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Carbohydrate Chemistry

VOLUME 14

Part I

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

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Part I

A Speicalist Periodical Report

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

A Review of the Literature Published during 1980

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Preface

This is the fourteenth in the Series of annual Specialist Periodical Reports on Carbohydrate Chemistry which aim to provide a comprehensive survey of publications covering carbohydrates in a concise and readable form; all journals for 1980 available to us by February 1981 have been abstracted.

In an endeavour to contain the prices of the volumes, and to expedite publication, it has been decided to publish the two parts of this Report separately. Further to these ends it has also been decided that Volume 15, covering the literature for 1981, and also to be published in two Parts, will be produced directly from authors' typescripts and we hope that this will prove to be an acceptable means of production.

With the proviso that the information is clearly presented and accurate, it is our belief that readers are more concerned about the speed of publication and the cheapness of the report, rather than its perfection in print. We expect Volume 15 to appear well before the end of 1983. We are always pleased to receive comments and suggestions which will serve to make the report more useful to its readership.

The same team of reporters responsible for Volume 13 are to be thanked for their assistance in producing this Volume; considerable effort is required to ensure that the report is both comprehensive on the one hand and yet concise and readable on the other, and we are conscious that we may not always have succeeded. We should again like to thank Dr R. Gigg for assistance with the literature survey.

Finally, I would like to thank Dr P. Gardam and Mrs L. A. Turrell at the Royal Society of Chemistry without whose assistance this report would not be possible.

May 1982 NEIL R. WILLIAMS

Contents

Abbreviations

The following abbreviations have been used:

Ac	acetyl
Ad	adenin-9-yl
Bn	benzyl
Bz	benzoyl
c.d.	circular dichroism
DBU	1,5-diazobicyclo5,4,0]undec-5-ene
DCC	dicyclohexylcarbodi-imide
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulphoxide
DNA	deoxyribonucleic acid
dpm	dipivaloylmethanato
e.s.r.	electron spin resonance
fod	2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionato
g.l.c.	gas–liquid chromatography
HMPT	hexamethylphosphotriamide
i.r.	infrared
LAH	lithium aluminium hydride
MCPBA	*m*-chloroperbenzoic acid
Ms	methanesulphonyl
NBS	*N*-bromosuccinimide
n.m.r.	nuclear magnetic resonance
o.r.d.	optical rotatory dispersion
py	pyridine
RNA	ribonucleic acid
THF	tetrahydrofuran
Thp	tetrahydropyranyl
TMS	trimethylsilyl
Ts	toluene *p*-sulphonyl
U	uracil-1-yl

Part I

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

By
B. E. Davison
R. J. Ferrier
A. C. Richardson
N. R. Williams

1

Introduction

Over 1200 references in Part I of this report for 1980 make plain the unceasing interest in the chemistry, and increasingly, the biochemistry of mono- and di-saccharides and their derivatives. The large amount of work on glycosides, which was noted last year, has been maintained and there seems no limit to the range of nucleoside analogues which continue to be reported, many of which show interesting biological properties. There is also no sign of an end to the number and diversity of carbohydrate-containing antibiotics being isolated, principally from strains of the remarkable soil actinomycetes, which provide formidable challenges to the synthetic chemist. Carbohydrates, notably glucose, continue to offer attractive chiral templates for the stereoselective synthesis of a wide range of chiral natural products, using reaction sequences that clearly display the ingenuity of the modern carbohydrate chemist. Carbohydrate chemistry is evidently in fine fettle!

An appreciation of William Ward Pigman[1] is contained in the 1980 issue of 'Advances in Carbohydrate Chemistry and Biochemistry', which also includes articles on the free-radical reactions of carbohydrates[2] and the synthesis of L-ascorbic acid.[3]

The latest text in the series 'Methods in Carbohydrate Chemistry' is devoted to general methods in carbohydrate chemistry, including procedures for separation and analysis of sugars, and the preparation of mono-, oligo-, and poly-saccharides and their derivatives.[4]

The final volume of the second edition of 'The Carbohydrates' has been published at last, being devoted principally to modified sugars and physical methods of analysis.[5]

Conformational nomenclature recommendations for five- and six-membered ring forms of monosaccharides and their derivatives are contained in a publication from the IUPAC–IUB Joint Commission on biochemical nomenclature.[6]

[1] A. Herp, *Adv. Carbohydr. Chem. Biochem.*, 1980, **37**, 1.
[2] C. Von Sonntag, *Adv. Carbohydr. Chem. Biochem.*, 1980, **37**, 7.
[3] T. C. Crawford and S. A. Crawford, *Adv. Carbohydr. Chem. Biochem.*, 1980, **37**, 79.
[4] 'Methods in Carbohydrate Chemistry', ed. R. L. Whistler and J. N. BeMiller, Academic, New York, 1980, Vol. 8.
[5] 'The Carbohydrates, Chemistry and Biochemistry', 2nd Edn., ed. W. Pigman and D. Horton, Academic, New York, 1980, Vol. 1B.
[6] *Eur. J. Biochem.*, 1980, **111**, 295.

2

Free Sugars

The radiation chemistry of carbohydrates has been reviewed in Russian,[1] and in English.[2]

A study of D-erythrose and D-threose in aqueous solution has shown the presence of >1% free aldehydic forms, 10–16% hydrated aldehyde, and the remainder as furanose forms; in the syrup dimeric forms predominate.[3]

A potential-energy function comprising harmonic terms for bond-length and valence-angle distortions with Lennard-Jones and coulomb terms for non-bonded interactions has been developed and shown to be able to reproduce structures of alkanes, alcohols, ethers, and α- and β-D-glucose. Good agreement was obtained for calculated and observed bond lengths and angles and for the free-energy differences between the two anomers.[4]

A journal issue containing reviews on the chemistry of carbohydrates with important food uses has appeared,[5] covering trehalose,[5a] sucrose,[5b] raffinose and melezitose,[5c] maltose,[5d] cellobiose,[5e] and lactose.[5f]

1 Isolation and Synthesis

Two disaccharides isolated from the dried twigs of *Sarcostemma brevistigma* have been shown to be β-D-digitoxopyranosyl-β-D-digitoxopyranoside and 4-*O*-(6-deoxy-2-*O*-methyl-β-D-allopyranosyl)-2,6-dideoxy-D-*xylo*-hexopyranose.[6,7] 3-*O*-Methyl-L-rhamnose has been isolated from hydrolysates of a *Rhizobium* capsular polysaccharide.[8]

A study of carbohydrates in human erythrocyte membranes during ageing has shown there is a homogeneous decrease in the concentrations of fucose, mannose, galactose, glucose, 2-acetamido-2-deoxy-D-glucose, and -D-galactose during ageing, although the relative proportions do not appear to change.[9]

[1] N. K. Kochetkov, L. I. Kudryashov, and M. A. Chlenov, 'Radiation Chemistry of Carbohydrates', Nauka, Moscow, USSR, 1978.

[2] N. K. Kochetkov, 'Radiation Chemistry of Carbohydrates', Pergamon, Oxford, England, 1979.

[3] S. J. Angyal and R. G. Wheen, *Aust. J. Chem.*, 1980, **33**, 1001.

[4] S. Melberg and K. Rasmussen, *J. Mol. Struct.*, 1979, **57**, 215 (*Chem. Abstr.*, 1980, **92**, 180469).

[5] Review issue of *Dev. Food Carbohydr.*, 1980, **2**; (*a*) C. K. Lee, *ibid.*, p. 1; (*b*) M. R. Jenner, *ibid.*, p. 91; (*c*) E. B. Rathbone, *ibid.*, p. 145; (*d*) E. Tarelli, *ibid.*, p. 187; (*e*) R. G. Edwards, *ibid.*, p. 229; (*f*), L. A. W. Thelwall, *ibid.*, p. 275.

[6] D. P. Khare, A. Khare, and M. P. Khare, *Carbohydr. Res.*, 1980, **79**, 287.

[7] D. P. Khare, S. S. Tiware, A. Khare, and M. P. Khare, *Carbohydr. Res.*, 1980, **79**, 279.

[8] L. K. Jackson, M. E. Slodki, M. C. Cadmus, K. A. Burton, and R. D. Plattner, *Carbohydr. Res.*, 1980, **82**, 154.

[9] D. Bladier, L. Gattegno, F. Fabia, G. Perret, and P. Cornillot, *Carbohydr. Res.*, 1980, **83**, 371.

D-[U-^{13}C]Galactose and [U-^{13}C]glycerol have been prepared by hydrolysis of [U-^{13}C]-2-hydroxy-1-(hydroxymethyl)ethyl-α-D-galactopyranoside formed by photosynthesis when the marine red alga *Gigartina corymbifera* was supplied with $^{13}CO_2$.[10] Photosynthesis has also been exploited in the formation of [U-^{11}C]glucose from $H_2{}^{11}CO_3$ by *Scenedesmus obtusiusculus*. A 50–70% yield was obtained in 0.5 h at 30 °C.[11] A 44% yield of D-[U-^{14}C]arabinose has been obtained by treatment of D-[U-^{14}C]glucose 2-nitrophenylhydrazone with ammoniacal sodium molybdate–hydrogen peroxide mixtures.[12] D-[5-^{3}H]Mannose and L-[5-^{3}H]gulose have been prepared by the route shown in Scheme 1.[13]

The Kiliani reaction with D-arabinose using [^{13}C]cyanide and [^{13}C, ^{15}N]cyanide has been investigated by means of ^{13}C n.m.r. spectroscopy. The reaction was shown to be complex, involving cyanohydrins, amides, lactones, amidines, and an imidate. The reaction, followed over the pH range 5.1–12.5, was shown to produce gluconate : mannonate ratios dependent upon the pH and not upon the presence of metal ions.[14]

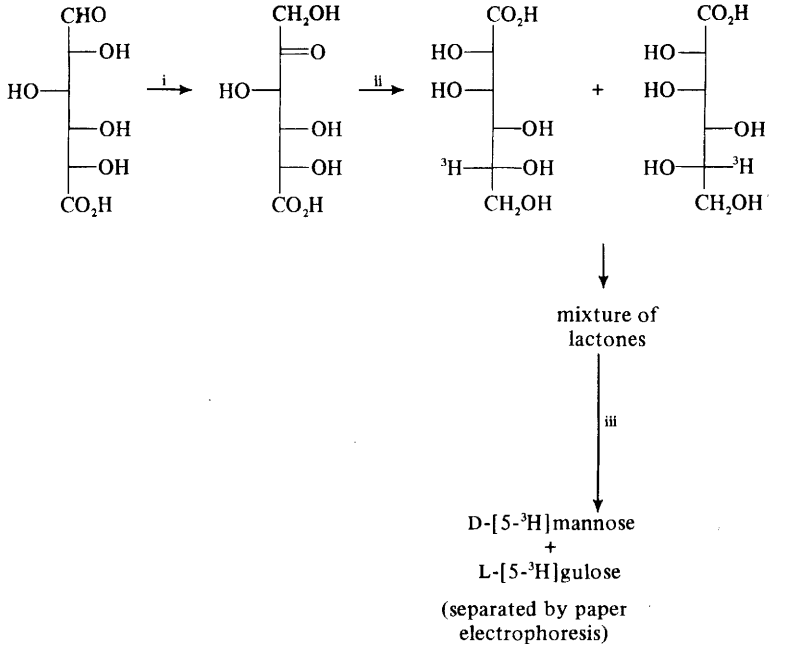
An abbreviated synthesis of penta-*O*-acetyl-α-D-altropyranose, and hence altrose, involves treatment of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside with acetic anhydride–sulphuric acid mixtures. The peracetate was obtained in 64% yield.[15]

The use of 4,5-dihydro-2-lithio-5-methyl-1,3,5-dithiazine instead of 2-lithio-1,3-dithian gives better results in the chain extension of sugars, the former being more reactive and the products more readily desulphurized.[16]

Chapter 7 contains a reference to a synthesis of L-idose among many reactions resulting from photobromination of penta-*O*-benzoyl-β-D-glucopyranose, and the synthesis of pure anhydrous D- and L-gulose *via* boronate esters of sugar lactones is covered in Chapter 16 (Schemes 1 and 2).

