez, and J.A. Escario, Eur. J. Med. Chem. - Chim. Ther., 1984, 19, 89 (Chem. Abstr., 1984, 101, 7580).
42 A. Billich, U. Stockhove, and H. Witzel, Nucleic Acid Res., 1983, 11, 7611 (Chem. Abstr., 1984, 100, 121 513).
43 R. Rico Gomez, and J. Rios Ruiz, An. Quim., Ser.C, 1983, 79, 36 (Chem. Abstr., 1984, 100, 7041).
44 E. Grinsteins, E. Liepins, and E.I. Stankevich, Khim. Geterotsikl. Soedin., 1984, 543 (Chem. Abstr., 1984, 101, 91384).
45 E. Stankevics, A. Dreimane, E. Liepins. A. Kemme, and J. Bleidelis, Nucleosides Nucleotides, 1983, 2, 155 (Chem. Abstr., 1984, 100, 22950).
46 A. Grouiller and J. Chattopadhyaya, Acta. Chem. Scand., Ser.B., 1984, 38, 367.
47 K. Hirota, Y. Kitade, T. Tomishi, and Y. Maki, J. Chem. Soc., Chem. Commun., 1984, 108.
48 J.P. Ferris and H. Yanagawa, J. Org. Chem., 1984, 49, 2121.
49 J. Koenig, and D. Cech, Z.Chem., 1984, 24, 209 (Chem. Abstr., 1984, 101, 230 925).
50 K. Kameyama, M. Sako, K. Hirota, and Y. Maki, J. Chem. Soc., Chem. Commun., 1984, 1658.
51 S.G. Zavgorodnii, N.V. Gnuchev, B.P. Gottikh, N.B. Dyatkina, and V.L. Florent'ev, Bioorg. Khim., 1984, 10, 681 (Chem. Abstr., 1984, 101, 230 915).
52 T. Ueda, H. Usui, S. Shuto, and H. Inoue, Chem. Pharm. Bull., 1984, 32, 3410.
53 T. Ueda, and S. Shuto, Nucleosides Nucleotides, 1984, 3, 295.
54 T. Ueda, S. Shuto, and H. Inoue, Nucleosides Nucleotides, 1984, 3, 173.
55 Z. Kazimierczuk, H.B. Cottam, G.R. Revankar, and R.K. Robins, J. Am. Chem. Soc., 1984, 106, 6379.
56 H.-D. Winkeler and F. Seela, Justus Liebigs Ann. Chem., 1984, 708.
57 F. Seela and H. Steker, Justus Liebigs Ann. Chem., 1984, 1719.
58 F. Seela and H. Steker, Tetrahedron Lett., 1984, 25, 5017.
59 L.P. Hawkins, J.C. Harvey, F.L. Boyd, Jr., D.C. Baker, and H.D.H. Showalter, Nucleosides Nucleotides, 1983, 2, 479.
60 J. Kimura, Y. Nishikubo, and O. Mitsunobu, Bull. Chem. Soc. Jpn., 1984, 57, 2017.
61 T. Yamaguchi and M. Saneyoshi, Chem. Pharm. Bull., 1984, 32, 1441.
62 S. Uesugi, T. Kaneyasu, J. Matsugi, and M. Ikehara, Nucleosides Nucleotides, 1983, 2, 373 (Chem. Abstr., 1984, 100, 139 542).
63 C. Lopez, T.C. Chou, K.A. Watanabe, and J.J. Fox, Dev. Mol. Virol., 1984, 4, 105 (Chem. Abstr., 1984, 101, 152 247).
64 R.A. Sharma, I. Kavai, R.G. Hughes, Jr., and M. Bobek, J. Med.Chem., 1984, 27, 410.
65 H.K. Misra, W.P. Gati, E.E. Knaus, and L.I. Wiebe, J. Heterocycl. Chem., 1984, 21, 773.
66 S. Ajmera, A.R. Bapat, K. Danenberg, and P.V. Danenberg, J. Med. Chem., 1984, 27, 11.
67 M. Von Janta-Lipinski, P. Langen, and D. Cech, Z. Chem., 1983, 23, 335 (Chem. Abstr., 1984, 100, 139 537).

68 S. Ozaki, Y. Watanabe, T. Hoshiko, S. Ii, and T. Kagawa, Nucleic Acids Symp. Ser., 1983, 12, 9 (Chem. Abstr., 1984, 100, 210 325).
69 K.S. Bhat and A.S. Rao, Indian J. Chem., Sect. B, 1983, 22B, 678 (Chem. Abstr., 1984, 100, 192 200).
70 K. Hirota, Y. Kitade, F. Iwami, and S. Senda, Chem. Pharm. Bull., 1984, 32, 2591.
71 C.F. Hummel and R.P. Carty, Nucleosides Nucleotides, 1983, 2, 249 (Chem. Abstr., 1984, 100, 51935).
72 V.E. Zaitseva, N.B. Dyatkina, A.A. Kraevskii, N.V. Skaptsova, O.V. Turina, N.V. Gnuchev, B.P. Gottikh, and A.V. Azhaev, Bioorg. Khim., 1984, 10, 670 (Chem. Abstr., 1984, 101, 192 378).
73 J.O. Jones and R.S. McElhinney, J. Chem. Res. Synop., 1984, 146.
74 A.L. Schifman and K.K. Ogilvie, Nucleosides Nucleotides, 1983, 2, 399.
75 K. Ramalingam and R.W. Woodard, J. Org. Chem., 1984, 49, 1291.
76 G. Cacciapuoti, M. Porcelli, F. Della Ragione, and M. Carteni-Farina, Bull. Mol. Biol.Med., 1983, 8, 199 (Chem. Abstr., 1984, 101, 73043).
77 J.S. Mills, G.C. Mills, and D.J. McAdoo, Nucleosides Nucleotides, 1983, 2, 465.
78 M.J. Robins, F. Hansske, N.H. Low, and J.I. Park, Tetrahedron Lett., 1984, 25, 367.
79 T. Ishikara, S. Oue, T. Itoh, A. Nomura, T. Veda, and Y. Mizuno, Nucleosides Nucleotides, 1984, 3, 413.
80 I. Saito, T. Morii, and T. Matsuura, Nucleic Acids Symp. Ser., 1983, 12 (Symp. Nucleic Acids Chem., 11th) 95 (Chem. Abstr., 1984, 101, 38768).
81 K. Antonakis, Advan. Carbohydr. Chem. Biochem., 1984, 42, 227.
82 R.P. Crews and D.C. Baker, Nucleosides Nucleotides, 1983, 2, 275 (Chem. Abstr., 1984, 100, 68640).
83 R.A. Ford, M. Gibson, H. Rawji, L. Hughes, R. Monserret, and A.P. Ollapally, Nucleosides Nucleotides, 1984, 3, 313.
84 J.A. Maurins, R.A. Paegle, A.A. Zidermane, M.J. Lidaks, E.I. Kvasyuk, and I.A. Mikhailopulo, Nucleosides Nucleotides, 1984, 3, 147.
85 L.N. Kulinkovich, and V.A. Timoshchuk, Khim. Prir. Soedin., 1983, 617 (Chem. Abstr., 1984, 100, 156 915).
86 L.N. Kulinkovich, and V.A. Timoshchuk, Zh. Obhch. Khim., 1983, 53, 1652 (Chem. Abstr., 1984, 100, 7021).
87 C.K. Chu, F.M. El-Kabbani, and B.B. Thompson, Nucleosides Nucleotides, 1984, 3, 1.
88 G. Handa, J. Singh, L.N. Nandi, and C.K. Atal, Phytochemistry, 1984, 23, 1779.
89 M. Ohno, Y. Ito, M. Arita, T. Shibata, K. Adachi, and H. Sawai, Tetrahedron, 1984, 40, 145.
90 K.W. Pankiewicz, K. Hirota, A. Matsuda, and K.A. Watanabe, Carbohydr. Res., 1984, 127, 227.
91 K.W. Pankiewicz, A. Matsuda, K.A. Watanabe, and J.J. Fox, Tetrahedron, 1984, 40, 33.
92 D.K. Buffel, B.P. Simons, J.A. Deceuninck, and G.J. Hoornaert, J. Org. Chem., 1984, 49, 2165.
93 D.T. Mao and V.E. Marquez, Tetrahedron Lett., 1984, 25, 2111.
94 C. Jiang, R.H. Baur, J.J. Dechter, and D.C. Baker, Nucleosides Nucleotides, 1984, 3, 123.
95 R.H. Baur and D.C. Baker, Nucleosides Nucleotides, 1984, 3, 77.
96 L. Huybrechts, D. Buffer, E. Freyne, and G. Hoornaert, Tetrahedron, 1984, 40, 2479.
97 I.F. Szabo, L. Somsak, and I. Farkas, Acta Chim. Hung., 1984, 115, 319.
98 J.G. Buchanan, N.K. Saxena, and R.H. Wightman, J. Chem. Soc. Perkin Trans. I, 1984, 2367.
99 E.M. Acton and K.J. Ryan, J. Org. Chem., 1984, 49, 528.
100 S.N. Bose, S. Kumar, R.J. H. Davies, S.K. Sethi, and J.A. McCloskey, J. Chem. Soc. Perkin Trans. I, 1984, 2421.
101 L.J.S. Knutsen, B.D. Judkins, W.L. Mitchell, R.F. Newton, and D.I.C. Scopes, J. Chem. Soc. Perkin Trans. I, 1984,

102 C.K. Chu, Heterocycles, 1984, 22, 345.
103 C.K. Chu, J. Heterocycl. Chem., 1984, 21, 389.
104 I. Maeba, F. Usami, and H. Furukawa, J. Org. Chem., 1984, 49, 1534.
105 M.A.E. Sallam and S.M.E. Abdel Mejid, Carbohydr. Res., 1984, 125, 85.
106 M.A.E. Sallam, Carbohydr. Res., 1984, 129, 33.
107 H. Ohno, T. Itoh, A. Nomura, and Y. Mizuno, Nucleosides Nucleotides, 1984, 3, 345.
108 Y.F. Shealy, J.D. Clayton, G. Arnett, and W.M. Shannon, J. Med. Chem., 1984, 27, 670.
109 Y.F. Shealy, C.A. O'Dell, W.M. Shannon, and G. Arnett, J. Med. Chem., 1984, 27, 1416.
110 R. Vince, J. Brownell, and S. Daluge, J. Med. Chem., 1984, 27, 1358.
111 R.A. Cadenas, J. Mosettig, and M.E. Gelpi, Carbohydr. Res., 1984, 133, 33.
112 Z.J. Lesnikowski, Wiad. Chem., 1983, 37, 91 (Chem. Abstr., 1984, 100, 51897).
113 G.M. Visser, J. van Westrenen, C.A.A. van Boeckel, and J.H. van Boom, J.R. Neth. Chem. Soc., 1984, 103, 141 (Chem. Abstr., 1984, 101, 111 329).
114 S.L. Beaucage, Tetrahedron Lett., 1984, 25, 375.
115 T. Shimidzu, K. Yamana, S. Maikuma, and Y. Oikawa, Nucleic Acids Symp. Ser., 1983, 12, 55 (Chem. Abstr., 1984, 100, 210 341).
116 S. Ueda and H. Takaku, Chem. Pharm. Bull., 1984, 32, 1650.
117 R. Charubala, E. Uhlmann, A.H. Beiter, and W. Pfleiderer, Synthesis, 1984, 965.
118 F. Himmelsbach, B.S. Schultz, T. Trichtinger, R. Charubala, and W. Pfleiderer, Tetrahedron, 1984, 40, 59.
119 M. Nishizawa, T. Kurihara, and T. Hata, Chem. Lett., 1984, 175.
120 R.W. Humble, G. Mackenzie, and G. Shaw, Nucleosides Nucleotides, 1984, 3, 363.
121 J. Jankowska and J. Stawiński, Synthesis, 1984, 408.
122 W.G. Bentrude and J. Tomasz, Synthesis, 1984, 27.
123 Z.J. Lesnikowski, W. Niewiarowski, W.S. Zieliński, and W. J. Stec, Tetrahedron, 1984, 40, 15.
124 B.V.L. Potter, F. Eckstein, and B. Uznanski, Nucleic Acids Res., 1983, 11, 7078 (Chem. Abstr., 1984, 100, 103 798).
125 A. Jager and J. Engels, Tetrahedron Lett., 1984, 25, 1437.
126 H.P. Albrecht, G.H. Jones, and J.G. Moffatt, Tetrahedron, 1984, 40, 79.
127 M. Morr, L.Ernst, and L. Grotjahn, Z. Naturforsch., B: Anorg. Chem., Org. Chem., 1983, 38B, 1665 (Chem. Abstr., 1984, 100, 192 204).
128 N.B. Tarusova, V.V. Shumyantsova, A.C. Krylov, M. Ya. Karpeiskii, and R.M. Khomutov, Bioorg. Khim., 1983, 9, 858 (Chem. Abstr., 1984, 100, 7026)
129 R. Lagunas, D. Pestana, and J.C. Diez-Masa, Biochemistry, 1984, 23, 955 (Chem. Abstr., 1984, 100, 86048).
130 K. Furusawa, T. Sakai, K. Tsuda, and Y. Shimura, Nucleic Acids Symp. Ser., 1983, 12, 21 (Chem. Abstr., 1984, 100, 210 326).
131 E. Albano-Garcia, and L.U. Colmenares, Nat. Appl. Sci. Bull., 1982, 34, 211 (Chem. Abstr., 1984, 100, 139 541).
132 H. Rosemeyer and F. Seela, Angew. Chem. Int. Ed. Engl., 1984, 23, 385.
133 P.P. Purygin and Z.P. Laletina, Izv. Akad. Nauk SSSR, Ser. Khim., 1983, 2621 (Chem. Abstr., 1984, 100, 139 576).
134 K. Keppeler, G. Keifer, and E. DeClercq, Arch. Pharm. (Weinheim, Ger), 1984, 317, 867 (Chem. Abstr., 1984, 101, 230 932).
135 G.K. Chu, Nucleosides Nucleotides, 1983, 2, 453.
136 J.A. Montgomery, H.J. Thomas, R.W. Brockman, and R.D. Elliott, J. Med. Chem., 1984, 27, 680.
137 J. Žemlička, Tetrahedron Lett., 1984, 25, 5619.
138 M. Melgarejo Sampedro and R. Robles Diaz, An. Quim., Ser. C, 1983, 79, 81 (Chem. Abstr., 1984, 100, 7042).
139 Y. Mizuno, K. Tsuchida, and H. Tampo, Chem. Pharm. Bull., 1984, 32, 2915.
140 J. Hollmann and E. Schlimme, Justus Liebigs Ann. Chem., 1984, 98.
141 R. Cosstick, A.S. Jones, and R.T. Walker, Tetrahedron, 1984, 40, 427.
142 L.M. Lerner, Carbohydr. Res., 1984, 127, 141.

143 T. Itaya, and T. Harada, J. Chem. Soc., Chem. Commun., 1984, 858.
144 V.K. Kansal, S. Funakoshi, P. Mangeney, P. Potier, B. Gillet, E. Guittet, and J.Y. Lallemand, Tetrahedron Lett., 1984, 25, 2351.
145 J.J. Prior, and D.V. Santi, J. Biol. Chem., 1984, 259, 2429 (Chem Abstr., 1984, 100, 134 479).
146 H. Lönnberg and E. Heikkinen, Acta Chem. Scand., Ser. B, 1984, 38, 673.
147 J. Cadet, L. Voituriez, M. Berger, L.S. Myers, Z. Naturforsch., B: Anorg. Chem., Org. Chem., 1983, 38B, 1643 (Chem. Abstr., 1984, 100, 192 203).
148 M. Mathlouthi, A.-M. Seuvre, and J.L. Koenig, Carbohydr. Res., 1984, 131, 1.
149 M. Mathlouthi, A.-M. Seuvre, and J.L. Koenig, Carbohydr. Res., 1984, 134, 23.
150 M.A. Viswamitra and N. Gautham, Proc.-Indian Acad. Sci., Chem. Sci., 1984, 93, 261 (Chem. Abstr., 1984, 101, 211 625).
151 D.B. Davies, M. MacCoss, and S.S. Danyluk, J. Chem. Soc., Chem. Commun., 1984, 536.
152 J. Uzawa and K. Anzai, Can. J. Chem., 1984, 62, 1555.
153 A. Joecks, H. Koeppel, K.D. Schleinitz, and D. Cech, J. Prakt. Chem., 1983, 325, 881 (Chem. Abstr., 1984, 100, 210 313).
154 M. Blandin and K. Jankowski, Rev. Latinoam. Quim., 1983, 14, 45 (Chem. Abstr., 1984, 100, 68641).
155 J. Doornbos, R. Charubala, W. Pfleiderer, and C. Antonis, Nucleic Acids Res., 1983, 11, 4569 (Chem. Abstr., 1984, 100, 7028).
156 J. Doornbos, J.L. Barascut, H. Lazrek, J.L. Imbach, J. van Westrenen, G.M. Wisser, J.H. van Boom, and C. Altona, Nucleic Acids Res., 1983, 11, 4583 (Chem. Abstr., 1984, 100, 7029).
157 J. Eagles, C. Javanaud, and R. Self, Biomed. Mass Spectrom., 1984, 11, 41 (Chem. Abstr., 1984, 101, 7579).
158 R.G. Teece, D. Slowikowski, and K.H. Schram, Biomed. Mass Spectrom., 1983, 10, 30 (Chem. Abstr., 1984, 100, 86040).

21
N.M.R. Spectroscopy and Conformational Features

1 Theoretical and General Considerations

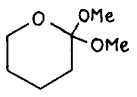
An attempt to derive the potential function for evaluation of the energy associated with the exo-anomeric effect has been made using differences in conformational energy for rotation about the carbon-carbon bond of 2-ethyltetrahydrofuran and rotation about the carbon-oxygen bond of 2-methoxytetrahydrofuran. The conformational energies were calculated using the PCILO method on the optimized conformer geometries.[1] The influence of the orientations of the 2- and 3-hydroxy groups on the puckering of the ring in (2S,3R)-tetrahydrofuran-2,3-diol and (3R)-tetrahydrofuran-3-ol has been calculated using SCF methods. In the E or W regions of the pseudorotation cycle there are no local energy minima. The local minima in the N and S regions are affected by different orientations of the hydroxy groups with energy differences of up to 12.2 kJ mol^{-1} for the diol and 6.9 kJ mol^{-1} for the monosubstituted compound. If statistical weightings of the possible rotomers are used to calculate N-S equilibrium constants, both states are equally populated; however, if the orientations of the hydroxy groups are restricted to those found in these molecular fragments in DNA double helices, the equilibrium shifts towards N. The results indicate that, in the vapour state, a unique one-dimensional N-S energy barrier does not exist but that there is a spectrum of barriers depending on the rotameric state of the hydroxy groups.[2] Monte Carlo calculations applied to deduce the preferred conformations of 1,2-diacetamido-1,2-dideoxy-β-D-glucopyranose and methyl 2-acetamido-2-deoxy-α-D-galactopyranoside have shown that restricted sets of angular variables could provide the energetically favoured conformations. Comparison with the known shapes was used to test the torsional potential functions.[3] Molecular mechanics calculations using the improved Allinger programme, MM2, have been applied to D-glucal and its triacetate: good approximations to the ring geometry were obtained, while rotamers about C-5 and C-6 were predicted to be g^+ for the D-glucal and gg or g^+ for the acetate.[4]

The Barfield modification of INDO SCF molecular orbital calcul-

ations has been used to examine the through-space effects in n.m.r. spectroscopy, and for studying the effect of phase angle pseudorotation on n.m.r. parameters; some THF ring structures were included as models for nucleosides.[5]

Coupling constants for vicinal protons in n.m.r. spectroscopy have been the subjects of a theoretical and computational study. Electronegativity as a source of additive correction for $J_{1'-2'}$ and $J_{2'-3'}$ was examined in two families of nucleoside. Variations in these coupling constants, and also $J_{3'-4'}$, were explained by conformational changes only, while $J_{1'-2'}$ and $J_{3'-4'}$ also varied with conformer population changes induced by the 2'-substituents and changes in the base; the population changes were quantifiable with respect to substituents at C-1' and C-2', which enabled the development of a computer programme (called SEARCH) optimizing phase angle of pseudorotation and the degree of pucker for a set of sugar ring coupling constants.[6] Theoretical conformational analysis has also been carried out on methyl β-cellobioside and methyl β-maltoside. The average values of ^{3}J for C-1 - H-4 and C-4' - H-1 and angle of rotation about the interglycosidic linkage were calculated and shown to fit the experimentally determined values. The exo-anomeric effect and intramolecular hydrogen bonding were considered unimportant.[7] The multiplicity of ^{13}C signals in n.m.r. spectroscopy observed in DMSO caused by partial deuteration of substituent hydroxy groups has been used to develop a new method for structural analysis in solution. The presence of a deuteroxy group causes an upfield shift of 0.09 - 0.12 p.p.m. for directly bonded hydroxy groups ($\Delta\beta$) and 0.07 p.p.m. for those in a vicinal relationship ($\Delta\gamma$). In partially deuterated vicinal diols, each carbon appears as a quartet arising from the HH, HD, DH, and DD species, and thus the central carbon atom of a contiguous triol displays eight components. The $\Delta\gamma$ effects in vicinal diols have been correlated with their cis or trans relationships, the former being about 0.02 p.p.m. and the latter between 0.04 and 0.05 p.p.m. in furanoid and pyranoid systems.[8] A detailed application of the method to the furanose and pyranose forms of aldo-pentoses and -hexoses and ketohexoses has shown its value as a structural method.[9] Assignment of ^{1}H and ^{13}C n.m.r. spectra by combination of homo- and hetero-nuclear shift-correlated two dimensional n.m.r. spectroscopy has been reported: the technique was applied to oligosaccharides related to arabino-xylan. The shifts found with mono- and disaccharides can be correlated with di- and trisaccharides from arabino-xylan, and allow precise assignments of

^{13}C chemical shifts.[10] On the basis of variable-temperature ^{1}H n.m.r. of the methoxy groups in 1,1-dimethoxyoxane (1) relative to that of other six-membered ring analogues, it has been claimed that the anomeric effect appears to slightly lower the barrier to conformational change rather than raise it, as has been suggested earlier (Deslongchamps *et al.*, *Can. J. Chem.*, 1975, *53*, 3029).[11] Application of continuous wave techniques and line shape analysis to wide-line n.m.r. spectra of D-xylose, D-mannose, D-glucose, D-fructose, and D-sorbose suggests that the lattice is effectively rigid in all except possibly D-fructose.[12] Previously published ^{13}C n.m.r. data for arabinosides and ribosides have been tabulated with correlation diagrams constructed in such a way that the data on new compounds can be used to assign the anomeric configurations and ring size.[13] Measurements of self-diffusion coefficients of carbo-



(1)

hydrates in solution have been obtained using an unmodified high-resolution n.m.r. spectrometer. The reordering was observed by turning off the field then reapplying it.[14] The cross-polarization magic-angle spinning ^{13}C n.m.r. (CPMAS) solid-state spectra of crystalline α-D-glucose hydrate, α-D-glucose, and β-D-glucose have been fully assigned with the aid of ^{13}C-labelled samples.[15] Changes in the relative positions of resonance lines on going from solid to solution have been demonstrated, and an erroneous earlier assignment (F.Horii, A.Hirai, and R.Kamura, *Polymer Bull.*, 1982, *8*, 63) of the solid-state spectrum of β-D-glucose corrected.

2 Acyclic Systems

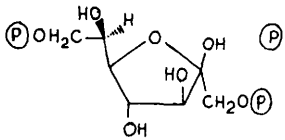
The structure of the tri-*O*-isopropylidene-D-glucitol has been re-investigated by means of a Bruker AG interactive n.m.r. programme called PANIC applied to the 250 MHz spectrum: it was shown that it is 1,3:2,4:5,6-tri-*O*-isopropylidene-D-glucitol and not the 1,2:3,5:4,6-isomer as earlier claimed.[16] The 400 MHz ^{1}H n.m.r. of tetritols, pentitols, and hexitols have been reported.[17] The predominant conformation of heptitols in aqueous solution has been determined by complete assignment of their ^{13}C n.m.r. spectra, using specifically deuterated compounds, and the results were found to be in good agree-

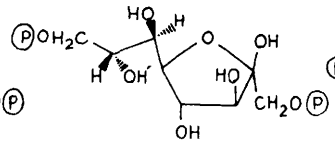
ment with those predicted by J.A.Mills in 1974.[18] Rotameric states in the acyclic forms of ketohexoses and deoxyketohexoses determined by c.d. are referred to in Chapter 22.

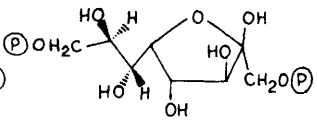
3 Furanose Systems

A series of benzoylated pentofuranosyl cyanides have been studied by ^{1}H n.m.r. and the preferred ring conformations and the conformer populations about C-5 - C-4 were determined.[19] Proton coupled ^{13}C n.m.r. spectra at 20 MHz and 80 MHz of D-arabino-1,4-lactone in deuterium oxide have been measured and by means of computer simulation the ^{2}J and ^{3}J values were derived.[20] The position of deuterium labels in organic molecules can be determined by a two-dimensional proton - deuterium spectroscopy experiment ($^{1}H/^{2}H$ COSY) in which the deuterium resonance can be correlated with the adjacent protons to which it is coupled. This was demonstrated for [4-^{2}H]-1,2:5,6-di-O-isopropylidene-D-allofuranose.[21] An analysis of X-ray-determined structures of five isomeric methyl 3,6-anhydro-hexofuranosides having the α- and β-D-gluco, α-L-ido, α- and β-D-manno configurations showed that the anomeric effect determines the conformation of the furanoid ring, which results in the quasi-axial orientation of the aglycone in all cases. Thus methyl 3,6-anhydro-α-L-idofuranoside adopts an almost ideal $^{E}_{2}$ conformation, whereas the β-D-gluco and β-D-manno isomers, having the same (R) configuration at the anomeric centre, have conformations intermediate between $^{E}_{2}$ and $^{1}_{2}T$. The related ^{2}E and $^{2}_{1}T$ conformations were found in the α-D-mannofuranoside which possesses (S) configuration at the anomeric centre, while the methyl 3,6-anhydro-α-D-glucofuranoside adopted a slightly distorted $^{O}_{1}T$ conformation. Except for the α-D-mannofuranoside in which the anhydro ring was C-6 exo, the C-6 endo conformation was found in all cases. A detailed comparison with the ^{1}H n.m.r. was made to ascertain the persistence of the solid-state conformation in solution.[22] The major contributing forms of D-altro-heptulose 1,7-diphosphate (2), D-glycero-D-altro-octulose 1,8-diphosphate (3), and D-glycero-D-ido-octulose 1,8-diphosphate, all intermediates in the recently discovered L-pentose phosphate pathway, have been determined by ^{13}C n.m.r. spectroscopy. The diphosphate (2) was found to consist of 74% β-furanose, 13% α-furanose, and 13% α-pyranose, the diphosphate (3) 74% β-furanose, 19% α-furanose, and 7% α-pyranose, and the diphosphate (4) 67% β-furanose, 14% α-furanose, and 19% α-pyranose.[23] The relationship

between $^{1}J_{(C1',H1')}$ and the glycosidic bond conformation of a series


(2)

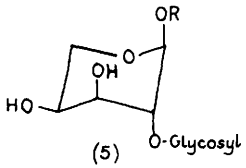

(3)


(4)

of pyrimidine cyclonucleosides has been established.[24] Complete assignment of the ^{1}H n.m.r. spectrum at 500 MHz and 300 MHz of the (2'→5')-linked trinucleoside diphosphate derived from 3'-deoxyadenosine has been achieved.[25]

4 Pyranose Systems

The effect of long-range virtual coupling on the appearance of the signal for the anomeric proton of pyranose rings has been investigated using simulated spectra. When the chemical shifts of H-2 and H-3 were closer than 0.05 p.p.m. severe distortion was observed in ABCD and ABCDE spin spectra.[26] It has been shown by 200 MHz ^{1}H n.m.r. spectroscopy that α-D-xylopyranosyl pyridinium bromide adopts the $^{1}\underline{C}_{4}$ conformation and α-D-glucopyranosyl pyridinium bromide the $^{1}\underline{S}_{3}$ form.[27] A series of synthetic 2-O-glycosylated α-L-arabinopyranosides has been investigated by n.m.r. spectroscopy. In certain cases unexpected shifts of C-3, C-4, and C-5 were observed in the ^{13}C n.m.r. spectra, together with the expected displacements of C-1 and C-2 resonances. These results, in combination with coupling constant data, were taken to indicate an increase in the contribution from the $^{1}\underline{C}_{4}$ conformer (5). The β-anomer did not show this effect on C-2 glycosylation.[28]

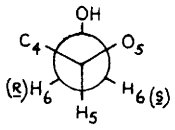

(5)

In the light of revised values for the conformational free energy of methyl and hydroxymethyl substituents at position 2 in tetrahydropyran (now believed to be 12.1 kJ mol^{-1} rather than the 7.5 kJ mol^{-1} reported by E.L.Eliel (J. Am. Chem. Soc., 1982, 104, 3635)), the conformations of ido- and altro-pyranose derivatives have been re-examined; it was shown that $^{4}\underline{C}_{1}$(D) conformations make a greater contrib-

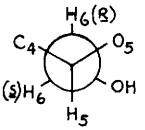
ution than predicted previously, and mixing with the $\underline{S}_2$ skew rather than the alternative chair conformation explains instances of poor agreement between vicinal H-H coupling constants and expected dihedral angles in the $^4\underline{C}_1$ (D) conformation.[29]

The ^{13}C n.m.r. spectra of several glucosides and acetylated glucosides of allylic and benzylic alcohols have been compared with the spectra of the corresponding methyl glucoside and of the parent alcohols. A correlation appears to exist between the shifts observed for chiral alcohols on glycosidation and the absolute configuration of their hydroxy groups.[30]

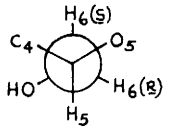
The n.m.r. spectra of sugars of the galactopyranose series have been the subject of a review in Japanese.[31] A study by ^{13}C n.m.r. spectroscopy of some aryl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranosides has been reported.[32] Conformational analysis of the C-6 group in 6-mono-deuterio derivatives of methyl α-D-glucopyranoside, methyl α-D-galactopyranoside, and their acetyl and benzoyl esters has been carried out using ^1H n.m.r. data. It was deduced that for the gluco series conformer (6) made the greatest contribution, followed by conformer (7), with only small amounts of conformer (8) present, whereas in the galacto series conformers (7) and (8) were present in equal amounts, with less of conformer (6). In all cases the proportions were solvent and substituent dependent.[33] Acetylation of



(6)



(7)

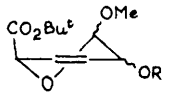


(8)

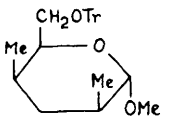
both O-4 and O-6 of methyl α- and β-D-glucopyranoside causes a reversal in the order of the chemical shifts of the 6 and 6' protons and may be used to detect when these positions are free; e.g., the point of linkage may be determined in disaccharides. Analogous effects are found in mannosides but not in galactosides.[34] The conformations adopted by cyclohexyl and (+)- and (-)-menthyl 6-O-trityl-D-glucopyranosides and their peracetylated derivatives have been examined by ^1H and ^{13}C n.m.r. spectroscopy.[35] Lanthanide shift and relaxation studies have been carried out on methyl 4,6-O-benzylidene-2,3-di-O-methyl-α-D-glucopyranoside using $Eu(fod)_3$, $Pr(fod)_3$, and $Yb(fod)_3$ for the former and $Gd(fod)_3$ for the latter: the coordination geometry was inferred. A variable-temperature experiment showed that $Yb(fod)_3$ was not undergoing fast

exchange at room temperature.[36] ^{13}C N.m.r. studies of the hydrolyzable tannins have led to the formulation of additive parameters for galloylation, hexahydroxydiphenoylation, and dehydrohexahydroxydiphenoylation shifts which enable the positions of the acyl groups on the D-glucopyranose ring to be determined.[37,38]

The conformational equilibria of methyl D-glucuronal, methyl D-galacturonal, methyl L-guluronal, and methyl L-alluronal and a number of related glycals have been compared by means of ^{1}H n.m.r. spectroscopy.[39] An n.m.r. study of t-butyl(methyl 3,4-dideoxy-DL-hex-3-enopyranoside)uronates and their 2-O-acetyl derivatives has shown that the unusual half-chair forms $^{O}H_{1}$ and $^{1}H_{O}$ are in equilibrium with substantial participation by those having pseudo-axial t-butoxycarbonyl groups (9). The dependence of the equilibriu on solvent polarity suggests that the so called "allylic effect" of the ester group is polar in nature and caused by a double bond - nc bond resonance (see Saunders et al., Can. J. Chem., 1977, 55, 1015) rather than by steric hindrance between the pseudo-equatorial groups and the hydrogen of the alkene.[40] The solution and CPMAS



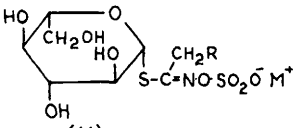
(9) R=H,Ac



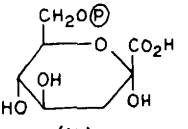
(10)

solid-state ^{13}C n.m.r. spectra of ethyl 2,3-dideoxy-α-D-erythro-hex-2-enopyranoside have been determined and compared with the X-ray crystal structure, which revealed that there were two symmetry-independent molecules present in the solid.[41] Methyl 2,3,4-trideoxy-2,4-di-C-methyl-6-O-trityl-α-D-lyxo-hexopyranoside (10) has the $^{4}C_{1}$ conformation in the solid state as determined by X-ray crystallography, but n.m.r. measurements suggest that the $^{1}C_{4}$ conformation is present in chloroform solution.[42]

A large range of glucosinolates of general formula (11) have been studied by ^{13}C n.m.r., for which complete assignments were achieved, and by ^{1}H n.m.r., for which partial assignments were



(11)



(12)

made.[43] A detailed structural analysis of 3-deoxy-D-*arabino*-heptulosonate 7-phosphate (12) has been carried out by means of ^{1}H and ^{13}C n.m.r. spectroscopy.[44]

5 Oligosaccharides

The ^{13}C n.m.r. data of oligosaccharides has been tabulated.[45]

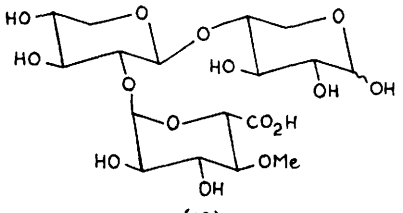
Regularities in the variation of chemical shifts and the glycosidation effects in the ^{13}C n.m.r. spectra of disaccharides have been found to depend on the configuration at the anomeric centre of the glycosidating pyranose and on the absolute configuration of both pyranose moieties. These empirical regularities are explained in terms of the spatial proton-proton interactions within the statistically averaged, or preferred, conformation near the glycosidic linkage. The applicability of these effects for the determination of the anomeric and absolute configuration and the sequence of pyranose residues in oligo- and poly-saccharides is discussed and the conformational properties of glycosidic linkages in disaccharides and disaccharide fragments of oligo- and polysaccharides compared on the basis of ^{13}C n.m.r. data.[46] A review of the conformational states of cellobiose, lactose, and maltose in solution includes a comparison of experimental and theoretical data.[47]

By means of 2D n.m.r. techniques, the ^{1}H, ^{13}C chemical shifts and ^{1}H-^{19}F *J* values of a series of fluorinated oligosaccharides have been determined. Selective spin flip pulse techniques were used to achieve homonuclear decoupling in the ^{1}H dimension as well as improved resolution and signal-to-noise ratios.[48]

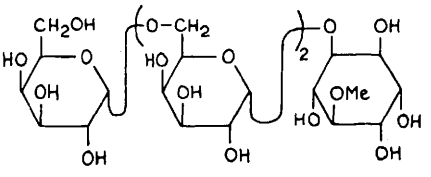
The assignment of acetyl resonances in ^{1}H n.m.r. spectra of 3-*O*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-D-xylopyranose has been achieved by means of acetylation with [$^{2}H_{3}$]acetic acid in the reducing residue. Differentiation of acetyl resonances in the reducing and non-reducing groups was thus permitted.[49] Methyl α- and β-D-glucopyranoside, methyl β-D-cellobioside, and methyl β-D-maltoside in DMSO have been examined (as models for cellulose and anylose) by normal and 2D ^{1}H n.m.r. spectroscopy. The 2D technique allows complete signal assignment of the hydroxy protons, in turn allowing assessment of the hydroxy group conformation from *J* values. H-Bonding was also observed through temperature dependence and dipolar phenomena.[50] Non-selective mono- and bi-selective spin-lattice relaxation rates, n.O.e. enhancements and ^{13}C-^{1}H *J* values have been assessed as a means of determining such stereochemical features

as the conformation about the glucosidic bond of 2,3,4,6,2',3'-hexa-O-acetyl-4-O-β-D-glucopyranosyl-1',6'-anhydro-β-D-glucopyranose. Methods were determined for the calculation of interproton distances which agree with results from X-ray crystallography.[51] The ^{13}C-chemical shifts of the non-reducing units and of the substituted units of several α-linked D-mannosyl-D-mannoses have been found to depend upon the position of linkage. A method for calculating shifts in any α-D-mannopyranosyl oligosaccharide is presented. Superconducting n.m.r. spectrometers were shown to give enough resolution to afford means of analyzing large oligosaccharides.[52]

A thorough literature survey of the ^{13}C n.m.r. data for aqueous solutions of mono-, di-, and oligosaccharides and their methyl derivatives has appeared. Analysis of the data gives a set of empirical rules for use in the structure determination of trisaccharides of known sugar composition.[53] The structures of 2'-fucosyllactose from echidna milk and of 3,2'-difucosyllactose from platypus milk have been determined by ^{13}C n.m.r. spectroscopy.[54] 2D-N.m.r. spectroscopy of an acidic trisaccharide obtained from birchwood using COSY homonuclear and heteronuclear shift-correlated techniques has shown the main component to be the aldotriuronic acid (13).[55]



(13)

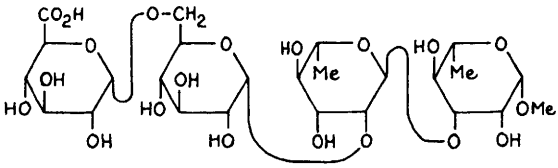


(14)

The trigalactosyl-pinetol (14), isolated from chick pea, has been characterized by ^{13}C n.m.r. spectroscopy.[56] A ^{13}C n.m.r. study of sialyl-oligosaccharides has shown that the exact conformation of the sialic acid residue depends upon the type of anomeric linkage to the β-D-galactose component, i.e., whether it is α-(2→3) or α-(2→6).[57]

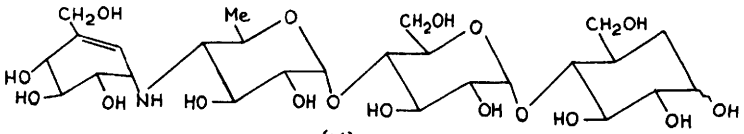
^{13}C-Spin-lattice relaxation rates have been determined for ganglioside micelles containing oligosaccharide units.[58] The ^{1}H and ^{13}C n.m.r. spectra of β-D-Gal(1→4)-β-D-GlcO$(CH_2)_8CO_2H$, β-D-GalNAc(1→4)-β-D-GalO$(CH_2)_8CO_2H$, and β-D-Gal(1→3)-β-D-GalNAcO$(CH_2)_8CO_2H$ have been used as a basis for signal assignments in the spectra of β-D-GalNAc(1→4)-β-D-Gal(1→4)-β-D-GlcO$(CH_2)_8CO_2H$ and β-D-Gal(1→3)-β-D-GalNAc(1→4)-β-D-Gal(1→4)-GlcO$(CH_2)_8$-

CO_2H, which are asialo-G_{M2} and asialo-G_{M1} related synthetic haptens. Conformations of all compounds were determined by ^1H n.O.e. methods and were found to be those predicted by HSEA calculations; these geometric features were discussed in relation to the biological properties of the gangliosides.[59] Transient n.O.e. in the rotating frame has been used to characterize the tetrasaccharide (15).[60]



(15)

^{13}C-N.m.r. lines have been assigned to the terminal, central and directly attached monosaccharide residues in a triterpenoid saponin with a trisaccharide moiety, on the basis of decreasing spin-lattice relaxation times, the so-called "partially relaxed Fourier transform" method.[61] The solution conformation of acarbose (16) has been determined by ^1H and n.O.e. n.m.r. techniques and compared with that predicted by hard-sphere exo-anomeric effect calculations.[62]

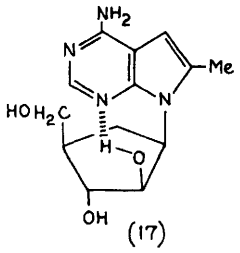


(16)

6 Nucleosides

The ^{13}C n.m.r. spectra of rigid cyclonucleosides of adenosine have been analyzed to obtain $^3J_{C1H}$ values which may be correlated with the presence of oxygen atoms at the carbon atoms involved.[63] The protonation of adenosine in strong acid has been studied by ^{13}C n.m.r. spectroscopy.[64] Complete assignment of the 500 MHz and 300 MHz ^1H n.m.r. spectra of various oligoarabinonucleotides has been achieved and their conformations thus determined.[65] The conformations adopted by some carbocyclic nucleoside analogues of tubercidin in DMSO-d_6 have been analyzed by ^1H n.m.r. spectroscopy, and syn-conformations were found to be preferred when an intramolecular bond

between the base and a C-2' or C-3' hydroxy group could form, e.g., as shown in formula (17).[66]



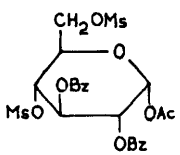
(17)

7 Other Molecules

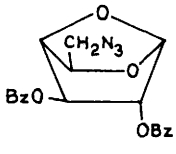
The conformations of the digitoxoside moiety and its 3,4-O-isopropylidenated analogue have been compared in eight cardiac digitoxosides (which were synthesized by modifications to the aglycone), using ^{1}H n.m.r. and X-ray data.[67] Seven glycopeptides of the series (α-Man)$_n$-Man-β-(1→4)-GlcNAc-β-(1→4)-GlcNAc-β-1-Asn, where n = 0,2,3, 4,5 and 6, have been examined by ^{13}C n.m.r. at 67.9 MHz. All compounds gave resolved spectra and nearly all lines were assigned by the combined application of deuterium exchange, pH studies, relaxation studies, carbon-hydrogen coupling constants, and comparison with known structures.[68]

8 N.m.r. of Nuclei Other Than ^{1}H or ^{13}C

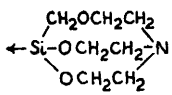
By labelling the dimesylate (18) at the anomeric centre with oxygen-1' the pathway leading to the 1,4-anhydro-derivative (19) on treatment with azide ion was investigated using ^{17}O n.m.r. spectroscopy. Chemical shifts induced in ^{13}C n.m.r. spectra by the introduction of oxygen-18 at C-1 were also used.[69]



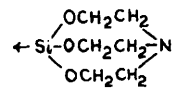
(18)



(19)



(20)



(21)

Data from ^{29}Si and ^{13}C n.m.r. spectra of several 2-carba-3-oxa-homosilatranyl (20) and silatranyl (21) derivatives of monosaccharide and other alcohols have been reported. The results showed no advantages over standard TMS derivatives.[70]

References

1 I.Tvaroska, Carbohydr. Res., 1984, 125, 155.
2 B.Lesyng and W.Saenger, Carbohydr. Res., 1984, 133, 187.
3 A.J.Duben and C.A.Bush, Proc. S. D. Acad. Sci., 1982, 61, 64 (Chem. Abstr., 1984, 100, 103 781).
4 W.Korytnyk and O.Dodson-Simmons, Carbohydr. Res., 1984, 131, 157.
5 F.A.A.De Leeuw, A.A.van Beuzekom, and C.Altona, J. Comput. Chem., 1983, 4, 438 (Chem. Abstr., 1984, 100, 22 268).
6 J.B.Chiasson, K.Jankowski, and W.Brostow, J. Bioelectr., 1983, 2, 93 (Chem. Abstr., 1984, 101, 152 241).
7 G.M.Lipkind, V.E.Verovsky, and N.K.Kochetkov, Carbohydr. Res., 1984, 133, 1.
8 J.Reuben, J. Am. Chem. Soc., 1984, 106, 2461.
9 J.Reuben, J. Am. Chem. Soc., 1984, 106, 6180.
10 J.Schraml, J.Hirsch, E.Petrakova, E.Krahe, and C.Bliefert, Collect. Czech. Chem. Commun., 1984, 49, 1605.
11 C.L.Perrin and O.Nunez, J. Chem. Soc., Chem. Commun., 1984, 333.
12 N.R.Jagannathan and R.Srinivasan, Indian J. Biochem. Biophys.,1984, 21, 142 (Chem. Abstr., 1984, 101, 111 288).
13 R.C.Beier and B.P.Mundy, J. Carbohydr. Chem., 1984, 3, 253.
14 L.D.Hall and S.D.Luck, Carbohydr. Res., 1984, 134, C1.
15 P.E.Pfeffer, K.B.Hicks, M.H.Frey, S.J.Opella, and W.L.Earl, J. Carbohydr. Chem., 1984, 3, 197.
16 P.Sohar and J.Kuszmann, Org. Magn. Reson., 1983, 21, 694 (Chem. Abstr., 1984, 100, 103 778).
17 G.E.Hawkes and D.Lewis, J. Chem. Soc., Perkin Trans. 1, 1984, 2073.
18 S.J.Angyal and R.Le Fur, Carbohydr. Res., 1984, 126, 15.
19 J.Zajicek, M.Budesinsky, and J.Farkas, Collect. Czech. Chem. Commun., 1984, 49, 235.
20 H.Wong, Aust. J. Chem., 1984, 37, 327.
21 S.J.Gould, V.Z.Palaniswamy, H.Bleich, and J.Wilde, J. Chem. Soc., Chem. Commun., 1984, 1075.
22 J.Kopf and P.Koll, Carbohydr. Res., 1984, 135, 29.
23 F.P.Francke, M.Kapuscinski, J.K.Macleod, and J.F.Williams, Carbohydr. Res., 1984, 125, 177.
24 D.B.Davies, M.MacCoss, and S.S.Danyluk, J. Chem. Soc., Chem. Commun., 1984, 536.
25 J.Doornbos, R.Charubala, W.Pfleiderer, and C.Antonis, Nucleic Acids Res., 1983, 11, 4569 (Chem. Abstr., 1984, 100, 7028).
26 J.Dahmen, T.Frejd, G.Gronberg, G.Magnusson, and G.Noori, Carbohydr. Res., 1984, 125, 161.
27 L.Hosie, P.J.Marshall, and M.L.Sinnott, J. Chem. Soc., Perkin Trans. 1, 1984, 1121.
28 K.Mizutani, A.Hayashi, R.Kasai, O.Tanaka, N.Yoshida, and T.Nakajima, Carbohydr. Res., 1984, 126, 177.
29 J.Auge and S.David, Tetrahedron, 1984, 40, 2101.
30 I.Horibe, S.Seo, Y.Yoshimura, and K.Tori, Org. Magn. Reson., 1984, 22, 428 (Chem. Abstr., 1984, 101, 230 876).
31 K.Izumi, Tanpakushitsu Kakusan Koso, 1984, 29, 282 (Chem. Abstr., 1984, 100, 192 157).
32 A.Talvitie, Finn. Chem. Lett., 1984, 22 (Chem. Abstr., 1984, 101, 73 021).
33 Y.Nishida, H.Ohrui, and H.Meguro, Tetrahedron Lett., 1984, 25, 1575.
34 V.S.Rao and A.S.Perlin, Can. J. Chem., 1983, 61, 2688.
35 T.Utamura and K.Koizumi, Yakugaku Zasshi, 1983, 103, 929 (Chem. Abstr., 1984, 100, 121 471).
36 P.McArdle, J.P.O'Reilly, E.Lee, and J.Simmie, Proc. R. Ir. Acad., Sect. B, 1983, 83, 115 (Chem. Abstr., 1984, 100, 6987).
37 T.Yoshida, T.Hatano, T.Okuda, M.U.Memon, T.Shingu, and K.Inoue, Chem. Pharm. Bull., 1984, 32, 1790.

38 Y.Toshida, T.Hatano, T.Okuda, M.U.Memon, T.Shingu, K.Inoue, and K. Fukushima, Tennen Yuki Kagobutsu Toronkai Koen Yoshishu, 1983, 158 (Chem. Abstr., 1984, 100, 175 141).
39 J.Thiem and P.Ossowski, J. Carbohydr. Chem., 1984, 3, 287.
40 J.Mieczkowski, A.Konowal, and A.Zamojski, Pol. J. Chem., 1983, 57, 75.
41 L.M.Wingert, J.R.Ruble, and G.A.Jeffrey, Carbohydr. Res., 1984, 128, 1.
42 M.Mori, T.Chuman, T.Fujimori, K.Kato, A.Ohkubo, and S.Toda, Carbohydr. Res., 1984, 127, 171.
43 I.J.Cox, A.B.Hanley, P.S.Belton, and G.R.Fenwick, Carbohydr. Res., 1984, 132, 323.
44 C.C.Garner and K.M.Herrman, Carbohydr. Res., 1984, 132, 317.
45 K.Bock, C.Pedersen, and H.Pedersen, Advan. Carbohydr. Chem. Biochem., 1984, 42, 193.
46 N.K.Kochetkov, O.S.Chizhov, and A.S.Shashkov, Carbohydr. Res., 1984, 133, 173.
47 G.M.Lipkind, V.G.Verovskii, and N.K.Kochetkov, Bioorg. Khim., 1983, 9, 1269 (Chem. Abstr., 1984, 100, 34 747).
48 T.C.Wong, V.Rutar, J.-S.Wang, M.Feather, and P.Kovac, J. Org. Chem., 1984, 49, 4358.
49 G.Excoffier, D.Gagnaire, and J.-P.Utille, Carbohydr. Res., 1984, 128, 217.
50 R.Nardin, J.Saint-Germain, M.Vincendon, F.Taravel, and M.Vignon, Nouv. J. Chim., 1984, 8, 305.
51 P.Dais, T.K.M.Shing, and A.S.Perlin, J. Am. Chem. Soc., 1984, 106, 3082.
52 A.Allerhand and E.Berman, J. Am. Chem. Soc., 1984, 106, 2400.
53 J.H.Bradbury and G.A.Jenkins, Carbohydr. Res., 1984, 126, 125.
54 G.A.Jenkins, J.H.Bradbury, M.Messer, and E.Trifonoff, Carbohydr. Res., 1984, 126, 157.
55 F.Cavagna, H.Deger, and J.Puls, Carbohydr. Res., 1984, 129, 1.
56 P.Nicolas, I.Gertsch, and C.Parisod, Carbohydr. Res., 1984, 131, 331.
57 E.Berman, Biochemistry, 1984, 23, 3754 (Chem. Abstr., 1984, 101, 55 471).
58 M.Nerz-Stormes and E.R.Thornton, J. Am. Chem. Soc., 1984, 106, 5240.
59 S.Sabesan, K.Bock, and R.U.Lemieux, Can. J. Chem., 1984, 62, 1034.
60 A.A.Bothner-By, R.L.Stephens, J.-M.Lee, C.D.Warren, and R.W.Jeanloz, J. Am. Chem. Soc., 1984, 106, 811.
61 T.Konoshima, T.Sawada, and T.Kimura, Chem. Pharm. Bull., 1984, 32, 4833.
62 K.Bock and H.Pedersen, Carbohydr. Res., 1984, 132, 142.
63 J.Uzawa and K.Anzai, Can. J. Chem., 1984, 62, 1555.
64 R.L.Benoit and M.Frechette, Can. J. Chem., 1984, 62, 995.
65 J.Doornbos, J.L.Barascut, H.Lazrek, J.L.Imbach, J.van Westrenen, G.M. Wisser, J.H.van Boom, and C.Altona, Nucleic Acids Res., 1983, 11, 4583 (Chem. Abstr., 1984, 100, 7029).
66 M.Legraverend, J.M.Lhoste, and E.Bisagni, Tetrahedron, 1984, 40, 709.
67 M.Kihara, K.Yoshioka, T.Deffo, D.S.Fullerton, and D.C.Rohrer, Tetrahedron, 1984, 40, 1121.
68 A.Allerhand and E.Berman, J. Am. Chem. Soc., 1984, 106, 2412.
69 A.Dessinges, S.Castillon, A.Olesker, T.T.Thang, and G.Lukacs, J. Am. Chem. Soc., 1984, 106, 450.
70 J.Schraml, A.M.Krapivin, A.P.Luzin, V.M.Kilesso, and V.A.Pestunovich, Collect. Czech. Chem. Commun., 1984, 49, 2897.

22
Other Physical Methods

1 I.r. Spectroscopy

Raman and i.r. spectra of crystalline D-fructose, L-sorbose, 5-deoxy-D-threo-hexulose (i.e., 5-deoxy-D-fructose), and D-arabinose in the 3100-3650, 2800-3000, and 200-1600 cm^{-1} regions and the Raman spectra in the 10-200 cm^{-1} region have been reported. Bands due to OH stretching were correlated with OH....H distances and results discussed in relationship to relative sweetness.[1] The hydrogen-bond system in crystalline α-D-glucopyranose has been analysed by i.r. spectroscopy at 18 and 300 K using the fine structure of the OH vibrational bands.[2] The i.r. spectra of the calcium chloride- and calcium bromide-α-L-arabinose tetrahydrate crystalline complexes, which have octacoordinate calcium(II) ions, have been studied.[3]

F.t.i.r. has been described as a powerful tool for the study of carbohydrates in solution, and bands characteristic of the anomeric forms of glucose and lyxose have been revealed by monitoring the mutarotation of pure anomers.[4,5] There is little difference, however, between spectra (i.r., and Raman scattering and absorption) of the furanose and pyranose forms of a given carbohydrate, so that vibrational spectroscopy has limited potential for studying equilibria of these forms in solution, as in the case of D-fructose.[4,6]

Previous assignments of bands characteristic of furanose and pyranose forms (Mathlouthi, Carbohydr. Res., 1980, 78, 225) were shown to be incorrect since these bands co-occur in the spectra of crystalline β-D-fructopyranose.[6] From the intensity of the carbonyl absorption in fructose solutions (the O-deuterated form in D_2O) relative to that of diethyl ketone, it was concluded that 0.9% of fructose was present as the open-chain form.[6] From a study of the i.r. spectra of peracetylated aryl glycosides, the value of bands in the 800-1000 cm^{-1} region for differentiating α- and β-anomers has been reassessed. The relative intensities of C-O-C stretching vibrations in the 1000-1100 cm^{-1} region and a band near 300 cm^{-1} for β-anomers only were suggested as criteria for differentiating anomeric peracetylated alkyl and aryl glycosides.[7]

The i.r. spectra of several aminoglycoside antibiotics, as well

as maltose and cellobiose, have been shown to be more sensitive, detailed, and characteristic at 78 K than at ambient temperature.[8] The f.t.-far-i.r. spectra (30-650 cm^{-1}) of polysaccharides and their constituent mono- and di-saccharides have been reported.[9] Raman spectra of carbohydrates have been recorded and configurationally specific signals reported; α-linked sugars gave bands at 850-860 and 920-940 cm^{-1}, while β-linked sugars gave bands at 885-900 and 950-965 cm^{-1}.[10]

A detailed i.r. study of D-glucuronic acid and its dehydrated Na^+, K^+, and Rb^+ salts, in which the cation is in six-fold co-ordination, has been reported.[11] The vibrational spectra of seven inositols and their O-deuterated counterparts have been correlated with force field calculations, and the spectra of other inositols not used in the study were predicted.[12] F.t.i.r. and laser Raman spectra of adenine, adenosine, thymine, and thymidine in the solid state have been subjected to detailed analysis.[13,14]

F.t.i.r.-vibrational circular dichroism of sugars is covered in Section 5.

2 Mass Spectrometry

A number of papers on fast atom bombardment (FAB) m.s. of carbohydrates have appeared. Matrix effects in the protonation of trehalose have been investigated. With matrices such as glycerol, and di- and tri-ethanolamine, protonated and solvated protonated ions were detected; mass analyzed kinetic ion (MIKE) spectra showed that desolvation contributes to the formation of protonated molecular ions.[15] FAB-m.s. has been useful for identifying cello- and malto-oligosaccharides and their corresponding alditols,[16] for sequencing and determining the site of sulphation in polysulphated oligosaccharides (D.P. 2,4,6, and 8) from enzymic digestion of chondroitin sulphate,[17] and for characterizing synthetic N-acetylmuramoyl-L-alanyl-D-isoglutamine[18] and the antibiotic kijanimicin and other nitro-sugar-containing compounds [which give both $(M+Na-NO_2)^+$ and $(M+Na-16)^+$ ions].[19] Negatively charged boronate cage compounds formed on the m.s. probe tip between boronic acids and trifunctional compounds such as sugars and nucleotides have been examined by FAB-m.s., the method proving useful for the analysis of such polyhydroxy compounds and for determining the affinity constants for their complexes.[20] Standard nucleosides and some related antibiotic analogues such as tubericidin have been

examined by a combination of FAB-m.s. with tandem m.s., with positive ion, negative ion, and collisionally activated decomposition spectra being recorded.[21] A combined t.l.c.-FAB-m.s. procedure has been developed for the rapid analysis of polar, high molecular weight, thermally unstable compounds and demonstrated on the glycopeptide bleomycin complex.[22] Molecular ions of underivatized nucleotides have been obtained by MBSA-FAB m.s.[23]

Field desorption (f.d.)-m.s. of sucrose has been studied in combination with optical microscopy. Emission occurs from nearly solid amorphous or glassy structures with many cavities.[24] The f.d.-m.s. of 38 anthracycline derivatives have been compared with those obtained using other soft ionization techniques; M^+ or MH^+ ions were always present, usually as the base peak.[25]

Negative ion in-beam c.i.-m.s. of several oligosaccharides has been shown to correspond to flash desorption c.i.-m.s. It gave not only the quasi-molecular ion of stachyose but also cluster ions of glucose and sucrose; accurate mass measurement was achieved for maltotriose.[26] Pseudomolecular ions, MH^+, of tetra- and penta-saccharides have been detected by in-beam e.i.-m.s.[27]

Matrix-assisted SIMS (secondary-ion m.s.) of aminoglycosides and neutral oligosaccharides in glycerol or a variety of amides (e.g., N-2-hydroxyethylformamide, α-pyrrolidone, or α-piperidone) has been reported; molecular ions and fragment ions were observed.[28–30]

E.i.-m.s. data on the following types of compounds have been detailed: perbenzoylated aldoses,[31] per(trifluoroacetylated) methyl glycosides of D-glycero-D-manno-heptose and L-glycero-D-manno-heptose in connection with methanolysis-g.c. analysis of lipopolysaccharides from Gram-negative bacterial cell outer membranes,[32] peracetylated methyl and acetyl glycofuranosides,[33] 17 partially methylated D-glycero-D-gluco-heptononitrile acetate derivatives,[34] benzoylated and/or acetylated aldosylamines (the presence of O-benzoyl groups increased the stability of high weight fragments),[35] permethylated N-methyl-N-phenyl-(3- and 4-O-α-D-glucopyranosyl-1-deoxy-D-glucitol-1-yl) amines derived from laminaran and maltose,[36] 11 O-isopropylidene and O-acetyl-O-isopropylidene derivatives produced by acetonation of D-glucitol, using zinc chloride as catalyst, and separated by capillary g.c.,[37] and per(trimethylsilyl)ated natural O-methyl inositols, separated by g.c.[38] A new fragment ion (1) has been found in the e.i.-m.s.

$$\overset{+}{O}{=}CH\text{-}O\text{-}Alditol$$

(1)

of per-O-alkylated, linear di- and tri-β-D-glucopyranosyl alditols containing 3-linked D-glucopyranosyl units but is not found when only 2-, 4-, or 6-linked units are present.[39]

The position of "native" O-methylation can be determined by m.s. following on-column per(trideuteromethyl)ation using tris(trideuteromethyl)anilinium hydroxide, the method being demonstrated for adenosine and 2'-O-methyladenosine.[40] Pyrolysis e.i.-m.s. has been used to identify nucleoside phosphites commonly used in the synthesis of oligonucleotides, with the separate thermal elimination of phosphite, protecting dimethoxytrityl, and heterocyclic base units allowing structure determination.[41]

E.i.- and c.i. (CH_4)-m.s. of alditol acetate derivatives following capillary g.c. separation have been reported in connection with the analysis of the carbohydrate components of bacteria; data for muramic acid, an unspecified heptose, and two amino-dideoxy-hexose components were included.[42] Similarly the e.i.- and c.i. (CH_4)-m.s. spectra of 2-di-N-methyl, 2-N-acetyl-, and 2-(N-acetyl)-N-methyl derivatives of 1,5-di-O-acetyl-7-O-(2-amino-2-deoxy-3,4,6-tri-O-methyl-α-D-glucopyranosyl)-2,3,4,6-tetra-O-methyl-L-glycero-D-manno-heptitol have been reported in connection with the methylation analysis of bacterial lipopolysaccharides.[43]

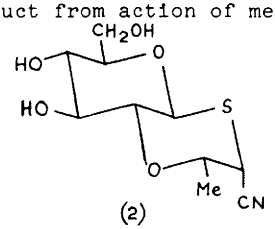
C.i.-m.s. (with i-C_4H_9, NH_3, or ND_3 as reagent gases) of a series of underivatized mono- to tri-saccharide menthyl glycosides have provided useful information about molecular weight and structural units, but could not differentiate stereoisomers.[44] The structures of the branched trisaccharides viridotriose A, B, and C(I) have been determined by permethylation-c.i.-m.s. (with i-C_4H_9 or NH_3 as reagent gases) following the analysis of the spectra of permethylated maltotriose, raffinose, melezitose, and stachyose as models.[45] Similarly, permethylated sialo-oligosaccharides obtained from gangliosides could be sequenced by c.i.-m.s. (NH_3).[46] Negative ion c.i.-m.s. (with a mixed H_2-N_2O reagent gas) of nucleosides has revealed only weak or non-existent $(M-H)^-$ peaks but observable fragment ions from the base and sugar moieties.[47]

3 X-Ray Crystallography

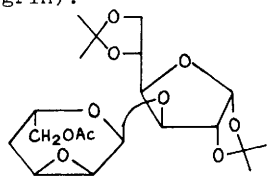
In an important analysis of stereoelectronic effects at the anomeric centre, the structures of 22 tetrahydropyranyl acetals

and α- and β-glucopyranosides have been compared to obtain a correlation between acetal C-O bond length and the electron demand of the aglycones. The pK_a's of the conjugate acids of the "leaving" groups were shown to be proportionate to the lengths of the C-O bond "broken".[48]

Specific crystal structures have been reported as follows:
Free Sugars and Simple Derivatives Thereof.- β-D-Allopyranose,[49] 2-deoxy-β-D-lyxo-hexose,[50] disodium α-D-glucopyranose 1-phosphate,[51] and a refinement of dipotassium α-D-glucopyranose 1-phosphate.[52]
Glycosides and Derivatives Thereof.- O-α-D-Mannopyranosyl-(1→3)-L-threonine,[53] ptaquiloside tetraacetate (a 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside of a tertiary alcohol aglycone),[54] methyl β-D-glucopyranoside tetranitrate,[55] tetraphyllin B [(1S,4S)-1-cyano-4-hydroxy-cyclo-pent-2-enyl β-D-glucopyranoside],[56] napoleogenin (a prosapogenin containing a 3,4-di-O-angeloyl-β-D-fucopyranosyl moiety),[57] octyl 1-thio-β-D-xylopyranoside (for which a disordered average structure was obtained),[58] and merosinigrin (2) (the product from action of methoxide on sinigrin).[59]



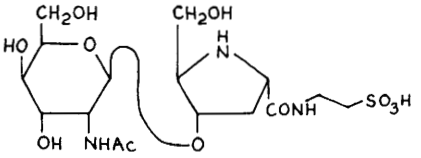
(2)



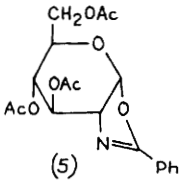
(3)

Di- and Tri-saccharides and Derivatives Thereof.- α-D-(1→4)-mannobiose,[60] 6-O-fructofuranosyl-sucrose monohydrate,[61] and sucrose octa-acetate (at 173 K).[62]
Anhydro-sugars.- The 2,3-anhydro-4-deoxy-α-L-ribo-hexopyranosyl-D-glucose derivative (3),[63] 1,6-anhydro-3,4-O-isopropylidene-β-D-galactopyranose,[64] and five isomeric methyl 3,6-anhydrohexofuranosides with the β-D-gluco-, α-L-ido-, β-D-manno-, α-D-gluco- and α-D-manno- configurations.[65]
Fluorine- and Nitrogen-containing Compounds.- 4-Deoxy-4-fluoro-β-D-fructopyranose,[66] 2,3-di-O-acetyl-1,6-anhydro-4-O-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)-β-D-gluco-pyranose,[67] the 2-acetamido-2-deoxy-D-gulopyranoside (4),[68] the oxazoline (5),[69] isopropyl 2-azido-2-deoxy-β-D-galacto-pyranoside,[70] the tetra-azido-disaccharide (6),[71] 5-amino-5-deoxy-D-gluconolactam,[72] the 5-amino-3,6-anhydro-5-deoxy-D-mannonolactam derivative (7),[73] the 4-amino-4-deoxy-DL-lyxofuranosylamine deri-vative (8),[74] 1'-(p-bromophenyl)-3'-ethyl-1',3',4',5'-tetrahydro-

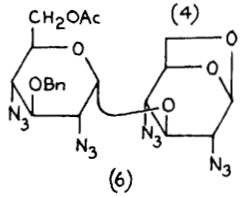
-1,2-dideoxy-D-glycero-D-gulo-heptofuranoso-[1,2-d]imidazole-2'-thione,[75] and N,N'-di(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl) phenylhydrazine.[76]



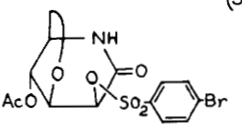
(4)



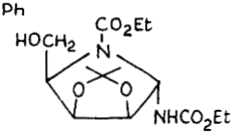
(5)



(6)

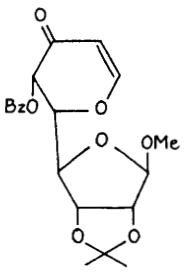


(7)

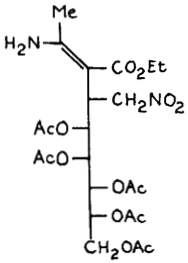


(8)

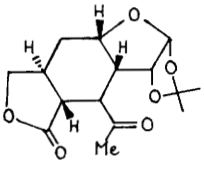
Unsaturated Compounds.- Ethyl 2,3-dideoxy-α-D-erythro-hex-2-enopyranoside,[77] 6-O-acetyl-2,3,4-trideoxy-α-DL-glycero-hex-2-enopyranose and the related chiral disaccharide, 3-O-(6-O-acetyl-2,3,4-trideoxy-α-L-glycero-hex-2-enopyranosyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose,[78] and the C-C linked disaccharide (9).[79]



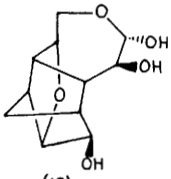
(9)



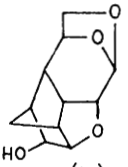
(10)



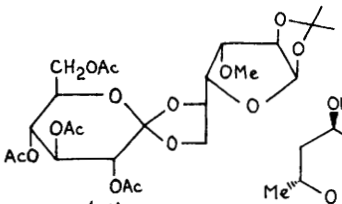
(11)



(13)

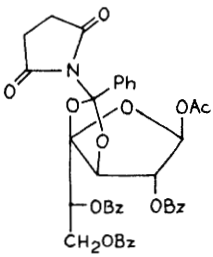


(12)



(14)

(15)



(16)

Branched-Chain Sugars.- Methyl 3-C-acetamidomethyl-3-chloro-2,3,6-trideoxy-4-O-methoxymethyl-α-L-arabino-hexopyranoside,[80] methyl 2,3,4-trideoxy-2,4-di-C-methyl-6-O-trityl-α-D-lyxo-hexo-

pyranoside,[81,82] 6-O-acetyl-2,3,4-trideoxy-4-C-ethenyl-3-C-(methyoxycarbonylmethyl)-α-D-lyxo-hexopyranose,[83] the 2-nonene derivative (10),[84] the intramolecular Diels-Alder-derived tetracycle (11),[85] and the two levoglucosenone-derived polycyclic derivatives (12)[86] and (13).[87]

Acid and Ulose Derivatives.- Lead(II) and sodium D-gluconates,[88] N-cyclohexyl-D-gluconamide,[89] the spiro-ortho-ester (14),[90] the cardenolide glycoside gomphoside (15),[91] and the hexos-4-ulose orthoimide derivative (16).[92]

Alditols.- 1,2:3,4:5,6-trianhydro-D-iditol [93] and 1,4:3,6-dianhydro-D-glucitol (at 100 K).[94]

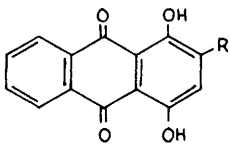
Nucleosides, Nucleotides, and Derivatives.- A new form of 2'-deoxyadenosine,[95] 5'-O-acetyl-2',3'-O-isopropylideneuridine,[96] 3',5'-di-O-acetylthymidine,[97] 2',3',5'-tri-O-acetyluridine,[98] 5-bromo-2',3'-O-isopropylideneuridine,[99] 6-(4-nitrobenzyl)thioinosine,[100] 5-(propyn-1-yl)-1-(β-D-arabinofuranosyl)uracil,[101] (E)-5-(2-bromovinyl)-2'-deoxyuridine,[102] 3-amino-1-(β-D-ribofuranosyl)-s-triazolo[5,1-c]-s-triazole,[103] 2'-deoxy-2'-fluoroadenosine,[104] and 2',3'-O-cyclohexylidene-4'-C-(2-methylpropen-3-yl)uridine.[105]

8,5'-Anhydro-8-hydroxy-9-(β-D-ribofuranosyl)adenine (a redetermination with a corrected crystal form and space group),[106,107] 5,5'-anhydro-5-benzenesulphonamido-1-(2',3'-O-isopropylidene-β-D-ribofuranosyl)imidazole-4-carbonitrile,[108] 5,2'-anhydro-5-(tosylamido)-1-(3'-O-tosyl-β-D-arabinofuranosyl)imidazole-4-carbonitrile,[109] 6,3'-anhydro-1-(4'-O-acetyl-2'-deoxy-β-D-xylopyranosyl)-6-methyluracil,[110] and 6,3':6,5'-dianhydro-5,5-dibromo-5,6-dihydro-6,6-dihydroxy-1-(β-D-xylofuranosyl)uracil.[111]

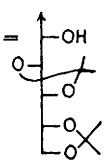
The iron(II) derivative of inosine-5'-monophosphate {[Fe(5'-IMP)$(H_2O)_5$].$2H_2O$},[112] calcium thymidine 5'-phosphate and calcium 2'-deoxyadenosine 5'-phosphate,[113] and disodium uridine diphosphoglucose.[52]

Antibiotics.- 4"-(p-Iodobenzenesulphonamido)oleandomycin.[114]

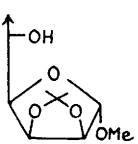
Others.- The anthraquinone derivatives (17) and (18),[115] and

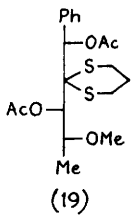


(17) R =



, (18) R =



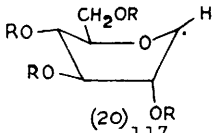


(19)

5-deoxy-1-C-phenyl-D-threo-pentulose derivative (19).[116]

4 E.s.r. Spectroscopy

Glycosyl radicals appear to adopt a conformation such that the half-occupied orbital at the radical centre is largely coplanar with the β-C-O bond (σ* orbital). The glucosyl radical thus adopts the boat conformation (20) whilst the mannosyl radical