A review in Russian on the synthesis of carbohydrates from formaldehyde has appeared.[17] An investigation of the formose reaction by g.c.–n.m.r. has shown that intermediate glycoaldehyde, glyceraldehyde, and dihydroxyacetone are present as mixtures of monomers, *e.g.* hydroxycarbonyl compounds, epoxides and hydrates, and dimers such as half and full acetals.[18] Further study of the barium chloride-catalysed formose reaction at pH 12 has shown that the main product forming 33% of the total sugars is the branched pentulose (1). The sugar yield reached a constant value at 70% completion of the reaction, *i.e.*, within

[10] V. H. Kollman, R. E. London, J. L. Hanners, C. T. Gregg, and T. W. Whaley, *J. Labelled Compd. Radiopharm.*, 1979, **16**, 833 (*Chem. Abstr.*, 1980, **93**, 186 689).
[11] E. Ehrin, E. Westman, S. O. Nilsson, J. L. G. Nilsson, L. Widen, T. Greitz, C. M. Larsson, J. E. Tillberg, and P. Malmborg, *J. Labelled Compd. Radiopharm.*, 1980, **17**, 453 (*Chem. Abstr.*, 1980, **93**, 186 692).
[12] V. Bílik, P. Biely, and M. Matulová, *Chem. Zvesti*, 1979, **33**, 782.
[13] H. S. Prihar and D. S. Feingold, *Carbohydr. Res.*, 1980, **86**, 302.
[14] R. M. Blazer and T. W. Whaley, *J. Am. Chem. Soc.*, 1980, **102**, 5082.
[15] K. Bock and M. B. Sommer, *Acta Chem. Scand., Ser. B*, 1980, **34**, 389.
[16] H. Paulsen, M. Stubbe, and F. R. Heiker, *Liebigs Ann. Chem.*, 1980, 825.
[17] T. I. Khomenko, M. M. Sakharov, and O. A. Golovina, *Usp. Khim.*, 1980, **49**, 1079 (*Chem. Abstr.*, 1980, **93**, 150 504).
[18] G. Harsch, M. Harsch, H. Bauer, and W. Voelter, *J. Chem. Soc. Pak.*, 1979, **1**, 95 (*Chem. Abstr.*, 1980, **93**, 186 690).



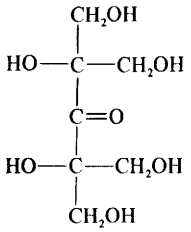
Reagents: i, pH 7.9, 100 °C; ii, NaB^3H_4; iii, B_2H_6

Scheme 1

25 min at 60 °C under nitrogen.[19] The presence of fructose as co-catalyst with *N,N*-diethylethanolamine has been shown to modify the reaction considerably. Use of the catalyst alone yields only pentaerythritol, whereas when fructose was present 2-hydroxymethyl-glycerol was the main product.[20] A stepwise mechanism of autocatalysis has been proposed for the formose reaction in the presence of calcium hydroxide on the basis of kinetic results.[21] Glucose, galactose, xylose, arabinose, and glyceraldehyde dimer have been identified in the product mixture from formaldehyde condensation in the presence of thiazolium ions.[22]

Treatment of 2,3,4,6-tetra-*O*-methyl-α,β-D-glucopyranose with 30% hydrogen peroxide in the presence of potassium hydroxide yields the products (2)–(7), thought to arise by decomposition of the hydroperoxide (8). Mechanistic schemes were proposed.[23] The formation of reductic acid from methyl β-D-*ribo*-hexosid-3-ulose by sulphuric acid treatment has been studied by ^{14}C-tracer

[19] Y. Shigemasa, S. Akagi, R. Nakashima, and S. Saito, *Carbohydr. Res.*, 1980, **80**, C1.
[20] T. Matsumoto, M. Komiyama, and S. Inoue, *Chem. Lett.*, 1980, 839.
[21] T. I. Khomenko, O. A. Golovina, M. M. Sakharov, O. V. Krylov, and A. H. Weiss, *React. Kinet. Catal. Lett.*, 1980, **13**, 407 (*Chem. Abstr.*, 1980, **93**, 220 983).
[22] J. Castells, F. Geijo, and F. Lopez-Calahorra, *Tetrahedron Lett.*, 1980, **21**, 4517.
[23] M. A. Salam and H. S. Isbell, *Carbohydr. Res.*, 1980, **82**, 253.



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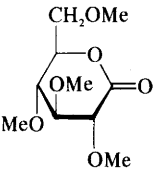

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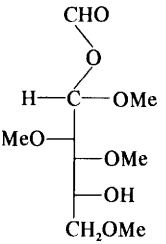

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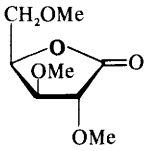

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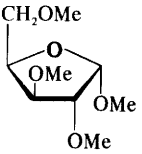

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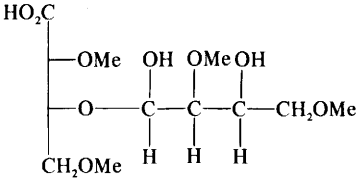

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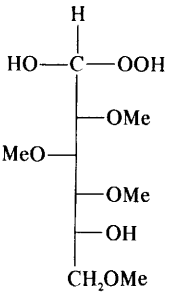

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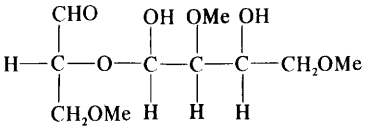


(7)

methods.[24] A caution on the use of labelled-glucose from several manufacturers due to contamination by labelled impurities has appeared. The impurities have been found to bind covalently to proteins and thus simulate non-enzymic glycosylation. This may render some previous results invalid where corroborative evidence is lacking.[25]

2 Physical Measurements

Laser–Raman spectroscopy of D-fructose in aqueous solution has given results for the proportions of furanose and pyranose similar to those from other tech-

[24] G. L. Lookhart, M. S. Feather, G. Lindgren, T. Popoff, and O. Theander, *Carbohydr. Res.*, 1980, **79**, 293.

[25] B. Trüeb, C. G. Holenstein, R. W. Fischer, and K. H. Winterhalter, *J. Biol. Chem.*, 1980, **255**, 6717.

niques.[26] A series of studies on the structure of aqueous solutions of D-glucose have been carried out, using electrical conductivity,[27] the dielectric characteristics at 0.01–7.5 M,[28] and proton relaxation times,[29] the latter being dependent on concentration, thus confirming the presence of glucose–water complexes. Data for the absorption frequencies and the rates of ultrasonic transmission in aqueous solutions of D-glucose at various concentrations have been published.[30] The lyoluminescence of sensitized glucose has been reported.[31] The catalytic effects of a series of cations on the decomposition of glucose and xylose have been evaluated. From the study of eighteen different metal ions, it was demonstrated that the trivalent cations were more effective than divalent cations.[32] By means of ^{13}C n.m.r. in $^{2}H_2O$ solution, the open-chain forms of D-fructose, L-sorbose, and D-tagatose have been shown to be present to the extent of 0.80, 0.25, and 0.30%, respectively.[33]

The kinetics of the thermal reactions of some disaccharides have been determined thermogravimetrically. The rate-determining step is the cleavage of the glycosidic bond, which is followed by the formation of anhydrohexopyranoses by elimination of water.[34] The heats of crystallization of sucrose in the 30–60 °C range vary between 11.6 and 19.5 kJ mol^{-1}.[35] A recent study of the previously reported enhanced solubility of sucrose in water when excess solid phase is present has failed to confirm the claim. It was concluded that the previous measurement was of a transitory occurrence.[36]

The free-radical reactions of carbohydrates as studied by radiation techniques have been reviewed.[37–39] The nature of the reactions of carbohydrates with hydroxy-radicals and hydrated electrons formed by pulse radiolysis has been investigated. Simple monosaccharides are unreactive towards the solvated electron but readily give unstable species with hydroxy-radicals. Aryl glycosides react readily with both in the manner of nucleophile and electrophile, respec-

[26] M. Mathlouthi and D. V. Luu, *Carbohydr. Res.*, 1980, **78**, 225.
[27] M. D. Adamenkova, S. N. Kartusov, V. I. Ermakov, and V. V. Shcherbakov, *Vestn. Mosk. Univ. Khim., Ser. 2*, 1980, **21**, 199 (*Chem. Abstr.*, 1980, **93**, 72 129).
[28] M. D. Adamenkova, S. N. Kartusov, V. I. Ermakov, and V. V. Shcherbakov, *Vestn. Mosk. Univ. Khim., Ser. 2*, 1980, **21**, 198 (*Chem. Abstr.*, 1980, **93**, 72 127).
[29] M. D. Adamenkova, V. I. Ermakov, and V. V. Makhlyarchuk, *Vestn. Mosk. Univ. Khim., Ser. 2*, 1980, **21**, 199 (*Chem. Abstr.*, 1980, **93**, 72 130).
[30] G. I. Maksimochkin, *Nauchn. Tr. Vses. Zaoch. Mashinostr. Inst.*, 1977, 155 (*Chem. Abstr.*, 1980, **93**, 72 116).
[31] J. S. Chazhoor and U. C. Mishra, *J. Lumin.*, 1979, **20**, 397 (*Chem. Abstr.*, 1980, **92**, 42 270).
[32] V. I. Krupenskii, *Khim. Drev.*, 1980, 49 (*Chem. Abstr.*, 1980, **93**, 114 863).
[33] G. J. Wolff and E. Breitmaier, *Chem.-Ztg.*, 1979, **103**, 232 (*Chem. Abstr.*, 1980, **92**, 6835).
[34] C. E. Weill, B. Carroll, and J. W. Liskowitz, *Thermochim. Acta*, 1980, **37**, 65 (*Chem. Abstr.*, 1980, **93**, 47 032).
[35] V. A. Mikhailik, I. G. Bazhal, and L. I. Trebin, *Zh. Fiz. Khim.*, 1980, **54**, 332 (*Chem. Abstr.*, 1980, **93**, 8407).
[36] A. van Hook, *Zuckerindustrie (Berlin)*, 1979, **104**, 511 (*Chem. Abstr.*, 1980, **92**, 42 820).
[37] C. von Sonntag, *Adv. Carbohydr. Chem. Biochem.*, 1980, **37**, 7.
[38] P. J. Baugh, *Stud. Phys. Theor. Chem.*, 1979, **6**, 115.
[39] H. Zegota and S. Bachman, *Wiad. Chem.*, 1979, **33**, 509 (*Chem. Abstr.*, 1980, **92**, 59 118).

tively.[40] Radiolysis of some monosaccharides at >20 mM in formate solution has been studied. The principal reaction is that with $\cdot CO_2^-$ which arises from the hydroxy-radical interacting with the formate ion: $\cdot OH + HCO_2^- \rightarrow H_2O + \cdot CO_2^-$. Therefore, in 100 mM formate, D-fructose gives 1-deoxy-D-*arabino*-hexulose and 1,3-dideoxy-D-*erythro*-hexulose, D-ribose gives 2-deoxy-D-ribose and 2-deoxy-D-ribitol, and D-glucose gives 2-deoxy-D-glucose and 2-deoxy-D-glucitol.[41] γ-Radiolysis of carbohydrates in the presence of salts and metal oxides leads to oxidation and degradation, yielding carbonyl compounds, carboxylic acids, and formaldehyde with sulphates and oxides but, interestingly from the point of view of the evolution of life, with nitrates a range of C_2–C_6 amino-acids were formed.[42] The pulse radiolysis of single crystals of sucrose at 6 K yields an absorption spectrum with λ_{max} 450–475 nm attributed to one form of a deeply trapped electron. The decay of this species with increasing temperature was reported.[43]

Using the e.s.r.–ENDOR technique, *X*-ray irradiation of single crystals of α-D-glucopyranose at 12 and 77 K has been shown to yield four free-radical species: two secondary alkoxy-radicals centred at O-2, a primary hydroxyalkyl radical at C-6, and a secondary hydroxyalkyl radical at C-3.[44]

Determination of the binding constants and their related enthalpy and entropy of activation for D-xylose and a series of n-alkyl β-D-xylopyranosides and their 1-thio-analogues to β-D-xylosidase from *Bacillus pumilus* has led to the conclusion that the enzyme does not distinguish between α- and β-D-xylopyranose.[45]

References to the conformations of β-gentiobiose and ketals of D-ribose and L-lyxose are contained in Chapter 20.