(20)

remains in the $^{4}C_{1}$ conformation.[117] An alkoxy radical with a partially delocalized unpaired electron has been produced by low-temperature X-irradiation of sucrose,[118] while similar treatment of methyl β-D-galactopyranoside produced the $^{\bullet}CH_2OR$ radical, both being characterized by e.s.r. techniques.[119] Radicals due to hydrogen abstraction by $^{\bullet}OH$ (Tl^{3+}-H_2O_2) from positions C-1 to C-5 in D-glucuronic and D-galacturonic acids have all been identified by e.s.r., although the C-5 radical predominated in the case of α-D-galacturonic acid and the polymeric equivalent, α-D-galacturonan.[120]

5 Polarimetry, Circular Dichroism, and Related Studies

A new polarimetric method for studying reaction kinetics has been applied to sucrose inversion in the presence of acid, the results being in good agreement with those previously obtained by classical methods.[121] Extended Bronsted plots and solvent isotope effects for the base-catalyzed mutarotation of glucopyranoses in water have been determined over a pK range of 17 using conventional polarimetry extended by a stopped flow polarimetric technique.[122] The Pfeiffer effect, in which optical activity is induced by complexation of aldoses with a racemic mixture tris-(pyridine-2,6-dicarboxylato)terbate(III), has been studied by circularly polarized luminescence spectroscopy. The inability of D-glyceraldehyde to induce optical activity was taken to mean that a hemiacetal ring-oxygen is necessary for the effect.[123]

Correlations have been drawn between the sign and intensity of the c.d. band at 250-275 nm and the point of attachment, absolute and anomeric configuration, ring size, and ring and rotational conformation of the sugar moiety in C-arabinofuranosyl

flavones.[124] The c.d. and conformational properties of acyclic derivatives of fructose, sorbose, tagatose, and four deoxy derivatives of fructose have been related.[125] It has been concluded that the c.d. properties of α-hydroxy-γ-lactones are determined by both the configuration and the conformation of the lactone.[126] The absolute configurations of stereoisomeric *in situ* complexes of glycols, including 1,2:5,6-di-*O*-isopropylidene-D-mannitol, with molybdenum(II) acetate dimer have been determined from the Cotton effects in their 300-400 nm c.d. spectra.[127] α-D- and β-L-*C*-nucleosides have been shown to display positive Cotton effects, while the β-D- and α-L-isomers display negative Cotton effects in their c.d. spectra.[128]

F.t.-i.r., vibrational c.d., a new technique using new instrumentation, has been applied to sugars. A vibrational band at *ca.* 1150 cm^{-1} appears to have a strong correlation with the sequential arrangement of hydroxy groups.[129]

References

1 W.A.Szarek, S.-L.Korppi-Tommola, H.F.Shurvell, V.H.Smith, and O.R.Martin, *Can. J. Chem.*, 1984, **62**, 1512.
2 V.G.Kachur, R.G.Zhbankov, N.V.Ivanova, and E.V.Korolik, *J. Mol. Struct.*, 1984, **117**, 303 (*Chem. Abstr.*, 1984, **101**, 130 986).
3 H.-A.Tajmir-Riahi, *Carbohydr. Res.*, 1984, **127**, 1.
4 D.M.Back, D.F.Michalska, and P.L.Polavarapu, *Appl. Spectrosc.*, 1984, **38**, 173 (*Chem. Abstr.*, 1984, **101**, 55 434).
5 D.F.Michalska, D.M.Back, and P.L.Polavarapu, *Carbohydr. Res.*, 1984, **131**, 29.
6 D.Steele, J.Lall, and J.Pamnani, *Carbohydr. Res.*, 1984, **133**, 313.
7 R.Varma, S.Y.Kulkarni, C.I.Jose, and V.S.Pansare, *Carbohydr. Res.*, 1984, **133**, 25.
8 A.Aszalos, *Appl. Spectrosc.*, 1984, **38**, 278 (*Chem. Abstr.*, 1984, **101**, 7 558).
9 S.K.Husain, J.B.Hasted, D.Rosen, E.Nicol, and J.R.Birch, *Infrared Phys.*, 1984, **24**, 209 (*Chem. Abstr.*, 1984, **101**, 230 894).
10 T.Monodane, K.Fukui, K.Tone, Y.Inoue, and C.Uchiyama, *Kyushu Shika Gakkai Zasshi*, 1983, **37**, 1028 (*Chem. Abstr.*, 1984, **101**, 152 198).
11 H.-A. Tajmir-Riahi, *Carbohydr.Res.*, 1984, **125**, 13.
12 M.R.Williams and R.H.Atalla, *J. Phys. Chem.*, 1984, **88**, 508 (*Chem. Abstr.*, 1984, **100**, 86 032).
13 M.Mathlouthi, A.-M.Seuvre, and J.L.Koenig, *Carbohydr. Res.*, 1984, **131**, 1.
14 M.Mathlouthi, A.-M.Seuvre, and J.L.Koenig, *Carbohydr. Res.*, 1984, **134**, 23.
15 G.Puzo and J.C.Prome, *Org. Mass Spectrom.*, 1984, **19**, 448 (*Chem. Abstr.*, 1984, **101**, 192 344).
16 C.Bosso, J.Defaye, A.Heyraud, and J.Ulrich, *Carbohydr. Res.*, 1984, **125**, 309.
17 S.A.Carr and V.N.Reinhold, *J. Carbohydr. Chem.*, 1984, **3**, 381.
18 L.R.Phillips, O.Nishimura, and B.A.Fraser, *Carbohydr. Res.*, 1984, **132**, 275.
19 B.N.Pramanik, A.K.Mallams, P.L.Bartner, R.R.Rossman, J.B.Morton, and J.H.McGlotten, *J. Antibiot.*, 1984, **37**, 818.
20 M.E.Rose, C.Longstaff, and P.D.G.Dean, *Biomed. Mass Spectrom.*, 1983, **10**, 512 (*Chem. Abstr.*, 1984, **100**, 121 506).

21 F.W.Crow, K.B.Tomer, M.L.Gross, J.A.McCloskey, and D.E.Bergstrom, Anal. Biochem., 1984, 139, 243 (Chem. Abstr., 1984, 101, 131 021).
22 T.D.Chang, T.M.Lee, and D.B.Borders, J. Antibiot., 1984, 37, 1098.
23 J.L.Aubagnac, F.M.Devienne, R.Combarieu, J.L.Barascut, J.-L.Imbach, and H.B.Lazrek, Org. Mass Spectrom., 1983, 18, 361 (Chem. Abstr., 1984, 100, 7050).
24 S.S.Wong, U.Giessmann, M.Karas, and F.W.Roellgen, Int. J. Mass Spectrom. Ion Processes, 1984, 56, 139 (Chem. Abstr., 1984, 101, 23 837).
25 B.Gioia, E.Arlandini, and A.Vigevani, Biomed. Mass Spectrom., 1984, 11, 35 (Chem. Abstr., 1984, 101, 7 556).
26 K.Tsujimoto, Y.Shida, M.Ohashi, and Y.Yamada, Shitsuryo Bunseki, 1984, 32, 115 (Chem. Abstr., 1984, 101, 152 218).
27 M.Ohashi, K.Tsujimoto, S.Funakura, K.Harada, and M.Suzuki, Spectrosc.: Int. J., 1983, 2, 260 (Chem. Abstr., 1984, 100, 156 901).
28 M.Suzuki and K.Harada, Spectrosc.: Int. J., 1983, 2, 267 (Chem. Abstr., 1983, 100, 156 914).
29 K.Harada, F.Ochiai, M.Suzuki, Y.Numajiri, T.Nakata, and K.Shizukuishi, Shitsuryo Bunseki, 1984, 32, 121 (Chem. Abstr., 1984, 101, 171 620).
30 K.I.Harada, F.Ochiai, M.Suzuki, and H.Kambara, Org. Mass. Spectrom., 1983, 18, 447 (Chem. Abstr., 1984, 100, 68 623).
31 N.B.D'Accorso and I.M.E.Thiel, Carbohydr. Res., 1984, 129, 43.
32 I.Brondz and I.Olsen, J. Chromatogr., 1984, 310, 261.
33 Yu.N.El'kin, T.I.Vakorina, and A.P.Shchedrin, Deposited Doc., 1982, VINITI 795 (Chem. Abstr., 1984, 100, 210 288).
34 T.I.Vakorina and Yu.N.El'kin, Deposited Doc., 1982, VINITI 6096 (Chem. Abstr., 1984, 100, 156 888).
35 C.A.Stortz, M.C.Matulewicz, and A.S.Cerezo, Carbohydr. Res., 1984, 133, 199.
36 E.G.Piotrowski, I.A.Low, S.Osman, and R.H.Liu, Org. Mass Spectrom., 1984, 19, 518 (Chem. Abstr., 1984, 101, 230 905).
37 É.Tomori, J.Kuszmann, and Gy.Horváth, J. Chromatogr., 1984, 286, 381.
38 R.G.Binder and W.F.Haddon, Carbohydr. Res., 1984, 129, 21.
39 J.K.Sharp and P.Albersheim, Carbohydr. Res., 1984, 128, 193.
40 R.G.Teece, D.Slowikowski, and K.H.Schram, Biomed. Mass Spectrom., 1983, 10, 30 (Chem. Abstr., 1984, 100, 86 040).
41 H.M.Schebez and H.R.Schulten, J. Anal. Appl. Pyrolysis, 1983, 5, 173 (Chem. Abstr., 1984, 100, 47 965).
42 M.D.Walla, P.Y.Lau, S.L.Morgan, A.Fox, and A.Brown, J. Chromatogr., 1984, 288, 399.
43 J.H.Banoub, F.Michon, D.H.Shaw, and R.Roy, Carbohydr. Res., 1984, 128, 203.
44 N.Takeda, K.Harada, M.Suzuki, A.Tatematsu, and I.Sakata, Biomed. Mass Spectrom., 1983, 10, 608 (Chem. Abstr., 1984, 100, 192 171).
45 K.Harada, S.Ito, N.Takeda, M.Suzuki, and A.Tatematsu, Biomed. Mass Spectrom., 1983, 10, 5 (Chem. Abstr., 1984, 100, 34 759).
46 Y.Tanaka, R.K.Yu, S.Ando, T.Ariga, and T.Itoh, Carbohydr. Res., 1984, 126, 1.
47 H.Seto, T.Okuda, T.Takesue, and T.Ikemura, Shitsuryo Bunseki, 1983, 31, 197 (Chem. Abstr., 1984, 100, 175 187).
48 A.J.Briggs, R.Glenn, P.G.Jones, A.J.Kirby, and P.Ramaswamy, J. Am. Chem. Soc., 1984, 106, 6200.
49 L.M.J.Kroon-Batenburg, P.van der Sluis, and J.A.Kanters, Acta Crystallogr., 1984, C40, 1863.
50 R.Puliti, C.A.Mattia, and G.Barone, Carbohydr. Res., 1984, 135, 47.
51 N.Narendra, T.P.Seshadri, and M.A.Viswamitra, Acta Crystallogr., 1984, C40, 1338.
52 Y.Sugawara and H.Iwasaki, Acta Crystallogr., 1984, C40, 389.
53 N.Darbon, Y.Oddon, J.-M.Lacombe, and A.A.Pavia, Carbohydr. Res., 1984, 130, 55.
54 S.Ohba, Y.Saito, I.Hirono, H.Niwa, M.Ojika, K.Wakamatsu, and K.Yamada, Acta Crystallogr., 1984, C40, 1877.

55 A.V.Nikitin, R.M.Myasnikova, V.I.Andrianov, V.N.Molchanov, A.I.Usov, S.I.Firgang, and A.I.Pertsin, Kristallografiya, 1984, 29, 489 (Chem. Abstr., 1984, 101, 46 754).

56 G.J.Gainsford, G.B.Russell, and P.F.Reay, Phytochemistry, 1984, 23, 2527.

57 Y.Chen, T.Takeda, Y.Ogihara, and Y.Iitaka, Chem. Pharm. Bull., 1984, 32, 3378.

58 S.Bhattacharjee, G.A.Jeffrey, Mol. Cryst. Liq. Cryst., 1983, 101, 247. (Chem. Abstr., 1984, 100, 43 428).

59 J.F.Richardson and M.H.Benn, Can. J. Chem., 1984, 62, 1236.

60 B.Sheldrick, W.Mackie, and D.Akrigg, Carbohydr. Res., 1984, 132, 1.

61 V.Ferretti, V.Bertolasi, G.Gilli, and C.A.Accorsi, Acta Crystallogr., 1984, C40, 531.

62 J.D.Oliver and L.C.Strickland, Acta Crystallogr., 1984, C40, 820.

63 J.W.Krajewski, P.Gluzinski, Z.Urbanczyk-Lipkowska, A.Banaszek, and M.Dobler, Carbohydr. Res., 1984, 134, 11.

64 F.H.Cano, C.Foces-Foces, J.Jimenez-Barbero, and M.Martin-Lomas, Carbohydr. Res., 1984, 127, 338.

65 J.Kopf and P.Köll, Carbohydr. Res., 1984, 135, 29.

66 J.Podlahová and J.Loub, Acta Crystallogr., 1984, C40, 1284.

67 J.G.Shelling, D.Dolphin, P.Wirz, R.E.Cobbledick, and F.W.B.Einstein, Carbohydr. Res., 1984, 132, 241.

68 S.Shinagawa, F.Kasahara, Y.Wada, S.Harada, and M.Asai, Tetrahedron, 1984, 40, 3465.

69 C.Foces-Foces, F.H.Cano, M.Bernabe, S.Penades, and M.Martin-Lomas, Carbohydr. Res., 1984, 135, 1.

70 N.Darbon, Y.Oddon, E.Guy, A.A.Pavia, J.P.Reboul, and G.Pèpe, Acta Crystallogr., 1984, C40, 292.

71 M.Strumpel, H.-J.Schmidt, P.Luger, and H.Paulsen, Carbohydr. Res., 1984, 125, 185.

72 H.Ogura, K.Furuhata, H.Takayanagi, N.Tsuzuno, and Y.Iitaka, Bull. Chem. Soc. Jpn., 1984, 57, 2687.

73 T.Niwa, T.Tsuruoka, H.Goi, Y.Kodama, J.Itoh, S.Inouye, Y.Yamada, T.Niida, M.Nobe, and Y.Ogawa, J. Antibiot., 1984, 37, 1579.

74 A.K.Forrest, R.R.Schmidt, G.Huttner, and I.Jibril, J. Chem. Soc., Perkin Trans. 1, 1984, 1981.

75 M.D.Estrada, A.Conde, and R.Márquez, Acta Crystallogr., 1984, C40, 898.

76 N.A.Chursina, B.K.Sadybakasov, I.F.Strel'tsova, V.A.Afanas'ev, M.Yu.Antipin, and Yu.T.Struchkov, Zh. Obshch. Khim., 1984, 54, 706 (Chem. Abstr., 1984, 101, 55 463).

77 L.M.Wingert, J.R.Ruble, and G.A.Jeffrey, Carbohydr. Res., 1984, 128, 1.

78 J.W.Krajewski, P.Gluziński, Z.Urbánczyk-Lipkowska, A.Banaszek, K.Vangehr, and P.Luger, Carbohydr. Res., 1984, 125, 203.

79 S.Danishefsky, C.J.Maring, M.R.Barbachyn, and B.E.Segmuller, J. Org. Chem., 1984, 49, 4564.

80 J.S.Brimacombe and T.J.R.Weakley, Carbohydr. Res., 1984, 126, 303.

81 Y.Chapleur, F.Germain, A.Aubry, and D.Bayeul, J. Carbohydr. Chem., 1984, 3, 443.

82 M.Mori, T.Chuman, T.Fujimori, K.Kato, A.Ohkubo, and S.Toda, Carbohydr. Res., 1984, 127, 171.

83 S.Leger, F.Belanger-Gariepy, S.Hanessian, and F.Brisse, Acta Crystallogr., 1984, C40, 1844.

84 R.Vega, M.J.Diánez, A.López-Castro, and R.Márquez, Acta Crystallogr., 1984, C40, 1941.

85 B.Fraser-Reid, Z.Benkö, R.Guilliano, K.M.Sun, and N.Taylor, J. Chem. Soc., Chem. Commun., 1984, 1029.

86 P.Bhate, J.Gallucci, and D.Horton, Acta Crystallogr., 1984, C40, 468.

87 M.G.Essig, F.Shafizadeh, T.G.Cochran, and R.E.Stenkamp, Carbohydr. Res., 1984, 129, 55.

88 T.Lis, Acta Crystallogr., 1984, C40, 374, 376.

89 N.Darbon, Y.Oddon, J.M.Lacombe, E.Decoster, A.A.Pavia, and J.P.Reboul, Acta Crystallogr., 1984, C40, 1105.

90 J.-P.Praly, G.Descotes, R.Faure, and H.Loiseleur, Acta Crystallogr., 1984, C40, 1206.
91 G.Ferguson, M.Parvez, H.T.A.Cheung, and T.R.Watson, J. Chem. Res., Synop., 1983, 277 (Chem. Abstr., 1984, 100, 121 476).
92 R.J.Ferrier, S.R.Haines, G.J.Gainsford, and E.J.Gabe, J. Chem. Soc., Perkin Trans. 1, 1984, 1683.
93 P.Köll, M.Oelting, and J.Kopf, Angew. Chem. Int. Ed. Engl., 1984, 23, 242.
94 H.van Koningsveld, J.A.Peters, and J.C.Jansen, Acta Crystallogr., 1984, C40, 519.
95 T.Sato, Acta Crystallogr., 1984, C40, 880.
96 T.P.Seshadri, N.Gautham, and M.A.Viswamitra, Acta Crystallogr., 1983, C39, 1706.
97 C.C.Wilson, J.N.Low, P.Tollin, and H.R.Wilson, Acta Crystallogr., 1984, C40, 1712.
98 J.N.Low and C.C.Wilson, Acta Crystallogr., 1984, C40, 1030.
99 Y.Yamagata, Y.Kobayashi, N.Okabe, K.Tomita, and T.Ueda, Nucleosides Nucleotides, 1983, 2, 327 (Chem. Abstr., 1984, 100, 103 808).
100 M.Soriano-Garcia, R.Parthasarathy, B.Paul, and A.R.P.Paterson, Acta Crystallogr., 1984, C40, 1897.
101 M.Cygler, W.F.Anderson, J.Giziewicz, and M.J.Robins, Can. J. Chem., 1984, 62, 147.
102 L.Parkanyi, A.Kalman, T.Kovacs, A.Szabolcs, and L.Otvos, Nucleic Acids Res., 1983, 11, 7999 (Chem. Abstr., 1984, 100, 121 514).
103 S.G.Wood, N.K.Dalley, R.D.George, R.K.Robins, and G.R.Revankar, Nucleosides Nucleotides, 1984, 3, 187.
104 K.Morishita, T.Hakoshima, T.Fujiwara, K.-i.Tomita, T.Kaneyasu, S.Uesugi, and M.Ikehara, Acta Crystallogr., 1984, C40, 434.
105 W.J.Cook, S.E.Ealick, and J.A.Secrist, Acta Crystallogr., 1984, C40, 885.
106 R.E.Marsh, Acta Crystallogr., 1984, C40, 712.
107 S.Sugio, H.Mizuno, K.Kitamura, K.Hamada, M.Ikehara, and K.-i.Tomita, Acta Crystallogr., 1984, C40, 712.
108 S.Sugio, K.Kitamura, H.Mizuno, A.Wakahara, M.Ikehara, and K.-i.Tomita, Acta Crystallogr., 1984, C40, 1608.
109 S.Sugio, H.Mizuno, K.Kitamura, M.Ikehara, and K.-i.Tomita, Acta Crystallogr. 1984, C40, 186.
110 Y.Yamgata, T.Fujiwara, K.-i.Tomita, S.Shuto, and T.Ueda, Acta Crystallogr., 1984, C40, 543.
111 M.Honjo, T.Maruyama, Y.Wada, and K.Kamiya, Chem. Pharm. Bull., 1984, 32, 2073.
112 M.V.Capparelli, D.M.L.Goodgame, P.B.Hayman, A.C.Skapski, and D.E.Hathway, FEBS Lett., 1983, 163, 241 (Chem. Abstr., 1984, 100, 139 538).
113 T.Sato, Acta Crystallogr., 1984, C40, 736, 738.
114 G.M.Bright, A.R.English, A.A.Nagel, J.A.Retsema, and F.C.Sciavolino, Antimicrob. Agents Chemother., 1984, 25, 113 (Chem. Abstr., 1984, 100, 175 174).
115 O.Johnson, D.W.Jones, D.J.Mincher, and G.Shaw, Nucleosides Nucleotides, 1983, 2, 367 (Chem. Abstr., 1984, 100, 139 524).
116 J.Thiem, H.-P.Wessel, M.Werk, and K.-H.Klaska, Justus Liebigs Ann. Chem., 1983, 2185.
117 J.Dupuis, B.Geise, D.Rüegge, H.Fischer, H.-G.Korth, and R.Sustmann, Angew. Chem. Int. Ed. Engl., 1984, 23, 896.
118 H.C.Box and E.E.Budzinski, J. Chem. Phys., 1983, 79, 4142 (Chem. Abstr., 1984, 100, 121 479).
119 W.A.Bernhard, T.L.Horning, and K.R.Mercer, J. Phys. Chem., 1984, 88, 1317 (Chem. Abstr., 1984, 100, 121 478).
120 B.C.Gilbert, D.M.King, and C.B.Thomas, Carbohydr. Res., 1984, 125, 217.
121 R.S.Roy and S.C.Chauhan, Acta Cienc. Indica, [Ser.] Chem., 1983, 9, 1 (Chem. Abstr., 1984, 101, 91 367).
122 H.Nielsen and P.E.Soerensen, Acta Chem. Scand., Ser. A, 1984, A38, 309.
123 H.G.Brittain, J. Chem. Soc., Dalton Trans., 1984, 1367.
124 W.Gaffield, E.Besson, and J.Chopin, Phytochemistry, 1984, 23, 1317.

125 S.Bystricky, T.Sticzay, and S.Kucar, Collect. Czech, Chem. Commun., 1984, 49, 828.
126 P.Welzel, H.-P.Bulian, A.Maulshagen, D.Müller, and G.Snatzke, Tetrahedron, 1984, 40, 3657.
127 J.Frelek and G.Snatzke, Fresenius' Z. Anal. Chem., 1983, 316, 261 (Chem. Abstr., 1984, 100, 121 490).
128 M.A.E.Sallam, Carbohydr. Res., 1984, 129, 33.
129 D.M.Back and P.L.Polavarapu, Carbohydr. Res., 1984, 133, 163.

23
Separatory and Analytical Methods

1 Chromatographic Methods

Gas-Liquid Chromatography.- The permethylation - "ionic hydrogenation" procedure developed by Gray and co-workers for the analysis of oligo- and poly-saccharides is covered extensively in Chapter 18. The procedure causes reductive cleavage of glycosidic bonds with the production of partially methylated anhydro-alditol derivatives, which are analysed by g.c. after acetylation.

Rules have been formulated for predicting the g.c. retention of carbohydrate derivatives based on a concept of "selective intermolecular force".[1]

Capillary g.c. analysis of amino-sugars as their alditol acetate derivatives using a nitrogen-phosphorus-selective detector has permitted increased selectivity and sensitivity, ca. 30-fold over flame-ionization detection.[2] All eight possible 2-amino-2-deoxy-hexitol peracetate isomers have been separated by capillary g.c. on a polyamide stationary phase, permitting the analysis of bacterial heteroglycans containing rare 2-aminohexoses and 2-amino-uronic acids.[3] Similarly, the carbohydrate components of other bacterial polymers have been determined by capillary g.c.-m.s. (both e.i. and c.i.), data for alditol acetates derived from muramic acid, an unspecified heptose, and two aminodideoxyhexoses being included.[4] Separations of partially methylated alditol acetates on various SCOT columns [5] and on a high-polarity bonded-phase (OV-275) capillary column [6] have been reported.

Acetate and nitrate esters of isosorbide (1,4:3,6-dianhydro-D-sorbitol) have been analysed by capillary g.c.; the nitrates are used as vasodilators and are synthesized via acetates.[7] The g.c. of 16 partially methylated methyl (methyl α-D-galacto- and manno-pyranosid)uronate peracetates [8] and the g.c.-m.s. of partially methylated sugars as their aldononitrile peracetates [9] have been reported. The glucuronic acid conjugate of trichloroethanol has been assayed in biological samples as its peracetylated or

pertrifluoroacetylated methyl ester using electron capture detection.[10] The capillary g.c.-m.s. analyses of acetylated mono- to tri-O-isopropylidene derivatives of D-glucitol[11] and D-mannitol[12] have been reported.

As a check on the reliability of sequential methanolysis, N-reacetylation, trimethylsilylation, and g.c. for sugar analysis, the propensity of alditols for forming anhydro-derivatives has been investigated. Xylitol, arabinitol, fucitol, glucitol, galactitol, 2-acetamido-2-deoxy-galactitol, and the alditols of N-acetylneuraminic acid were all prone to form anhydrides, while 2-amino-2-deoxy-galactitol and -glucitol, 2-acetamido-2-deoxy-glucitol, and mannitol were not.[13] The g.c.-m.s. of eight isomeric per(trimethylsilyl)ated 6-deoxyhexitols has been reported,[14] while complex mixtures of hydroxy-mono- and di-carboxylic acids resulting from alkaline degradation of wood polysaccharides have been converted to their ammonium salt form (to avoid lactone formation) and analysed by trimethylsilylation-capillary g.c.[15]

Mono- to penta-saccharides present in soy beans have been analysed as their trimethylsilylated oxime derivatives; an effective procedure for obtaining single peaks from these reducing sugars consisted of dehydrating them by distillation of isopropanol prior to oxime formation.[16]

Thin Layer Chromatography.- In connection with their work on the thermal-u.v. method for detecting sugars after t.l.c. or p.c., Alperin and co-workers have now described a reproducible solubilization of the fluorescent derivatives generated by heating glucose or glucosamine on silica gel absorbent and certain properties of these fluorescers.[17] A sulphosalicylic acid-sulphuric acid spray reagent has been evaluated for the detection of reducing sugars on silica t.l.c. plates.[18]

Aminopropyl-bonded silica t.l.c. plates have been prepared by treatment of commercial precoated silica gel h.p.t.l.c. plates with a 1% (3-aminopropyl)triethoxysilane solution. The resulting plates permit good separations of monosaccharides, simple derivatives thereof, and disaccharides,[19] especially after impregnation with sodium dihydrogen phosphate to eliminate glycosylamine formation (*c.f.* analogous pH adjustment recommended for h.p.l.c. of reducing sugars on amino-bonded silica, Vol. 16, p.253).[20]

The constituents of complex glycolipids have been determined

after methanolysis using a silica gel t.l.c. - flame ionization detection system (Chromarod SII), the sugar components thus being present as methyl glycosides.[21] Oligo(D-galactosiduronic acids) of DP = 1-9 have been separated on cellulose in connection with a polygalacturonase enzyme assay.[22]

High Pressure Liquid Chromatography.- In connection with the development of a post-column packed-bed reactor for use in the analysis of non-reducing sugars (c.f. Vol.14, p.211), a polystyrene-based strongly acidic cation exchanger has been found which can hydrolyze sucrose and related oligosaccharides at 80°C and can be coupled to a subsequent fluorophore- or chromophore-producing reactor to enable high sensitivity in detection.[23]

Post-column derivatization of reducing sugars with 2-cyanoacetamide, and electrochemical detection of the readily oxidized products, has permitted their detection down to very low levels, e.g., 20 pmol for glucose.[24]

The anomers of twelve aldoses have been separated on cation exchange resins in the sodium form (at 25°C) or the calcium form (at 4°C), and in some cases a peak corresponding to the furanose forms has also been observed. Post-column derivatization with 2-cyanoacetamide was used to render the method sufficiently sensitive for use in biological analyses.[25] Separations of free sugars on silica gel columns have been reported using ethyl formate - methanol - water eluents.[26] The h.p.l.c. of 24 carbohydrates on a polystyrene-based strong cation exchange resin in the H^+-form has been included in a paper covering a wide range of alcohols, aldehydes, ketones, and acids; all 24 elute in a narrow range due to the low selectivity of this column for this compound class.[27] Free sugars and polyols present in lens, erythrocytes, and plasma have been analysed as their per-nitrobenzoate derivatives on silica.[28]

Several studies on the separation of oligosaccharides have appeared. The retention of malto- and cello-oligosaccharides (from polymer hydrolysis) on reversed-phase columns has been studied with respect to eluent composition (i.e., salt, methanol, or pentan-1-ol in water), silica pore size, and alkyl chain length (C_8 vs. C_{18}).[29] Similarly the effect of a range of additives on the elution of malto- and isomalto-oligosaccharides from a reversed-phase column (Dextropak) with an aqueous eluent has been examined. Surfactants (anionic, cationic, or non-ionic), tetra-

methylurea, or organic solvents hastened elution and permitted larger oligomers to be separated in acceptable times. Neutral inorganic salts considerably increased retention and permitted the separation of some compounds poorly resolved using water alone, e.g., isomaltotetraose and the branched 3^3-α-D-glucosylisomaltose. The mechanism by which these changes in retention are induced was discussed.[30] Several columns have been examined for their ability to separate the mono- to oligo-saccharides and their degradation products formed on acidic, hydrothermal, or enzymatic hydrolysis of biomass. Toyo Soda's TSK PW column and an anion-exchange column were useful for oligomers of DP 1-ca. 8, a cation-exchange column proved effective for separating monosaccharides and various aldehydic and ketonic degradation products, and a μ-Spherogel-Carbohydrate column was useful for separating isomeric pentoses and hexoses.[31] Enzymatic hydrolysis products from lactose, i.e., glucose, galactose, and especially oligosaccharides arising due to transgalactolytic activity, have been analyzed on a new Ca^{2+}-form ion-exchange resin.[32] Fructose oligosaccharides (DP 2-30) have been separated on a dynamically coated amine-modified silica gel column (i.e., using 1,4-diaminobutane in the eluent).[33]

A number of naturally occurring glycosides and sugar esters have been analysed by h.p.l.c. Cyanogenic glucosides in complex plant extracts have been separated by reversed-phase h.p.l.c. and selectively detected (down to picomoles) using a post-column enzyme reactor (a glycosidase immobilized on glass or silica support), followed by alkaline release and electrochemical detection of cyanide.[34] The degree of glycosylation of flavonols has been determined by h.p.l.c. separation of the perbenzoylated derivatives using a u.v. diode-array detector, which provides a measure of the number of benzoate chromophoric groups.[35] Forty flavonol glycosides have been separated on a C_8-reversed-phase column using gradient elution.[36] The reversed-phase separation of C-glycosyl-flavone isomers of varying ring form, anomeric configuration, and glycosyl moiety has been reported.[37] Caffeoylated phenylethyl glycosides have been separated on both preparative and analytical scales, on a polyamide-6 column.[38] Hydroxycinnamic acid derivatives of glucose, and their esters with quinic acid, have been separated into two groups by column chromatography on polyamide, followed by reversed-phase h.p.l.c. analysis.[39] Similarly, the reversed-phase separation of eleven hydroxycinnamic acid esters of quinic acid has been reported.[40]

Ester and ether glucuronides of diflusinal (2',4'-difluoro-4-hydroxy-3-biphenylcarboxylic acid) have been separated by reversed-phase h.p.l.c. and their identities confirmed through acid, base, or enzymic prehydrolysis of samples.[41]

Free muramic acid in human serum has been determined, as an indicator of bacterial cell wall debris, by separation on a silica-based strong cation exchanger, post-column reaction with bis(1,10-phenanthroline)copper(II), and amperometric detection of the derived copper(I) species.[42] Sensitive reversed-phase analyses of neuraminic acid and KDO (3-deoxy-D-*manno*-oct-2-ulosonic acid) as their *p*-nitrophenylhydrazone derivatives have been reported.[43]

D-Gluconic acid and 5-keto-, 2-keto-, and 2,5-diketo-D-gluconic acids in biological fluids have been determined on an anion-exchange resin in the formate form.[44] L-Ascorbic acid (vitamin C) has been determined in blood by enzymic oxidation to dehydro-L-ascorbic acid, condensation with *o*-phenylenediamine to form a quinoxaline derivative, and reversed-phase separation with fluorimetric detection.[45] Reversed-phase analyses of L-ascorbic acid[46] and its 2-sulphate[47] with electrochemical detection have been detailed.

A wide range of aminoglycoside antibiotics has been analysed on reversed-phase columns. A general procedure using volatile perfluorocarboxylic acids as ion-pairing reagents has permitted the preparative isolation of components by lyophilization.[48] Samples of gentamicin complex from different origins have been analysed by both h.p.l.c. and ^{13}C-n.m.r. spectroscopy and the results compared.[49] Amikacin has been determined as its *N*-(2,4,6-trinitrophenyl)ated derivative.[50] An automated analysis of six aminoglycosides in blood employed pre-column derivatization with *o*-phthaldehyde,[51] while another analysis of four aminoglycosides employed ion-pair chromatography, post-column derivatization with *o*-phthalaldehyde, and fluorescence detection.[52]

Pirlimycin, an antibiotic in the lincosaminide family, has been analysed (reversed-phase) as its fluorescent *N*-(9-fluorenylmethyloxycarbonyl)-derivative,[53] while the nikkomycins, a group of nucleoside-peptide antibiotics, have been separated by h.p.l.c. and identified with the aid of a photodiode array detector.[54]

Many separations of nucleosides and related materials have been reported, the majority using reversed-phase columns. Electrochemical detection of adenosine and other purine nucleosides and bases has been shown to be more sensitive than u.v.-detection and

in many cases rivals fluorescence detection without requiring post-column derivatization; minimum detectable limits in the 0.05-0.50 pmole range were reported.[55] A novel experimental Cerenkov photon absorption detector, which monitored the absorption of u.v. photons generated by the Cerenkov effect (viz. photons given off by the β-particles from a ^{90}Sr source), has been demonstrated with nucleosides, detection limits being 3-30 ng at present.[56] Nucleosides, in particular pseudouridine, released on enzymic hydrolysis of tRNA have been purified on a phenylboronate gel column prior to h.p.l.c. analysis.[57] In determining adenosine, inosine, and hypoxanthine in plasma, specific enzyme-induced peak shifts, e.g., adenosine to inosine with adenosine deaminase, have been used for peak verification.[58] Post-column eluent pH adjustment has been used to assist in the identification of purines and pyrimidines and their nucleosides; it is non-destructive and results in distinctive changes in u.v. and fluorescence spectra.[59] A detailed optimization of the quantitative analysis of major and modified nucleosides (both ribo- and deoxyribo-types) from enzymic DNA hydrolysis has been reported.[60] The remaining reversed-phase h.p.l.c. analyses that have been reported are as follows: S-adenosylmethionine in rat tissue,[61] hypoxanthine arabinoside in plasma,[62] the products from action of formaldehyde on deoxynucleosides, with rapid isolation and ^{1}H-n.m.r. analysis revealing them to be products of N-hydroxymethylation at the exocyclic amine of the base moiety,[63] and the new anticancer C-nucleoside 2-β-D-ribofuranosylthiazole-4-carboxamide (Tiazofurin), in urine[64] and plasma.[65]

Ion-pair h.p.l.c. of nucleosides and bases has been probed, the counter-ion, pH, temperature, organic modifiers in the eluent, and the alkyl chain length of the stationary phase being varied to find optimum parameters.[66] Improvements to the conventional h.p.l.c. analysis on anion-exchange resin of adenosine and its mono- to tri-phosphates have been reported.[67] Thymidine, cytidine, uridine, guanosine and adenosine have been nicely separated by h.p.l.c. on a "dihydroxyboryl-agarose" matrix, in which cross-linked agarose beads have spacer arms bearing N-linked m-aminophenylboronic acid groups; retention was due to complexation of the cis-diol group in the ribonucleosides with the boronate ligand.[68] Separations of 2',3'- and 3',5'-cyclic monophosphates of 5-fluorocytidine (on an APS Hypersil column) [69] and arsenic mononucleotides and related materials [70] have been reported.

Column Chromatography.- Automated amino acid analyzers have been utilized for the following analyses: i) sugars and amino acids released from glycoproteins, amino-sugars including N-acetylneuraminic acid being analyzed on a cation-exchange column, and neutral sugars being separated by anion-exchange chromatography with a borate buffer as eluent and with post-column detection using ninhydrin and copper bicinchoninate reagents,[71] ii) 2-O-(α-D-glucopyranosyl)-β-D-galactopyranosyl and β-D-galactopyranosyl hydroxylysines (present in urine of patients with spinal cord injury and due to collagen degradation) using a Li^+-form cation-exchange resin and ninhydrin colourimetric detection,[72] and iii) lactulose in the presence of a variety of sugars, especially a large excess of lactose as found in sterilized milk, by anion-exchange chromatography as outlined in i) above.[73]

In connection with the preparative separation of glucose and fructose on Ca^{2+}-form cation-exchange resins, the effect of increasing on-column sugar concentrations on the bonding of these sugars has been determined.[74]

2 Electrophoresis

Organic acids from alkaline degradation of D-glucose in the presence and absence of oxidizing agents, including 5- and 6-carbon isosaccharinic acids, have been analyzed by isotachophoresis.[75]

3 Other Analytical Methods

An amplification method for the titrimetric determination of L-rhamnose has been described, in which oxidation with periodate in aqueous acid yields six equivalents of IO_3^-, equivalent to 18 I_3^-, that are titrated with 36 equivalents of $S_2O_3^{2-}$.[76]

EDTA and Ca^{2+} ions have been shown to interfere with the 3,5-dinitrosalicylate reducing sugar assay, leading to lower and higher results, respectively.[77] Colourimetric determination of the aminoglycoside antibiotics neomycin and toburamycin has been effected using o-hydroxyhydroquinonephthalein-uranium(VI) complex as reagent.[78]

References

1 S.Jin, Fenzi Kexue Yu Huaxue Yanjiu, 1983, 3, 17 (Chem. Abstr., 1984, 100, 121 459).

2 R.J.Whenham, J. Chromatogr., 1984, 303, 380.
3 T.Kontrohr and B.Kocsis, J. Chromatogr., 1984, 291, 119.
4 M.D.Walla, P.Y.Lau, S.L.Morgan, A.Fox,and A.Brown, J. Chromatogr., 1984, 288, 399.
5 G.M.Iskander and H.Ibn Oaf, Dokl. Bolg. Akad. Nauk, 1983, 36, 791 (Chem. Abstr., 1984, 100, 139 523).
6 A.Bacic, P.J.Harris, E.W.Hak, and A.E.Clarke, J. Chromatogr., 1984, 315, 373.
7 N.Russeva, N.Dimova, G.Spyrov, and M.Jurovska, J. Chromatogr., 1984, 295, 255.
8 V.I.Grishkovets, V.N.Paukov, and V.Y.Chirva, Khim. Prir. Soedin., 1983, 558 (Chem. Abstr., 1984, 100, 121 502).
9 G.R.Tanner and I.M.Morrison, J. Chromatogr., 1984, 299, 252.
10 M.Ikeda, H.Hattori, Y.Koyama, and S.Ohmori, J. Chromatogr., 1984, 307, 111.
11 É.Tomori, J.Kuszmann, and Gy. Horváth, J. Chromatogr., 1984, 286, 381.
12 É.Tomori and J.Kuszmann, J. Chromatogr., 1984, 299, 87.
13 G.J.Gerwig, J.P.Kamerling, and J.F.G.Vliegenthart, Carbohydr. Res., 1984, 129, 149.
14 T.Niwa, K.Yamada, T.Ohki, A.Saito, and M.Mori, J. Chromatogr., 1984, 336, 345.
15 R.Alén, K.Niemelä, and E.Sjöström, J. Chromatogr., 1984, 301, 273.
16 I.Molnár-Perl, M.Pintér-Szakács, Á.Kovágó, and J.Petróczy, J. Chromatogr., 1984, 295, 433.
17 D.M.Alperin, N.D.Iusem, V.Idoyaga-Vargas, and H.Carminatti, J. Chromatogr., 1984, 295, 123.
18 B.Ray, P.K.Ghosal, S.Thakur, and S.Ghosh Majumdar, J. Chromatogr., 1984, 315, 401.
19 L.W.Doner, C.L.Fogel, and L.M.Biller, Carbohydr. Res., 1984, 125, 1.
20 L.W.Doner and L.M.Biller, J. Chromatogr., 1984, 287, 391.
21 M.Tanaka, K.Takase, J.Ishii, T.Itoh, and H.Kaneko, J. Chromatogr., 1984, 284, 433.
22 O.Markovic and A.Slezárik, J. Chromatogr., 1984, 312, 492.
23 P.Vrátný, R.W.Frei, U.A.Th.Brinkman, and M.W.F.Nielen, J. Chromatogr., 1984, 295, 355.
24 S.Honda, T.Konishi, and S.Suzuki, J. Chromatogr., 1984, 299, 245.
25 S.Honda, S.Suzuki, and K.Kakehi, J. Chromatogr., 1984, 291, 317.
26 S.Iwata, T.Narui, K.Takahashi, and S.Shibata, Carbohydr. Res., 1984, 133, 157.
27 R.Pecina, G.Bonn, E.Burtscher, and O.Bobleter, J. Chromatogr., 1984, 287, 245.
28 M.Petchey and M.J.C.Crabbe, J. Chromatogr., 1984, 307, 180.
29 L.A.Th.Verhaar, B.F.M.Kuster, and H.A.Claessens, J. Chromatogr., 1984, 284, 1.
30 N.W.H.Cheetham and G.Teng, J. Chromatogr., 1984, 336, 161.
31 G.Bonn, R.Pecina, E.Burtscher, and O.Bobleter, J. Chromatogr., 1984, 287, 215.
32 H.F.Betschart and J.E.Prenosil, J. Chromatogr., 1984, 299, 498.
33 W.Praznik, R.H.F.Beck, and E.Nitsch, J. Chromatogr., 1983, 303, 417.
34 L.Dalgaard and L.Brimer, J. Chromatogr., 1984, 303, 67.
35 F.Siewek and R.Galensa, J. Chromatogr., 1984, 294, 385.
36 J.B.Harborne and M.Boardley, J. Chromatogr., 1984, 299, 377.
37 C.Lardy, M.-L.Bouillant, and J. Chopin, J. Chromatogr., 1984, 291, 307.
38 C.C.S.Chapple and B.E.Ellis, J. Chromatogr., 1984, 285, 171.
39 M.Winter and K.Herrmann, J. Chromatogr., 1984, 315, 243.
40 H.Morishita, H.Iwahashi, N.Osaka, and R.Kido, J. Chromatogr., 1984, 315, 253.
41 J.R.Veenendaal and P.J.Meffin, J. Chromatogr., 1984, 307, 432.
42 N.Watanabe, J. Chromatogr., 1984, 316, 495.
43 P.A.McNicholas, M.Batley, and J.W.Redmond, J. Chromatogr., 1984, 315, 451.
44 J.D.Blake, M.L.Clarke, and G.N.Richards, J. Chromatogr., 1984, 312, 211.
45 A.J.Speek, J.Schrijver, and W.H.P.Schreurs, J. Chromatogr., 1984, 305, 53.

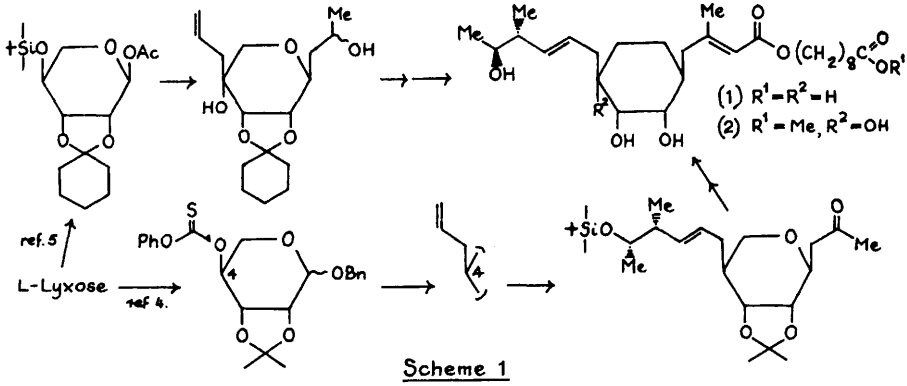
46 D.Sybilska, K.Duszczyk, and M.Przasnyski, J. Chromatogr., 1984, 298, 352.
47 C.S.Tsao, M.Young, S.M.Rose, J. Chromatogr., 1984, 308, 306.
48 G.Inchauspé and D.Samain, J. Chromatogr., 1984, 303, 277.
49 P.J.Claes, R.Busson, and H.Vanderhaeghe, J. Chromatogr., 1984, 298, 445.
50 P.M.Kabra, P.K.Bhatnager, and M.A.Nelson, J. Chromatogr., 1984, 307, 224.
51 L.Essers, J. Chromatogr., 1984, 305, 345.
52 T.Kawamoto, I.Mashimo, and S.Yamauchi, J. Chromatogr., 1984, 305, 373.
53 J.A.Shah and D.J.Weber, J. Chromatogr., 1984, 309, 95.
54 H.-P.Fiedler, J. Chromatogr., 1984, 316, 487.
55 R.J.Henderson, Jr. and C.A.Griffin, J. Chromatogr., 1984, 298, 231.
56 K.Jones and D.J.Malcolme-Lawes, J. Chromatogr., 1984, 291, 21.
57 T.Russo, F.Salvatore, and F.Cimino, J. Chromatogr., 1984, 296, 387.
58 J.Ontyd and J.Schrader, J. Chromatogr., 1984, 307, 404.
59 S.P.Assenza and P.R.Brown, J. Chromatogr., 1984, 289, 355.
60 C.W.Gehrke, R.A.McCune, M.A.Gama-Rosa, M.Ehrlich, and K.C.Kuo, J. Chromatogr., 1984, 301, 199.
61 J.Wagner, C.Danzin, S.Huot-Olivier, N.Claverie,and M.G.Palfreyman, J. Chromatogr., 1984, 290, 247.
62 G.A.Smith, K.M.Giacomini, C.T.Smith, P.B.Gregory, W.S.Robinson, T.C.Merigan, and T.F.Blaschke, J. Chromatogr., 1984, 307, 410.
63 F.A.Beland, N.F.Fullerton, and R.H.Heflich, J. Chromatogr., 1984, 308, 121.
64 N.M.Meltzer and L.A.Sternson, J. Chromatogr., 1984, 307, 216.
65 R.W.Klecker, Jr. and J.M.Collins, J. Chromatogr., 1984, 307, 361.
66 P.A.Perrone and P.R.Brown, J. Chromatogr., 1984, 307, 53.
67 D.-S.Hsu and S.S.Chen, J. Chromatogr., 1984, 311, 396.
68 S.Hjertén and D.Yang, J. Chromatogr., 1984, 316, 301.
69 A.H.Csarnyi, J.Beres, M.Vajda, S.K.Sethi, and J.A.McCloskey, J. Chromatogr., 1984, 285, 226.
70 R.Lagunas, D.Pestana, and J.C.Diez-Masa, Biochemistry, 1984, 23, 935 (Chem. Abstr., 1984, 100, 86 048).
71 Dj.Josić, R.Hofermaas, Ch. Bauer, and W.Reutter, J. Chromatogr., 1984, 317, 35.
72 G.P.Rodriguez and J.Claus-Walker, J. Chromatogr., 1984, 308, 65.
73 R.S.Ersser and J.D.Mitchell, J. Chromatogr., 1984, 307, 393.
74 P.E.Barker and S.Thawait, J. Chromatogr., 1984, 295, 479.
75 Ľ.Repášová, J.Polonský, M.Košík, and Š.Vodný, J. Chromatogr., 1984, 286, 347.
76 V.Zaharans and A.Valdniece, Khim. Prir. Soedin., 1984, 21 (Chem. Abstr., 1984, 100, 210 281).
77 D.W.M.Leung and T.A.Thorpe, Phytochemistry, 1984, 23, 2949.
78 Y.Fujita, I.Mori, and S.Kitano, Chem. Pharm. Bull., 1984, 32, 1214.

24
Synthesis of Enantiomerically Pure Non-carbohydrate Compounds

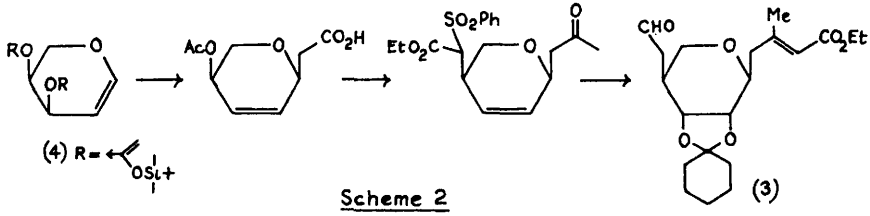
The use of carbohydrates as chiral starting materials for the synthesis of chiral non-carbohydrate products has been reviewed,[1,2] and an article on chelation or non-chelation control in addition reactions of chiral α- and β-alkoxy-carbonyl compounds includes carbohydrate examples, particularly of organometallic additions extending the carbon chain stereoselectively.[3]

1 Antibiotics and their Components

Syntheses have been reported for pseudomonic acid C (1)[4] and the closely related methyl deoxypseudomonate B (2),[5] both starting from L-lyxose and using a variety of organometallic reagents to extend the sugar chain at C-1 and C-5 (Scheme 1), and L-arabinose has been used to prepare the intermediate (3), a known precursor for pseudomonic acid, utilizing a Claisen rearrangement of the arabinal derivative (4)(Scheme 2).[6]

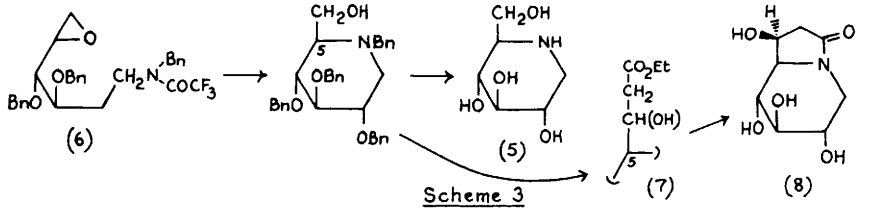


Scheme 1



Scheme 2

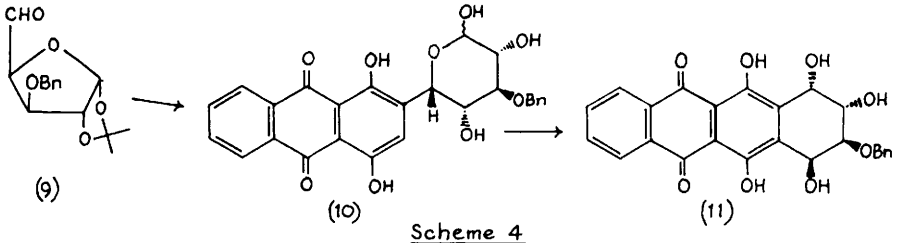
The conversion of D-glucose to 1-deoxy-nojirimycin (5) has been described, an N-benzyl-glucosylamine being converted to the amino-oxiran (6) which could be cyclized to the required piperidine derivative; alternatively, sequential Swern oxidation at C-6 and condensation with acetate lithium enolate led to the corresponding chain-extended imine (7) which could be de-N-protected by hydrogenolysis and then cyclized to give (+)-castanospermine (8), thus establishing the absolute configuration of this alkaloid (Scheme 3).[7]



Scheme 3

Another paper describes the preparation of 1-deoxy-mannojirimycin (the C-2 epimer of (5)) either from D-mannose (with double inversion at C-5) or from D-glucose (with inversion at C-2).[8]

Further work has been reported on using sugars to elaborate chiral anthracyclines. The xylo-dialdose derivative (9) can be condensed with leuco-quinizarin leading to the derivative (10), which was then cyclized by the Marschlak procedure to the optically pure anthracyclinone (11)(Scheme 4).[9] Full details of the Diels-Alder

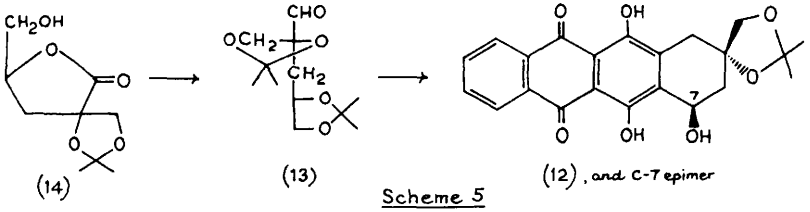


Scheme 4

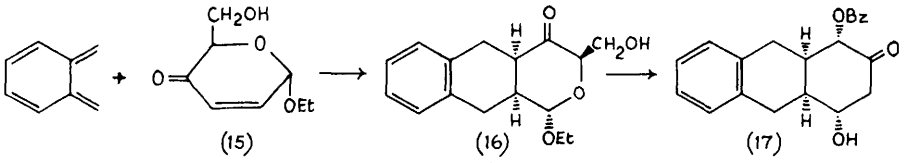
synthesis of 4-demethoxy-daunomycinone (Vol.17,p.247) have been published.[10] The closely related 4-demethoxy-anthracyclinone (12) has been obtained in optically active form by condensing the branched-chain sugar (13) prepared from isosaccharino-1,4-lactone (14)(from lactose) with leuco-quinizarin and cyclizing as for (11) (Scheme 5); other anthracyclinones were also prepared from (14).[11] An alternative Diels-Alder procedure using the glycenosidulose (15) with o-xylylene led to the tricyclic product (16), which was rearranged by Ferrier's procedure to the chiral tricycle (17)(Scheme 6).[12]

D-Glucose has been used as a source material for a synthesis of

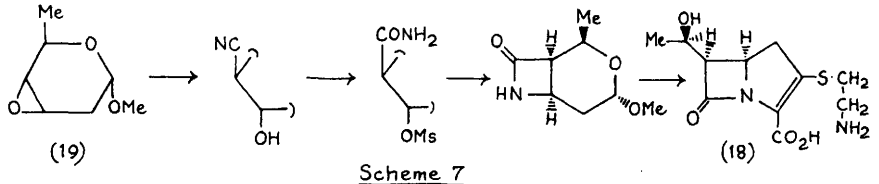
6-epithienamycin (18) via the dideoxyoxiran (19)(Scheme 7).[13] A synthesis of the carbapenem SQ 27860 (20) used the dideoxyaminosugar acid (21) prepared from D-glucosamine.[14]



Scheme 5

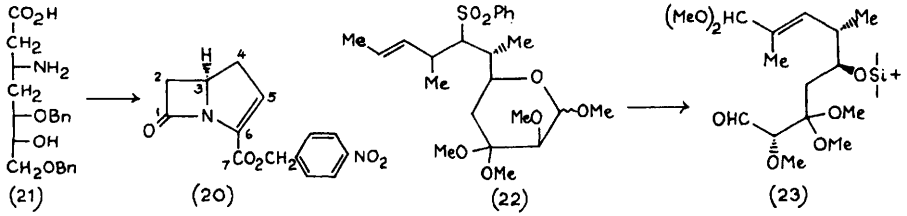


Scheme 6

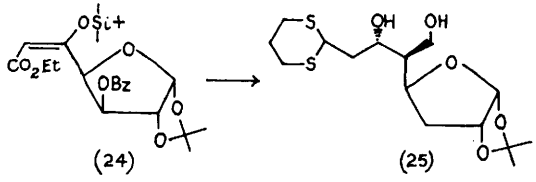


Scheme 7

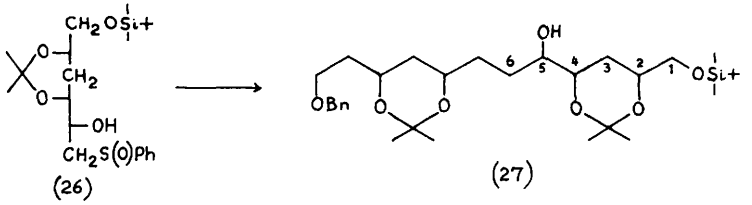
A number of fragments of macrolide rings have been synthesized from carbohydrates. D-Mannose has served as a source of the acyclic structure (22) via the glycosidulose derivative (23), and this was then incorporated into the ansa macrolactam precursor maytansinol.[15]



The diacetone-glucose derived intermediate (24) provides a route to the synthon (25) which can be used in the synthesis of amphotericin

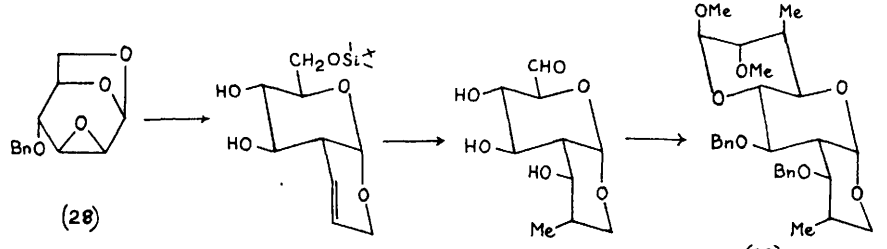


B.[16] Another laboratory has reported the conversion of diacetone-L-glucose to a 3-deoxy-ribo-hexitol, and hence to the deoxy-arabino-hexitol (26), which could then be condensed with a similar polyol derived from (S)-malic acid to furnish the C-1 → C-12 unit in amphotericin B (27).[17] The dianhydro-sugar (28) has been developed as a



(26) (27)

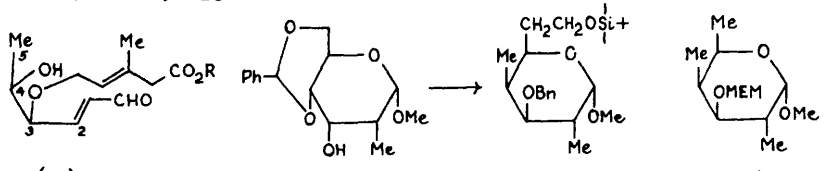
starting material for the preparation of the key intermediate (29) (Scheme 8) required for the ansa chain in rifamycin, and the use of carbohydrates for synthesizing such acyclic chains with many chiral centres was discussed generally, including the concept of pyranosidic homologation.[18] Full details of the synthesis of the C-19 → C-29



(28) (29)

Scheme 8

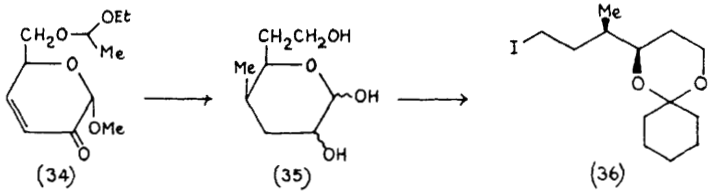
fragment in rifamycin S have been published (see Vol. 16,p.270).[19] 5-Deoxy-1,2-cyclohexylidene-D-xylofuranose has been used to prepare the macrolide fragment (30)(sugar chain numbering) by O-3 etherification with subsequent 1,2-periodate cleavage and Wittig condensation.[20] Likewise the 2-C-methyl sugar (31) can furnish the derivatives (32) and (33) which are respectively the protected forms of the C_3-C_8 and C_9-C_{13} sections of the oleandomycin macrocycle.[21]



(30) (31) (32) (33)

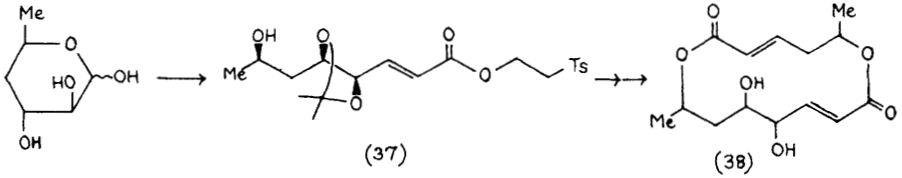
A synthesis of the ionophore antibiotic A 23187 (calcimycin) has been completed, using D-glucose as a source of the enone (34), and

hence the 4-C-methyl sugar (35) and the iodohexanediol derivative (36), which could then be condensed with the previously reported fragment (see Vol. 15,p.257).[22] 4,6-Dideoxy-D-arabino-hexopyranose



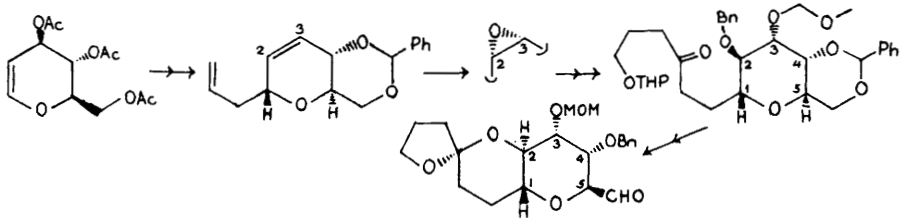
(34) (35) (36)

has provided the octenoic acid derivative (37) which was then esterified with 5-tetrahydropyranyloxy-hex-2-enoic acid and subsequently cyclized to give the plant pathogen metabolite colletodiol (38).[23,24]



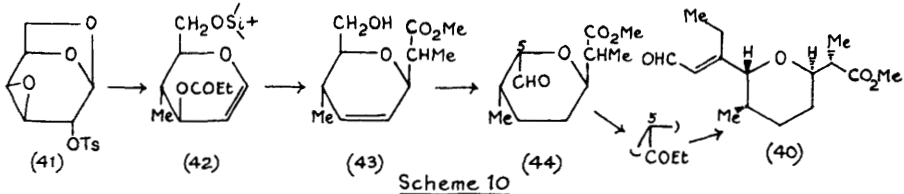
(37) (38)

A fragment (39)(sugar chain numbering) of the polyether marine toxin okadaic acid has been synthesized from D-glucal triacetate (Scheme 9).[25] D-Glucose also provides the chiral source for the



Scheme 9 (39)

fragment (40), which represents part of indanomycin, the dianhydro sugar (41) leading successively to the glycal (42), the dihydropyran (43), the aldehyde (44), and hence to (40)(Scheme 10).[26]

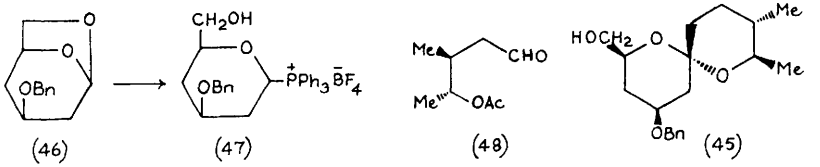


(41) (42) (43) (44) (40)

Scheme 10

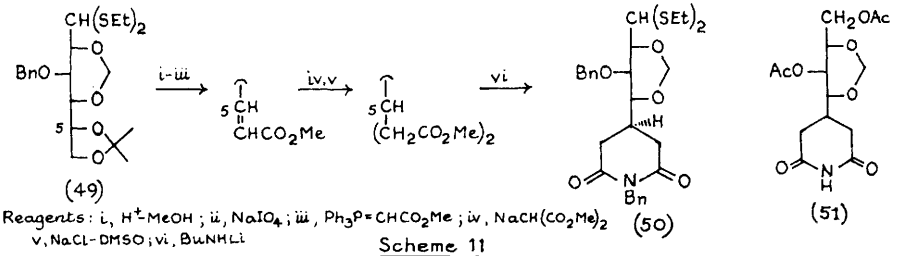
Studies towards the synthesis of a fragment of the antibiotic ionomycin involving branched-chain sugar intermediates are referred to in Chapter 14.

The dioxaspiro [5,5] undecane (45), a building block for the anti-parasitic agents milbemycin and avermectin, has been constructed in enantiomerically pure form from the dideoxy-sugar anhydride (46), which yields the phosphonium salt (47) on treatment with triphenyl-phosphonium tetrafluoroborate; the ylide derived from (47) was condensed with the aldehyde (48) and cyclized stereospecifically to give (45).[27]



(46) (47) (48) (45)

The D-glucose derivative (49) serves as a convenient source for preparing both enantiomers of the precursor (50) for the antitumour compound sesbanimide. Scheme 11 outlines the synthesis of the D-enantiomer; the L-form was obtained by demasking the aldehyde at C-1, forming the imide ring as before, and finally generating the dithioacetal following periodate cleavage of the terminal diol.[28]



(49) (50) (51)

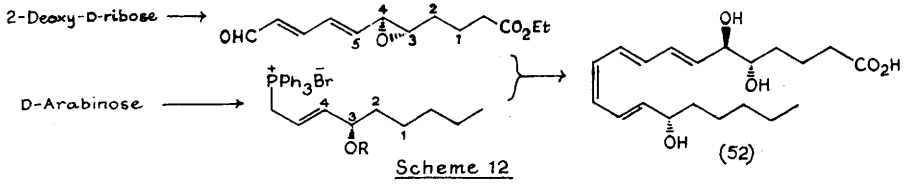
Reagents: i, H^+-MeOH; ii, $NaIO_4$; iii, $Ph_3P{=}CHCO_2Me$; iv, $NaCH(CO_2Me)_2$ v, NaCl-DMSO; vi, BuNHLi

Scheme 11

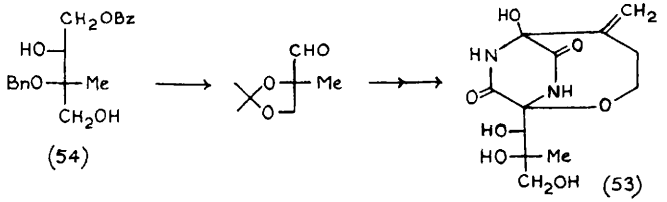
A very similar sequence to the closely related analogue (51) has been described, starting from D-sorbitol (a source of 2,4;3,5-di-O-methylene-L-xylose).[29] A possible stereostructure for lipoxin A (52) has been synthesized from 2-deoxy-D-ribose and D-arabinose derivatives (sugar chain numbering)(Scheme 12).[30]

A chiral synthesis of bicyclomycin (53) has been reported which utilizes the branched-chain threitol (54), derived from D-glucose, to provide the trihydroxy sidechain.[31]

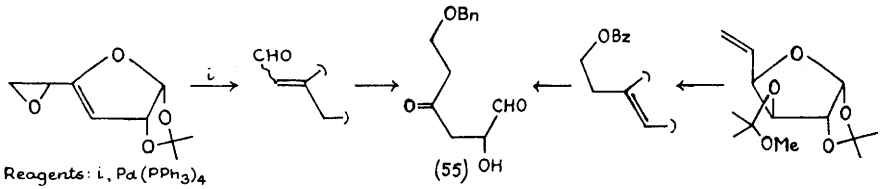
Two routes from D-glucose to (-)-pentenomycin have been explored, both involving the keto-aldehyde (55) which cyclizes in aldol



Scheme 12



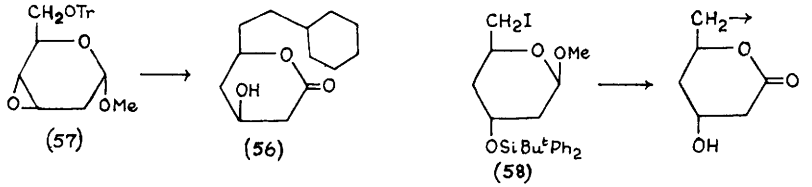
fashion to the corresponding cyclopentenone derivative; one route utilized a novel palladium-catalysed rearrangement of alkenyloxiran to enal (Scheme 13).[32]



Scheme 13

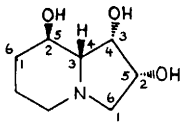
2 Enzyme Inhibitors

A synthesis of the lactone part (56) of the coenzyme A reductase inhibitor compactin has been reported, starting from compound (57) derived from triacetyl-D-glucal.[33] The chiral intermediate (58), derived also from triacetyl-D-glucal, has been converted to the corresponding lactone and incorporated (via C-6 substitution) in a synthesis of the compactin relative (+)-dihydromevinolin.[34]



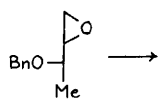
Several syntheses of the α-mannoside inhibitor (-)-swainsonine (59) have been recorded, using either D-mannose[35,36] or

D-glucose[37,38] as the chiral starting material, the former being converted to a 4-amino-4-deoxy-D-mannose intermediate, the latter to a 3-amino-3-deoxy-D-mannose derivative. The adenosine deaminase inhibitor (+)-EHNA (60) has been prepared using L-ascorbic acid as the source of the chiral oxiran precursor (61).[39]



(59)

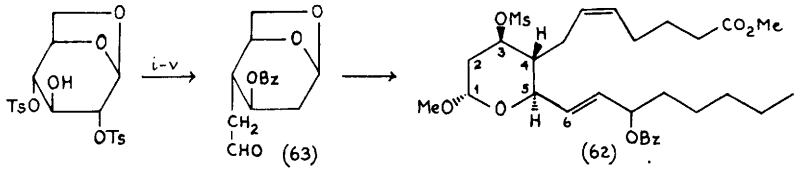
mannose numbering exocyclic
glucose numbering endocyclic



(61) (60)

3 Prostanoids and Related Compounds

The marine prostanoid clavulone has been synthesized enantiospecifically, D-mannitol being used to supply the chiral C-4 allylic alcohol unit.[40] 1,6-Anhydro-D-glucose provides a source for the thromboxane precursor (62) via the branched-chain sugar (63) (Scheme 14).[41] Six 8,15-dihydroxy derivatives of arachidonic acid (8,15-LTB compounds) have been prepared, deriving chiral centres

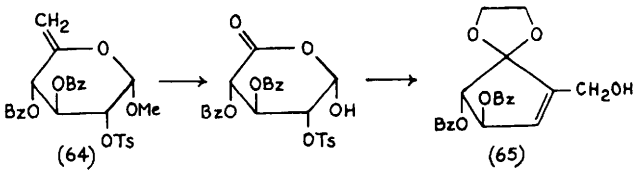


(63) (62)

Reagents: i, MeO^-; ii, $CH_2{=}CHCH_2MgCl$-CuI; iii, Et_3BHLi; iv, BzCl-Py; v, O_3

Scheme 14

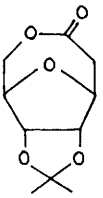
from carbon-3 in 2-deoxy-4,5-O-isopropylidene-D- or -L-erythro-pentose obtained from arabinose.[42] Another communication describes the use of 2-deoxy-D-erythro-pentose to prepare the 11S,12S-oxido derivative of 5Z,7E,9E,14Z-eicosatetraenoic acid (i.e.,11S,12S,-LTA_4).[43] Routes to functionalized cyclopentene derivatives from 6-deoxy-hex-5-enopyranosides have been explored, e.g., (64)→(65).[44]



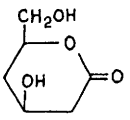
(64) (65)

4 Lactones

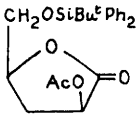
The synthesis and resolution of the bicyclic lactone (66)(actually obtained from a non-carbohydrate precursor) has been described, and its use in the synthesis of C-nucleosides was also extensively surveyed.[45] D-Ribonolactone serves as a convenient chiral source for the lactone (67) required for nonactic acid studies,[46] and also provides a convenient entry to optically active pheromones and aromas possessing γ-alkyl-γ-lactone structures, e.g., compounds (68) and their 2,3-dihydro analogues [47] and the valerolactones (69).[48]

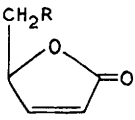


(66)

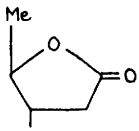


(67)



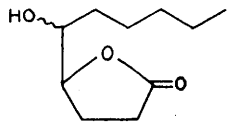


(68) R = Me, Bu

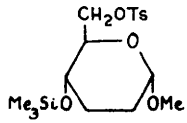


(69) R = H, OH

D-Ribose has been used to synthesize the epimeric alkylated γ-lactones (70), until recently thought to be anthracycline biosynthesis regulators.[49] Another paper describes the synthesis of the 5-(R)-epimer by alkylation of the 6-O-tosyl ester (71) with lithium dibutylcuprate; the author concludes that this approach to extending the carbon chain of carbohydrates compares very favourably with the more usual three-stage sequence of oxidation-Wittig reaction-reduction.[50]

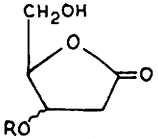


(70)

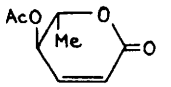


(71)

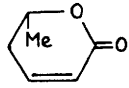
2,3-O-Isopropylidene-D-glyceraldehyde (from D-mannitol) reacts stereoselectively with organometallic or Wittig reagents leading to either erythro- or threo-β-substituted glyconic acids and hence lactones (72).[51]



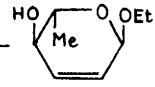
(72)



(74)