3 Isomerizations

The kinetics and mechanism of the acid-catalysed reactions of methylated trioses have been determined and the results were shown to be in good agreement with quantum mechanical calculations of charge distributions in substrates and intermediates.[46] The same group has studied the kinetics and mechanism of acid–base-catalysed enolization of glycolaldehyde and methoxyacetaldehyde by polarography. Deuterium incorporation was used to establish the mechanism.[47]

[40] J. S. Moore, K. G. Kemsley, J. V. Davies, and G. O. Phillips, *Stud. Phys. Theor. Chem.*, 1979, **6** (Radiat. Biol. Chem.: Res. Dev.), 99 (*Chem. Abstr.*, 1980, **92**, 94 647).

[41] Y. Kito, S. Kawakishi, and M. Namiki, *Agric. Biol. Chem.*, 1980, **44**, 2695.

[42] M. A. Khenokh, E. A. Kuzicheva, and N. V. Tsupkina, *Zh. Evol. Biokhim. Fiziol.*, 1980, **16**, 216 (*Chem. Abstr.*, 1980, **93**, 204 990).

[43] G. V. Buxton and G. A. Salmon, *Chem. Phys. Lett.*, 1980, **73**, 304 (*Chem. Abstr.*, 1980, **93**, 220 992).

[44] K. P. Madden and W. A. Bernhard, *J. Phys. Chem.*, 1979, **83**, 2643.

[45] H. Kersters-Hilderson, E. van Doorslaer, and C. K. DeBruyne, *Carbohydr. Res.*, 1980, **78**, 163.

[46] M. Fedoroňko, P. Temkovic, V. Mihálov, and I. Tvaroška, *Carbohydr. Res.*, 1980, **87**, 51.

[47] M. Fedoroňko, P. Temkovic, J. Königstein, V. Kováčik, and I. Tvaroška, *Carbohydr. Res.*, 1980, **87**, 35.

The conditions of Ohno and Ward[48a] have been shown to provide more than one pathway for the isomerization of D-glucose in acidic solutions.[48b] The conversion of aqueous solutions of D-glucose to D-fructose, D-mannose and D-arabinose by Dowex $1 \times 2(OH^-)$ required strongly basic resins, with better results being obtained at 30 °C than at 50 °C. The evidence suggested that glucose only reacted when it combined with resin, that a carbonyl group at C-1 is necessary for degradation, and that C-1 is lost as formic acid in forming arabinose.[49] Dioxobis(pentane-2,4-dionato-*O*,*O'*)molybdenum(VI) in DMF catalyses epimerization of aldoses at C-2 with no side products. Thus at 50 °C for 5 h D-glucose or D-mannose gave an equilibrium mixture of the former to the latter of 55 : 45. Under similar conditions D-galactose gave 32% D-talose, L-rhamnose gave 55% L-quinovose, and L-arabinose gave 36% L-ribose.[50]

4 Oxidation

Studies on the kinetics of oxidation of D-glucose and D-ribose,[51] and of D-erythrose and DL-glyeraldehyde[52] by chromium(IV) and vanadium(V) in perchloric acid medium have shown that the reaction is first order in oxidant and substrate in each case. Although the reactions are catalysed by acid, the dependence on pH is complex. Free radicals were produced in the reaction. A mechanism was proposed[52] on the basis of the determined activation parameters. The proposal that the formation of free radicals is the rate-determining step has also been made for the vanadium(V) oxidation of L-arabinose. Similar dependencies on concentrations of substrate and oxidant and on pH were reported.[53] The kinetics of oxidation of D-galactose and D-mannose by mercury(I), mercury(II), and silver nitrates at 100 °C have been determined, and the activation energy found to be in the range 80–100 kJ mol^{-1}. The principal products were the corresponding aldonic acids.[54] An investigation of the kinetics of oxidation of maltose and cellobiose by Nessler's reagent [mercury(II) iodide and sodium hydroxide] has shown that the rates are independent of initial mercury(II) concentration, first order in sugar concentration, and retarded by increasing iodide ion concentration. A mechanism involving intermediate enediols with $[HgI_3]^-$ as the reacting species was proposed.[55]

[48] (*a*) Y. Ohno and K. Ward, jun., *J. Org. Chem.*, 1961, **26**, 3928; (*b*) T. P. Mawhinney, M. A. Madson, and M. S. Feather, *Carbohydr. Res.*, 1980, **86**, 147.

[49] K. Koizumi and Y. Okada, *Yakugaku Zasshi*, 1980, **100**, 183 (*Chem. Abstr.*, 1980, **93**, 8398).

[50] Y. Abe, T. Takizawa, and T. Kunieda, *Chem. Pharm. Bull.*, 1980, **28**, 1324.

[51] K. K. Sengupta and S. N. Basu, *Carbohydr. Res.*, 1980, **80**, 223.

[52] K. K. S. Gupta and S. N. Basu, *Carbohydr. Res.*, 1980, **86**, 7.

[53] R. P. Bhatnagar and A. G. Fadnis, *Monatsch. Chem.*, 1980, **111**, 927 (*Chem. Abstr.*, 1980, **93**, 220 987).

[54] V. I. Krupenskii, *Zh. Obshch. Khim.*, 1980, **50**, 1397 (*Chem. Abstr.*, 1980, **93**, 132 707).

[55] M. P. Singh, R. K. Singh, A. K. Singh, and A. Srivastava, *Indian J. Chem. Soc., Sect. A*, 1980, **19**, 547 (*Chem. Abstr.*, 1980, **93**, 220 994).

5 Other Reactions

The thermolysis of sucrose in DMSO has been shown to yield a fructofuranosyl carbonium ion and α-D-glucose, which subsequently anomerizes. If the latter is generated in the presence of benzyl alcohol, benzyl α- and β-fructofuranosides result. The carbonium ion was thought to be the precursor for the formation of 2,6-anhydrofructofuranose in thermolysis reactions of sucrose.[56]

An examination of the role of anthraquinone in alkaline wood-pulping processes has been carried out using cellobiose, glucose, and glycoaldehyde as model substrates. Each gave a wide range of acid products.[57]

The biosynthetic pathway for the incorporation of glucose into cellulose has been studied by using D-[1-^{13}C]glucose, D-[6-^{13}C]glucose, and D-[U-^{13}C]glucose in admixture with unlabelled glucose as substrates for *Acetobacter xylinium*, and detecting the presence of the label in the cellulose hydrolysate by ^{13}C n.m.r.[58]

The pH profile for the mutarotation of 6-thio-D-fructose has been determined. The general conclusion was reached that all sugars with sulphur-containing rings show base-catalysed mutarotations several orders of magnitude faster than ring-opening.[59]

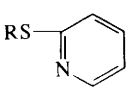
[56] L. Poncini and G. N. Richards, *Carbohydr. Res.*, 1980, **87**, 209.
[57] L. Löwendahl and O. Samuelson, *Acta Chem. Scand., Ser. B*, 1979, **33**, 531.
[58] D. Y. Gagnaire and F. R. Taravel, *Eur. J. Biochem.*, 1980, **103**, 133.
[59] C. E. Grimshaw, W. W. Cleland, and R. L. Whistler, *Carbohydr. Res.*, 1980, **82**, 353.

3
Glycosides

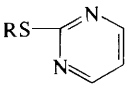
1 *O*-Glycosides

A review has appeared on the occurrence of the α-D-galactopyranosidic linkage in the plant kingdom, covering sucrose, alditol, and lipid derivatives.[1] Two reviews published in Japanese have covered recent advances in glycosidation methods (glycosyl halides, 1,2-orthoesters, glycosyl esters, and glycal derivatives as glycosylating agents),[2] and the synthesis of oligosaccharide blood-group determinants [Le^a, A, B, H (type I and II)], with particular reference to (i) efficient α-glucosylation, (ii) use of protecting groups, (iii) fucose derivatives, and (iv) common derivatives used as synthetic intermediates.[3]

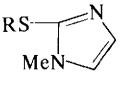
Synthesis of Monosaccharide Glycosides. – An improved method of glycosylation uses the reagents (1)–(3), which form alcohols under acidic conditions but, more importantly, they react readily with alcohols in the presence of mercury(II) salts. Compound (1) with, for example, 2-chloroethanol in acetonitrile in the presence of mercury(II) nitrate gave the α-glycoside in high yield at 25 °C.[4] A further glucosylation method uses 2,3,4,6-tetra-*O*-benzyl-α-D-glucose and alcohols together with *p*-nitrobenzenesulphonyl chloride, silver triflate, and triethylamine. Yields were high; the α:β ratios ranged from 1:2.5 to 1:5.[5] A more novel procedure for the preparation of D-mannopyranosides involves treatment of the α-2,3 : 4,6-*O*-isopropylidene derivative with tris(dimethylamino)-phosphine in carbon tetrachloride at low temperatures to give a phosphonium intermediate with the α-configuration. This, treated with silver toluene-*p*-sulphonate and alcohols, gives glycosides in good yield for simple primary and secondary alcohols but with poor specificity; with t-butyl alcohol the α-manno-



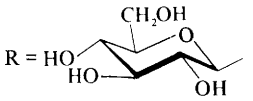
(1)



(2)



(3)



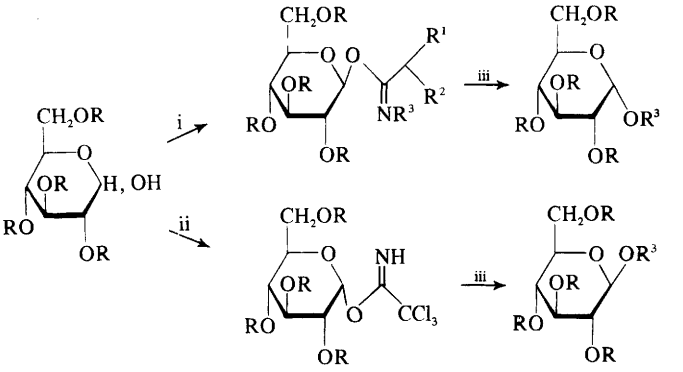
[1] P. M. Dey, *Adv. Carbohydr. Chem. Biochem.*, 1980, **37**, 283.
[2] H. Tsutsumi and Y. Ishido, *Yuki Gosei Kagaku Kyokaishi*, 1980, **38**, 473 (*Chem. Abstr.*, 1980, **93**, 95 492).
[3] T. Kondo and T. Goto, *Kagaku (Kyoto)*, 1979, **34**, 406 (*Chem. Abstr.*, 1980, **92**, 147 052).
[4] S. Hanessian, C. Bacquet, and N. Lehong, *Carbohydr. Res.*, 1980, **80**, C17.
[5] S. Koto, T. Sato, N. Morishima, and S. Zen, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1761.

side was obtained specifically in 50% yield. The method was also found applicable to the preparation of β-1-thiomannosides and to disaccharides.[6]

Continuing their work on glycosylation *via* stabilized O-1–metal intermediates, Schmidt and co-workers have developed procedures for the preparation of α- and β-D-mannofuranosides. 2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranose, treated with sodium hydride in the presence of a crown ether, gives the α-sodio-derivative which, with primary alcohol (including sugar) triflates, leads to the α-glycosides. Alternatively, in the absence of crown ether, the β-sodio-derivative, which is stabilized by co-ordination from the *cis*-oxygen atoms, is obtained, and this affords access to the β-anomers.[7] In analogous fashion, 2,3,4-tri-*O*-benzyl-D-glucose is convertible into the stabilized β-potassio-salt which, with triflates of primary alcohols (again including sugar derivatives), leads to β-compounds. On the other hand, when oxygen-6 of the starting material is substituted, this stabilization does not occur, α-salts are favoured, and α-glycosides result.[8]

The same group have examined glycosyl imidates as specific precursors of both α- and β-D-glucopyranosides (see Scheme 1).[9]

The stereoselectivity of the uncatalysed O-1 methylation of free sugars with diazomethane has been correlated with the preferred conformations of the thermodynamically favoured anomers.[10] More specific studies of methyl glycosides relate to the acid-catalysed methanolysis of α-D-glucofuranose 1,2:3,5-bis(phenylboronate), which gives the α- and β-glucofuranosides in the ratio of



Reagents: i, $R^1R^2C{=}C{=}NR^3$; ii, $CCl_3C{\equiv}N$; iii, $R^3OH{-}BF_3$, R = Ac or Bn

Scheme 1

[6] F. Chretiew, Y. Chapleur, B. Castro, and B. Gross, *J. Chem. Soc., Perkin Trans. 1*, 1980, 381.
[7] R. R. Schmidt, M. Reichrath, and V. Moering, *Tetrahedron Lett.*, 1980, **21**, 3561.
[8] R. R. Schmidt, V. Moering, and M. Reichrath, *Tetrahedron Lett.*, 1980, **21**, 3565.
[9] R. R. Schmidt and J. Michel, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 731.
[10] M. E. Gelpi and R. A. Cadenas, *An. Asoc. Quim. Argent.*, 1978, **66**, 327 (*Chem. Abstr.*, 1980, **93**, 72 201).

1:1.7 and provides a suitable route to the β-anomer.[11] The methyl tetrosides have been prepared by way of the 1,2-*O*-isopropylidene acetals of the sugars and their 3-ethers,[12] and methyl α- and β-D-gulopyranosiduronic acid have been made from D-*glycero*-D-*gulo*-heptose (readily available from D-glucose by the cyanohydrin addition) by glycosidation, separation of the heptopyranosides, periodate cleavage to give the 6-aldehydes, and oxidation with bromine in the presence of strontium carbonate.[13]

Allyl glycosides have been used to link glucose to proteins: reductive ozonolysis of allyl α-D-glucopyranoside giving an aldehyde. This, on reductive amination, afforded the 2-aminoethyl glycoside which was coupled by standard methods.[14] Vinyl ethers are produced by treatment of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose with ethyl vinyl ether in a vinyl-exchange reaction induced by mercury(II) acetate and toluene *p*-sulphonic acid. In addition, however, 1-ethoxyethyl and 1-ethoxybut-3-enyl glycosides are formed concurrently.[15]

Transglucosylation, using different enzymes, from maltose and cellobiose to the enantiomers of *trans*-cyclohexane-1,2-diol gave stereochemically discrete α- and β-monoglycosides.[16]

Some *para*-substituted phenyl β-D-glucopyranosides have been prepared and their cleavage by β-glucosidases studied together with some aryl glycosylamine analogues.[17] Similarly, an extensive set of substituted phenyl α-D-mannopyranosides (and thio-analogues) have been examined for insulin-like and insulin-antagonistic properties.[18] The photobromination of phenyl tetra-*O*-benzoyl-β-D-glucopyranoside leads to the incorporation of bromine at C-5, and reduction of the product affords a new route to phenyl α-L-idopyranoside (see Chapter 6).

A variety of glycosylated compounds of interest for natural product studies have been prepared. 3-*O*-(6-Deoxy-6-sulpho-α-D-glucopyranosyl)-1,2-di-*O*-hexadecanoyl-L-glycerol was made by way of 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranosyl chloride (from 1,6-anhydro-tri-*O*-benzyl-β-D-glucopyranose) as glycosylating agent. The sulphonic acid group was introduced by oxidation of the 6-thiosugar.[19] Russian workers have also made α-D-glucopyranosyl derivatives of glycerol by use of α-glycosyl bromides and 1,2-*O*-isopropylidene-glycerol.[20] Mono-, di-, and tri-β-D-galactopyranosides of the triol (4) have been prepared by treatment of the corresponding methyl ester with tetra-*O*-acetyl-α-D-galacto-

$$(HOH_2C)_3C{-}NHCO(CH_2)_4CONHNH_2$$

(4)

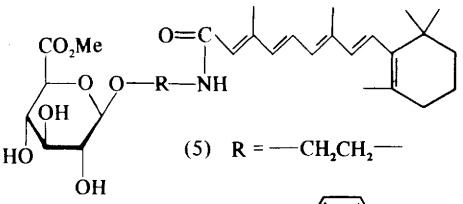
[11] J. Briggs, I. R. McKinley, and H. Weigel, *Carbohydr. Res.*, 1980, **80**, 340.
[12] J. Jary and M. Marek, *Collect. Czech. Chem. Commun.*, 1980, **45**, 3571.
[13] T. Anthonsen and M. A. E. Sallam, *Carbohydr. Res.*, 1980, **78**, 368.
[14] M. A. Bernstein and L. D. Hall, *Carbohydr. Res.*, 1980, **78**, C1.
[15] H.-M. Dettinger, J. Lehmann, and K. Wallenfels, *Carbohydr. Res.*, 1980, **87**, 63.
[16] K. Itano, K. Yamasaki, C. Kihara, and O. Tanaka, *Carbohydr. Res.*, 1980, **87**, 27.
[17] G. Legler, M. L. Sinnott, and S. G. Withers, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1376.
[18] P. L. Durette and T. Y. Shen, *Carbohydr. Res.*, 1980, **81**, 261.
[19] R. Gigg, A. A. E. Penglis, and R. Conant, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2490.
[20] L. V. Volkova, S. A. Suvorova, V. Veres, N. G. Morozova, and R. P. Evstigneeva, *Zh. Obshch. Khim.*, 1979, **49**, 2148 (*Chem. Abstr.*, 1980, **92**, 129 203).

pyranosyl bromide in nitromethane in the presence of mercury(II) cyanide. The products were bonded to bovine serum albumin and their effects on the hepatic galactose-binding system were studied.[21] Uvarova and colleagues have published three reports on the glucosylation of sterols and triterpenoid alcohols using (*a*) acetylated glycosyl halides in the presence of mercury(II), cadmium, and silver salts,[22,23] and (*b*) the 1,2-orthoester method.[24]

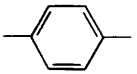
Syntheses of 2-amino-2-deoxy-D-glucopyranosyl derivatives of terpene alcohols by standard procedures have been reported[25] and allyl and benzyl glycosides of compounds having long-chain acyl groups (lauroyl, stearoyl, *etc.*) attached to the amino-group have been prepared to test their immunostimulatory activities.[26]

Methyl 2,3,4-tri-*O*-benzyl-D-glucuronate has been converted into the corresponding α-glycopyranosyl bromide and the α- and β-chlorides. These reacted with carbohydrate alcohols at room temperature with poor stereoselectivity, but at −15 °C the α,β ratios were satisfactorily high. It was proposed that, at low temperatures, the acetonitrile present as solvent reacted initially with the glycosyl carbonium ions to give intermediates with the β-configuration.[27] The common β-glucuronide glycosylating agent methyl tri-*O*-acetyl-α-D-glucopyranuronosyl bromide has been used to prepare uronosides of 5-hydroxy-*N*,*N*-dimethyltryptamine,[28] 5β-pregnane-3α,17,20α-triol, and the corresponding preg-6-ene[29] and deoxycholic acid.[30] Similarly, the retinamides (5) and (6) have been synthesized by way of the intermediate glycosidic amines.[31]

Several glycosylations of cyclitol derivatives are referred to in Chapter 18.



(5) R = —CH_2CH_2—

(6) R = 

[21] H. Kawaguchi, M. Kuhlenschmidt, S. Roseman, and Y. C. Lee, *Arch. Biochem. Biophys.*, 1980, **205**, 388.
[22] N. I. Uvarova, L. N. Atopkina, and G. B. Elyakov, *Carbohydr. Res.*, 1980, **83**, 33.
[23] L. N. Atopkina and N. I. Uvarova, *Khim. Prir. Soedin.*, 1980, 205 (*Chem. Abstr.*, 1980, **93**, 150417).
[24] N. F. Samoshina and N. I. Uvarova, *Khim. Prir. Soedin.*, 1979, 334 (*Chem. Abstr.*, 1980, **92**, 76868).
[25] C. Prakash, T. Cheng, and I. K. Vijay, *Carbohydr. Res.*, 1980, **84**, C9.
[26] M. Kiso, H. Nishiguchi, and A. Hasegawa, *Carbohydr. Res.*, 1980, **81**, C13.
[27] R. R. Schmidt and E. Rücker, *Tetrahedron Lett.*, 1980, **21**, 1421.
[28] L. S. Krasavina, M. M. Vigdorchik, K. F. Turchin, and N. N. Suvorov, *Tezisy Dokl. Sov.-Indiiskii Simp. Khim. Prir. Soedin., 5th*, 1978, 42 (*Chem. Abstr.*, 1980, **93**, 186704).
[29] G. Cooley, A. E. Kellie, and P. Samarajeewa, *J. Steroid Biochem.*, 1980, **13**, 359 (*Chem. Abstr.*, 1980, **93**, 132746).
[30] J. Oehlke, *Pharmazie*, 1979, **34**, 383 (*Chem. Abstr.*, 1980, **92**, 59167).
[31] M. I. Dawson and P. D. Hobbs, *Carbohydr. Res.*, 1980, **85**, 121.

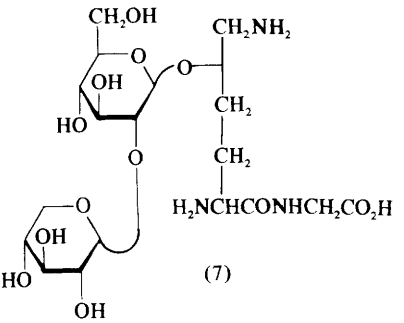
Synthesis of Disaccharides and their Derivatives. – In this Section compounds are categorized according to the nature of the non-reducing sugars; other disaccharide syntheses are referred to in the next Section.

Reduction of 3-ketosucrose with sodium borohydride gives mainly α-D-allopyranosyl-β-D-fructofuranoside, and deuterium can be incorporated by this approach. Various derivatives of the disaccharide were prepared, including the 6,1′,6′-tritrityl ether, the 6,6′-ditrityl ether, the penta-acetate, and the hexa-acetate derivable from these, and the 6,6′-dichloro-6,6′-dideoxy-compound.[32]

In the area of non-reducing disaccharides it has been found that treatment of 2,3,4,6-tetra-*O*-benzyl-D-glucose, -D-mannose, and -D-galactose with trifluoroacetic anhydride in DMF gives the α,α- and α,β-dimers in the ratio 2:1 (the method can also be applied to give heterodisaccharides).[33] α,α-Trehalose has been converted by way of the 6,6′-ditrityl ether and its hexa-acetate into the 6,6′-dicarboxylic acid (Jones reagent for the oxidation).[34]

1,2-Thio-orthoesters in the D-*gluco*-, D-*galacto*-, D-*manno*-, and L-*rhamno*-series have been shown to react with primary and secondary trityl ethers of monosaccharides in the presence of trityl perchlorate to give 1,2-*trans*-related disaccharides in good yield.[35] More specifically, glycosylation of benzyl 4,6-*O*-benzylidine-α-D-glucopyranoside by the Koenigs–Knorr method gave mainly the 2-*O*-β-linked product (sophorose derivative), whereas laminaribiose derivatives were obtained by initial selective benzoylation at O-2.[36] The same worker then investigated the glycosylation of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside with tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of silver triflate and 1,1,3,3-tetramethylurea and obtained the 2-linked-β-disaccharide in 28% yield as well as the 3-linked isomer and the trisaccharide.[37] 6-*O*-(α-D-Glucopyranosyl)-2-deoxy-D-*arabino*-hexose was prepared from maltose and the deoxy-sugar by transglycosylation using an α-glucosidase.[38]

The disaccharide dipeptide (7) was synthesized by initial condensation using 3,4,6-tri-*O*-acetyl-2-*O*-levulinyl-α-D-glucopyranosyl bromide, and the terminal



(7)