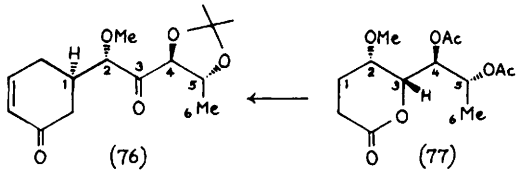


(73)



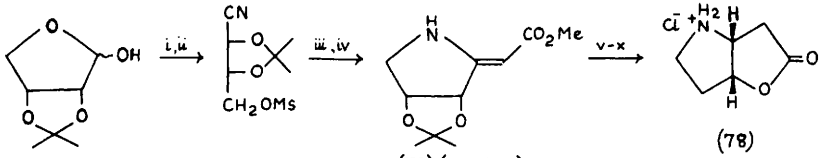
(75)

Diacetyl-L-rhamnal has been used to synthesize (S)-parasorbic acid (73) and other 5-S-hydroxy six-carbon synthons via the unsaturated lactone (74) or the glycenoside (75).[52] A standard Wittig reaction has been used to convert a D-galactose derivative to the aureolic acid aglycone (76)(sugar numbering) via the lactone (77).[53]



(76) (77)

2,3-O-Isopropylidene-D-erythrose has been used to prepare the precursor (78), previously used in synthesizing the pyrrolizidine alkaloid (+)-retronecine, via the intermediate enamino-glyconic acid (79) as outlined in Scheme 15.[54]



(79) (Z:E, 30:1)

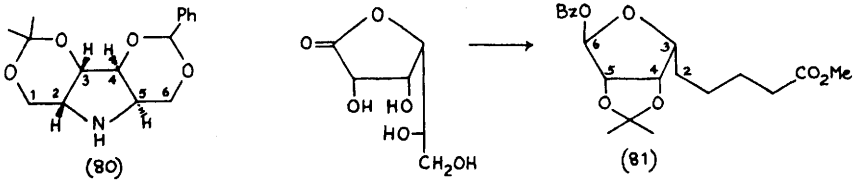
Reagents: i, NH_2OH; ii, MsCl-Py; iii, $BrCH_2CO_2Me$-Zn; iv, DBU; v, $NaBH_3CN$; vi, BnOCOCl-NEt_3; vii, H_3O^+; viii, $(\text{thiourea})_2CS$-Py; ix, Bu_3SnH; x, H_2-Pd

Scheme 15

5 Miscellaneous Compounds

A review on phospholipids in biomembranes includes a summary of synthetic routes from 3,4-O-isopropylidene-D-mannitol.[55]

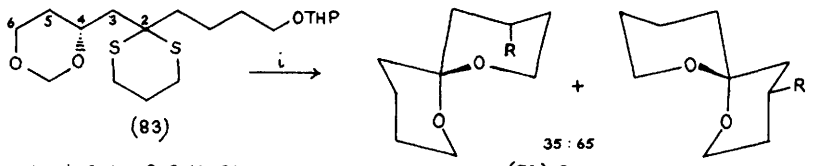
D-Glucosamine serves as a source of the chiral pyrrolidine derivative (80)(sugar numbering).[56] A new multistep synthesis of



(80) (81)

(+)-biotin has been described, using D-glucuronolactone as a chiral source for the precursor (81)(glucose numbering) via the L-gulono-γ-lactone.[57] Both enantiomers of the insect pheromone 1,7-dioxaspiro[5,5]undecane (82)(R=H) have been synthesized from D-glucose via its 3,5-dideoxy analogue which was then converted to the

dithiane derivative (83)(glucose numbering)(Scheme 16).[58]

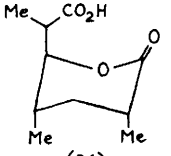


(83) (82) R = OH

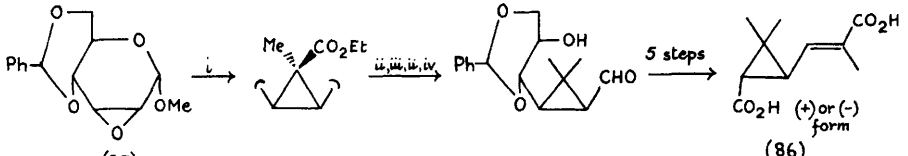
Reagents : i, $CuCl_2$-CuO, Me_2CO-H_2O

Scheme 16

Laevoglucosenone provides short, stereoselective routes to chiral synthons leading to (-)-δ-multistriatin and (+)-Prelog-Djerassi lactonic acid (84)(see also Vol.16, p.265).[59] The allo-oxiran (85) (obtained from D-glucose) has been used as the chiral control in a synthesis of chrysanthemic acids (86)(Scheme 17), the cyclopropane ring being formed by Wadsworth-Emmons reaction.[60]



(84)



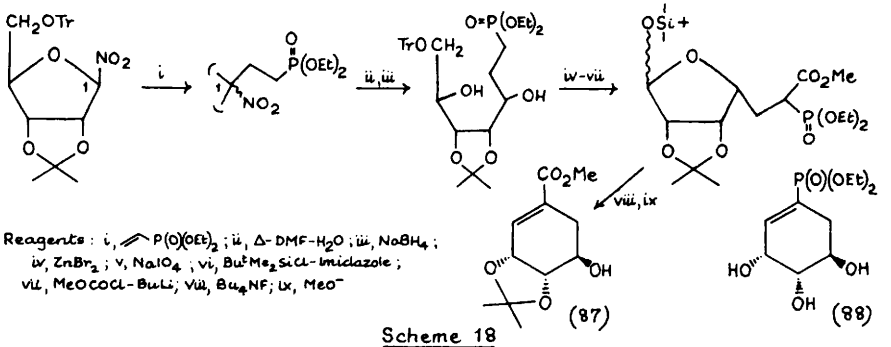
(85) (86)

Reagents : i, $(EtO)_2P(O)CHMeCO_2Et$ - NaH - 160°, press. ; ii, LAH ; iii, MsCl - Py ; iv, H_2O

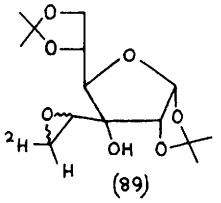
Scheme 17

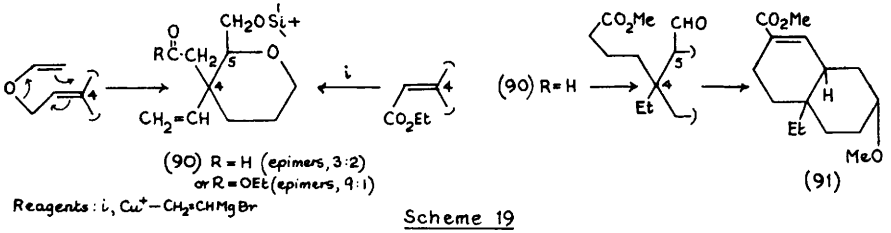
A synthesis of shikimic acid (87) proceeds from D-ribose as outlined in Scheme 18; use of diethyl phosphorochloridate in step (vii) likewise yielded the diethyl phosphonate analogue (88).[61] Chiral control in a synthesis of chiral acetic acid has been achieved using the standard 3-osulose derived from D-glucose as the source of the diastereoisomeric oxirans (89), each of which was then sequentially reduced with lithium aluminium tritiide and oxidized with periodate.[62]

D-Glucose has been used to prepare the geminally substituted branched-chain sugar derivatives (90), as shown in Scheme 19; the ethanal derivative was then used to prepare the bicycle (91) required for the synthesis of the trichothecane verrucarol.[63] In another report, Fraser-Reid's group describe an approach to sesqui-



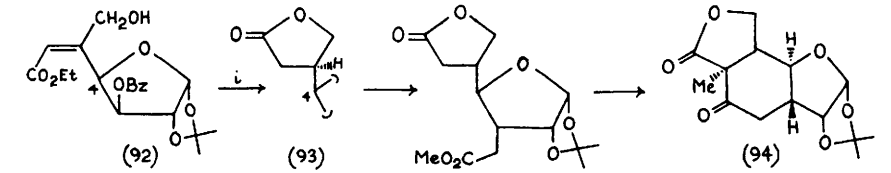
Scheme 18





Scheme 19

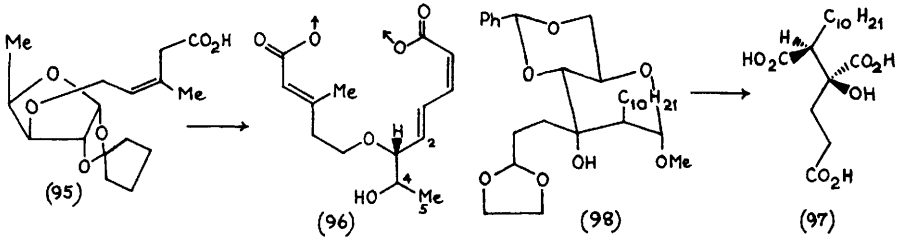
terpene lactones utilizing "off-template"stereocontrol in the reduction of the unsaturated branched-chain sugar (92) obtained from D-glucose to give the lactone (93), which was then elaborated to give the sesquiterpene (94)(Scheme 20).[64]



Scheme 20

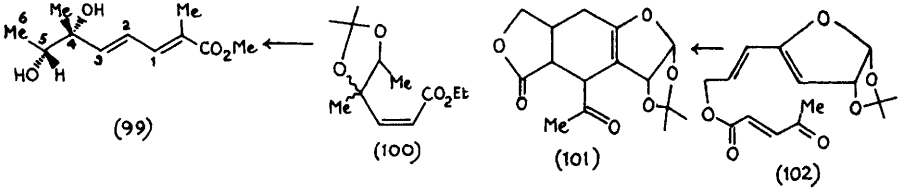
D-Xylose has been used as a starting material for the synthesis of the macrocyclic loop of the anti-leukaemic trichothecanoids baccharin B5 and roridin E, which contains the C-6' and C-13' asymmetric centres. Standard transformations on crystalline

1,2;3,5-di-O-cyclopentylidene-α-D-xylofuranose led to the derivative (95) and hence to the named compounds which contain the fragment (96)(sugar numbering) attached via ester links to the terpene verrucarol or a deoxy analogue.[65] The anhydro alloside (85) has

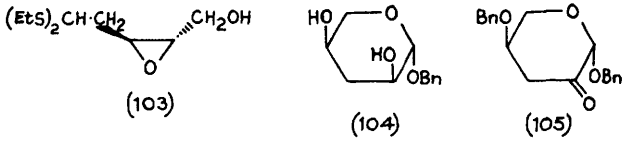


served to establish the stereochemistry of the fungal metabolite spiculisporic acid A (97), which was prepared by oxidative degradation of the doubly branched-chain sugar (98) obtained from (85) utilizing stereoselective organometallic reactions of the oxiran and subsequently derived 3-ulose.[66]

The structures and stereochemistry of citreodiol (99)(sugar numbering) and epicitreodiol, metabolites of Penicillium citreoviride, have been determined by synthesis of their antipodes from L-rhamnose; two routes led to the epimeric branched-chain glycenonic esters (100), which were converted to (99) and its epimer by a conventional Wittig sequence.[67] An intramolecular Diels-Alder



reaction gave the tricyclic derivative (101) from the diene (102) derived from D-glucose; the double bond in (101) was exclusively hydrogenated on the face anti to the dioxalan ring.[68] L-Arabinose serves as a source of the chiral epoxide (103),[69] and the chiral



synthons (104) and (105) and their enantiomers have been obtained from L- and D- arabinose.[70]

References

1 T.D.Inch, Tetrahedron, 1984, 40, 3161.
2 N.K.Kochetkov, A.F.Sviridov, M.S.Ermolenko, et al., "Carbohydrates in the Synthesis of Natural Compounds",(Nauka: Moscow, USSR), 1984.
3 M.T.Reetz, Angew. Chem. Int. Ed. Engl., 1984, 23, 556.
4 G.E.Keck, D.F.Kachensky, and E.J.Enholm, J. Org. Chem., 1984, 49, 1462.
5 A.P.Kozikowski and K.L.Sorgi, Tetrahedron Lett., 1984, 25, 2085.
6 D.P.Curran and Y.-G.Suh, Tetrahedron Lett., 1984, 25, 4179.
7 R.C.Bernotas and B.Ganem, Tetrahedron Lett., 1984, 25, 165.
8 G.W.J.Fleet, M.J.Gough, and T.K.M.Shing, Tetrahedron Lett., 1984, 25, 4029.
9 D.J.Mincher and G.Shaw, J. Chem. Soc. Perkin Trans. 1, 1984, 1279.
10 R.C.Gupta, P.A.Harland, and R.J.Stoodley, Tetrahedron, 1984, 40, 4657.
11 F.Bennani, J.-C. Florent, M.Koch, and C.Monneret, Tetrahedron, 1984, 40, 4669; Tetrahedron Lett., 1984, 25, 3975.
12 S.Chew and R.J.Ferrier, J. Chem. Soc., Chem. Commun., 1984, 911.
13 A.Knierzinger and A.Vasella, J. Chem. Soc., Chem. Commun., 1984, 9.
14 M.Miyashita, N.Chida, and A.Yoshikoshi, J. Chem. Soc., Chem. Commun., 1984, 195.
15 M.Kitamura, M.Isobe, Y.Ichikawa, and T.Goto, J. Am. Chem. Soc., 1984, 106, 3252.
16 D.Liang, H.W.Pauls, and B.Fraser-Reid, J. Chem. Soc., Chem. Commun., 1984, 1123
17 S.Masamune, P.Ma, H.Okumoto, J.W.Ellingboe, and Y.Ito, J. Org. Chem., 1984, 49, 2834.
18 B.Fraser-Reid, L.Magdzinski, and B.Molino, J. Am. Chem. Soc., 1984, 106, 731.
19 S.Hanessian, J.-R.Pougny, and I.K.Boessenkool, Tetrahedron, 1984, 40, 1289.
20 W.C.Still, C.Gennari, J.A.Noguez, and D.A.Pearson, J. Am. Chem. Soc., 1984, 106, 260.
21 S.S.Costa, A.Olesker, T.T.Thang, and G.Lukacs, J. Org. Chem., 1984, 49, 2338
22 Y.Nakahara, A.Fujita, and T.Ogawa, J. Carbohydr. Chem., 1984, 3, 487.
23 H.Tsutsui and O.Mitsunobu, Tetrahedron Lett., 1984, 25, 2159,2163.
24 O.Mitsunobu, Chem. Future, Proc. IUPAC Congr., 29th, 1983 (Pub. 1984), 189 (Chem. Abstr., 1984, 101, 23829).
25 Y.Ichikawa, M.Isobe, and T.Goto, Tetrahedron Lett., 1984, 25, 5049.
26 M.P.Edwards, S.V.Ley, S.G.Lister, B.D.Palmer, and D.J.Williams, J. Org. Chem., 1984, 49, 3503.
27 J.Godoy, S.V.Ley, and B.Lygo, J. Chem. Soc., Chem. Commun., 1984, 1381.
28 G.W.J.Fleet and T.K.M.Shing, J. Chem. Soc., Chem. Commun., 1984, 835.
29 M.J.Wanner, G.-J.Koomen, and U.K.Pandit, Heterocycles, 1984, 22, 1483.
30 J.Adams, B,J,Fitzsimmons, and J.Rokach, Tetrahedron Lett., 1984, 25, 4713.
31 J.Yoshimura, M.Yamaura, T.Suzuki, and H.Hashimoto, Chem. Lett., 1984, 2157.
32 S.Achab, J.-P.Cosson, and B.C.Das, J. Chem. Soc., Chem. Commun., 1984, 1040.
33 T.Rosen, M.T.Taschner, and C.H.Heathcock, J. Org. Chem., 1984, 49, 3994.
34 J.R.Falck and Y.-L.Yang, Tetrahedron Lett., 1984, 25, 3563.
35 N.Yasuda, H.Tsutsumi, and T.Tayaka, Chem. Lett., 1984, 1201.
36 G.W.J.Fleet, M.J.Gough, and P.W.Smith, Tetrahedron Lett., 1984, 25, 1853.
37 M.H.Ali, L.Hough, and A.C.Richardson, J. Chem. Soc., Chem. Commun., 1984, 447.
38 T.Suami, K.Tadano, and Y.Iimura, Chem. Lett., 1984, 513.
39 E.Abushanab, M.Bessodes, and K.Antonakis, Tetrahedron Lett., 1984, 25, 3841.
40 H.Nagaoka, T.Miyakoshi, and Y.Yamada, Tetrahedron Lett., 1984, 25, 3621.
41 V.N.Kalè and D.L.J.Clive, J. Org. Chem., 1984, 49, 1554.
42 B.J.Fitzsimmons and J.Rokach, Tetrahedron Lett., 1984, 25, 3043.
43 R.Zamboni, S.Milette, and J.Rokach, Tetrahedron Lett., 1984, 25, 5835.
44 R.J.Ferrier and S.R.Haines, Carbohydr. Res., 1984, 130, 135.
45 T.Sato, Y.Hayakawa, and R.Noyori, Bull. Chem. Soc. Jpn., 1984, 57, 2515.
46 S.V.Attwood and A.G.M.Barrett, J. Chem. Soc. Perkin Trans. 1, 1984, 1315.
47 J.Cardellach, J.Font, and R.M.Ortuno, J. Heterocycl. Chem., 1984, 21, 327.
48 C.Papageorgiou and C.Benezra, Tetrahedron Lett., 1984, 25, 6041.
49 R.D.Cooper, V.B.Jigajinni, and R.H.Wightman, Tetrahedron Lett., 1984, 25, 5215.

50 J.-R.Pougny, Tetrahedron Lett., 1984, 25, 2363.
51 J.Mulzer, M.Kappert, G.Huttner, and I.Jibril, Angew. Chem. Int. Ed. Engl., 1984, 23, 704.
52 F.W.Lichtenthaler, F.D.Klingler, and P.Jarglis, Carbohydr. Res., 1984, 132, C1.
53 R.W.Franck, C.S.Subramaniam, T.V.John, and J.F.Blount, Tetrahedron Lett., 1984, 25, 2439.
54 J.G.Buchanan, G.Singh, and R.H.Wightman, J.Chem. Soc., Chem. Commun., 1984, 1299.
55 H.Eibl, Angew. Chem. Int. Ed. Engl., 1984, 23, 257.
56 C.Morin, Tetrahedron Lett., 1984, 25, 3205.
57 T.Ravindranathan, S.V.Hiremath, D.Rajagopala Reddy, and A.V.R.Rao, Carbohydr. Res., 1984, 134, 332.
58 H.Redlich and W.Francke, Angew. Chem. Int. Ed. Engl., 1984, 23, 519.
59 M.Mori, T.Chuman, and K.Kato, Carbohydr. Res., 1984, 129, 73.
60 B.J.Fitzsimmons and B.Fraser-Reid, Tetrahedron, 1984, 40, 1279.
61 S.Mirza and A.Vasella, Helv. Chim. Acta, 1984, 67, 1562.
62 K.Kobayashi, K.Kakinuma, and H.G.Floss, J. Org. Chem., 1984, 49, 1290.
63 D.B.Tulsham and B.Fraser-Reid, Tetrahedron, 1984, 40, 2083.
64 M.Georges, T.F.Tam, and B.Fraser-Reid, J. Chem. Soc., Chem. Commun., 1984, 1122.
65 W.C.Still, C.Gennari, J.A.Noguez, and D.A.Pearson, J. Am. Chem. Soc., 1984, 106, 260.
66 S.Brandänye, O.Dahlman, B.Lindquist, A.Måhlén, and L.Mörch, Acta Chem. Scand., Ser. B, 1984, 38, 837.
67 Y.Shizuri, S.Nishiyama, D.Imai, S.Yamamura, H.Furukawa, K.Kawai, and N.Okada, Tetrahedron Lett., 1984, 25, 4771.
68 B.Fraser-Reid, Z.Benkö, R.Guilliano, K.M.Sun, and N.Taylor, J. Chem. Soc., Chem. Commun., 1984, 1029.
69 C.Morin, J. Chem. Res., Synop., 1983, 275.
70 L.Pettersson, T.Frejd, and G.Magnusson, J. Org. Chem., 1984, 49, 4540.

Author Index

In this index the number given in parentheses is the chapter number, which is followed by the relevant reference number(s) within that chapter.

Abashev, Yu.P., (9) 53; (10) 14
Abate, V., (2) 37
Abbas, S.A., (3) 66, 69; (4) 38, 43, 50, 51
Abbas, S.H., (4) 33, 34
Abbasov, E.M., (17) 23
Abdelmejid, S.M.E., (20) 105
Abe, R., (19) 33
Abuaan, M.M., (9) 58; (12) 12
Abubakirov, N.K., (3) 32
Abushanab, E., (24) 39
Accorsi, C.A., (22) 61
Achab, S., (24) 32
Achmatowicz, O., jun., (13) 14; (15) 8
Acton, E.M., (3) 148; (19) 32, 42; (20) 99
Adachi, K., (3) 9; (19) 58; (20) 89
Adam, M.J., (8) 9
Adams, A.D., (19) 67
Adams, J., (24) 30
Adams, T.C., (14) 8, 15
Adinolfi, M., (4) 53, 68
Adlersberg, M., (7) 58
Aebischer, B., (10) 25; (13) 23
Afanas'ev, V.A., (14) 36; (22) 76
Afza, N., (7) 71; (8) 32; (9) 17, 18, 21-23
Aglietto, M., (3) 35
Ahmed, K., (3) 22
Ajito, K., (7) 46; (9) 56
Ajmera, S., (20) 66
Akhlebinin, A.K., (7) 66
Akimoto, K., (19) 15
Akrigg, D., (22) 60
Albano-Garcia, E., (6) 14; (20) 131
Albersheim, P., (22) 39
Albert, R., (8) 28; (19) 9, 10
Albrecht, H.P., (20) 126
Aldag, R., (5) 20
Alemany, A., (4) 48
Alen, R., (23) 15
Alexander, J., (19) 36
Alfoldi, J., (17) 31
Ali, M.H., (9) 71; (24) 37
Allerhand, A., (21) 52, 68
Alperin, D.M., (23) 17
Altona, C., (20) 156; (21) 5, 65
Ambrose, M.G., (5) 4; (7) 43
Ames, M.M., (10) 18
Ameta, S.C., (2) 56
Anderle, D., (7) 6
Andersen, B., (2) 52
Anderson, L., (3) 80
Anderson, W.F., (22) 101
Andersson, F., (15) 1
Ando, S., (4) 7; (22) 46
Andrews, G.C., (16) 40
Andrianov, V.I., (22) 55
Andronova, T.M., (9) 53; (10) 14
Angyal, S.J., (2) 1, 27; (18) 4; (21) 18
Anker, D., (9) 8, 30
Annaka, M., (19) 15
Anteunis, M.J.O., (5) 38; (6) 1
Antipin, M.Yu., (22) 76
Antonakis, K., (3) 143; (20) 81; (24) 39
Antonis, C., (20) 155; (21) 25
Anufriev, V.F., (3) 26
Anzai, K., (2) 152; (21) 63
Araki, K., (2) 22, 66
Araki, Y., (3) 156
Arbuzov, B.A., (7) 67
Areces Bravo, P., (10) 50, 51
Argoudelis, A.D., (19) 76
Ariga, T., (4) 7; (22) 46
Arita, M., (3) 9; (19) 58; (20) 89
Arlandini, E., (22) 25
Armistead, D.M., (3) 149
Armour, M.-A., (17) 5-8
Arnett, C.D., (8) 13
Arnett, G., (19) 70; (20) 108, 109
Arpone, A., (19) 43
Arshava, B.M., (12) 24, 25
Asai, M., (7) 76; (22) 68
Asano, N., (18) 37; (19) 3, 7
Assenza, S.P., (23) 59
Astles, D.J., (12) 4
Aszalos, A., (22) 8
Atal, C.K., (20) 88
Atalla, R.H., (22) 12
Atta-Ur-Rahman, (9) 12; (14) 14
Attwood, S.V., (24) 46
Aubagnac, J.L., (22) 23
Aubry, A., (14) 30; (22) 81
Auge, C., (4) 32, 40; (16) 22
Auge, J., (21) 29
Avalos Gonzalez, M., (9) 25, 26; (10) 19, 20, 43
Aver'yanova, V.M., (7) 4
Axt, E.M., (18) 34

Azhaev, A.V., (20) 72
Azhayev, A.V., (9) 14; (10) 23
Azmy, B., (20) 12
Azuma, I., (9) 49-51; (11) 4, 11, 12
Bachmann, D., (16) 46
Bacic, A., (23) 6
Back, D.M., (22) 4, 5, 129
Baczynskyj, L., (19) 76
Baer, H.H., (3) 50, 51; (12) 4
Baggett, N., (2) 24; (5) 31
Bailey, A.A.T., (2) 40
Bairamova, N.E., (4) 52
Baker, D.C., (19) 70; (20) 59, 82, 94, 95
Bakinovskii, L.V., (3) 90, 91; (4) 52; (6) 17
Bako, P., (5) 24
Bakos, J., (17) 18
Bambury, R.E., (20) 20, 21
Banaszek, A., (3) 100; (5) 33; (22) 63, 78
Bannister, B., (11) 13; (19) 78
Banoub, J.H., (3) 82; (22) 43
Bapat, A.R., (2) 66
Baraldi, P.G., (20) 16
Barascut, J.L., (20) 156; (21) 65; (22) 23
Barbachyn, M.R., (3) 147; (22) 79
Bardos, T.J., (20) 32
Barker, P.E., (23) 74
Barker, R., (2) 33; (3) 122
Barna, J.C.J., (19) 73
Barnhart, M., (19) 71
Barone, G., (2) 37; (3) 125; (4) 53; (22) 50
Barrett, A.G.M., (3) 151; (24) 46
Barrette, E.-P., (12) 6
Bartner, P.L., (19) 26; (22) 19
Basterrechea, Rey, M., (3) 1; (4) 25
Basu, D., (17) 24
Basu, S.N., (2) 65
Bates, R.B., (18) 38
Batley, M., (23) 43
Batta, G., (4) 15; (10) 33
Bauer, Ch., (23) 71
Bauer, H., (2) 18, 19; (7) 17
Bauer, T., (15) 12
Baumann, W., (16) 24
Baur, R.H., (20) 94, 95
Bayeul, D., (14) 30; (22) 81
Beaulage, S.L., (20) 114
Becchi, M., (3) 95
Beck, R.H.F., (23) 33
Bednarski, M., (14) 42
Beerman, H., (14) 13
Beetz, T., (5) 29; (10) 22; (13) 3
Beier, R.C., (21) 13
Beiter, A.H., (20) 117
Beland, F.A., (23) 63
Belanger-Gariepy, F., (22) 83
Bellanato, J., (3) 6; (14) 31
Belton, P.S., (21) 43
Belzecki, C., (14) 39
Be Miller, J.N., (3) 139
Benbow, J.A., (17) 26
Benezra, C., (24) 48
Benkö, Z., (22) 85; (24) 68
Benn, M.H., (3) 129, 130; (22) 59
Bennani, F., (24) 11
Bennek, J.A., (3) 115, 116; (18) 25
Benoit, R.L., (21) 64
Bentrude, W.G., (20) 122
Benz, G., (11) 15, 16; (19) 52
Benzing-Purdie, L., (10) 7
Beranek, J., (20) 38
Beres, J., (23) 69
Berger, M., (20) 147
Berger, S., (16) 38
Bergogne, M.-C., (20) 37
Bergstrom, D.E., (22) 21
Berman, E., (21) 52, 57, 68
Bernabe, M., (22) 69
Bernet, B., (16) 5
Bernhard, W.A., (22) 119
Bernotas, R.C., (24) 7
Berti, M., (19) 74
Bertolasi, V., (20) 16; (22) 61
Bessodes, M., (24) 39
Besson, E., (22) 124
Beszczynski, M., (9) 59
Betschart, H.F., (23) 32
Betz, R., (16) 20
Bhakuni, D.S., (20) 17
Bhat, K.S., (20) 69
Bhate, P., (22) 86
Bhatnager, P.K., (23) 50
Bhattacharjee, S., (22) 58
Bieber, M., (8) 42
Biely, P., (2) 28
Biermann, C.J., (2) 62
Bigler, P., (4) 10, 20
Bilik, V., (2) 28; (17) 31
Biller, L.M., (23) 19, 20
Billich, A., (20) 42
Binder, R.G., (18) 35; (22) 38
Binder, T.P., (3) 53; (11) 7; (12) 7
Binkley, R.W., (5) 4; (7) 13, 43, 74
Birch, E.J., (9) 67
Birch, J.R., (22) 9
Birkenmeyer, R.D., (19) 79
Birnbach, S., (3) 23
Bisagni, E., (21) 66
Blake, D.A., (3) 70
Blake, J.D., (23) 44
Blanchard, P., (19) 69
Blanc-Muesser, M., (11) 9
Blandin, M., (20) 154
Blaschke, T.F., (23) 62
Bleich, H., (21) 21
Bleidelis, J., (20) 45
Bliefert, C., (4) 4; (21) 10
Blount, J.F., (24) 53
Blunden, S.J., (17) 34
Boardley, M., (23) 36
Bobek, M., (20) 64
Bobleter, O., (23) 27, 31
Bock, K., (3) 39; (4) 3, 44, 64; (12) 16; (16) 12; (21) 45, 59, 62
Boessenkool, I.K., (24) 19
Bognar, R., (18) 39
Bonin, M., (3) 144
Bonn, G., (23) 27, 31
Borders, D.B., (19) 75; (22) 22
Borisenko, A.A., (17) 23
Borisov, E.V., (7) 66
Borowski, E., (19) 38

Borrachero Moya, P., (3) 6
Bose, S.N., (20) 100
Bosso, C., (4) 6; (22) 16
Bothner-By, A.A., (21) 60
Bottle, S., (7) 40
Bouillant, M.L., (3) 167; (23) 37
Bovee, W.M.M.J., (17) 35
Bovin, N.V., (4) 39
Bowie, J.U., (18) 26
Box, H.C., (22) 118
Box, V.G.S., (14) 26
Boyd, F.L., jun., (19) 59; (20) 59
Bradbury, J.H., (4) 26; (21) 53, 54
Brade, H., (3) 89; (16) 21
Brandänge, S., (24) 66
Brandstetter, H.H., (3) 87; (16) 23
Braun, H., (10) 26
Brawnell, G.L., (8) 15
Brdar, B., (20) 7
Brennan, P.J., (9) 2; (14) 4
Breuer, E., (10) 48; (17) 7
Briggs, A.J., (22) 48
Bright, G.M., (19) 25; (22) 114
Brimacombe, J.S., (9) 58; (12) 12; (14) 12; (22) 80
Brimer, L., (23) 34
Brinkman, U.A.Th., (23) 23
Brisse, F., (22) 83
Brittain, H.G., (22) 123
Brockman, R.W., (20) 136
Brockway, C., (14) 27
Brondz, I., (22) 32
Broser, E., (3) 20
Brostow, W., (21) 6
Broughton, H.B., (3) 151
Brown, A., (22) 42; (23) 4
Brown, E., (7) 79; (10) 13
Brown, J.M., (3) 49
Brown, K.L., (20) 30
Brown, P.R., (23) 59, 66
Brown, R.J., (12) 26
Brown, R.K., (3) 10
Brownell, J., (20) 110
Buchanan, J.G., (19) 46, 60, 64, 65; (20) 98; (24) 54
Buchanan, S., (2) 48
Buddrus, J., (7) 17
Budzinski, E.E., (22) 118
Budesinsky, M., (3) 28; (8) 22; (9) 68; (21) 19
Buffel, D., (3) 161
Buffel, D.K., (20) 92
Buffer, D., (20) 96
Bukharov, V.G., (7) 4
Bulian, H.-P, (14) 7; (16) 35; (22) 126
Bullock, M.W., (19) 85
Bulychev, Yu. N., (20) 14
Bundle, D.R., (4) 28, 49
Burak, K., (3) 51
Burke, S.D., (3) 149
Burtscher, E., (23) 27, 31
Burzynska, M.H., (15) 8
Bush, C.A., (21) 3
Bushnev, A.S., (3) 48
Buss, V., (9) 5
Busson, R., (23) 49
Bystricky, S., (22) 125
Cacciapuoti, G., (20) 76
Cadenas, R.A., (20) 111
Cadet, J., (20) 147
Cai, M., (3) 157
Calvo-Mateo, A., (9) 73; (12) 11; (13) 20; (14) 24
Camarasa, M.J., (9) 73; (10) 12; (12) 11; (13) 20; (14) 24; (20) 41
Campbell, M.M., (18) 46, 47
Cano, F.H., (22) 64, 69
Canonico, P.G., (19) 67
Capek, K., (9) 60
Capek, P., (5) 6
Capillon, J., (3) 37, 38
Capkova, J., (9) 60
Capparelli, M.V., (22) 112
Card, P.J., (8) 25
Cardellach, J., (16) 13a; (24) 47
Cardillo, G., (9) 27; (12) 13
Carlström, A.-S., (3) 71; (4) 24, 36, 54
Carminatti, H., (23) 17
Carr, S.A., (22) 17
Carteni-Farina, M., (20) 76
Carty, R.P., (20) 71
Carver, J.P., (4) 22
Cassai, E., (20) 16
Cassinelli, G., (19) 43
Castillon, S., (5) 35; (21) 69
Castronuova, G., (2) 37; (3) 125
Cavagna, F., (21) 55
Cavalleri, B., (19) 74
Ceccherelli, P., (3) 45
Cech, D., (8) 35; (20) 49, 67, 153
Cerezo, A.S., (22) 35
Cerny, I., (3) 28; (9) 9, 68
Cerny, M., (8) 22; (9) 9, 68
Cha, J.K., (18) 9
Chambert, R., (11) 6
Chan, M., (16) 43
Chan, Y. M., (6) 20
Chang, F.W., (18) 6
Chang, R.D., (19) 75; (22) 22
Chapleur, Y., (3) 152; (14) 30; (18) 40; (22) 81
Chapple, C.C.S., (23) 38
Charon, D., (3) 76, 77; (7) 59
Charubala, R., (20) 117, 118, 155; (21) 25
Chatterjee, V., (2) 65
Chattopadhyaya, J., (20) 46
Chauhan, S.C., (22) 121
Chavis, C., (10) 3
Cheetham, N.W.H., (23) 30
Chembert, R., (3) 52
Chen, C.-M., (5) 1, 14; (7) 27; (14) 5
Chen, D., (3) 157
Chen, F.-H., (3) 42
Chen, S.S., (23) 67
Chen, S.-Y., (3) 160; (13) 19; (16) 13
Chen, Y., (22) 57
Cherepinskii-Malov, V.D., (7) 67
Chernyak, A.Ya., (4) 31
Chernyshev, A.I., (19) 84
Cheung, H.T.A., (22) 91
Chew, S., (24) 12