[32] L. Hough and E. O'Brien, *Carbohydr. Res.*, 1980, **84**, 95.
[33] A. A. Pavia, J.-M. Rocheville, and S. N. Ung, *Carbohydr. Res.*, 1980, **79**, 79.
[34] A. Liav and M. B. Goren, *Carbohydr. Res.*, 1980, **84**, 171.
[35] L. V. Backinowsky, Y. E. Tsvetkov, N. F. Balan, N. E. Byramova, and N. K. Kochetkov, *Carbohydr. Res.*, 1980, **85**, 209.
[36] K. Takeo, *Carbohydr. Res.*, 1980, **86**, 151.
[37] K. Takeo, *Carbohydr. Res.*, 1980, **87**, 147.
[38] S. Chiba and O. Yamana, *Agric. Biol. Chem.*, 1980, **44**, 549.

unit was attached, after removal of the levulinyl unit with hydrazine, by use of a tetra-*O*-benzyl-β-D-glucopyranosylimidate.[39] Octyl and dodecyl β-D-lactoside and dodecyl β-D-cellobioside and -maltoside have been synthesized as analogues of octyl β-D-glucoside for use as solubilizing agents for membrane proteins and activators of cytochrome oxidases. The Koenigs–Knorr reaction was used with an improved workup procedure for these detergents. The dodecyl maltoside was the most useful of these glycosides.[40]

A highly selective route to β-D-mannopyranosides involves the use of α-D-mannopyranosyl sulphonates as glycosylating agents. Toluene-*p*-sulphonates and 1-*O*-(2,2,2-trifluoroethylsulphonyl) esters were used, and a derivative of methyl 6-*O*-β-D-mannopyranosyl-α-D-mannopyranoside was synthesized.[41] Likewise, conditions were optimized for the preparation of 1,2- and 1,6-linked β-D-galactopyranosyl derivatives of D-glucose and D-galactose using the same glycosyl sulphonate derivatives.[42] In related work, tetra-*O*-acetyl-α-D-galactopyranosyl bromide has been used to prepare disaccharide derivatives with β-D-galactopyranosyl units bonded to O-3, O-4, and O-6 of 6-aminohexyl 2-acetamido-2-deoxy-β-D-glucopyranosides[43] and O-4 of 2-acetamido-2-deoxy-D-galactose.[44] Alternatively, 4-*O*-α-D-galactopyranosyl-L-rhamnose has been prepared by use of tetra-*O*-benzyl-α-D-galactopyranosyl bromide in the presence of tetraethylammonium bromide and the product was then converted into a trisaccharide bearing a glucose unit at O-2 of the rhamnose moiety.[45] A transferase from bovine milk allows the preparation of β-D-galactopyranosyl disaccharides using UDP-galactose and an acceptor, and in this way lactose and the [1-^{13}C]labelled analogue have been prepared.[46] The ^{1}H and ^{13}C n.m.r. spectra of some galactose-containing disaccharides related to ABH and Lewis human-blood-group determinants are referred to in Chapter 20.

Condensation of tri-*O*-acetyl-α-D-xylopyranosyl bromide with benzyl 3,4-di-*O*-benzyl-β-D-xylopyranoside afforded a synthesis of 2-*O*-β-D-xylopyranosyl-D-xylose,[47] and condensation with the three diacetates of methyl β-D-xylopyranoside led to the isomeric (1→2), (1→3), and (1→4)linked xylobiosides. The main products were the β-bonded disaccharides, but small proportions of α-compounds were also obtained.[48] A penicillium β-D-xylosidase has been used to transfer a xylose unit from one phenyl β-D-xylopyranoside to another to produce (1→4) and (1→3)linked phenyl β-xylobiosides; some corresponding triosides and higher glycosides were also obtained.[49]

[39] H. J. Koeners, C. Schattenkerk, J. Verhoeven, and J. H. van Boom, *Tetrahedron Lett.*, 1980, **21**, 2373.
[40] P. Rosevear, T. Vanaken, J. Baxter, and S. Ferguson-Miller, *Biochemistry*, 1980, **19**, 4108.
[41] V. K. Srivastava and C. Schuerch, *Carbohydr. Res.*, 1980, **79**, C13.
[42] H. F. Vernay, E. S. Rachaman, R. Eby, and C. Schuerch, *Carbohydr. Res.*, 1980, **78**, 267.
[43] J. Vernon, S. Roseman, and Y. C. Lee, *Carbohydr. Res.*, 1980, **82**, 59.
[44] S. S. Rana, J. J. Barlow, and K. L. Matta, *Carbohydr. Res.*, 1980, **84**, 353.
[45] P. Fügedi, A. Liptàk, P. Nánási, and A. Neszmélyi, *Carbohydr. Res.*, 1980, **80**, 233.
[46] H. A. Nunez and R. Barker, *Biochemistry*, 1980, **19**, 489.
[47] P. Kovác and E. Petráková, *Chem. Zvesti*, 1980, **34**, 537.
[48] P. Kovác, *Collect. Czech. Chem. Commun.*, 1980, **45**, 892.
[49] M. Claeyssens, R. D. Brown, F. Deleyn, and C. K. de Bruyne, *J. Carbohyr., Nucleosides, Nucleotides*, 1980, **7**, 203.

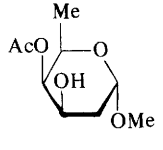
Naturally occurring hydroxyanthraquinone β-glycosides of 6-*O*-β-D-xylopyranosyl-D-glucose (primeverose) and 6-*O*-α-L-rhamnopyranosyl-D-glucose (rutinose) have been prepared by use of the acetylated glycosyl halides.[50]

Considerable attention has been given to the preparation of L-rhamnose-containing disaccharides, and several rhamnosylating agents have been used. The 2,3,4-tri-*O*-acetylglycosyl bromide was employed to obtain the 2-, 3-, and 4-linked α-rhamnosyl-L-rhamnoses[51–54] and 3-*O*-α-L-rhamnopyranosyl-D-galactose,[55] and a useful reagent for obtaining β-linkages is 4-*O*-acetyl-2,3-*O*-carbonyl-α-L-rhamnopyranosyl bromide by which the following disaccharides have been produced: 3-*O*-β-L-rhamnopyranosyl-D-galactose,[55] 4-*O*-β-L-rhamnopyranosyl-L-rhamnose,[56, 57] 6-*O*-β-L-rhamnopyranosyl-D-glucose[56, 57] and -D-galactose.[56, 57] 4-*O*-Benzoyl-2,3-*O*-cyclohexylidene-α-L-rhamnosyl bromide again gives β-glycosides and has been used in the synthesis of 3- and 4-linked rhamnobioses and 4-*O*-β-L-rhamnopyranosyl-D-glucose.[58]

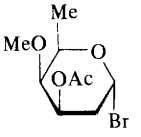
Two unusual epoxydisaccharides isolated from plants are referred to in the natural product section below.

Considerable effort has gone into the synthesis of deoxy-derivatives of disaccharides, particularly by Thiem and his colleagues, because of their significance in natural products. Mannobiose was converted into the 3′,6,6′-trideoxy-derivative *via* a 6,6′-dideoxy-compound which afforded the 3′-bromo-3′-deoxy-analogue with 2-acetoxyisobutyryl bromide. In parallel fashion, the 2,3′,6,6′-tetradeoxydisaccharide was made by way of a 2,6,6′-tri-iodo intermediate. These deoxy-products are related to deoxydisaccharides that occur in micro-organism metabolism.[59]

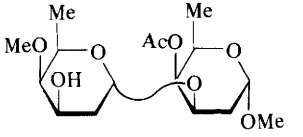
Photochemical dideoxygenation of methyl 2,6-di-*O*-acetyl-3,4-*O*-isopropylidene-α-D-galactopyranoside gave access to the dideoxy-derivatives (8) and (9)



(8)

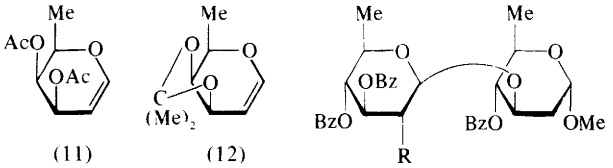


(9)



(10)

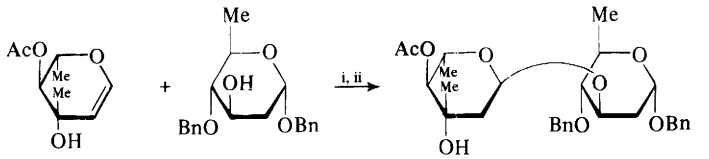
[50] B. Vermes, L. Farkas, and H. Wagner, *Phytochemistry*, 1980, **19**, 119.
[51] D. Schwarzenbach and R. W. Jeanloz, *Carbohydr. Res.*, 1980, **81**, 323.
[52] S. Josephson and D. R. Bundle, *J. Chem. Soc., Perkin Trans. 1*, 1980, 297.
[53] A. Liptàk, P. Nánási, A. Neszmélyi, and H. Wagner, *Tetrahedron*, 1980, **36**, 1261.
[54] V. Pozsgay and P. Nanasi, *Symp. Pap. – IUPAC Int. Symp. Chem. Nat. Prod., 11th*, 1978, **3**, 73 (*Chem. Abstr.*, 1980, **92**, 42 276).
[55] V. I. Torgov, V. N. Shibaev, A. S. Shashkov, and N. K. Kochetkov, *Bioorg. Khim.*, 1980, **6**, 1860.
[56] L. V. Backinowsky, N. F. Balan, A. S. Shashkov, and N. K. Kochetkov, *Carbohydr. Res.*, 1980, **84**, 225.
[57] L. V. Backinowsky, N. F. Balan, A. S. Shashkov, and N. K. Kochetkov, *Biorg. Khim.*, 1980, **6**, 464.
[58] T. Iversen and D. R. Bundle, *Carbohydr. Res.*, 1980, **84**, C13.
[59] J. Thiem and A. Sievers, *Chem. Ber.*, 1980, **113**, 3505.



(11) (12)

(13) R = H
(14) R = OH

condensation of which led to the disaccharide (10), a derivative of a constituent of chromomycin A_3.[60] Otherwise, condensation between compound (8) and the glycal derivative (11) in the presence of *N*-iodosuccinimide gave access to a 2-deoxy-2-iodo product, which also afforded a derivative of the chromomycin A_3 disaccharide. The β-linked isomeric product was obtained by use of similar procedures and the isopropylideneglycal (12).[61] In related work the same group produced the tetra- and tri-deoxy-disaccharides (13) and (14) starting from a dibenzylidene derivative of laminaribiose containing an iodo-group at C-2 and using the *N*-bromosuccinimide method to introduce bromine at the primary positions. Reductions at the 2-positions were effected using tributyltin hydride, and the carbon–iodine bond was cleaved together with a xanthate ester group which was introduced at an intermediate stage.[62] A branched-chain derivative of the chromomycin A_3 disaccharide was then made as outlined in Scheme 2.[63]

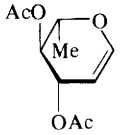


Reagents: i, *N*-iodosuccinimide; ii, Pd/C–H_2

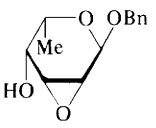
Scheme 2

Condensation of the glycal ester (15) with the epoxide (16), catalysed by boron trifluoride, then gave an unsaturated disaccharide derivative from which the pentadeoxy-compound (17) was made. This is a derivative of a disaccharide that occurs in anthracyclin antibiotics.[64] The closely related dimer (18) was also prepared using the same glycal derivative and methyl 2,3-anhydro-6-bromo-6-deoxy-α-D-allopyranoside. Inversion at C-5 of the product was effected by hydrogenation of the derived 6-deoxy-5-enose compound.[65] This work also led

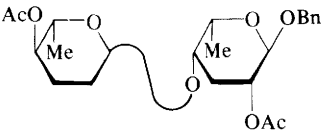
[60] J. Thiem and B. Meyer, *Chem. Ber.*, 1980, **113**, 3058.
[61] J. Thiem and B. Meyer, *Chem. Ber.*, 1980, **113**, 3067.
[62] J. Thiem and H. Karl, *Chem. Ber.*, 1980, **113**, 3039.
[63] J. Thiem and J. Elvers, *Chem. Ber.*, 1980, **113**, 3049.
[64] J. Thiem, M. Holst, and J. Schwentner, *Chem. Ber.*, 1980, **113**, 3488.
[65] J. Thiem, H.-W. Kluge, and J. Schwentner, *Chem. Ber.*, 1980, **113**, 3497.



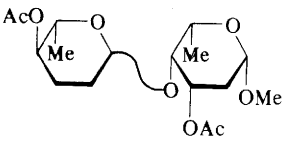
(15)



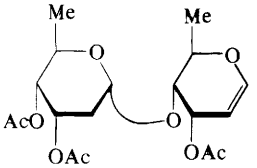
(16)



(17)



(18)



(19)

to the synthesis of a 2,6,2′,6′-tetradeoxydisaccharide which in turn afforded the glycal (19), and a trisaccharide (see later).[66]

Reference is made in Chapter 8 to the synthesis of a 3-amino-2,3,6,2′,6′-pentadeoxydisaccharide which occurs in anthracycline antibiotics and, in Chapter 12, to the preparation of unsaturated and derived deoxydisaccharides.

Synthesis of Tri- and Higher-saccharides. – As synthetic methods improve, more attention is being given to the synthesis of trisaccharides, and even more complex saccharides are being produced by specific methods. A major stimulus remains the importance of many compounds of these classes in biological systems.

Condensation between the acetylated glycosyl bromide derived from the β-1,4-linked xylobiose and methyl 2,3-anhydro-β-L-lyxopyranoside afforded a route to the glycoside of the β-1,4-xylose-linked trimer,[67] amd the isomeric (1→3),(1→4)-β-linked trisaccharide was obtained by standard glycosylation of a methyl 4-*O*-β-D-xylopyranosyl-D-xyloside derivative having a free hydroxyl group at C-3′.[68]

In the area of hexose homotrimers crystalline laminaritriose has been isolated from the hydrolysate of sclerotia,[69] and the three isomeric trimers comprising D-glucose substituted at O-2,O-6; O-3,O-6; O-4,O-6 by α-D-glucopyranosyl units have been synthesized as their 2-(4-aminophenyl)ethyl α-glycosides by use of 2,3,4-tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-1-*O*-toluene-*p*-sulphonyl-D-glucopyranose as glycosylating agent. These were then coupled *via* the amino-groups to bovine serum albumin to give antigenic determinants of the branch points of natural dextrans.[70] In the galactose series 6-*O*-β-D-galactopyranosyl-D-galactose was synthesized as a fully substituted derivative with an acetate group at O-6′. This ester was specifically cleaved and the resulting dimer was again

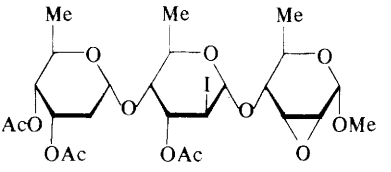
[66] J. Thiem, P. Ossowski, and J. Schwentner, *Chem. Ber.*, 1980, **113**, 955.
[67] P. Kovác, *Chem. Zvesti*, 1980, **34**, 234.
[68] P. Kovác and J. Hirsch, *Carbohydr. Res.*, 1980, **79**, 303.
[69] Y. Ueno and K. Kato, *Carbohydr. Res.*, 1980, **80**, 212.
[70] R. Eby and C. Schuerch, *Carbohydr. Res.*, 1980, **79**, 53.

treated with 6-*O*-acetyl-3,4-di-*O*-benzyl-2-*O*-benzoyl-α-D-galactopyranosyl toluene-*p*-sulphonate to give, after deblocking, methyl 6-*O*-β-D-galactopyranosyl-(1→6)-*O*-β-D-galactopyranosyl-(1→6)-*O*-β-D-galactopyranoside.[71] The use of the levulinyl group as a blocking function has been illustrated in the synthesis of 2-*O*-β-D-galactopyranosyl-(1 → 2)-β-D-galactopyranosyl-(1 → 6)-D-galactose[72] (Chapter 6).

Several heterotrisaccharides containing 6-deoxyhexoses have been reported. 6-*O*-α-L-Fucopyranosyl-lactose was prepared by use of 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl bromide and 1,2,3,6,2′,3′-hexa-acetyl-lactose;[73] 2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl bromide was used with a lactose 1,2,3,6,2′,6′-hexaester to provide 3′-*O*-α-L-fucopyranosyl-lactose, the β-anomer being obtained by use of the tribenzylglycosyl bromide.[74] L-Rhamnose-containing trisaccharides to have been reported are α-D-galactopyranosyl-(1→2)-α-D-mannopyranosyl-(1→4)-L-rhamnose,[75] 4-*O*-(α-D-galactopyranosyl)-2-*O*-(β-D-glucopyranosyl)-L-rhamnose,[76] α-D-mannopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→3)-D-galactose,[55,77] α-D-mannopyranosyl-(1→4)-β-L-rhamnopyranosyl-(1→3)-D-galactose,[55] β-D-mannopyranosyl-(1 → 4)-α-L-rhamnopyranosyl-(1 → 3)-D-galactose,[78] 6-*O*-(α-D-glucopyranosyl)-3-*O*-(α-L-rhamnopyranosyl)-D-galactose,[55] and β-D-glucopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→3)-D-galactose.[77]

Trifluoroacetolysis of human erythrocyte membranes released β-D-galactopyranosyl-(1 → 4)-β-D-galactopyranosyl-(1 → 4)-D-glucose and 2-*O*-(α-L-fucopyranosyl)-3-*O*-(α-D-galactopyranosyl)-D-galactose.[79]

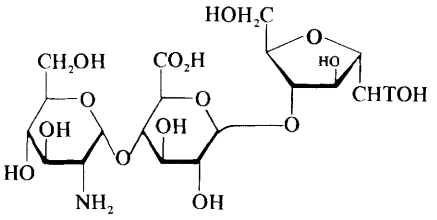
Thiem's interest in deoxydisaccharides has been extended into related trisaccharides, the glycal derivative (19) having been condensed with methyl 2,3-anhydro-6-deoxy-α-D-allopyranoside in the presence of *N*-iodosuccinimide to give the product (20).[66]



(20)

[71] V. K. Srivastava, S. J. Sondheimer, and C. Schuerch, *Carbohydr. Res.*, 1980, **86**, 203.
[72] H. J. Koeners, J. Verhoeven, and J. H. van Boom, *Tetrahedron Lett.*, 1980, **21**, 381.
[73] H. H. Baer and S. A. Abbas, *Carbohydr. Res.*, 1980, **83**, 146.
[74] H. H. Baer and S. A. Abbas, *Carbohydr. Res.*, 1980, **84**, 53.
[75] P. J. Garegg, H. Hultberg, and C. Lindberg, *Carbohydr. Res.*, 1980, **83**, 157.
[76] P. Fügedi, A. Liptàk, P. Nánási, and A. Neszmélyi, *Carbohydr. Res.*, 1980, **80**, 233.
[77] V. I. Betaneli, M. V. Ovchinnikov, L. V. Backinowsky, and N. K. Kochetkov, *Carbohydr. Res.*, 1980, **84**, 211.
[78] V. I. Betaneli, M. V. Ovchinnikov, L. V. Backinowsky, and N. K. Kochetkov, *Dokl. Akad. Nauk SSSR*, 1980, **251**, 108 (*Chem. Abstr.*, 1980, **93**, 204 942).
[79] A. Lundblad, S. Svensson, B. Löw, L. Messeter, and B. Cedergren, *Eur. J. Biochem.*, 1980, **104**, 323.

The occurrence of 2-amino-2-deoxyhexoses in many naturally occurring trisaccharides has stimulated the synthesis of several such compounds. Two reports have appeared on the preparation of the branched trisaccharide 2-acetamido-2-deoxy-4-*O*-(α-L-fucopyranosyl)-3-*O*-(β-D-galactopyranosyl)-D-glucose which is the Le^a blood-group antigenic determinant;[80, 81] the chloroacetyl, 2-tetrahydrofuranyl, and *p*-nitrobenzoyl groups were used as unusual protecting functions during these syntheses. 2-Acetamido-2-deoxy-4-*O*-(β-D-galactopyranosyl)-3-*O*-(β-D-xylopyranosyl)-D-glucose, which is related to this trisaccharide and is also a derivative of lactosamine, has been specifically synthesized.[82] The xylosyl substituent protects the β-D-galactoside bond from enzymic hydrolysis. *N*-Acetyl-lactosamine has been condensed, by way of the intermediate oxazoline, on to the 3- and 6-positions of D-galactose to give linear trimers with the amino-sugar in the central position,[83] and the linear compound α-L-fucopyranosyl-(1→2)-β-D-galactopyranosyl-(1→3)-2-acetamido-2-deoxy-D-galactose, with the amino-sugar at the reducing position, was prepared as its α-phenyl glyoside.[84] The tritiated trisaccharide derivative (21), with an amino-sugar at the non-reducing end, has been obtained by partial deaminative degradation of heparin.[85]



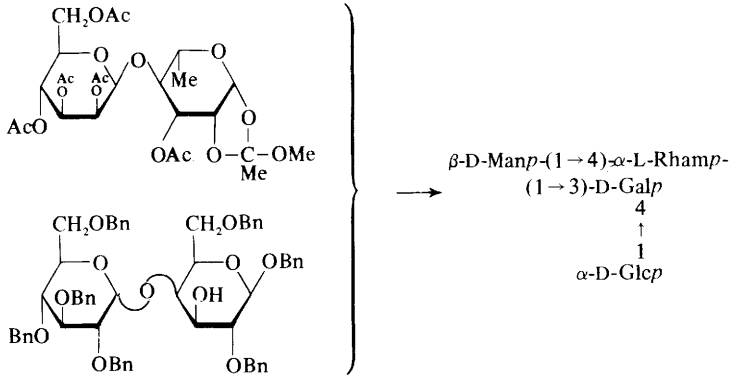
(21)

In the field of trimers containing two amino-sugars, *O*-β-D-mannopyranosyl-(1→4)-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→4)-2-acetamido-2-deoxy-D-glucose has been made by way of a disaccharide oxazoline derivative as glycosylating agent.[86] An alternative method involves analogous preparation of the isomer with a substituted β-D-glucopyranosyl unit in the non-reducing position. Specific removal of an acetate at O-2″, oxidation with DMSO–acetic anhydride, and reduction with sodium borohydride led to the *manno*-epimer.[87]

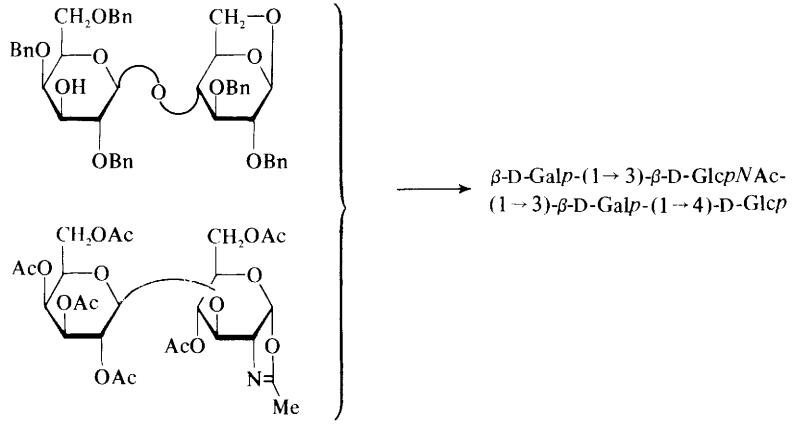
[80] N. V. Bovin, S. E. Zurabyan, and A. Ya. Khorlin, *Bioorg. Khim.*, 1980, **6**, 789 (*Chem. Abstr.*, 1980, **93**, 150 521).
[81] N. V. Bovin, S. E. Zurabyan, and A. Ya. Khorlin, *Bioorg. Khim.*, 1980, **6**, 242 (*Chem. Abstr.*, 1980, **93**, 72 155).
[82] S. Oguri, H. Ishihara, and S. Tejima, *Chem. Pharm. Bull.*, 1980, **28**, 35.
[83] C. Auge, S. David, and A. Veyrieres, *Nouv. J. Chim.*, 1979, **3**, 491 (*Chem. Abstr.*, 1980, **92**, 94 653).
[84] S. S. Rana, J. J. Barlow, and K. L. Matta, *Carbohydr. Res.*, 1980, **87**, 99.
[85] U. Klein and K. von Figura, *Carbohydr. Res.*, 1980, **78**, 249.
[86] C. D. Warren, C. Augé, M. L. Laver, S. Suzuki, D. Power, and R. W. Jeanloz, *Carbohydr. Res.*, 1980, **82**, 71.
[87] C. Augé, C. D. Warren, R. W. Jeanloz, M. Kiso, and L. Anderson, *Carbohydr. Res.*, 1980, **82**, 85.