Chiang, P.K., (19) 61
Chiasson, J.B., (21) 6
Chida, N., (18) 49, 50; (24) 14
Chikashita, H., (7) 29, 36; (9) 54
Chirva, V.Ya., (5) 9-11; (16) 28-30; (23) 8
Chiu, J.S., (19) 16
Chiu, S.H.L., (19) 85
Chizhov, O.S., (21) 46
Chmielewski, M., (13) 14; (14) 39
Cho, I.H., (15) 10
Choay, J., (4) 41, 67
Chou, T.C., (20) 63
Chopin, J., (3) 167; (22) 124; (23) 37
Chowdhary, M.S., (7) 15
Chowdhury, B.L., (20) 17
Chretien, F., (18) 40
Christ, W.J., (18) 9
Christian, R., (3) 88; (4) 58; (16) 21
Chu, C.K., (20) 87, 102, 103
Chu, G.K., (20) 135
Chucholowski, A., (3) 127, 135; (10) 2
Chudek, J.A., (18) 1
Chuman, T., (14) 33; (21) 42; (22) 82; (24) 59
Chun, M.W., (8) 7
Chung, S., (12) 18
Chung, W.K., (8) 7
Chursina, N.A., (22) 76
Cimino, F., (23) 57
Cirovic, M., (19), 2
Cisneros, x., (7) 68, (10) 21
Cuicanu, I., (5) 2
Claes, P.J., (23) 49
Claessens, H.A., (23) 29
Clarke, A.E., (23) 6
Clarke, M.L., (23) 44
Classon, B., (3) 99; (8) 40
Claus-Walker, J., (23) 72
Claverie, N., (23) 61
Clayton, J.D., (20) 108
Clive, D.L.J., (24) 41
Cobbledick, R.E., (8) 27; (22) 67
Coccia, R., (3) 45
Cochran, T.G., (22) 87
Coetzee, I., (9) 75
Cole, J.R., (18) 38
Cole-Hamilton, D.J., (16) 41
Collins, J.M., (23) 65
Collins, P.M., (3) 46; (9) 31
Coll Manchado, F., (4) 25
Colmenares, L.U., (6) 14; (20) 131
Combarieu, R., (22) 23
Conde, A., (22) 75
Conn, E.E., (7) 30
Cook, A.F., (19) 62
Cook, P.D., (19) 67
Cook, S.J., (3) 49
Cook, W.J., (22) 105
Cooper, R.D., (24) 49
Cory, J.G., (19) 61
Cosson, J.-P., (24) 32
Cosstick, R., (20) 141
Costa, S.S., (24) 21
Cottam, H.B., (20) 13, 55
Couto, A., (3) 58
Cox, I.J., (21) 43
Crabbe, M.J.C., (2) 53; (23) 28
Crews, R.P., (20) 82
Cristescu, C., (20) 6
Crow, F.W., (22) 21
Csarnyi, A.H., (23) 69
Csuk, R., (16) 31
Culver, C.A., (19) 55
Curini, M., (3) 45
Curran, D.P., (24) 6
Cusack, P.A., (17) 34
Cygler, M., (22) 101
Dabrowski, J., (4) 5
Dabrowski, U., (4) 5
D'Accorso, N.B., (7) 14; (22) 31
Dahlbender, B., (7) 31
Dahlhoff, W.V., (17) 33
Dahlman, O., (24) 66
Dahmen, J., (3) 71; (4) 24, 36, 54; (21) 26
Daido, Y., (10) 45, 46
Dais, P., (21) 51
Dalgaard, L., (10) 6; (23) 34
Dalgue, S., (20) 110
Dalley, N.K., (19) 67; (20) 10, 11, 13; (22) 103
Daman, M.E., (17) 29
Danenberg, K., (20) 66
Dangre, A.J., (2) 44
Daniel, J.R., (14) 19
Danilov, L.L., (7) 61
Danishefsky, S., (3) 147; (13) 1; (14) 42; (22) 79
Danyluk, S.S., (20) 151; (21) 24
Danzin, C., (23) 61
Darbon, N., (22) 53, 70, 89
Darise, M., (3) 42
Das, B.C., (24) 32
Das, P.K., (3) 117
David, S., (4) 32; (5) 27; (16) 22; (21) 29
Davidson, R.B., (20) 13
Davies, D.B., (20) 151; (21) 24
Davies, R.J.H., (20) 100
Davis, H.F., (3) 117
Davison, I.R., (18) 1
Dawe, R.D., (3) 141; (13) 8; (16) 4
Dax, K., (8) 28; (19) 9, 10
Dean, P.D.G., (7) 78; (22) 20
Debono, M., (19) 71
Debost, J.-L., (6) 3
De Bruyn, A., (5) 38; (6) 1
De Bruyne, C.K., (3) 109
Deceuninck, J.A., (20) 92
Dechter, J.J., (20) 94
De Clercq, E., (19) 61; (20) 134
Decoster, E., (22) 89
Dedek, V., (8) 35
Defaye, J., (2) 27; (3) 51, 52; (4) 6; (11) 3, 6, 9; (22) 16
Deffo, T., (3) 22; (21) 67
Deger, H., (21) 55
De Gourcy, C., (10) 3
De Lahaye, P., (3) 101
De Lange, J., (3) 25
De Las Heras, F.G., (9) 73; (12) 11; (13) 20; (14) 24; (20) 41
de Lederkremer, Rr.M., (3) 58; (12) 15; (16) 11
De Leeuw, F.A.A., (21) 5
Dellamonica, G., (3) 167
Della Ragione, F., (20) 76
Delzer, J., (19) 51
Denisenko, V.A., (3) 15
De Paoli, A., (19) 74
Depew, M.C., (16) 42, 43

Depezay, J.-C., (9) 40; (14) 22
Descotes, G., (3) 119, 120; (7) 39; (22) 90
Deshong, P., (9) 33; (12) 23
Dessinges, A., (5) 35; (8) 12; (21) 69
Devienne, F.M., (22) 23
Dewaele, C., (3) 101
De Wit, G., (2) 49
Dianez, M.J., (22) 84
Dicken, C.M., (9) 33
Diez-Masa, J.C., (20) 129; (23) 70
Dill, K., (17) 29
Dimare, M., (12) 26
Dimova, N., (23) 7
Diolez, C., (3) 77; (7) 59
Dittel, W., (18) 52
Dittrich, P., (18) 32
Dmitriev, B.A., (4) 31, 46
Dobler, M., (3) 100; (5) 33; (22) 63
Doboszewski, B., (4) 30; (8) 2
Dodson-Simmons, O., (21) 4
Dokolina, E.V., (3) 48
Dolezalova, J., (8) 22
Dolle, R.E., 93) 127, 131, 135; (8) 4; (10) 2
Dolphin, D., (8) 27; (22) 67
Donald, A.S.R., (4) 62
Doner, L.W., (19) 20
Doornbos, J., (20) 155, 156; (21) 25, 65
Dorland, L., (16) 26
Doyle, R.J., (7) 47
Drasar, P., (3) 28
Dreimane, A., (20) 45
Driguez, H., (3) 52; (11) 3, 6, 9
Driller, H., (20) 34
Driscoll, J.S., (20) 8
Drivas, I., (9) 8
Dropkin, D., (2) 23
Duben, A.J., (21) 3
Dubois, M.A., (3) 167
Duchaussoy, P., (4) 41, 67
Duddeck, H., (19) 80
Dudyez, L.W., (20) 26
Du Mortier, C., (12) 15
Dunnigan, D.A., (19) 2, 21
Dupeyre, D., (4) 61
Dupuis, J., (22) 117
Dureault, A., (9) 40; (14) 22
Duszczyk, K., (23) 46
Dvortsak, P., (6) 8
Dyatkina, N.B., (9) 14; (10) 23; (20) 51, 72
Dyong, I., (13) 13
Eagles, J., (20) 157
Ealick, S.E., (22) 105
Earl, W.L., (2) 51; (21) 15
Ebringerova, A., (4) 13
Eby, R., (5) 5; (7) 5; (8) 20
Eckstein, F., (20) 124
Eder, H., (3) 46
Edwards, M.P., (24) 26
Egan, R.S., (19) 2
Egge, H., (4) 5
Ehrenkaufer, R.E., (8) 8, 10
Ehrler, R., (9) 5
Ehrlich, M., (23) 60
Eibl, H., (24) 55
Einstein, F.W.B., (8) 27; (22) 67
Eisermann, D., (13) 11
Ekborg, G., (3) 72, 75
El Ashry, E.S., (10) 40; (16) 45
Elia, V., (2) 37; (3) 125
El Kabbani, F.M., (20) 87
El Kilany, Y., (10) 40; (16) 45
El'kin, Yu.N., (22) 33, 34
Ellenberger, S.R., (9) 44; (14) 15
Ellingboe, J.W., (24) 17
Elliott, R.D., (20) 136
Ellis, B.E., (23) 38
Elmaleh, D.R., (8) 15
El Sadek, M.M., (3) 81
El Sekily, M.A., (10) 47
El-Shenawy, H.A., (3) 62; (4) 14
Elsner, A., (7) 38
El-Sokkary, R.I., (9) 69
Emsley, J., (7) 60; (18) 53
Endo, K., (7) 32
Engel, J., (3) 5
Engels, J., (20) 125
English, A.R., (19) 25; (22) 114
Enholm, E.J., (3) 127a; (24) 4
Ermakova, N.P., (16) 44
Ermolenko, M.S., (14) 29; (24) 2
Ernst, K., (19) 51
Ernst, L., (20) 127
Ersser, R.S., (23) 73
Esaki, S., (3) 54, 97; (7) 34
Escario, J.A., (20) 41
Essers, L., (23) 51
Essig, M.G., (14) 43; (22) 87
Estrada, M.D., (22) 75
Esquivel, B., (7) 33
Eswarakrishnan, S., (8) 23
Eto, Y., (19) 30
Evans, S.V., (18) 31
Evstigneeva, R.P., (3) 48
Excoffier, G., (3) 92; (4) 61; (21) 49
Fahmy, K., (10) 47
Falck, J.R., (24) 34
Falkowski, L., (9) 59; (19) 38
Fang, J.-R., (19) 19
Farkas, I., (10) 33, 52; (20) 97
Farkas, J., (21) 19
Fateev, A.N., (2) 43
Faure, R., (22) 90
Feather, M., (21) 48
Feeley, D.T., (20) 20, 21
Feeney, J., (4) 62
Felber, H., (10) 26
Fellows, L.W., (18) 31
Fenichel, L., (5) 24
Fenwick, G.R., (21) 43
Ferguson, G., (22) 91
Fernandez, F., (17) 30
Fernandez Bertran, J., (17) 30
Fernandez Bolanos, J., (10) 49
Fernandez-Bolanos, J.M., (9) 25, 26; (10) 19, 20
Fernandez Cirelli, A., (16) 11
Fernandez-Resa, P., (10) 12; (20) 12
Ferretti, V., (22) 61
Ferrier, R.J., (3) 132; (6) 18; (7) 7; (8) 33, 38; (13) 22; (22) 92; (24) 12, 44
Ferris, J.P., (20) 2, 48
Fiala, R., (19) 85
Fiedler, H.-P., (19)

51; (23) 54
Field, S.J., (19) 65
Finlander, P., (20) 15
Firgang, S.I., (7) 73; (22) 55
Fischer, H., (22) 117
Fisher, J.R., (16) 41
Fitzsimmons, B.J., (24) 30, 42, 60
Flechtner, T.W., (9) 19
Fleet, G.W.J., (18) 31, 48; (24) 8, 28, 36
Florent, J.-C., (3) 144; (24) 11
Florent'ev, V.L., (20) 51
Floss, H.G., (24) 62
Flowers, H.M., (7) 49
Foces-Foces, C., (22) 64, 69
Fogel, C.L., (23) 19
Font, J., (16) 13a; (24) 47
Ford, C.W., (18) 33
Ford, R.A., (20) 83
Forrest, A.K., (9) 46, 47; (22) 74
Fortin, R., (5) 28
Foster, R., (18) 1
Fourray, J.L., (19) 69
Fox, A., (22) 42; (23) 4
Fox, J.J., (19) 66; (20) 63, 91
Franck, R.W., (13) 6; (18) 18; (24) 53
Francke, F.P., (7) 54; (21) 23
Francke, W., (24) 58
Franz, R., (9) 5
Fraser, B.A., (9) 48; (22) 18
Fraser-Reid, B., (3) 141, 146; (5) 37; (9) 10, 11, 20; (12) 9; (13) 8, 9, 16; (14) 10, 11, 25, 26, 35, 41; (16) 4; (22) 85; (24) 16, 18, 60, 63, 64, 68
Frechette, M., (21) 64
Frei, R.W., (23) 23
Freiberg, L.A., (19) 21
Frejd, T., (3) 71; (4) 24, 36, 54; (21) 26; (24) 70
Frelek, J., (17) 32; (22) 127
Frey, M.H., (2) 51; (21) 15
Freyne, E., (3) 161; (20) 96
Friebolin, H., (16) 24, 25
Frolova, V.I., (19) 84
Fronza, G., (14) 23; (19) 43
Frost, J.W., (16) 17
Fuchs, B., (1) 4
Fuentes Mota, J., (10) 50, 51
Fuganti, C., (14) 23
Fujie, H., (3) 29
Fujimori, T., (21) 42; (22) 82
Fujisawa, H., (20) 27
Fujita, A., (24) 22
Fujita, E., (9) 63
Fujita, Y., (23) 78
Fujiwara, A., (19) 39
Fujiwara, T., (9) 2; (14) 4; (22) 104, 110
Fukase, H., (18) 37; (19) 7
Fukuda, Y., (19) 56
Fukui, K., (22) 10
Fukuoka, E., (2) 47
Fukushima, K., (7) 22; (21) 38
Fukuyasu, H., (19) 49
Fullerton, D.S., (3) 22, 27; (21) 67
Fullerton, N.F., (23) 63
Funabashi, M., (18) 22
Funakoshi, S., (20) 144
Funakura, S., (22) 27
Furihata, K., (19) 27
Furuhata, K., (9) 4; (22) 72
Furukawa, H., (20) 104; (24) 67
Furusawa, K., (20) 130
Gabe, E.J., (6) 18; (8) 33; (22) 92
Gadelle, A., (2) 27
Gaffield, W., (22) 124
Gagnaire, D., (3) 92; (21) 49
Gagnier, R.P., (20) 18
Gainsford, G.J., (6) 18; (8) 33; (22) 56, 92
Gal, J., (10) 17, 18
Galbis Perez, J.A., (9) 25, 26; (10) 19, 20, 31, 43, 50, 51; (18) 15
Galensa, R., (23) 35
Gallucci, J., (22) 86
Galoyan, A.A., (8) 6
Gama-Rosa, M.A., (23) 60
Ganem B., (24) 7
Garcia Bala, M.C., (10) 44
Garcia Barros, F.J., (9) 61
Garcia Fernandez, G., (4) 25
Garcia-Hierro, J.I.F., (10) 50; (10) 51
Garcia-Lopez, M.T., (10) 12
Garcia-Lopez, T., (20) 9
Garcia Poza, D., (14) 18
Garcia Ruiz, P.A., (3) 56
Garcia Seguar, R., (3) 162; (5) 36
Garegg, P.J., (1) 2; (3) 99; (8) 29, 34, 40; (13) 21; (18) 55
Garner, C.C., (16) 18; (21) 44
Gaset, A., (18) 29
Gati, W.P., (20) 65
Gautham, N., (20) 150; (22) 96
Gautheron, C., (4) 32; (16) 22
Gehrke, C.W., (23) 60
Geigert, J., (18) 5
Geise, B., (22) 117
Gelas, J., (6) 3
Gelpi, M.E., (20) 111
Gennari, C., (24) 20, 65
George, R.D., (20) 10, 11; (22) 103
Georges, M., (5) 37; (9) 10, 20; (12) 9; (14) 10; (24) 64
Germain, F., (14) 30; (22) 81
Gertsch, I., (21) 56
Gerwig, G.J., (18) 20; (23) 13
Geze, M., (19) 69
Ghosal, P.K., (23) 18
Ghosh Majumdar, S., (23) 18
Giacomini, K.M., (23) 62
Gibbs, D.E., (7) 70
Gibson, M., (20) 83
Giese, B., (14) 37, 38
Giessman, U., (22) 24
Gilbert, B.C., (16) 33; (22) 120
Gillard, J.W., (5) 28
Gillet, B., (20) 144
Gilli, G., (22) 61
Gillies, D.G., (17) 34

Gimenez Gracia, M.P., (10) 49
Gioia, B., (19) 43; (22) 25
Girodeau, J.-M., (19) 14; (19) 18
Giuliano, R.M., (14) 9
Giziewicz, J., (22) 101
Glaudemans, C.P.J., (3) 61, 63, 72, 75
Glebova, Z.I., (17) 14
Glenn, R., (22) 48
Glennon, R.A., (20) 25
Gluzinski, P., (3) 100; (5) 33; (22) 63, 78
Gnichtel, H., (14) 40
Gnuchev, N.V., (20) 51, 72
Godoy, J., (24) 27
Goebel, R.J., (20) 13
Goewey, G.S., (7) 13
Goguadze, M.I., (18) 10
Goi, H., (9) 1; (19) 77; (22) 73
Goldstein, I.J., (3) 70
Golovach, S.N., (7) 4
Gomez Guillen, M., (9) 61
Gomez Perez, C., (16) 19
Gomez-Sanchez, A., (3) 6; (14) 31, 32
Gomtsyan, A.R., (4) 52
Gonsalez-Gomez, J.A., (14) 37
Good, F., (5) 34
Goodby, J.W., (3) 124
Goodgame, D.M.L., (22) 112
Goodman, J.F., (19) 55
Goodman, L., (12) 6
Goren, M.B., (5) 12; (7) 41, 48, 49, 75
Gorrichon, J.P., (18) 29
Gorskova, R.P., (14) 3
Gosselin, (20) 37
Goto, T., (8) 5; (24) 15, 25
Gottikh, B.P., (20) 51, 72
Gough, M.J., (24) 36
Gould, S.J., (21) 21
Goya, P., (20) 12
Grasselli, P., (14) 23
Gray, G.R., (3) 115, 116; (18) 24-27
Gray, K., (15) 9
Greenberg, N., (19) 66
Gregory, P.B., (23) 62
Grenier-Loustalot, M.-F., (3) 119
Grethe, G., (9) 42, 43
Grief, V., (16) 16
Grierson, D.s., (3) 144
Griffin, C.A., (23) 55
Griffin, G.W., (3) 117, 118
Grigor'Eva, O.N., (17) 22
Grinsteins, E., (20) 44
Grishkovets, V.I., (5) 9-11; (16) 28-30; (23) 8
Gröninger, K., (14) 38
Gronberg, G., (21) 26
Gross, M.L., (22) 21
Grotjahn, L., (7) 31; (20) 127
Grouiller, A., (20) 46
Grund, H., (9) 5
Grundler, G., (3) 83
Grynkiewicz, G., (2) 10; (3) 139; (8) 2; (13) 12a; (18) 28
Gu, F., (20) 5
Guarneri, M., (20) 16
Guenther, M., (17) 10
Guilliano, R., (22) 85; (24) 68
Guindon, Y., (3) 114; (5) 28; (8) 36
Guittet, E., (20) 144
Gumprecht, C., (14) 40
Gunnarsson, A., (3) 110; (16) 7
Gupta, H.L., (2) 56
Gupta, K.C., (2) 69
Gupta, P.K., (19) 67; (20) 17
Gupta, R.B., (13) 6; (18) 18
Gupta, R.C., (3) 43; (24) 10
Gurarii, L.I., (7) 67
Gurjar, M.K., (8) 19, 37; (9) 57; (15) 6
Guy, E., (22) 70
Haake, P., (16) 37
Habash-Marino, M., (2) 23
Habermeier, H., (3) 105
Hadamczyk, D., (4) 29
Haddon, W.F., (18) 35; (22) 38
Hagan, W.J., jun., (20) 2
Hagel, P., (2) 23
Hague, E., (7) 2
Hahn, C.S., (15) 10
Hain, W., (5) 21
Haines, S.R., (3) 132; (6) 18; (7) 7; (8) 33, 38; (13) 22 92; (29) 44
Hak, E.W., (23) 6
Hakimelahi, G.H., (7) 72
Hakimi, J.M., (20) 30
Hakoshima, T., (22) 104
Halat, M.J., (20) 18
Hall, L.D., (8) 9; (21) 14
Hamacher, K., (3) 57; (11) 10
Hamada, K., (22) 107
Hamada, M., (19) 68
Hamada, Y., (9) 35, 36
Hamaguchi, H., (15) 7
Hamatsu, T., (19) 15
Hamblin, M.R., (19) 64
Hamid, H.A., (10) 40; (16) 45
Hamill, R.L., (19) 71
Hanaya, T., (17) 6
Handa, G., (20) 88
Haneda, T., (19) 63
Hanessian, S., (3) 134; (22) 83; (24) 19
Hanfland, P., (4) 5
Hanley, A.B., (21) 43
Hansske, F., (15) 5; (20) 35, 78
Hanvey, C.J., (19) 59
Harada, K., (2) 16; (19) 20; (22) 27-30, 44, 45
Harada, K.I., (4) 9; (19) 82
Harada, S., (7) 76; (22) 68
Harada, T., (20) 143
Haradahira, T., (8) 16, 17; (13) 15
Harangi, J., (4) 15
Harborne, J.B., (23) 36
Harland, P.A., (3) 43; (24) 10
Harris, P.J., (23) 6
Harsh, G., (2) 18, 19; (18) 17
Harsch, M., (2) 18; (18) 17
Harvey, J.C., (20) 59
Hase, T., (3) 103
Hasegawa, A., (6) 4-6, 11; (7) 57; (9) 15, 16, 49-51; (11) 4, 11, 12
Hasegawa, E., (4) 56
Hashimoto, H., (9) 32; (14) 16, 21; (24) 31
Hashimoto, J., (20) 31
Hashimoto, S., (3) 19; (8) 3
Hashimoto, T., (3) 27,

41
Hasted, J.B., (22) 9
Hata, T., (20) 119
Hatano, T., (7) 22, 23; (21) 37, 38
Hathway, D.E., (22) 112
Hattori, H., (23) 10
Hattori, M., (3) 136
Hauser, F.M., (9) 44; (14) 8, 15
Havel, M., (3) 28
Haverkamp, J., (16) 26
Hawkes, G.E., (21) 17
Hawkins, L.D., (19) 59
Hawkins, L.P., (20) 59
Hawthorne, M.F., (13) 12
Hay, G.W., (2) 25; (8) 2
Hayakawa, Y., (19) 27, 29; (24) 45
Hayashi, A., (3) 94; (21) 28
Hayashi, K., (12) 3
Hayashi, M., (3) 19; (8) 3
Hayashi, Y., (20) 31
Hayatsu, H., (7) 25
Hayman, P.B., (22) 112
Heald, J.K., (20) 1
Heathcock, C.H., (24) 33
Hedbys, L., 93) 65
Heflich, R.H., (23) 63
Heil, B., (17) 18
Heiker, F.-R., (19) 81
Heikkinen, E., (20) 146
Hemmi, H., (16) 48
Henderson, R.J., jun., (23) 55
Hengemihle, F.H., (3) 121
Hengeveld, J.E., (16) 16
Herchman, M., (3) 64; (4) 23
Hermans, J.P.G., (3) 79
Herranz, R., (20) 9, 19
Herrington, T.M., (3) 126
Herrman, K.M., (16) 18; (21) 44
Herrmann, K., (23) 39
Herscovici, J., (3) 143
Heyraud, A., (4) 6; (22) 16
Hicks, K.B., (2) 51; (21) 15
Higuchi, W.I., (19) 70
Hikichi, K., (3) 166
Hildebrandt, J., (19) 12
Hillenkamp, F., (16) 46
Himmelsbach, F., (20) 118
Hioki, Y., (9) 49, 51; (11) 4, 12
Hirano, S., (5) 13; (7) 42
Hirao, I., (20) 36
Hiremath, S.V., (24) 57
Hirono, I., (22) 54
Hirose, Y., (19) 47; (20) 4
Hiroto, K., (20) 47, 50, 70, 90
Hirsch, J., (4) 4, 17, 45; (21) 10
Hitz, W.D., (8) 25
Hiyame, T., (9) 37, 38
Hjerten, S., (23) 68
Ho, P.-T., (12) 18
Ho, Y.K., (20) 32
Hoes, C., (3) 25
Hofermans, R., (23) 71
Hoffman, J.J., (18) 38
Hokimoto, K., (13) 18; (16) 10
Hollman, J., (20) 140
Holman, M.J., (19) 62
Holzapfel, C.W., (7) 10, 11; (9) 75
Honda, S., (23) 24, 25
Hong, N., (9) 12; (14) 14
Honjo, M., (22) 111
Hoornacrt,G., (3) 161; (20) 96
Hoornaert, G.J., (20) 92
Horgan, R., (1) 20
Horibe, I., (21) 30
Horrii, S., (18) 37; (19) 7
Horino, I., (19) 30
Horita, K., (16) 17
Horlock, P.L., (19) 21
Horning, T.L., (22) 119
Horton, D., (3) 17; (6) 2, 3; (19) 35; (22) 86
Horvat, S., (11) 5
Horvath, Gy., (22) 37; (23) 11
Hoshiko, T., (2) 27, 68
Hoshino, T., (19) 39
Hosie, L., (10) 5; (21) 27
Hosoda, H., (3) 29; (3) 31
Hosomi, A., (3) 140
Hough, L., (7) 15; (8) 24, 26; (9) 71; (24) 37
Hranisavljevic, J.T., (3) 158; (5) 32
Hrebabecky, H., (20) 38
Hronewski, L.J.J., (2) 25
Hsu, D.-S., (23) 67
Hubler, P.M., (2) 36
Hughes, L., (20) 83
Hughes, R.E., (16) 47
Hughes, R.G., jun., (20) 64
Humble, R.W., (20) 120
Hummel, C.F., (20) 71
Hunt, A.H., (19) 71
Hunter, S.W., (9) 2; (14) 4
Huot-Olivier, S., (23) 61
Husain, S.K., (22) 9
Husson, H.-P., (3) 144
Hutchinson, D.W., (7) 50
Hutchinson, J.P., (8) 23
Huttner, G., (9) 47; (22) 74; (24) 51
Huttunen, E., (7) 77
Huybrechts, L., (3) 161; (20) 96
Hwang, C.K., (8) 31
Ibn Oaf, H., (23) 5
Ichikawa, S., (15) 11
Ichikawa, Y., (24) 15, 25
Idmoumaz, H., (3) 120
Ido, T., (8) 11
Idoyaga-Vargas, V., (23) 17
Iga, Y., (4) 56
Ignacio Andres, J., (20) 9, 19
Ignatova, L.A., (10) 15; (20) 28
Ii, S., (20) 68
Iimura, Y., (9) 72; (18) 43; (24) 38
Iitaka, Y., (19) 45; (22) 57, 72
Ikeda, A., (7) 46; (9) 56
Ikeda, D., (19) 11
Ikeda, M., (23) 10
Ikeda, Y., (18) 42; (19) 13
Ikegimi, F., (10) 36
Ikehara, M., (20) 62; (22) 104, 107-109
Ikemura, T., (22) 47
Ikenaka, T,. (9) 29
Ikura, M., (3) 166
Imai, D., (24) 67
Imamura, K., (19) 29

Imanaka, H., (19) 48
Imbach, J.-L., (10) 3., (20) 37, 156; (21) 65; (22) 23
Imoto, M., (3) 78
Inaba, T., (4) 56
Inch, T.D., (24) 1
Inchauspe, G., (23) 48
Inoi, T., (7) 29
Inokawa, S., (7) 65; (14) 28; (17) 1, 3., 5-8
Inoue, H., (2) 52, 54
Inoue, K., 97) 22, 23; (21) 37, 38
Inoue, M., (19) 24
Inoue, S., (2) 17; (18) 54
Inoue, T., (3) 155
Inoue, Y., (22) 10
Inouye, H., (16) 36
Inouye, S., 99) 1; (10) 54; (19) 77; (22) 73
Irie, S., (2) 15
Isac Garcia, J., (3) 165
Isakov, I., (18) 14
Isakov, V.V., (14) 3
Ishida, H., (5) 4; (7) 57; (9) 15
Ishido, Y., (3) 156; (19) 8; (20) 36
Ishii, J., (23) 21
Ishii, K., (19) 28
Ishikara, T., (20) 79
Ishikura, T., (19) 37, 40, 41
Ishimaru, K., (7) 19; (14) 6
Iskander, G.M., (23) 5
Isobe, M., (24) 15, 25
Ison, E.R., (2) 25; (18) 13
Isono, K., (19) 50
Itaya, T., (20) 143
Ito, S., (22) 45
Ito, T., (17) 28; (19) 49
Ito, Y., (3) 9; (20) 89; (24) 17
Itoh, J., (9) 1; (19) 77; (22) 73
Itoh, K., (3) 156
Itoh, T., (4) 7; (20) 24, 79, 107; (22) 46; (23) 21
Itoh, Y., (4) 55
Iusem, N.D., (23) 17
Ivanova, N.V., (22) 2
Iversen, T., (4) 28; (18) 55
Iwagawa, T., (3) 103
Iwahashi, H., (23) 40
Iwami, F., (20) 70
Iwasa, T., (19) 53
Iwasaki, H., (22) 52
Iwasawa, H., (19) 11
Iwasawa, Y., (18) 45; (18) 49
Iwata, M., (19) 54
Iwata, R., (8) 11
Iwata, S., (23) 26
Izquierdo Cubero, I., (14) 17, 18; (16) 15
Izumi, K., (21) 31
Jackson, R.J., (3) 126
Jacobsen, D.W., (20) 30
Jacobsen, S., (7) 12
Jacquet, F., (18) 29
Jacquinet, J.-C., (4) 41, 67
Jagannathan, N.R., (21) 12
Jager, A., (20) 125
Jaeger, V., (9) 5, 34
Janado, M., (2) 2
Janecek, F., (4) 13
Jankowska, J., (20) 121
Jankowski, K., (20) 154; (21) 6
Jansen, J.C., (22) 94
Jaret, R.S., (19) 16
Jarglis, P., (24) 52
Jarosz, S., (15) 12
Jary, J., (5) 7, 8; (9) 60, 70; (16) 2
Jarzebski, A., (9) 59
Jasinska, J., (20) 40
Javanaud, C., (20) 157
Jaworska, A., (3) 96; (4) 16
Jeanloz, R.W., (3) 81; (4) 40; (21) 60
Jeffrey, G.A., (3) 123; (21) 41; (22) 58, 77
Jegge, S., (4) 12
Jenkins, G.A., (4) 26; (21) 53, 54
Jenkins, I.D., (7) 40; (11) 8
Jenkins, J.K., (19) 16
Jennings, H.J., (2) 42
Jerabkova, J., (5) 7
Jericevic, Z., (11) 5
Jeronic, L.O., (16) 11
Jesthi, P.K., (17) 13
Jewett, D.M., (8) 8, 10
Jezo, I., (9) 65; (12) 8
Jiang, C., (20) 94
Jibril, I., (9) 47; (22) 74; (24) 51
Jigajinni, V.B., (24) 49
Jimenez-Barbero, J., 922) 64
Jimeno, M.L., (4) 48; (20) 12
Jiminez Requejo, J.L., (9) 25, 26; (10) 19, 20, 43
Jin, H., (4) 19
Jin S., (23) 1
Jo, I., (19) 31
Joecks, A., (20) 153
Johansson, R., (5) 18, 19; (6) 21, 22; (8) 34; (13) 21; (18) 55
Johdo, O., (19) 40
John, T.V., (24) 53
Johne, S., (3) 33
Johnson, J.H., (19) 72
Johnson, O., (22) 115
Johnston, J.C., (7) 13
Jokei, S., (7) 29, 36; (9) 54
Jolad, S.D., (18) 38
Jones A.S., (20) 141
Jones, D.W., (22) 115
Jones, E., (16) 47
Jones, G.H., (20) 126
Jones, J.O., (20) 73
Jones, K., (23) 56
Jones, P.G., (22) 48
Jose, C.I., (22) 7
Josic, Dj., (23) 71
Joullie, M.M., (3) 160; (13) 20; (16) 13
Judkins, B.D., (20) 101
Jülich, E., (9) 28
Junge, B., (19) 81
Jurczak, J., (5) 22, 23; (14) 39; (15) 12; (18) 8
Jurovska, M., (23) 7
Kabir, A.K.M.S., (8) 24, 26
Kabra, P.M., (23) 50
Kachensky, D.F., 93) 127a; (24) 4
Kachur, V.G., (22) 2
Kagawa, T., (20) 68
Kahiya, S., (3) 54
Kakehi, K., (23) 25
Kakinuma, K., (2) 29; (24) 62
Kale, A., (2) 54
Kale, V.N., (24) 41
Kalman, A., (22) 102
Kaluza, Z., (14) 39
Kambara, H., (4) 9; (22) 30
Kambara, T., (16) 48
Kameda, Y., (18) 37, 43; (19) 3, 7
Kamerling, J.P., (16)

26; (18) 20; (23) 13
Kameyama, K., (20) 50
Kamigauchi, T., (18) 42
Kamiya, K., (22) 111
Kamiya, S., (3) 97; (7) 34
Kanai, K., (9) 66
Kanaoka, M., (7) 35
Kane, P.D., (3) 150
Kaneda, M., (3) 102
Kaneko, H., (23) 21
Kaneyasu, T., (20) 62; (22) 104
Kansal, V.K., (20) 144
Kanters, J.A., (2) 6; (22) 49
Kaplun, A.P., (3) 48
Kappert, M., (24) 51
Kapuscinski, M., (7) 54; (21) 23
Karas, M., (16) 46; (22) 24
Kardosova, A., (5) 6
Karlivans, V., (7) 80
Karmen, A., (2) 4
Karpeiskii, M.Ya., (7) 63; (20) 128
Kasahara, F., (7) 76; (22) 68
Kasai, R., (3) 7, 42, 94; (21) 28
Kashiwadi, Y., (7) 26
Kasumi, T., (8) 5
Katagiri, N., (19) 63
Kataoka, M., (16) 48
Kato, H., (7) 35
Kato, K., (14) 33; (19) 68; (21) 42; (22) 82; (24) 59
Kato, T., (9) 66
Katsuno, T., (13) 18; (16) 10
Katsuta, S., (3) 102
Katz, E., (10) 48; (17) 17
Kavai, I., (20) 64
Kawabata, K., (9) 63
Kawai, A., (9) 35, 36
Kawai, H., (19) 27
Kawai, K., (24) 67
Kawai, Y., (19) 48
Kawaide, A., (6) 4; (9) 15
Kawaizumi, F., (2) 38
Kawamoto, T., (23) 52
Kawauchi, N., (14) 16
Kaye, A.D., (18) 46
Kazimierczuk, Z., (20) 23, 55
Keck, G.E., (3) 127a; (24) 4
Kefurt, K., (5) 8; (9) 70; (16) 2
Kefurtova, Z., (5) 8; (9) 70; (16) 2
Keglevic, D., (9) 52
Keifer, G., (20) 134
Keller, T.H., (3) 129
Kelly, D.R., (14) 41
Kemme, A., (20) 45
Kempen, H.J.M., (3) 25
Kennett, R., (19) 85
Keppeler, K., (20) 134
Kerek, F., (5) 2
Kersters-Hilderson, H., (3) 109
Kesarwani, R.N., (2) 67
Khalafi-Nezhad, A., (7) 72
Khan, R., (3) 49
Khanna, I., (19) 36
Khare, A., (4) 18, 60; (21) 1
Khare, M.P., (4) 18, 60; (12) 1
Khare, N.K., (4) 18
Khazova, O.A., (2) 63; (16) 1
Khodyreva, N.V., (3) 108
Khomutov, R.M., (7) 63; (20) 128
Khorlin, A.Ya., (4) 39; (9) 53; (10) 14
Kida, T., (19) 30
Kido, R., (23) 40
Kieboom, A.P.G., (2) 3, 49; (17) 35
Kiely, D.E., (15) 9
Kihara, M., (3) 22, 27; (21) 67
Kikino, H., (7) 32
Kikot, B.S., (16) 44
Kilesso, V.M., (21) 70
Kim, D., (8) 7
Kim, I.-K., (19) 61
Kim, K.S., (15) 10
Kim, M.H., (8) 7
Kimura, I., (19) 82
Kimura, J., (20) 60
Kimura, M., (2) 12; (9) 41; (12) 21; (14) 2; (18) 7
Kimura, T., (7) 27; (21) 61
Kimura, Y., (19) 33, 34
King, D.K., (2) 34
King, D.M., (16) 33; (22) 120
Kinomura, K., (7) 28
Kinoshita, M., (19) 15
Kinoshita, T., (10) 16
Kirby, A.J., (22) 48
Kise, N., (16) 3
Kishi, T., (12) 2; (13) 17
Kishi, Y., (18) 9
Kiso, M., (6) 4-6, 11; (7) 57; (9) 15, 16, 49-51; (11) 4, 11, 12
Kist'yan, G.K., (17) 16
Kitade, Y., (20) 47, 70
Kitagawa, I., (3) 106; (18) 42; (19) 1, 13
Kitagawa, S., (5) 13
Kitahata, S., (3) 42
Kitajima, T., (4) 57
Kitamura, K., (22) 107-109
Kitamura, M., (24) 15
Kitano, S., (23) 78
Kitatsuji, E., (3) 22, 27
Kiyota, Y., (3) 106
Klaska, K.-H., (2) 74; (22) 116
Klausener, A., (12) 5
Klecker, R.W., jun., (23) 65
Klemer, A., (8) 42; (14) 13; (18) 41
Klenke, K., (13) 11
Klinger, F.D., (24) 52
Kloosterman, M., (5) 30
Knaus, E.E., (20) 65
Knierzinger, A., (24) 13
Knirel, Y.A., (4) 46
Knowles, J.R., (16) 17
Knutsen, L.J.S., (20) 101
Kobayashi, A., (2) 14
Kobayashi, K., (3) 102; (9) 37, 38; (24) 62
Kobayashi, M., (3) 106; (7) 65
Kobayashi, N., (3) 156
Kobayashi, S., (3) 8, 154
Kobayashi, Y., (22) 99
Kobe, J., (20) 7
Koch, M., (24) 11
Kochak, G., (7) 24
Kocharova, N.A., (4) 46
Kochetkov, N.K., (3) 16, 74, 90, 91; (4) 1, 31, 46, 52; (7) 68; (14) 29; (21) 7, 46, 47; (24) 2
Kocioenski, P., (14) 27
Kocsis, B., (23) 3
Kodaka, M., (3) 107
Kodama, J., (9) 1
Kodama, Y., (19) 77; (22) 73
Koekemoer, J.M., (7)

10, 11; (9) 75
Köll, P., (5) 41; (7) 44; (13) 11; (18) 19; (22) 65, 93
Koenig, J., (20) 49
Koenig, J.L., (20) 148, 149; (22) 13, 14
König, W.A., (19) 51
Koeppel, H., (20) 153
Kövago, A., (23) 16
Koh, Y.N., (9) 6
Kohata, K., (4) 33, 34
Kohla, M., (18) 41
Kohne, B., (18) 56
Koholic, D.J., (7) 74
Kohsaka, M., (19) 48
Koikov, L.N., (8) 6
Koizumi, K., (21) 35
Kojima, M., (8) 16, 18; (13) 15; (19) 49
Kolina, J., (2) 28
Koll, P., (21) 22
Komander, H., 95) 41; (7) 44
Komori, T., (19) 48
Kon, K., (19) 44
Kondo, A., (6) 6
Kondo, S., (19) 11, 28
Kondo, T., (10) 29
Kondo, Y., (5) 13; (6) 6; (7) 8, 45; (19) 54
Konigstein, J., (4) 13
Konishi, T., (23) 24
Konopski, L., (3) 2
Konoshima, T., (7) 37; (21) 61
Konowal, A., (12) 27; (21) 40
Kontrohr, T., (23) 3
Koomen, G.-J., (24) 29
Kopf, J., (18) 19; (21) 22; (22) 65, 93
Korak, A., (18) 32
Korbukh, I.A., (20) 14
Korolik, E.V., (22) 2
Koroteev, M.P., (3) 16; (7) 66, 68, 69; (8) 30; (10) 21; (17) 21-23
Korppi-Tommola, S.-L (2) 5; (22) 1
Korth, H.-G., (22) 117
Korytnyk, W., (3) 128; (21) 4
Kosik, M., (23) 75
Kosma, P., (4) 47
Koster, R., (17) 33
Kothari, S., (2) 70
Koto, S., (4) 21
Kou, O., (2) 34
Kovac, P., (3) 61, 63; (21) 48
Kovacs, T., (22) 102
Kovago, A., (2) 50
Kowollik, W., (9) 18
Koyama, M., (19) 49, 54
Koyama, T., (19) 50
Koyama, Y., (23) 10
Kozikowski, A.P., (24) 5
Kraevskii, A.A., (20) 72
Krahe, E., (4) 4; (21) 10
Krajewski, J.W., (3) 100; (5) 33; (22) 63, 78
Kramer, K.J., (16) 39
Krapivin, A.M., (21) 70
Krepinsky, J.J., (4) 22
Kresze, G., (10) 26; (18) 52
Krishna, B., (2) 64
Kroh, L., (9) 7; (10) 4
Krohn, K., (3) 20
Kroll, S.J., (19) 79
Kroon-Batenburg, L.M.J., (2) 6; (22) 49
Kruggel, F., (19) 80
Krupenskii, V.I., (2) 57-60
Krylov, A.C., (7) 63; (20) 128
Kuan, F.-H., (3) 156
Kubler, D.G., (2) 48
Kucar, S., (7) 6; (22) 125
Kühlmeyer, R., (19) 5
Kuhn, S., (4) 5
Kulhanek, M., (8) 22
Kulinkovich, L.N., (16) 27; (20) 85, 86
Kulkarni, S.Y., (22) 7
Kumar, A., (19) 64, 65
Kumar, S., (20) 100
Kumar, S.D., (19) 70
Kunberger, G., (2) 34
Kung, H., (20) 32
Kunisch, F., (19) 80
Kunz, H., (3) 12, 23, 145; (13) 4, 10
Kuo, C.H., (18) 51
Kuo, K.C., (23) 60
Kuo, K.T., (18) 6
Kuo, Y.-H., (10) 36
Kuraishi, T., (5) 1; (7) 27
Kurath, P., (19) 2
Kuriacose, J.C., (2) 75, 76
Kurihara, T., (20) 119
Kurz, J., (19) 81
Kusakabe, H., (19) 50
Kusamoto, S., (7) 56
Kuster, B.F.M., (23) 29
Kustova, I.L., (16) 44
Kusumoto, S., (3) 78
Kuszmann, J., (6) 7-9; (18) 12; (21) 16; (22) 37; (23) 11, 12
Kuwajima, I., (3) 155
Kuyama, H., (3) 93
Kuzovkov, A.D., (19) 84
Kvarnström, I., (3) 163
Kvasyuk, E.I., (20) 84
Kyogoku, Y., (3) 106
Lacombe, J.-M., (22) 53, 89
Lagunas, R., (20) 129; (23) 70
Laletina, Z.P., (20) 133
Lall, J., (2) 46; (22) 6
Lallemand, J.Y., (2) 144
Lambein, F., (10) 36
Lambert, W.J., (19) 70
Lancelin, J.-M., (3) 133; (13) 5; (17) 20; (18) 23
Landi, M., (19) 74
Landor, S.R., (6) 19, 20
Langen, P., (20) 67
Langendoen, A., (3) 25
Lanzetta, R., (4) 53
Laonigro, G., (4) 53
Lardy, C., (23) 37
Larsen, C., (7) 70
Larsen, K.E., (10) 35
Larson, P.O., (3) 65
Lartey, P.A., (16) 16
Lastres. R.D.G., (10) 32
Lau, P.Y., (22) 42; (23) 4
Lawrimore, J.T., (2) 62
Lawton, G.C., (20) 20, 21
Lazrek, H., (20) 156; (21) 65
Lazrek, H.B., (22) 23
Lebuhn, R., (4) 37, 65, 66
Lederman, I., (4) 41, 67
Lednicer, D., (19) 36
Lee, C.M., (9) 6
Lee, C.-M., (16) 16
Lee, C.N., (18) 6
Lee, D.-S., (3) 112, 113
Lee, E., (21) 36
Lee, J.-M., (21) 60

Lee, M.S., (10) 37
Lee, P.R., (19) 31
Lee, T.M., (19) 75; (22) 22
Lee, Y.C., (3) 138
Le Fur, R., (18) 4; (21) 18
Leger, S., (22) 83
Leginus, J.M., (9) 33; (12) 23
Legler, G., (9) 28
Le Goffic, F., (19) 14, 18
Legraverend, M., (21) 66
Lehmann, J., (4) 12
Lehnert, R., (5) 21
Lelievre, J., (9) 67
Lemieux, R.U., (4) 27, 35; (21) 59
Lendering, U., (5) 41; (7) 44
Leonard, N.J., (20) 29
Lerner, L.M., (12) 10; (20) 142
Lesnaya, N.A., (16) 44
Lesnikowski, Z.J., 97) 51; (20) 112, 123
Lesyng, B., (21) 2
Leung, D.W.M., (23) 77
Leung, T.-W.C., (19) 73
Levanevskii, O.E., (2) 20
Levinsky, A.B., (4) 31
Levy, S., (8) 15
Lewis, C., (19) 79
Lewis, D., (21) 17
Ley, S.V., (24) 26, 27
Lfrom, A.H., (3) 22
Lhoste, J.M., (21) 66
Li, L., (3) 157
Li, W.S., (8) 31
Liang, D., (24) 16
Liang, Y.-T., (16) 39
Liav, A., (5) 12; (7) 41, 48, 49, 75
Lichtenthaler, F.W., (24) 52
Lidaks, M.J., (20) 84
Liepins, E., (20) 44, 45
Lillard, D.W., (16) 39
Liman, U., (20) 33
Lindberg, B., (18) 55
Lindquist, B., (24) 66
Linscheid, M., (7) 17
Lipkind, G.M., (21) 7, 47
Liptak, A., (4) 15
Lis, T., (22) 88
Liska, F., (8) 35
Liss, R.H., (19) 21
Lister, S.G., (24) 26
Litvinov, I.A., (7 67
Liu, R.H., (22) 36
Livni, E., (8) 15
Lönn, H., (3) 85
Lönnberg, H., (20) 146
Lönngren, J., (3) 85
Lohmann, W., (16) 46
Loibner, H., (19) 12
Loiseleur, H., (22) 90
Long, G.W., (3) 153
Longstaff, C., (7) 78; (22) 20
Lopez, C., (19) 66; (20) 63
Lopez Aparicio, F.J., (3) 164, 165; (14) 17; (16) 15
Lopez-Castro, A., (22) 84
Lopez Herrera, F.J., (3) 162; (5) 36; (16) 19
Lopez Sastre, J.A., (3) 165
Lorentzen, J.P., (3) 84
Loub, J., (22) 66
Low, I.A., (22) 36
Low, J.N., (22) 97, 98
Low, N.H., (20) 78
Lowe, D., (14) 26
Lu, P.W., (16) 39
Lubineau, A., (5) 26
Luck, S.D., (21) 14
Luger, P., (14) 40; (22) 71, 78
Lukacs, G., (5) 35; (8) 12; (21) 69; (24) 21
Lundsten, J., (3) 110
Lundt, E., (3) 39
Lundt, I., (3) 98; (12) 16; (16) 12
Lutsenko, A.I., (7) 68, 69; (8) 30; (17) 22
Luzin, A.P., (21) 70
L'vov, V.L., (4) 46
Lygo, B., (24) 27
Lyutik, A.L., (3) 48
Ma, P., (24) 17
MacCoss, M., (20) 151; (21) 24
MacKay, D., (9) 10, 20; (12) 9; (14) 10
Machida, Y., (3) 137
Maciejewski, A., (10) 39
Mackenzie, G., (20) 120
Mackie, W., (22) 60
Mackiewiczowa, D., (20) 40
MacLean, D.B., (3) 163
Macleod, J.K., (7) 54; (21) 23
Madej, D., (15) 5; (20) 35
Maeba, I., (20) 104
Maeda, K., (19) 68
Maeda, M., (8) 16, 18
Maedo, M., (13) 15
Magdzinski, L., (24) 18
Magnusson, G., (3) 71; (4) 24, 36, 54; (21) 26; (24) 70
Mahlen, A., (24) 66
Maikuma, S., (7) 52; (20) 115
Majima, M., (3) 24
Maki, Y., (20) 47, 50
Makin, S.M., (12) 24, 25
Malabarba, A., (19) 73, 74
Malcolme-Lawes, D.J., (23) 56
Malik, A., (7) 71; (8) 32; (9) 17, 18, 21-23
Mal'kova, V.P., (9) 53; (10) 14
Mallams, A.K., (19) 26; (22) 19
Malleron, A., (5) 26
Mal'tsev, S.D., (7) 61
Mancera, M., (14) 31, 32
Mancy, S., (10) 47
Manfredini, S., (20) 16
Mangeney, P., (20) 144
Mangoni, L., (4) 53, 68
Mann, J., (3) 150
Manservigi, R., (20) 16
Mao, D.T., (20) 8, 93
Marais, C.F., (7) 10, 11
Marchis-Mouren, G., (11) 9
Margalith, E., (10) 48
Maring, C.J., (3) 147; (22) 79
Marino, G., (4) 68
Markham, K.R., (3) 167
Marko, L., (17) 18
Markovic, O., (23) 22
Marquez, R., (22) 75, 84
Marquez, V.E., (20) 8, 93
Marquez Archilla, F., (10) 8
Marsh, R.E., (22) 106
Marshall, P.J., (10) 5; (21) 27
Martin, O.R., (2) 5; (19) 17; (22) 1
Martinez, A.S., (15) 2,

3
Martinez, M., (7) 33
Martinez-Fernandez, A.R., (20) 41
Martin-Lomas, M., (4) 48; (22) 64, 69
Martin Madero, C., (10) 44
Martinovskaya, E.G., (2) 8
Maruyama, T., (22) 111
Masamune, S., (24) 17
Mashimo, I., (23) 52
Maslinska-Solich, J., (6) 13
Maslov, I.A., (2) 8
Masson, M., (19) 14, 18
Mathieu, C., (4) 32
Mathlouthi, M., (20) 148, 149; (22) 13, 14
Matsuba, A., (2) 16
Matsuda, A., (20) 90, 91
Matsuda, K., (19) 6
Matsue, H., (3) 24
Matsugi, J., (20) 62
Matsui, K., (18) 37; (19) 3, 7
Matsui, Y., (3) 136, 137
Matsumoto, T., (3) 166; (12) 17; (19) 33
Matsumura, Y., (15) 7
Matsunaga, I., (3) 34
Matsuno, K., (19) 56
Matsuura, T., (20) 80
Matsuzawa, Y., (19) 41
Matta, K.L., (3) 66, 69; (4) 33, 34, 38, 43, 50, 51
Mattia, C.A., (22) 50
Matulewicz, M.C., (22) 35
Matulova, M., (7) 6
Maulshagen, A., (14) 7; (16) 35; (22) 126
Maurins, J.A., (20) 84
Maynard, C.M., (7) 47
Mazerska, Z., (19) 38
McAdoo, D.J., (20) 77
McAlpine, J.B., (19) 2
McArdle, P., (21) 36
McCloskey, J.A., (19) 50; (20) 100; (22) 21; (23) 69
McCormick, J.E., (11) 14
McCune, R.A., (23) 60
McElhinney, R.S., (11) 14; (20) 73
McGarvey, G.J., (2) 12; (9) 41; (12) 21; (14) 2; (18) 7
McGaw, B.A., (1) 20
McGimpsey, W.G., (16) 42
McGinnis, G.D., (2) 62; (3) 121
McGlotten, J.H., (19) 26; (22) 19
McKernan, P.A., (19) 67; (20) 13
McNeal, C.J., (7) 64
McNicholas, P.A., (23) 43
Medvedeva, N.G., (2) 21
Meerwald, I., (6) 9; (18) 12
Meffin, P.J., (23) 41
Meguro, H., (2) 30; (8) 41; (21) 33
Meigs, C., (2) 48
Meldal,, M., (4) 44, 64
Melgarejo Sampedro, M., (10) 30; (20) 138
Meltzer, N.M., (23) 64
Melua, N.S., (18) 10
Melumad, D., (10) 48; (17) 17
Memon, M.U., (7) 22, 23; (21) 37, 38
Mendez-Castrillon, P., (10) 12
Mentech, J., (7) 39
Mercer, K.R., (22) 119
Merigan, T.C., (23) 62
Merkel, K.E., (19) 71
Merten, H., (13) 13
Messer, M., (4) 26; (21) 54
Metras, F., (3) 119
Metzger, J.O., (5) 41
Meuwly, R., (10) 24, 25; (13) 23
Meyer, B., (4) 37; (7) 44
Meyer, R.B., jun., (17) 13
Michalska, D.F., (22) 4, 5
Michel, J., (2) 9; (7) 81
Michon, F., (3) 82
Michon, F., (22) 43
Mieczkowski, J., (21) 40
Mieth, G., (7) 38
Mihalov, V., (4) 13
Mikhailopulo, I.A., (20) 84
Milat, M.-L., (4) 40
Milenkovic, L., (8) 39
Milette, S., (24) 43
Miljkovic, D., (8) 39
Miljkovic, D.A., (3) 158; (5) 32, 40
Miljkovic, M., (2) 23
Miller, K.J., (10) 18
Miller, R., (2) 78
Mills, G.C., (20) 77
Mills, J.S., (20) 77
Mincher, D.J., (22) 115; (24) 9
Mircheva, I., (18) 14
Mirza, S., (24) 61
Misawa, T., (8) 41
Misra, H.K., (20) 65
Misra, K., (7) 24
Mitchell, J.D., (23) 73
Mitchell, W.L., (20) 101
Mitscher, L.A., (19) 36
Mitsuhashi, H., (12) 3
Mitsunobu, O., (20) 60; (24) 23, 24
Mitsuo, N., (3) 40, 41
Mitt, T., (9) 43
Miwa, T., (20) 39
Miyahara, Y., (2) 38
Miyakoshi, T., (24) 40
Miyasaka, T., (9) 63
Miyashita, M., (24) 14
Miyata, N., (19) 50
Miyazaki, C., (10) 9
Miyoshi, E., (2) 14
Mizsak, S.A., (19) 76
Mizuno, H., (22) 107-109
Mizuno, Y., (20) 24, 79, 107, 139
Mizuta, E., (12) 2; (13) 17
Mizutani, K., 93) 42, 94; (21) 28
Moczulska, A., (7) 3; (10) 1
Mörch, L., (24) 66
Moering, U., (3) 11
Moffatt, J.G., (20) 126
Molchanov, V.N., (22) 55
Molino, B., (24) 18
Molloy, R.M., (19) 71
Molnar-Perl, I., (2) 50; (23) 16
Mols, O., (6) 3
Mondange, M., (3) 76, 77; (7) 59
Mondelli, R., (19) 43
Monma, M., (8) 11
Monneret, C., (3) 144
Monnert, C., (24) 11
Monodane, T., (22) 10
Monserret, R., (20) 83
Montejano, Y.D., (20) 30

Montgomery, J.A., (20) 136
Moreland, M., (18) 5
Morgan, S.L., (22) 42; (23) 4
Morgenlie, S., (2) 31
Mori, H., (19) 44
Mori, I., (23) 78
Mori, K., (7) 25
Mori, M., (14) 33; (18) 2; (21) 42; (22) 82; (23) 14; (24) 59
Morii, T., (20) 80
Morin, C., (6) 10; (12) 17; (24) 56, 69
Morin-Allory, L., (3) 133; (13) 5; (17) 20; (18) 23
Morioka, H., (19) 30
Morishima, N., (4) 21
Morishita, H., (23) 40
Morishita, K., (22) 104
Morita, M., (2) 47
Morita, N., (10) 45, 46
Morozov, A.A., (2) 20
Morr, M., (20) 127
Morrison, I.M., (23) 9
Morton, H.E., (3) 114; (8) 36
Morton, J.B., (19) 26; (22) 19
Mosbach, K., (3) 65
Mosettig, J., (20) 111
Mosher, C.W., (19) 32
Movlik, S.P., (17) 24
Müller, B., (3) 145; (13) 10
Müller, D., (14) 7; (16) 35; (22) 126
Müller, H., (19) 51
Mueller, I., (9) 5
Müller, L., (19) 81
Mueller, N., (16) 31
Mueller, S.L., (19) 2
Mukaiyama, T., (2) 11, 13; (3) 3, 4, 8, 154; (6) 15, 16; (19) 57; (20) 31, 39
Mukhanov, V.I., (16) 44
Mukherjee, R., (18) 34
Mukmenev, E.T., (7) 67
Muleka, K., (3) 143
Muller, G., (7) 39
Mulzer, J., (24) 51
Munavu, R.A., (7) 16; (17) 25
Mundy, B.P., (21) 13
Munesada, K., (3) 103
Murakami, F., (3) 42
Murakami, M., (6) 15, 16
Murakami, T., (5) 1, 14; (7) 27; (14) 5
Murakoshi, I., (10) 36
Murata, H., (17) 7
Murphy, R.C., (9) 2; (14) 4
Muzutani, K., (3) 7
Myasnikova, R.M., (22) 55
Myers, L.S., (20) 147
Myers, R.W., 93) 138
Nagabhushan, T.L., (19) 16
Nagakura, N., (16) 36
Naganawa, H., (19) 28
Nagao, Y., (9) 63
Nagaoka, H., (6) 16; (24) 40
Nagaoka, M., (3) 30
Nagataki, S., (3) 34
Nagel, A.A., (19) 25; (22) 114
Nagyvar, J., (7) 64
Naitoh, S., (15) 7
Nakagawa, M., (19) 27
Nakagawa, T., (12) 3
Nakahara, Y., (24) 22
Nakai, Y., (2) 47
Nakaji, T., (4) 63
Nakajima, S., (2) 47
Nakajima, T., (3) 94; (21) 28
Nakamura, H., (19) 45
Nakamura, Y., (12) 14; (17) 5
Nakanishi, K., (7) 35
Nakashima, R., (2) 16
Nakashima, T.T., (17) 5-8
Nakata, T., (22) 29
Namai, S., (3) 137
Nambara, T. (3) 29, 31
Nand, K.C., (2) 54, 55, 68
Nandi, L.N., (20) 88
Narasaka, K., (12) 22; (20) 39
Nardin, R., (3) 55; (21) 50
Narendra, N., (22) 51
Narita, H., (12) 3
Narui, T., (23) 26
Nashed, M.A., (3) 80
Nasheed, M.A., (9) 69
Nasseri-Noori, B., (7) 17; (17) 25
Nassr, M.A.M., (10) 41
Nawwar, M.A.M., (7) 17
Neeser, J.R., (8) 9
Negishi, T., (9) 64
Neidleman, S.L., (18) 5
Nelson, M.A., (23) 50
Nerz-Stormes, M., (21) 58
Nesal'tsev, Yu.V., (14) 36
Newton, R.F., (20) 101
Niazi, S.B., (7) 60; (18) 53
Nicol, E., (22) 9
Nicolaou, K.C., (3) 127, 131, 135; (8) 4, 31; (10) 2
Nicolas, P., (21) 56
Nicoll-Griffith, D., (14) 34
Nicotra, F., (3) 142; (13) 24; (17) 11, 12
Nielen, M.W.F., (23) 23
Nielsen, H., (22) 122
Niemelä, K., (23) 15
Nieves, R., (20) 12
Niewiarowski, W., (20) 123
Nifant'ev, E.E., (3) 16; (7) 66, 68, 69; (8) 30; (10) 21; (17) 21-23
Nifant'ev, N.E., (3) 90, 91; (6) 17
Niida, T., (9) 1; (19) 49, 77; (22) 73
Nikiforuk, J.H., (10) 7
Nikitin, A.V., (22) 55
Nikolaeva, N.N., (2) 63; (16) 1
Nimura, N., (10) 16
Ninomiya, K., (5) 1; (19) 3
Nishida, K., (3) 102
Nishida, Y., (2) 30; (21) 33
Nishide, K., (9) 37, 38
Nishikubo, Y., (20) 60
Nishimura, H., (7) 20, 21; (18) 36
Nishimura, O., (9) 48; (22) 18
Nishimura, Y., (19) 28
Nishioka, I., (7) 18-21, 26; (14) 6; (18)
Nishiyama, S., (24) 67
Nishizaki, H., (10) 9
Nishizawa, M., (20) 119
Nishizawa, N., (19) 54
Nitsch, E., (23) 33
Niwa, H., (3) 93; (22) 54
Niwa, T., (9) 1; (18) 2; (19) 49, 77; (22) 73; (23) 14
Nobe, M., (9) 1; (19) 77; (22) 73
Noguchi, N., (14) 5

Noguez, J.A., (24) 20, 65
Nohara, T., (3) 104
Nomura, A., (20) 24, 79, 107
Nomura, H., (2) 38
Nonaka, G., (7) 18-21, 26; (14) 6; (18) 36
Noori, G., (3) 71; (4), 36, 54; (21) 26
Norberg, T., (3) 99
Noumi, K., (5) 13
Novik, E.R., (3) 108
Novikov, V.L., (3) 15
Novotny, M., (2) 4
Noyori, R., (3) 19; (8) 3; (24) 45
Nukada, T., (4) 57
Numajiri, Y., (22) 29
Numazawa, M., (3) 30
Nunata, A., (13) 18; (16) 10
Nunez, O., (21) 11
Nuss, D.M., (20) 30
Obara, H., (3) 136, 137
Occhiai, F., (4) 9; (22) 29, 30
Ochoa, C., (20) 12
O'Connor, C.J., (2) 40
Odagawa, A., (19) 29
Oddon, Y., (22) 53, 70, 89
O'Dell, C.A., (20) 109
Oelting, M., (18) 19; (22) 93
Oga, T., (7) 28
Ogasawara, K., (5) 39
Ogata, M., (3) 30
Ogawa, K., (19) 83
Ogawa, M., (19) 83
Ogawa, S., (3) 42; (18) 45, 49, 50
Ogawa, T., (3) 21, 88; (4) 57; (8) 17; (18) 49
Ogawa, Y., (9) 1, (19) 44, 77; (22) 73
Ogihara, Y., (10) 11; (22) 57
Ogawa, T., (24) 22
Ogilvie, K.K., (20) 74
Ogura, H., (9) 4; (22) 72
Oh, T., (2) 12; (9) 41; (12) 21; (14) 2; (18) 7
Ohashi, M., (4) 8; (22) 26, 27
Ohba, K., (19) 49
Ohba, S., (22) 54
Ohe, Y., (7) 42
Ohgushi, T., (4) 56
Ohki, S., (9) 66
Ohki, T., (18) 2; (23) 14
Ohkubo, A., (21) 42; (22) 82
Ohleyer, E., (11) 3
Ohmori, S., (23) 10
Ohno, H., (20) 107
Ohno, M., (3) 9; (19) 58; (20) 89
Ohrai, K., (20) 27
Ohrui, H., (2) 30; (8) 41; (21) 33
Ohshima, M., (6) 15, 16
Ohta, K., (12) 2; (13) 17
Ohtani, K., (3) 7
Ohtsuka, Y., (2) 38
Oikawa, Y., (5) 16, 17; (7) 52; (20) 115
Ojika, H., (3) 93
Ojika, M., (22) 54
Okabe, N., (22) 99
Okachi, R., (19) 22, 23
Okada, K., (18) 54
Okada, N., (24) 67
Okada, S., (3) 42
Okai, H., (7) 28; (10) 9, 10
Okazaki, H., (12) 2; (13) 17
Okuda, T., (7) 22, 23, 25; (21) 37, 38; (22) 47
Okumoto, H., (24) 17
Olechno, J.D., (7) 30
Olesker, A., (5) 35; (8) 12; (21) 69; (24) 21
Oliver, J.D., (22) 62
Ollapally, A.P., (20) 83
Olsen, I., (22) 32
Olsson, K., (2) 78
Olsson, R.A., (19) 61
Oltvoort, J.J., (3) 79; (5) 30; (9) 55
Omae, H., (8) 16
Omichi, K., (9) 29
Omoto, S., (19) 54
Omura, S., (19) 22-24
Ontyd, J., (23) 58
Ooi, Y., (3) 41
Opella, S.J., (2) 51; (21) 15
O'Reilly, J.P., (21) 36
Orena, M., (9) 27; (12) 13
Orgeret, C., (11) 3
Orito, S., (3) 106
Ortuno, R.M., (16) 13a; (24) 47
Osaka, N., (23) 40
Oshikawa, T., (7) 65
Osman, S., (22) 36
Ossowski, P., (3) 18; (4) 59; (13) 2; (21) 39
Otake, N., (19) 27, 29
Otero, D.A., (18) 30
Otsuka, S., (18) 11
Otter, B.A., (20) 18
Otvos, L., (22) 102
Ouchi, T., (7) 29, 36; (9) 54
Oue, S., (20) 79
Overend, W.G., (9) 31
Ovodov, Y.S., (14) 3
Owa, M., (4) 21
Owens, M., (2) 48
Oya, M., (9) 64
Ozaki, M., (9) 50; (11) 11
Ozaki, S., (20) 27, 68
Paal, M., (3) 67, 68; (4) 29
Pacak, J., (8) 22
Pacheco, H., (9) 8, 30
Paegle, R.A., (20) 84
Pai, F.-C., (12) 21
Palacids Albarran, J.C., (9) 25, 26; (10) 19, 20, 43
Palaniswamy, V.Z., (21) 21
Palfreyman, M.G., (23) 61
Palmer, B.D., (24) 26
Palmer, A.J., (19) 21
Pal'yants, N.Sh., (3) 32
Pamnani, J., (2) 46; (22) 6
Panasyuk, S.L., (2) 43
Pandey, S.P., (2) 69
Pandit, U.K., (24) 29
Pando, E., (10) 44
Pang, Q., (3) 36
Pankiewicz, K.W., (20) 90, 91
Panov, V.P., (1) 3
Pansare, V.S., (22) 7
Pant, C., (14) 27
Panter, T., (18) 14
Panza, L., (17) 11
Papageorgiou, C., (24) 48
Papahatjis, D.P., (3) 131; (8) 4
Paphassarang, S., (3) 95
Paquet, F., (3) 86
Parekh, S., (7) 64

Parisod, C., (21) 56
Park, J.I., (20) 78
Parkanyi, L., (22) 102
Parrilli, M., (4) 53, 68
Parthasarathy, R., (22) 100
Parvez,, M., (22) 91
Pate, B.D., (8) 9
Patel, A., (7) 64
Paterson, A.R.P., (22) 100
Patil, V.J., (8) 19; (9) 57
Paukov, V.N., (23) 8
Paul, B., (3) 128; (22) 100
Pauls, H.W., (9) 11; (14) 11; (24) 16
Paulsen, H., (3) 67, 68, 84; (4) 29, 37, 42, 65, 66; (18) 44; (22) 71
Pavia, A.A., (22) 53, 70, 89
Pazur, J.H., (1) 1
Pearce, C.J., (19) 19
Pearson, D.A., (24) 20, 65
Pecina, R., (23) 27, 31
Pedersen, C., (3) 39; (4) 3; (12) 16; (16) 12; (21) 45
Pedersen, E.B., (20) 15
Pedersen, H., (4) 3; (21) 45, 62
Penades, S., (22) 69
Pepe, G., (22) 70
Perdomo, A., (17) 30
Pedrocchi-Fantoni, G., (14) 23
Pedulli, G.F., (16) 42
Pei, Y., (5) 3
Pellicciari, R., (3) 45
Pelmore, H., (17) 26
Pelyvas, I., (18) 39
Peng, S., (3) 157
Perego, R., (3) 142; (17) 12
Periotto, V., (20) 16
Perlin, A.S., (3) 59, 12, 113, 159; (21) 34, 51
Pernemalm, P.-A., (2) 78
Pernikis, R., (7) 80
Perrin, C.L., (21) 11
Perrone, P.A., (23) 66
Pertsin, A.I., (22) 55
Perun, T.J., (19) 21
Peseke, K., (10) 52
Pestana, D., (20) 129; (23) 70
Pestunovich, V.A., (21) 70
Petchey, M., (23) 28
Peters, J.A., (17) 35; (22) 94
Peters, T., (4) 37
Petit-Glatron, M.-F., (3) 52; (11) 6
Petitou, M., (4) 41, 67
Petrakova, E., (4) 4, 17, 45; (21) 10
Petrie, C.R., (20) 13
Petroczy, J., (2) 50; (23) 16
Pettersson, L., (24) 70
Pfander, H., (4) 10, 20
Pfeffer, P.E., (2) 51; (21) 15
Pfleiderer, W.,(20) 117, 118, 155; (21) 25
Phillips, L.R., (9) 48; (22) 18
Picq, D., (9) 8, 30
Piekarska, B., (3) 60
Pietraszkiewicz, M., (5) 22, 23
Pike, V.W., (19) 21
Pikul, S., (18) 8
Pineau, R., (19) 14, 18
Pinter-Szakacs, M., (2) 50; (23) 16
Pinto, B.M., (4) 49
Piotrowski, E.G., (22) 36
Piper, I.M., (3) 163
Piskorz, C.F., (4) 38, 50, 51
Plaza Lopez-Espinosa, M., (3) 164
Plepis, E., (7) 80
Plessas, N.R., (3) 70
Plusquellec, D., (7) 79; (10) 13
Plyamovatyi, A.Kh., (7) 67
Podlahova, J., (22) 66
Poh, B.-L., (2) 7
Pohlid, H., (9) 19
Polavarapu, P.L., (22) 4, 5, 129
Polenov, V.A., (17) 16
Polonik, S.G., (3) 13, 14
Polonsky, J., (23) 75
Poncet, S., (3) 52; (11) 6
Pongrack, M., (9) 52
Ponty, A., (19) 80
Popsavin, V.J., (3) 158; (5) 32, 40
Porcelli, M., (20) 76
Portal Olea, M.D., (14) 17, 18; (16) 15
Potier, P., (20) 144
Potocki, J.F., (8) 8, 10
Potter, B.V.L., (20) 124
Pougny, J.-R., (16) 14; (24) 19, 50
Poulton, J.E., (7) 30
Povzar, V., (3) 28
Praefcke, K., (18) 56
Prahst, A., (3) 98
Praly, J.-P., (3) 119, 120; (22) 90
Pramanik, B.N., (19) 26; (22) 19
Praznik, W., (23) 33
Prenosil, J.E., (23) 32
Preobrazhenskaya, M.N., (16) 44; (20) 14
Presti, E., (19) 71
Priebe, W., (3) 17; (19) 35
Prince, S., (3) 121
Prince, S.E., (2) 62
Prior, J.J., (20) 145
Prinzbach, H., (9) 76; (19) 4, 5
Prome, J.C., (22) 15
Przasnyski, M., (23) 46
Pugashova, N.M., (7) 66
Puliti, R., (22) 50
Puls, J., (21) 55
Purygin, P.P., (20) 133
Puzo, G., (22) 15
Quintiliani, M., (2) 77
Quivoron, C., (3) 37, 38
Rabinowitz, I.N., (2) 34
Racz, V.M., (9) 31
Radatus, B., (3) 50
Radomski, J., (3) 60
Raemy, A., (2) 39
Rahman, A., (14) 41
Rahman, MD.D., (19) 8
Rai, R.C., (2) 61
Raifel'd, Yu,E., (12) 24, 25
Rajagopal, S., (2) 75, 76
Rajagopala Reddy,D., (24) 57
Rajaram, J., (2) 75, 76
Ram, B., (2) 35
Ramalingam, K., (20) 75
Rama Rao, A.V., (8) 19
Ramaswamy, P., (22) 48
Rana, S.S., (3) 66; (4) 38