A further closely related trimer, *O*-β-D-galactopyranosyl-(1→4)-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→4)-2-acetamido-2-deoxy-D-glucose has been produced by use of a transferase enzyme.[46]

In the tetrasaccharide series the 2 + 2 approach is illustrated (Scheme 3) by the synthesis of the repeating unit of the O-specific polysaccharide of *S. muensler* and *S. minneapolis*.[88] The same strategy has led to 'lacto-*N*-tetraose' (Scheme 4).[89] However, the alternative sequential approach was used in the synthesis of *O*-α-L-rhamnopyranosyl-(1→2)-*O*-α-L-rhamnopyranosyl-(1→3)-*O*-α-L-rhamnopyranosyl-(1→3)-2-acetamido-2-deoxy-D-glucose as its β-8-methoxycarbonyloctyl glycoside, which was required for bonding to proteins and cell surfaces.[90]



Scheme 3

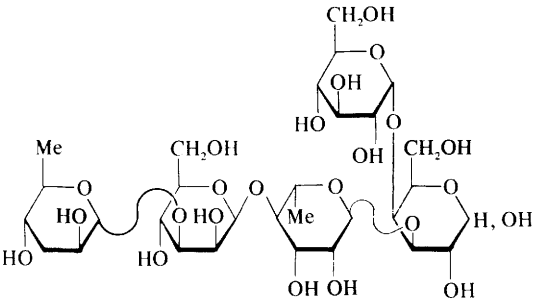


Scheme 4

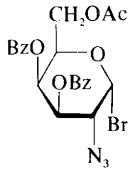
[88] N. K. Kochetkov, V. I. Torgov, N. N. Malysheva, A. S. Shashkov, and E. M. Klimov, *Tetrahedron*, 1980, **36**, 1227.

[89] T. Takamura, T. Chiba, H. Ishihara, and S. Tejima, *Chem. Pharm. Bull.*, 1980, **28**, 1804.

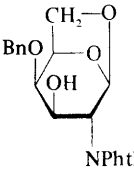
[90] D. R. Bundle and S. Josephson, *Carbohydr. Res.*, 1980, **80**, 75.



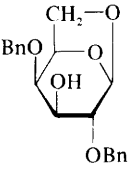
(22)



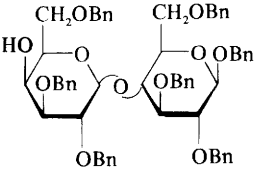
(23)



(24)



(25)



(26)

O-(2-Acetamido-2-deoxy-β-D-galactopyranosyl)-(1→3)-β-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-D-glucose is a product of trifluoroacetolysis of human erythrocyte membranes.[79]

Block synthesis has also been employed to produce the pentasaccharide repeating unit (22) of the O-specific polysaccharide of *S. strasbourg*. The ortho-ester method allowed condensation between units from which the disaccharide at the reducing end and the trisaccharide at the non-reducing end were derived.[91] Compounds (23)–(26) were used in the synthesis of the linear compound α-D-gal NAc-(1→3)-β-D-gal NAc-(1→3)-α-D-gal-(1→4)-β-D-gal-(1→4)-D-glc which is the pentasaccharide of Forssman antigen. Monomers (23) and (24) were condensed, and the dimer was converted to the glycosyl bromide; this was coupled with the anhydride (25) and the trimer, in turn, was converted into its corresponding bromide which was condensed with the dimer (26).[92]

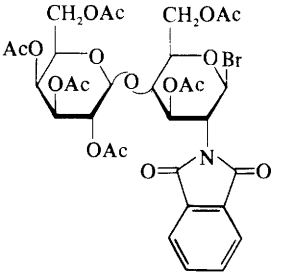
Work related to glycoprotein chemistry led to a pentasaccharide by condensation of benzyl 3,6-di-*O*-benzyl-α-D-mannopyranoside with two equivalents of the disaccharide derivative (27), and the latter glycosylating agent with benzyl 2,4-di-*O*-benzyl-3,6-di-*O*-(3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-α-D-mannopyranoside afforded a branched heptasaccharide.[93]

O-Glycosides Isolated from Natural Products. – As usual, this Section is highly selective; many examples with simple and complex glycosyl substituents have been reported.

[91] N. K. Kochetkov, V. I. Torgov, N. N. Malysheva, and A. S. Shashkov, *Tetrahedron*, 1980, **36**, 1099.

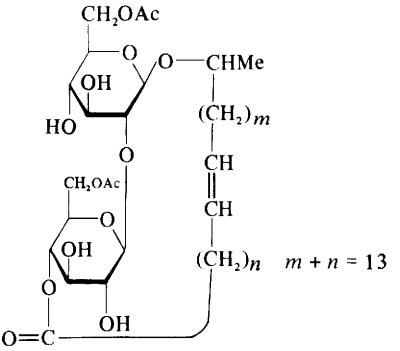
[92] H. Paulsen and F. R. Heiker, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 902.

[93] J. Arnarp and J. Lonngren, *J. Chem. Soc., Chem. Commun.*, 1980, 1000.



(27)

Two interesting, non-reducing epoxydisaccharides have been isolated as follows: 3,4-anhydro-2,6-dideoxy-β-D-*lyxo*-hexopyranosyl 6-deoxy-3-*O*-methyl-β-D-allopyranoside (by hydrolysis of a pregnane glycoside) from dried twigs of *Sarcostemma brevistigma*,[94] and 3,4-anhydro-2,6-dideoxy-β-D-*ribo*-hexopyranosyl 6-deoxy-3-*O*-methyl-β-D-allopyranoside from dried stems of *Gymnema tingens*.[95] β-D-Galactofuranose has been detected in a complex galactolipid,[96] and a most unusual cyclic lactone structure (28) has been assigned to a 17-hydroxyoctadecenoic acid disaccharide glycoside.[97]

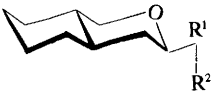


(28)

The triterpene β-altropyranosides virescenoside A and B give broad-line ^{13}C spectra because of intermolecular association through hydrogen bonding. Addition of methanol results in normal line widths; T_1 and T_2 values were measured as a function of methanol concentrations.[98]

[94] D. P. Khare, A. Khare, and M. P. Khare, *Carbohydr. Res.*, 1980, **81**, 275.
[95] D. P. Khare, A. Khare, and M. P. Khare, *Carbohydr. Res.*, 1980, **81**, 285.
[96] N. G. Clarke, G. P. Hazlewood, and R. M. C. Dawson, *Biochem. J.*, 1980, **191**, 561.
[97] S. Ito, M. Kinta, and S. Inoue, *Agric. Biol. Chem.*, 1980, **44**, 2221.
[98] N. Bellavita, J.-M. Bernassau, P. Ceccherelli, M. S. Raju, and E. Wenkert, *J. Am. Chem. Soc.*, 1980, **102**, 17.

Hydrolysis and Other Reactions. – The kinetics of the acid-catalysed hydrolysis of the conformationally rigid acetals (29) and (30) were studied as models for anomeric methyl pyranosides.[99]



	R^1	R^2
(29)	H	OMe
(30)	OMe	H

Increasing the acid concentration during the sulphuric acid-catalysed hydrolysis of the methyl D-glucopyranosides at 70 °C led to a small decrease in ΔH^* and a larger decrease in $T\Delta S^*$. Since the reaction mechanism is still A-1 this indicates that water of hydration is released in passing to the transition state. This solvation was further studied by use of Zucker–Hammett plots; ΔH^* and ΔS^* values were also recorded for the hydrolyses of the methyl galactopyranosides, methyl α-D-mannopyranoside and methyl β-L-arabinopyranoside.[100] Detailed studies have been carried out on the acid-catalysed solvolysis of phenyl α- and β-D-glucopyranoside in ethanol–2,2,2-trifluoroethanol mixtures, and related work was done on the anomeric glucopyranosyl fluorides and other glucosyl derivatives. It was concluded that the ratios of anomeric products depend upon the assistance provided to the leaving groups by the solvent.[101]

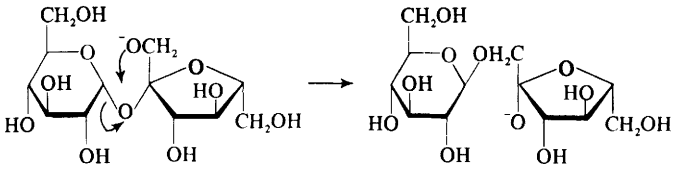
Glycosides of 2-acetamido-2-deoxy-β-D-gluco- and -galacto-pyranoside hydrolyse readily in 48% aqueous hydrofluoric acid provided the aglycone is not a cyclic sugar residue. In consequence, chitotriose is degraded to chitobiose only after the terminal reducing unit has been converted to the alditol.[102] The acid-catalysed hydrolysis and methanolysis of some 4-chlorophenyl aldofuranosides have been studied in the presence of calcium ions, and the effects of the salt were correlated with the ion-complexing abilities of the glycosides. These were determined for the calcium ion complexes of methyl aldofuranosides in aqueous solution using an ion-selective electrode and correlated with chromatographic mobilities on strong cation resins in the Ca^{2+} form.[103] The kinetics of the hydrolysis of methyl 2,3,4-tri-*O*-methyl-α- and -β-L-arabinopyranoside and methyl 2,3,5-tri-*O*-methyl-α-L-arabinofuranoside have been investigated.[104]

The cleavage of sugars from the steroidal glycoside solasodine on acid hydrolysis was followed by h.p.l.c. methods, and a kinetic model was developed to describe the process.[105]

[99] P. van Eikeren, *J. Org. Chem.*, 1980, **45**, 4641.
[100] T. J. Painter, *Carbohydr. Res.*, 1980, **82**, 362.
[101] M. L. Sinnott and W. P. Jencks, *J. Am. Chem. Soc.*, 1980, **102**, 2026.
[102] H. J. Jennings and C. Lugowski, *Can. J. Chem.*, 1980, **58**, 2610.
[103] H. Lönnberg and A. Vesala, *Carbohydr. Res.*, 1980, **78**, 53.
[104] V. I. Kadentsev, A. G. Kaimarazov, and O. S. Chizhov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1979, 1911 (*Chem. Abstr.*, 1980, **92**, 6874).
[105] P. G. Crabbe and C. Fryer, *Chem. Eng. Commun.*, 1980, **4**, 135 (*Chem. Abstr.*, 1980, **93**, 8451).