Randall, J.L., (3) 127, 131, 135; (8) 4; (10) 2
Ranucci, E., (3) 35
Rao, A.S., (20) 69
Rao, A.V.R., (8) 37; (9) 57; (15) 6; (24) 57
Rao, V.S., (3) 159; (21) 34
Rateb, L., (9) 69
Rathmann, R., (19) 51
Rauwald, H.W., (3) 168
Ravindranathan, T., (24) 57
Rawji, H., (20) 83
Ray, B., (23) 18
Raynaud, J., (3) 95
Reay, P.F., (22) 56
Rebolledo Vicente, F., (10) 50, 51
Reboul, J.P., (22) 70, 89
Redlich, H., (24) 58
Redmond, J.W., (23) 43
Reed, R.H., (18) 1
Reetz, M.T., (24) 3
Reichman, U., (19) 66
Reichrath, M., (3) 11
Reinhold, V.N., (22) 17
Remiszewski, S.W., (9) 45
Rensch, R., (16) 24
Repasova, L., (23) 75
Retsema, J.A., (19) 25; (22) 114
Reuben, J., (21) 8, 9
Reutter, W., (23) 71
Revankar, G.R., (19) 67; (20) 10, 11, 13, 23, 55; (22) 103
Rhee, R.P., (9) 44
Ricard, A., (3) 37, 38
Richards, E.L., (9) 67
Richards, G.N., (23) 44
Richardson, A.C., (7) 15; (8) 24, 26; (9) 71; (24) 37
Richardson, J.F., (3) 130; (22) 59
Rico, M., (14) 32
Rico Gomez, R., (10) 30; (20) 43
Reitschel, E.T., (3) 89; (16) 21
Riley, D., (16) 16
Rinehart, K.L., (18) 3
Rinehart, K.L., (jun)., (19) 19
Riordan, J.M., (15) 9
Rios Ruiz, J., (20) 43
Robert-Gero, M., (19) 69
Robins, M.J., (15) 5; (20) 35, 78; (22) 101
Robins, R.K., (19) 67; (20) 10, 11, 13, 23, 55; (22) 103
Robinson, W.S., (23) 62
Robles Diaz, R., (3) 164, 165; (20) 138
Robyt, J.F., (3) 53; (11) 7; (12) 7
Rodriguez, A., (17) 30
Rodriguez, G.P., (23) 72
Rodriguez Fernandez, M.E., (4) 25
Rodriquez-Hahn, L., (7) 33
Röben, W., (18) 44
Roellgen, F.W., (22) 24
Rohrer, D.C., (3) 22, 27; (21) 67
Rokach, J., (24) 30, 42, 43
Rolf, D., (3) 115, 116; (18) 25, 27
Rollin, P., (3) 44; (13) 7
Romhanyi, I., (10) 52
Ronchetti, F., (3) 142; (13) 24; (17) 11, 12
Roosz, M., (9) 17
Rosado, F., (14) 31, 32
Rose, M.E., (7) 78; (22) 20
Rose, S.M., (23) 47
Rosemeyer, H., (20) 132
Rosen, D., (22) 9
Rosen, T., (24) 33
Rosenbrook, W., jun., (19) 2
Rosik, J., (5) 6
Rosmarinowsky, J., (16) 46
Rossman, R.R., (19) 26; (22) 19
Roth, K., (3) 168
Roulleau, F., (7) 79; (10) 13
Roush, W.R., (12) 26
Roy, R., (2) 42; (3) 82; (22) 43
Roy, R.S., (22) 121
Roy, S., (20) 17
Ruble, J.R., (21) 41; (22) 77
Rudnicka, I., (6) 13
Rüegge, D., (22) 117
Ruggeri, G., (3) 35
Ruiz, P.A., (15) 2, 3
Ruiz Contreras, R., (10) 49
Rumyantseva, S.A., 93) 16; (7) 68; (10) 21; (17) 22
Runsink, J., (12) 5
Rusjakovski, B., (20) 7
Russell, G.B., (22) 56
Russeva, N., (23) 7
Russo, G., (3) 142; (13) 24; (17) 12
Russo, T., (23) 57
Rutar, V., (21) 48
Rya, E.K., (20) 32
Ryan, K.J., (3) 148; (19) 42; (20) 99
Rychener, M., (4) 10, 20
Sabesan, S., (4) 27; (21) 59
Sada, T., (5) 14
Sadybakasov, B.K., (22) 76
Saenger, W., (21) 2
Saiki, Y., (5) 1, 14; (7) 27; (14) 5
Sainsbury, M., (18) 46, 47
Saint-Germain, J., (3) 55; (21) 50
Saito, A., (18) 2; (23) 14
Saito, I., (20) 80
Saito, K., (3) 166
Saito, S., (2) 16
Saito, Y., (22) 54
Sakai, T., (20) 130
Sakari, N., (19) 8; (20) 36
Sakakibara, T., (10) 27, 28
Sakamoto, Y., (7) 36; (9) 54
Sakanaka, O., (19) 56
Sakane, K., (19) 48
Sakata, I., (22) 44
Sakata, Y., (3) 140
Sako, M., (20) 50
Sakuma, M., (2) 22
Sakurai, H., (3) 140
Salanski, P., (5) 23; (14) 39
Sallam, M.A.E., (20) 105, 106; (22) 128
Salvatore, F., (23) 57
Samain, D., (23) 48
Samoshina, N.F., (3) 15
Samra, A.K., (2) 24; (5) 31
Samuel, J., (8) 21
Samuelsson, B., (5) 18, 19; (6) 21, 22; (8) 34, 40; (13) 21
Sandri, S., (9) 27;

(12) 13
Saneyoshi, M., (20) 61
San Feliz, A., (10) 12
Sano, H., (19) 22-24
Santi, D.V., (20) 145
Sarel, S., (10) 48; (17) 17
Sarfati, S.R., (3) 77; (7) 59
Sasai, H., (19) 56
Sasajima, K., (2) 32
Sasajima, K.-I., (12) 19, 20
Sasaki, H., (14) 28
Sasaki, N., (2) 38
Sato, K., (10) 29; (14) 16, 20, 21
Sato, K.-I., (9) 32
Sato, T., (15) 11; (22) 95, 113; (24) 45
Savino, V., (2) 37; (3) 125
Sawa, T., (19) 40, 41
Sawada, H., (19) 53
Sawada, T., (7) 37; (21) 61
Sawai, H., (3) 9; (19) 58; (20) 89
Sawaki, M., (10) 10
Saxena, N.K., (20) 98
Scharf, H.-D., (12) 5
Schauer, R., (16) 26
Schebez, H.M., (22) 41
Scheer, P., (9) 18
Schifman, A.L., (20) 74
Schleifer, L., (1) 4
Schleinitz, K.D., (20) 153
Schleiper, C.A., (20) 22
Schlimme, E., (20) 140
Schmid, W., (9) 24
Schmidt, D.D., (19) 81
Schmidt, H., (16) 25
Schmidt, H.-J., (22) 71
Schmidt, R.R., (2) 9; (3) 11, 83; (7) 53, 81; (9) 46, 47; (16) 20; (22) 74
Schneller, S.W., (19) 61
Schoenen, F.J., (3) 149
Schohe, R., (9) 5, 34
Schrader, J., (23) 58
Schram, K.H., (20) 158; (22) 40
Schraml, J., (4) 4, 45; (21) 10, 70
Schreurs, W.H.P., (23) 45
Schrijver, J., (23) 45
Schröder, G., (5) 20, 21
Schubert, J., (19) 4
Schueller, A.M., (7) 14; (10) 32
Schuerch, C., (3) 61; (4) 14; (5) 5, 34; (7) 5
Schulten, H.R., (3) 105; (22) 41
Schultz, B.S., (20) 118
Schulz, G., (3) 89; (4) 47, 58; (16) 21
Schumacher, D., (19) 16
Schwab, W., (9) 5
Schwarting, W., (5) 41
Schweizer, T.F., (2) 39
Schwesinger, B., (9) 76
Schwesinger, R., (9) 76; (19) 4, 5
Sciavolino, F.C., (19) 25; (22) 114
Scopes, D.I.C., (20) 101
Secrist, J.A., (22) 105
Seela, F., (20) 33, 34, 56-58, 132
Segmuller, B.E., (3) 147; (22) 79
Seib, P.A., (16) 39
Seifert, K., (3) 33
Seigner, C., (11) 9
Seiner, V.S., (19) 55
Seki, E., (9) 49, 51; (11) 4, 12
Self, R., (4) 68; (20) 157
Seligmann, O., (4) 15
Semenov, S.G., (3) 108
Senda, S., (20) 70
Sen Gupta, K.K., (2) 65
Seno, K., (9) 63
Seo, K., (17) 4
Seo, S., (21) 30
Sereno, J., (9) 42
Serianni, A.S., (2) 33; (3) 122
Serino, A.J., (13) 12
Serrano, Blazquez, J.A., (9) 61; (10) 8, 31; (18) 15
Seshadri, T.P., (22) 51, 96
Sethi, S.K., (19) 50; (20) 100; (23) 69
Seto, H., (19) 27; (22) 47
Setoguchi, Y., (19) 39
Setoi, M., (19) 48
Seuvre, A.-M., (20) 148, 149; (22) 13, 14
Sezaki, M., (19) 49
Shafizadeh, F., (14) 43; (22) 87
Shah, J.A., (23) 53
Shallenberger, R.S., (2) 41
Shannon, W.M., (19) 70; (20) 108, 109
Sharghi, H., (7) 72
Sharma, K., (2) 61
Sharma, M.N., (8) 20
Sharma, R.A., (20) 64
Sharma, V.K., (2) 61
Sharp, J.K., (22) 39
Shashkov, A.S., (4) 46; (5) 11; (7) 73; (14) 36; (16) 30; (21) 46
Shashkus, J., (16) 37
Shaw, D.H., (3) 82; (22) 43
Shaw, G., (20) 120; (22) 115; (24) 9
Shchedrin, A.P., (22) 33
Shealy, Y.F., (20) 108, 109
Sheldrick, B., (22) 59
Shelling, J.G., 8 (27); (22) 67
Sherr, B., (9) 6
Shiba, T., (7) 56
Shibaev, V.N., (3) 74; (7) 61
Shibai, H., (19) 30
Shibata, K., (5) 15; (7) 9
Shibata, S., (10) 11; (23) 26
Shibata, T., (3) 9; (20) 89
Shida, Y., (4) 8; (22) 26
Shigemasa, Y., (2) 16
Shimada, N., (19) 68
Shimamoto, T., (3) 78
Shimauchi, Y., (19) 37
Shimidzu, T., (7) 52; (20) 115
Shimizu, E., (3) 104
Shimura, Y., (20) 130
Shinagawa, S., (7) 76; (22) 68
Shing, T.K.M., (18) 48; (21) 51; (24) 8, 28
Shing, T.M., (3) 59
Shingu, T., (7) 22, 23; (21) 37, 38
Shinmitsu, K., (4) 11, 63
Shioiri, T., (9) 35, 36
Shirai, T., (2) 14
Shiraishi, S., (2) 22, 66
Shishniashvili, M.E.,

(18) 10
Shiue, C.Y., (8) 13
Shizukuishi, K., (22) 29
Shizuri, Y., (24) 67
Shoda, S., (2) 13; (3) 3, 8, 154; (20) 31
Shomura, T., (19) 49
Shono, T., (15) 7; (16) 3
Showalter, H.D.H., (19) 59; (20) 59
Shukla, S.N., (2) 67
Shumyantseva, V.V., (7) 63; (20) 128
Shurvell, H.F. (22) 1
Shutalev, A.D., (10) 15; (20) 28
Shuto, S., (20) 52-54; (22) 110
Shvets, V.I., (3) 48
Siemsen, L., (3) 51
Siewek, F., (23) 35
Simat, B., (3) 22
Simkovic, I., (4) 13
Simmie, J., (21) 36
Simoni, D., (20) 16
Simons, B.P., (20) 92
Simpson, R., (18) 30
Sinaÿ, P., (3) 44, 86, 133; (4) 41, 67; (13) 5, 7; (16) 14; (17) 20; (18) 23
Sinclair, H.B., (18) 21
Singh, A.K., (2) 64
Singh, B., (2) 64
Singh, G., (24) 54
Singh, J., (20) 88
Singh, M.P., (2) 70
Singh, P.D., (19) 72
Singh, S., (7) 47
Sinnott, M.L., (10) 5; (21) 27
Sinnwell, V., (4) 37
Sisneros, K., (3) 16
Sjöström, E., (23) 15
Skapski, A.C., (22) 112
Skaptsova, N.V., (20) 72
Slavica, B.S. (5) 40
Slezarik, A., (23) 22
Slowikowski, D., (20) 158; (22) 40
Smiatacz, Z., (7) 3; (10) 1
Smit, P., (9) 62; (10) 38
Smith, C.T., (23) 62
Smith, D., (19) 60
Smith, G.A., (23) 62
Smith, P.J., (17) 34
Smith, P.W., (18) 31; (24) 36
Smith, S.L., (2) 4
Smith, V.H., (2) 5; (22) 1
Snatzke, G., (14) 7; (16) 35; (17) 32; (22) 126, 127
Soerensen, P.E., (22) 122
Sof'ina, Z.P., (16) 44
Sohar, P., (6) 7; (21) 16
Sokoloski, E.A., (3) 61
Sokolov, V.M., (3) 108
Sokolowski, J., (20) 40
Solan, V.C., (20) 32
Solanki, S.K., (2) 56
Somsak, L., (10) 33, 52; (20) 97
Song, Y.H., (15) 10
Sonola, O.O., (6) 19, 20
Sookyova, E., (17) 31
Sorgi, K.L., (24) 5
Soriano-Garcia, M., (22) 100
Sorokina, I.B., (9) 53; (10) 14
Souleman, A.M.A., (7) 17
Spanjer, H.H., (3) 25
Speek, A.J., (23) 45
Sprinson, D.B., (7) 58
Spyrov, G., (23) 7
Srinivasan, R., (21) 12
Srivastava, A., (2) 64
Srivastava, M.L., (2) 35
Srivastava, R.M., (3) 10; (14) 41
Stamatatos, L., (16) 14
Stanaszek, R.S., (19) 2
Stanek, J., jun., (5) 7
Stanek, Ya.Ya., (2) 21
Staniewski, J., (5) 25
Stankevich, E.I., (20) 44
Stankevics, E., (20) 45
Stawiński, J., (20) 121
Stec, W.J., (20) 123
Steele, D., (2) 46; (22) 6
Stefanska, B., (9) 59; (19) 38
Steiger, K.-M., (4) 29
Stein, H., (19) 80
Steker, H., (20) 57, 58
Stenkamp, R.E., (22) 87
Stephens, R.L., (21) 60
Stepinski, J., (3) 60
Stern, A., (2) 45
Stern, J.H., (2) 36
Stern, K.F., (19) 79
Sternson, L.A., (23) 64
Stevenson, T.M., (20) 29
Stewart, A.O., (9) 13
Sticzay, T., (22) 125
Still, W.C., (24) 20, 65
Stockhove, U., (20) 42
Stolyarova, T.V., (3) 108
Stone, T.E., (17) 13
Stoodley, R.J., (3) 43; (24) 10
Stork, G.A., (9) 62; (10) 38
Stortz, C.A., (22) 35
Strack, D., (7) 31
Strazzolini, P., (19) 73, 74
Streicher, W., (19) 12
Strel'tsova, I.F., (22) 76
Strickland, L.C., (22) 62
Struchkov, Yu.T., (7) 67; (22) 76
Strumpel, M., (22) 71
Stud, M., (20) 12
Stütz, A.E., (8) 28; (19) 9, 10
Stumpp, M., (7) 53
Su, T.-L., (19) 66
Suami, T., (9) 39, 66, 72; (18) 43, 45, 49, 50; (19) 56; (24) 38
Subero, C., (4) 48
Subramaniam, C.S., (24) 53
Sudoh, R., (10) 27, 28
Suga, A., (9) 39
Sugawara, H., (6) 12
Sugawara, T., (20) 24
Sugawara, Y., (22) 52
Sugimoto, M., (3) 88; (4) 57
Sugio, S., (22) 107-109
Sugita, N., (19) 53
Sugiura, M., 97) 65
Sugiyama, T., (6) 12
Suh, H., (3) 153
Suh, Y.-G., (24) 6
Sukharevich, V.I., (2) 21
Sumitomo, H., (5) 39
Sun, K.M., (22) 85; (24) 68
Sunazuka, T., (19) 22, 23
Sustmann, R., (22) 117
Suzomoto, T., (16) 3
Suzuki, K., (10) 57

Suzuki, M., (2) 16; (4) 9; (19) 20, 33, 34, 82; (22) 27-30, 44, 45
Suzuki, N., (19) 56
Suzuki, S., (23) 24, 25
Suzuki, T., (24) 31
Svahn, B.-M., (8) 23
Svensson, S., (3) 65, 110; (16) 7
Sviridov, A.F., 914) 29; (24) 2
Sybilska, D., (23) 46
Sykes, R.B., (19) 55
Symons, M.C.R., (17) 26
Szabo, I.F., (20) 97
Szabo, L., (3) 76, 77; (7) 59
Szabo, P., (3) 77; (7) 59
Szabolcs, A., (22) 102
Szarek, W.A., 92) 5, 25; (3) 163; (8) 2; (18) 13; (19) 17; (22) 1
Szekeres, G.L., (20) 32
Szmant, H.H. (7) 16; (17) 25
Sztaricskai, F., (18) 39
Szymanowski, J., (5) 25
Szymanski, M., (10) 39
Taba, K.M., (17) 33
Tabusa, F., (19) 57
Tachimori, Y., (10) 27, 28
Tadanier, J., (16) 16
Tadano, K., (9) 72; (18) 43; (24) 38
Tadono, K., (9) 39
Tadra, M., (8) 22
Tajima, K., (16) 34
Tajmir-Riahi, H.-A., (16) 32; (17) 27; (22) 3, 11
Takagi, M., (10) 45, 46
Takagi, Y., (9) 74
Takahashi, H., (3) 103; (19) 15
Takahashi, K., (15) 11; (23) 26
Takahashi, N., (19) 63
Takahashi, T., (8) 11
Takahashi, Y., (3) 21, 166; (8) 17; (19) 45
Takaku, H., (7) 62; (20) 116
Takami, E., (19) 82
Takao, S., (9) 63
Takase, K., (23) 21
Takatsuki, Y., (19) 40
Takaya, T., (19) 6
Takayanagi, H., (22) 72
Takeda, N., (2) 16; (22) 44, 45
Takeda, T., (10) 11; (22) 57
Takedo, K., (4) 11
Takeichi, H., (3) 40
Takemura, T., (13) 18; (16) 10
Takenaka, K., (19) 13
Takeo, K., (4) 63; (5) 15; (7) 9
Takesue, T., (22) 47
Takeuchi, M., (18) 37 (19) 3, 7
Takeuchi, T., (19) 40, 41, 45
Takezawa, M., (19) 30
Takita, T., (19) 68
Talhouk, J.W., (15) 9
Tallman, A., (2) 48
Talvitie, A., (21) 32
Tam, T.F., (24) 64
Tamba, M., (2) 77
Tampo, H., (20) 139
Tamura, M., (7) 28; (10) 9, 10
Tamura, Z., (3) 34
Tanabe, K., (19) 29
Tanahashi, T., (16) 36
Tanaka, A., (18) 11
Tanaka, H., (19) 22, 23, 37
Tanaka, M., (23) 21
Tanaka, N., (5) 1, 14; (14) 5
Tanaka, O., (3) 7, 42, 94; (21) 28
Tanaka, R., (3) 54, 97; (7) 34
Tanaka, T., (5) 16, 17; (7) 18, 19; (14) 6
Tanaka, Y., (4) 7; (22) 46
Tang, P.W., (3) 111
Tanino, H., (18) 54
Tanner, G.R., (23) 9
Taravel, F., (3) 55; (21) 50
Tarraga Tomas, A., (3) 56
Tartakovsky, E., (1) 4
Taru, M., (7) 2
Tarusova, N.B., (7) 63; (20) 128
Taschner, M.T., (24) 33
Tashiro, S., (19) 53
Tatchell, A.R., (6) 19, 20
Tatematsu, A., (22) 44, 45
Tatsuta, K., (19) 15, 45
Tayaka, T., (24) 35
Taylor, K.G. (7) 47
Taylor, N., (22) 85; (24) 68
Taylor, N.F., (8) 21
Teece, R.G., (20) 158; (22) 40
Tejani, S.M., (20) 25
Tejima, S., (4) 55
Temeriusz, A., (3) 60
Tempesta, M.S., (18) 38
Templeton, C., (3) 121
Teng, G., (23) 30
Teraji, T., (19) 48
Terashima, S., (19) 33, 34
Teresa Garcia Lopez, M., (20) 19
Tewson, T.J., (8) 14
Thakur, S., (23) 18
Thang, S., (11) 8
Thang, T.T., (5) 35; (8) 12; (21) 69, (24) 21
Thanh, L.P., (17) 15
Thawait, ., (23) 74
Thieffrey, A., (5) 27
Thiel, I.M.E., (14) 7; (10) 32; (22) 31
Thiem, J., (2) 73, 74; (3) 18, 98; (4) 2, 59; (13) 2, 13; (17) 10; (21) 39; (22) 116
Thomas, C.B., (16) 33; (22) 120
Thomas, H.J., (20) 136
Thompson, B.B., (20) 87
Thompson, R..D., (19) 61
Thornalley, P.D., (2) 45, 53
Thornton, E.R., (3) 47; (21) 58
Thorpe, T.A., (23) 77
Tietz, H., (4) 42
Timoshchuk, F.A., (16) 27; (20) 85, 86
Timpa, J.D., (3) 117, 118
Tiwari, K.N., (4) 18, 60; (12) 1
Toad, S., (21) 42; (22) 82
Tohyama, H., (19) 49
Toke, L., (5) 24
Tolkach, A.M., (3) 13, 14
Tollin, P., (22) 97
Toma, L., 93) 142; (13) 24; (17) 11, 12

Toman, R., (5) 6
Tomasini, C., (9) 27; (12) 13
Tomasz, J., (20) 122
Tomer, K.B., (22) 21
Tomic, S., (11) 5
Tomimatsu, T., (3) 104
Tomishi, T., (20) 47
Tomita, K., (22) 99
Tomita, K.-i., (22) 104, 107-110
Tomori, E., (6) 8, 9; (18) 12; (22) 37; (23) 11, 12
Tone, K., (22) 10
Tong, G.L., (19) 32
Torgov, V.I., (3) 74
Tori, K., (21) 30
Torihara, M., (19) 13
Toriumi, K., (17) 28
Torri, G., (4) 41, 67
Torssell, K.B.G., (10) 35
Toshida, Y., (21) 38
Toyama, A., (10) 16
Toyokuni, T., (18) 49, 50
Tracy, M., (3) 148; (19) 42
Travesedo, I.C., (15) 2, 3
Trichtinger, T., (20) 118
Trifonoff, E., (4) 26; (21) 54
Trigalo, F., (3) 77; (7) 59
Trivedi, K.K., (7) 24
Trnka, T., (9) 9, 68
Trska, P., (9) 60
Tsai, H., (19) 16
Tsai, T.Y.R., (4) 19
Tsang, R., (13) 16; (14) 25, 26, 35
Tsao, C.S., (23) 47
Tsubomura, T., (17) 28
Tsuchida, K., (20) 139
Tsuchiya, T., (7) 46; (8) 1; (9) 56, 74
Tsuda, K., (20) 130
Tsuda, Y., (7) 1, 2
Tsuji, T., (19) 30
Tsujimoto, K., (4) 8; (22) 26, 27
Tsukamoto, S., (12) 3
Tsumura, N., (8) 5
Tsunekawa, K., (7) 65
Tsuruoka, T., (9) 1; (19) 54, 77; (22) 73
Tsutsui, H., (24) 23
Tsutsumi, H., (19) 6; (24) 35
Tsuzono, N., (22) 72
Tucker, L.C.N., (9) 58; (12) 12
Tulsham, D.B., (24) 63
Tulshian, D.B., (3) 146; (13) 9; (14) 25, 26
Turina, O.V., (20) 72
Turner, W.N., (19) 16
Turnowsky, F., (19) 12
Tvaroska, I., (11) 1, 2; (21) 1
Tymiak, A.A., (18) 3; (19) 55
Ubukata, M., (19) 50
Uchida, I., (19) 48
Uchiyama, C., (22) 10
Ueda, N., (2) 16
Ueda, S., (7) 62; (20) 116
Ueda, T., (20) 52-54; (22) 99, 110
Ueno, Y., (9) 39
Uesugi, S., (20) 62; (22) 104
Ugolini, A., (3) 134
Uhlmann, E., (20) 117
Ulrich, J., (4) 6; (22) 16
Umezawa, H., (19) 11, 28, 40, 41, 45, 68
Umezawa, S., (7) 46; (9) 56, 74
Unger, F.M., (3) 89; (4) 47, 58; (16) 21
Unkovskii, B.V., (10) 15; (20) 28
Uramoto, M., (19) 50
Urbanczyk-Lipkowska, Z. (3) 100; (5) 33; (22) 63, 78
Usami, F., (20) 104
Uskokovic, M.R., (9) 42, 43
Usov, A.I., (7) 73; (22) 55
Usui, H., (20) 52
Usui, T., (9) 74
Utagawa, T., (19) 47; (20) 4
Utamura, T., (21) 35
Utille, J.-P., (3) 92; (4) 61; (21) 49
Uvarova, N.I., (3) 13-15, 26
Uzawa, J., (20) 152; (21) 63
Uzlova, L.A., (17) 14, 16
Uznanski, B., (20) 124
Vajda, M., (23) 69
Vakorina, T.I., (22) 33, 34
Valdniece, A., (23) 76
Valpuesta Fernandez, M., (3) 162; (5) 36; (16) 19
Van Aelst, S.F., (5) 29
Van Bekkum, H., (2) 3, 49
Van Berkel, T.J.C., (3) 25
Van Beuzekom, A.A., (21) 5
Van Boeckel, C.A.A., (3) 73, 79; (5) 29; (9) 55; (10) 22; (13) 3; (20) 113
Van Boom, J.H., (3) 25, 73, 79; (5) 30; (9) 55; (10) 22; (13) 3; (20) 113, 156; (21) 65
Vancheesan, S., (2) 75, 76
Vanderhaeghe, H., (23) 49
Van Der Marel, G.A., (3) 79; (9) 55
Van Der Plas, H.C., (9) 62; (10) 38
Van Der Sluis, P., (22) 49
Van Doorslaer, E., (3) 109
Vangehr, K., (22) 78
Van Koningsveld, H., (22) 94
Van Opstal, O., (3) 109
Van Rijsbergen, R., (5) 38; (6) 1
Van Westrenen, J., (20) 113, 156; (21) 65
Varela, O., (3) 17; (6) 2; (19) 35
Varela, O.J., (16) 11
Varma, R., (22) 7
Varnum, D.A., (8) 15
Vasella, A., (10) 24-26; (13) 23; (16) 5; (24) 13, 61
Vasil'ev, A.V., (17) 23
Vasil'ev, Yu.B., (2) 63; (16) 1
Vazquez, I.M., (7) 14
Vazquez De Miguel, L.M., (9) 61
Veda, T., (20) 79
Veenendal, J.R., (23) 41
Vega, R., (22) 84
Veksler, V.I., (10) 42; (16) 8
Vemura, A., (20) 27

Verez Bencomo, V., (3) 1, 2, 44; (4) 25; (13) 7
Verhaar, L.A.Th., (23) 29
Verovskii, V.G., (21) 47
Verovsky, V.E., (21) 7
Verzele, M., (3) 101
Veysoglu, T., (19) 36
Viden, I., (7) 55
Viet, C., (11) 3
Vig, R., (3) 69
Vigevani, A., (19) 43; (22) 25
Vignon, M., (3) 55; (21) 50
Vikrishchuk, N.I., (17) 14
Vince, R., (20) 110
Vincendon, M., (3) 55; (21) 50
Vinogradov, E.V., (4) 46
Visser, G.M., (20) 113
Viswamitra, M.A., (20) 150; (22) 51, 96
Vliegenthart, J.F.G., (16) 26; (18) 20; (23) 13
Vodny, S., (23) 75
Voelter, W., 92) 18, 19; (7) 71; (8) 32; (9) 17, 21-23; (18) 17
Voituriez, L., (20) 147
Volodin, Yu.Yu., (16) 44
Vondeyn, W., (18) 44
Von Janta-Lipinski, M., (20) 67
Von Platen, A.E., (9) 75
Vos, J.N., (10) 22; (13) 3
Voznij, Y.V., (8) 6
Vratny, P., (23) 23
Vukojevic, N., (8) 39
Vuorinen, T., (2) 72; (15) 4; (16) 6
Vyas, D.M., (2) 25
Wada, K., (12) 3
Wada, M., (3) 166
Wada, Y., (7) 76; (22) 68, 111
Wadsworth, J., (18) 5
Wagner, H., (3) 105; (4) 15
Wagner, J., (23) 61
Waites, W.J., (19) 70
Wakahara, A., (22) 108
Wakamatsu, K., (22) 54
Waldmann, H., (3) 12
Waldstatten, P., (4) 58
Walker, R.T., (20) 141
Walla, M.D., (22) 42; (23) 4
Walton, D.J., (18) 13
Walz, B., (5) 21
Wan, J.K.S., (16) 42, 43
Wang, C.Y., (10) 37
Wang, J.-S., (21) 48
Wang, S., (5) 3
Wanner, M.J., (24) 29
Warr, S.M., (18) 48
Warren, C.D., (3) 81; (4) 40; (21) 60
Washburn, W.H., (19) 2
Watanabe, K., (3) 156
Watanabe, K.A., (19) 66; (20) 63, 90, 91
Watanabe, M., (6) 12
Watanabe, N., (23) 42
Watanabe, Y., (20) 27, 68
Watkins, W.M., (4) 62
Watson, T.R., (22) 91
Weakley, T.J.R., (14) 12; (22) 0
Weaver, J.M., (20) 20, 21
Webb, R.R., (13) 1
Weber, D.J., (23) 53
Webster, K.T., (5) 5; (7) 5
Weidmann, H., (16) 31
Weiler, L., (14) 34
Weinreb, S.M., (9) 45
Weiss, A., (7) 38
Weiss, M.M., (18) 52
Weissmüller, J., (3) 145; (13) 4, 10
Welch, J.T., (8) 23
Welzel, P., (14) 7; (16) 35; (19) 80; (22) 126
Wemple, J., (20) 20-22
Wender, N.L., (18) 51
Werk, M., (2) 74; (22) 116
Wessel, H.-P., (2) 73, 74; (4) 28; (22) 116
Westerduin, P., (3) 73, 79
Westphal, G., (9) 7; (10) 4
Whenham, R.J., (23) 2
Whistler, R.L., (14) 19; (17) 2
Whittle, R.R., (9) 33, 45
Wiebe, L.I., (20) 65
Wielogorski, Z., (19) 36
Wiesner, K., (4) 19
Wightman, R.H., (19) 60, 64, 65; (20) 98; (24) 49, 54
Wilcox, C.S., (3) 153
Wilde, J., (21) 21
Wiley, P.F., (19) 76
Williams, D.H., (19) 73
Williams, D.J., (24) 26
Williams, J.F., (7) 54; (21) 23
Williams, J.M., (2) 12; (3) 111; (9) 41; (12) 21; (14) 2; (18) 7, 16
Williams, M.R., (22) 12
Williams, R.E., (2) 42
Williams, R.M., (9) 13
Williams, T.H., (9) 42, 43
Wilson, C.C., (22) 97, 98
Wilson, H.R., (22) 97
Wingert, L.M., (21) 41; (22) 77
Winkeler, H.-D, (20) 56
Winnik, F.M., (4) 22
Winter, M., (23) 39
Wirz, P., (8) 27; (22) 67
Wisser, G.M., (20) 156; (21) 65
Witczak, Z.J., (9) 3; (10) 34; (14) 19; (17) 2, 19; (20) 3
Witzel, H., (20) 42
Witzel, T., (14) 37
Wojtczak, J., (10) 39
Wolf, A.P., (8) 13
Wolff, S.P., (2) 53
Wolgemuth, R.L., (19) 32, 36
Wong, H., (16) 9; (21) 20
Wong, S.S., (22) 24
Wong, T.C., (4) 35; (21) 48
Wood, S.G., (20) 10, 11; (22) 103
Woodard, R.W., (20) 75
Wozniak, L., (19) 85
Wray, V., (7) 31
Wright, G.E., (20) 26
Wroblewski, A.E., (2) 26; (17) 9
Wünsche, C., (19) 81
Wydila, J., (3) 47
Yadav, J.S., (8) 19, 37; (9) 57; (15) 6
Yagisawa, N., (19) 68
Yakimova, G.V., (2) 20

Yakovlev, V.I., (2) 21
Yakshina, N.V., (17) 16
Yamada, K., (3) 93; (18) 2; (22) 54; (23) 14
Yamada, N., (19) 44
Yamada, T., (10) 57
Yamada, Y., (4) 8; (9) 1; (19) 77; (22) 26, 73; (24) 40
Yamagata, Y., (22) 99, 110
Yamaguchi, T., (18) 37; (19) 7; (20) 61
Yamamoto, H., (7) 65; (14) 28; (17) 1, 3, 5-8
Yamamoto, K., (13) 18; (16) 10; (17) 8
Yamamoto, M., (3) 78; (7) 56
Yamamura, S., (24) 67
Yamana, K., (7) 52; (20) 115
Yamane, M., (2) 17
Yamashita, H., (9) 66
Yamashita, K., (6) 12; (18) 11; (19) 22, 23
Yamashita, M., (7) 65; (17) 5-8; (19) 48
Yamauchi, S., (23) 52
Yamaura, M., (24) 31
Yanagawa, H., (20) 48
Yanagisawa, S., (2) 14
Yanagiya, M., (3) 166
Yang, D., (23) 68
Yang, Y.-L., (24) 34
Yano, S., (2) 71; (7) 35; (17) 28
Yano, Y., (8) 16, 18; (13) 15
Yartseeva, I.V., (16) 44
Yashunskii, D.V., (14) 29
Yasuda, N., (19) 6; (24) 35
Yasui, A., (6) 5, 11; (9) 16
Yasumori, T., (9) 32; (10) 29; (14) 16, 20, 21
Yates, A.D., (4) 62
Yavarzadeh, R., (18) 46, 47
Yelland, L.J., (3) 129
Yoakim, C., (3) 114; (5) 28; (8) 36
Yokohama, H., (3) 29, 31
Yokose, K., (19) 83
Yokota, A., (2) 32; (12) 19, 20
Yokoyama, Y.S., (3) 155
Yonemitsu, O., (5) 16, 17
Yoneta, T., (19) 8
Yoo, B.K., (15) 10
Yoshida, N., (3) 94; (21) 28
Yoshida, T., (7) 22, 23; (21) 37
Yoshikawa, M., (18) 37, 42; (19) 7, 13
Yoshikawa, S., (2) 71; (17) 28
Yoshikoshi, A., (24) 14
Yoshimoto, A., (19) 37, 40, 41
Yoshimoto, K., (7) 1, 2
Yoshimura, H., (3) 78
Yoshimura, J., (9) 12, 32; (10) 29; (14) 1, 14, 16, 20, 21; (24) 31
Yoshimura, S., (12) 3
Yoshimura, Y., (21) 30
Yoshioka, K., (3) 27; (21) 67
Yoshioka, S., (18) 22
Yoshioka, T., (5) 17; (19) 37
Yoshizaki, M., (7) 35
Young, D.W., (19) 65
Young, M., (23) 47
Yu, R.K., (4) 7; (22) 46
Yurchenko, N.N., (7) 61
Zähner, H., (19) 51
Zähringer, U., (3) 89; (16) 21
Zaharans, V., (23) 76
Zaitseva, V.E., (20) 72
Zajicek, J., (21) 19
Zama, Y., (20) 36
Zamboni, R., (24) 43
Zamocky, J., (7) 6
Zamojski, A., (2) 10; (3) 96; (4) 16, 30; (12) 27; (13) 14; (21) 40
Zamora Mata, F., (10) 49
Zarrinmayeh, H., (7) 72
Zavgorodnii, S.G., (20) 51
Zbiral, E., (3) 87; (9) 24; (16) 23
Zehavi, U., (3) 64; (4) 23
Zeisig, R., (8) 35
Zemek, J., (7) 6; (9) 65; (12) 8
Zemlicka, J., (22) 137
Zemlyakov, A.E., (5) 10, 11; (16) 28-30
Zen, S., (4) 21
Zenk, M.H., (16) 36
Zharkov, A.A., (17) 21
Zhbankov, R.G., (1) 3; (22) 2
Zhdanov, Yu.A., (17) 14, 16
Zhu, T., (5) 3
Zidermane, A.A., (20) 84
Zielinski, W.S., (20) 123
Zil'berg, L.L., (12) 24, 25
Zirotti, C., (14) 24
Zoll, A., (3) 167
Zong, Y., (3) 36
Zubieta, J., (8) 23
Zubkov, V.A., (14) 3
Zurabyan, S.E., (9) 53; (10) 14
Zurenko, G.E., (19) 79
Zvonkova, E.N., (3) 48

Other Publications

The following publications also published by the Royal Society of Chemistry may be of interest to those involved in organic and bio-organic chemistry:

The Chemical Regulation of Biological Mechanisms
Special Publication No. 42
(1982) Softcover 330pp ISBN 0 85186 855 X

Index of Reviews in Organic Chemistry 1985 (IROC 85)
(1986) Softcover 65pp ISBN 0 85186 589 5

Molecular Aspects of Toxicology
(1984) Hardcover 319pp ISBN 0 85186 068 0

Molecular Biology and Biotechnology
Special Publication No. 54
(1986) Softcover 348pp ISBN 0 85186 985 8

Pharmacokinetics of Cardiovascular, Central Nervous System, and Antimicrobial Drugs
(1985) Hardcover 468pp ISBN 0 85186 937 8

Recent Advances in the Chemistry of Insect Control
Special Publication No. 53
(1985) Softcover 336pp ISBN 0 85186 965 3

Recent Advances in the Chemistry of β-Lactam Antibiotics
3rd International Symposium 1984
Special Publication No. 52
(1985) Softcover 399pp ISBN 0 85186 955 6

Third SCI-RSC Medicinal Chemistry Symposium
Special Publication No. 55
(1986) Softcover 396pp ISBN 0 85186 616 6

Further details on coverage and prices of these and any other RSC publications are obtainable from:
Sales and Promotion Department, The Royal Society of Chemistry, Burlington House, London W1V 0BN