Examinations of the trifluoroacetolysis of methyl α-L-arabinofuranoside and its methylated derivatives have revealed that the glycoside itself is quite stable under conditions in which the 2,3,5-trimethyl ether is solvolysed. This follows from the initial esterification of the glycoside and, in consequence, monomethyl ethers were substantially stable, while dimethyl ethers were significantly cleaved.[106] The work was extended to an examination of the effects of hydroxyl groups in the aglycones of tetra- and 2,3,4-tri-*O*-methyl-D-glucopyranosides in protecting the glycosidic bonds against trifluoroacetolysis.[107]

Further work on the mechanism of the alkaline degradation of sucrose, using substituted derivatives, supported an earlier hypothesis[108a] which invoked 1-*O*-β-D-glucopyranosyl-D-fructose as an intermediate (Scheme 5).[108b]



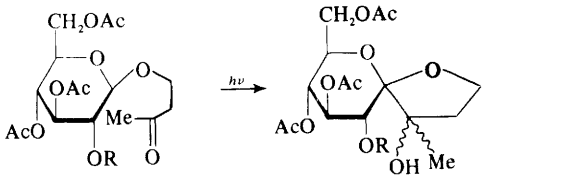
Scheme 5

In the area of glycosidases, the binding constants for xylose, a series of n-alkyl β-D-xylopyranosides and their 1-thio-analogues with the β-D-xylosidase of *B. pumilis* were determined. Hydrolytic $\Delta H°$, $\Delta G°$, and $\Delta S°$ values were obtained, and it was found that the enzyme does not distinguish between the anomers of the free sugar.[109] An extension of this work considered the effects of cyclic, substituted, and branched aglycones on the binding of the glycosides, but no pattern emerged.[110] Several techniques were used to study the stereochemistry of the hydrolysis of trehalose by a trehalase from the flesh fly *Sarcophaga barbata*. Equal proportions of α- and β-D-glucose were initially formed, and the anomeric hydroxy-group of the β-anomer was derived from the solvent; it was concluded that the hydrolysis proceeds by a bimolecular nucleophilic substitution reaction involving inversion at the anomeric centre undergoing substitution.[111] The disaccharide unit of collagen (2-*O*-α-D-glucopyranosyl-β-D-galactopyranosyl-hydroxylysine) is hydrolysed by an enzyme which has been isolated from rat spleen. Normal α-glucosidases do not cleave the terminal sugar from this compound and the new enzyme does not hydrolyse neutral α-gluco-

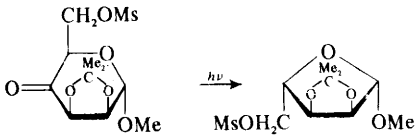
[106] L.-E. Franzen and S. Svensson, *Acta Chem. Scand., Ser. B*, 1980, **34**, 133.
[107] L.-E. Franzen and S. Svensson, *Acta Chem. Scand., Ser. B*, 1980, **34**, 171.
[108] (*a*) G. W. O'Donnell and G. N. Richards, *Aust. J. Chem.*, 1973, **26**, 2041; (*b*) M. Manley-Harris, W. Moody, and G. N. Richards, *ibid.*, 1980, **33**, 1041.
[109] H. Kersters-Hilderson, E. van Doorslaer, and C. K. de Bruyne, *Carbohydr. Res.*, 1980, **78**, 163.
[110] E. van Doorslaer, H. Kersters-Hilderson, and C. K. de Bruyne, *Carbohydr. Res.*, 1980, **78**, 317.
[111] K. H. Clifford, *Eur. J. Biochem.*, 1980, **106**, 337.

sides (*e.g.*, methyl α-D-glucopyranoside or maltose). It is therefore assumed that the amino-group of the hydroxylysine is required for binding. Acetylation of this group greatly reduces the hydrolysis rate.[112]

The effects of the anomeric configuration and the presence of acetoxy-groups at C-2 on the photocyclization of 3-oxobutyl glycopyranosides (Scheme 6) have been studied. β-Compounds react preferentially, and C-2 acetoxy-groups participate in the reactions.[113] A further photochemical reaction provides means of making L-ribofuranosides from D-mannoside derivatives *via* ketonic intermediates (Scheme 7).[114] *C*-Glycosidic ketones behave similarly (see below).



Scheme 6

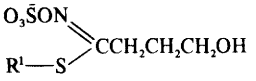


Scheme 7

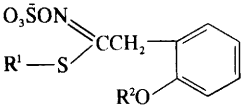
Two further studies have been reported on the radical reactions occurring following *X*-ray irradiation of methyl α-D-glucopyranoside, especially at low temperatures. At 12 K a primary alkoxy-radical is generated that is distinguishable from a similar radical produced at higher temperatures, and the difference is attributed to hydrogen-bonding factors.[115] After irradiation at 77 K, the crystals were warmed and several reactions of the initial primary radical were characterized.[116]

The ^{13}C n.m.r. spectra of a set of xylose-based oligosaccharides are referred to in Chapter 20.

[112] H. Hamazaki and K. Hotta, *Eur. J. Biochem.*, 1980, **111**, 587.
[113] G. Remy, L. Cottier, and G. Descotes, *Can. J. Chem.*, 1980, **58**, 2660.
[114] P. M. Collins and A. S. Travis, *J. Chem. Soc., Perkin Trans. 1*, 1980, 779.
[115] K. P. Madden and W. A. Bernhard, *J. Chem. Phys.*, 1980, **72**, 31.
[116] K. P. Madden and W. A. Bernhard, *J. Phys. Chem.*, 1980, **84**, 1712 (*Chem. Abstr.*, 1980, **93**, 47 096).



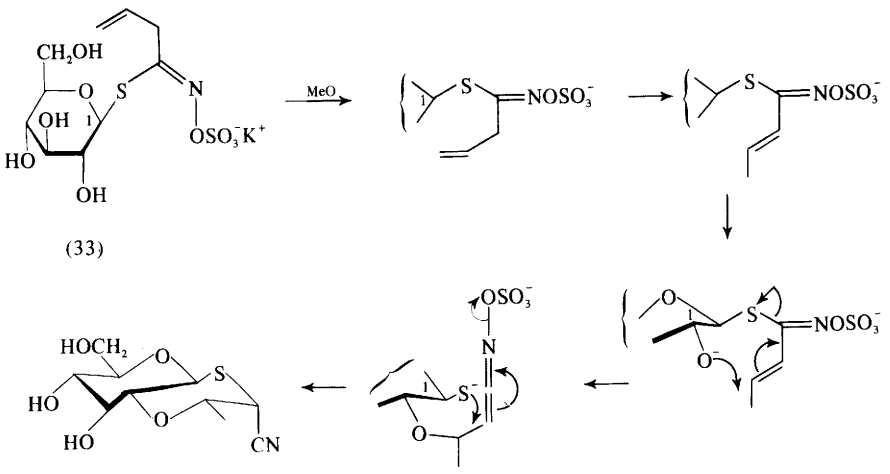
(31)



(32) R^1 = β-D-glucopyranosyl
R^2 = α-L-rhamnopyranosyl

2 *S*-Glycosides

New glucosinolates continue to be reported, *e.g.*, compounds (31) and (32) from the seeds of *Malcolmia maritima*[117] and from *Reseda odorata*,[118] respectively. The latter paper also describes the isolation of 2-hydroxy-2-methylpropyl- and 2-hydroxy-2-phenyl-glucosinolate from *R. alba* and *R. luteola*, respectively. A compound, 'merosinigrin' isolated many years ago as a by-product of the alkaline treatment of sinigrin (33) has been shown to be (34) (Scheme 8).[119]



(33)

(34)

Scheme 8

A range of thioglycosides (35) with cholesteryl-containing side-chains were prepared by published methods from D-glucose, D-mannose, D-galactose, 2-acetamido-2-deoxy-D-glucose, 2-acetamido-2-deoxy-D-galactose, L-fucose, L-arabinose, D-xylose, *N*-acetyl-D-neuraminic acid, lactose, and cellobiose. They were required for the investigation of glycolipids in cell-surface recognition studies.[120]

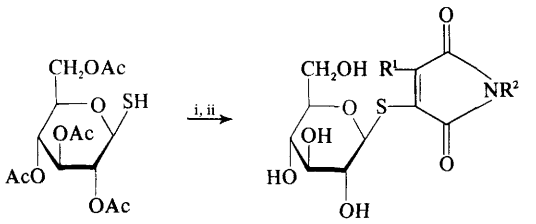
[117] M. E. Daxenbichler, G. F. Spencer, and W. P. Schroeder, *Photochemistry*, 1980, **19**, 813.
[118] O. Olsen and H. Soerenson, *Phytochemistry*, 1979, **18**, 1547 (*Chem. Abstr.*, 1980, **92**, 181 560).
[119] M. Benn, *Can. J. Chem.*, 1980, **58**, 1892.
[120] M. M. Ponpipom, R. L. Bugianesi, and T. Y. Shen, *Can. J. Chem.*, 1980, **58**, 214.

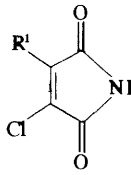
Sugar-S-$(CH_2)_6$-O-cholesteryl

(35)

For work on insulin-like and insulin-antagonist properties, a range of substituted phenyl and benzyl 1-thio-α-D-mannopyranosides were prepared either by alkylation of the 1-thiosugar or by use of glycosylthiourea derivatives.[18]

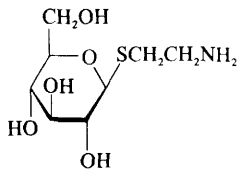
Glycosylthiomaleimides were synthesized as indicated in Scheme 9,[121] and the 2-aminoethylglycoside (36) was obtained from the same starting material by alkylation with 2-phthalimidoethyl chloride.[122]





Reagents: i, R^1 = *p*-MeC_6H_4 or *p*-$MeOC_6H_4$, R^2 = Ph, Me, H, or Bn; ii, MeO^-

Scheme 9



(36)

3 *C*-Glycosides

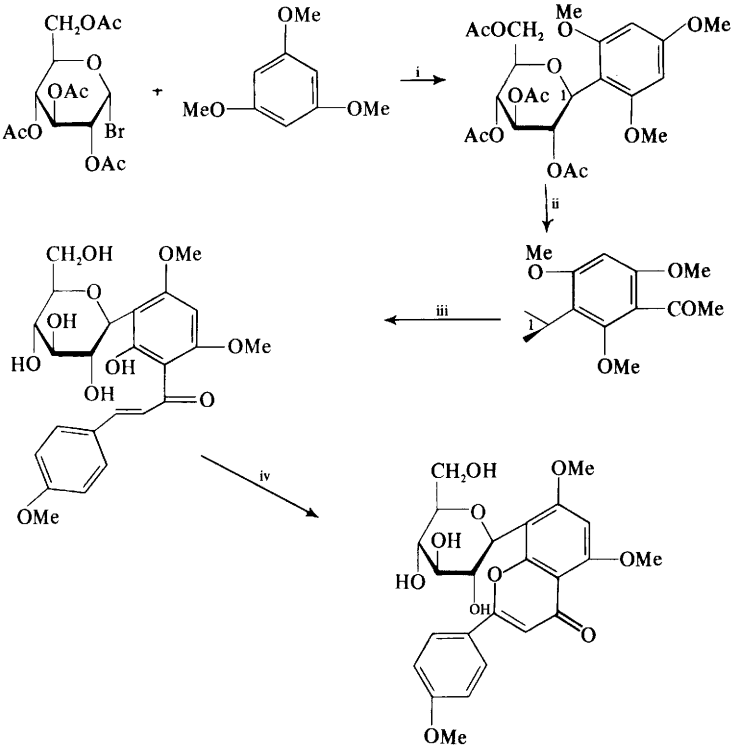
A review 'From sugars to *C*-glycosides *via* unusual carbohydrate derivatives' has appeared.[123]

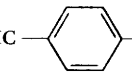
Derivatives of *C*-glycosides with ketonic groups within pyranose rings lose carbon monoxide on photoirradiation, and lead to furanoid analogues.[114]

[121] M. M. Al-Holly, M. Augustin, J. Faust, and M. Koehler, *Pharmazie*, 1979, **34**, 645 (*Chem. Abstr.*, 1980, **93**, 47 093).

[122] A. Juodvirsis and L. I. Khondo, *Liet. TSR Mokslu Akad. Darb., Ser. B*, 1980, 27 (*Chem. Abstr.*, 1980, **93**, 239 845).

[123] J. M. J. Tronchet, *Colloq.-Inst. Natl. Sante Rech. Med.*, 1978 (Publ. 1979), 81 (Nucleosides, Nucleotides, Appl. Biol.), 117 (*Chem. Abstr.*, 1980, **92**, 76 803).

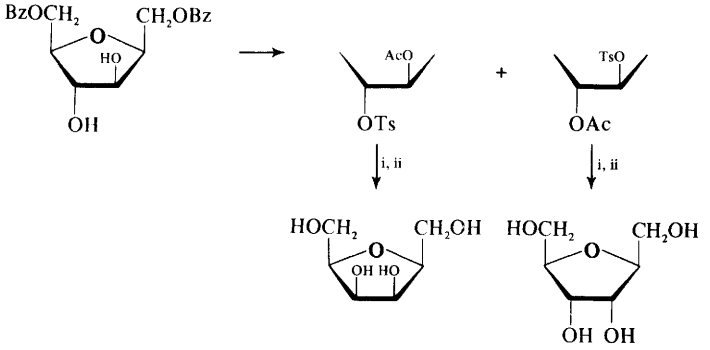


Reagents: i, ZnO, ii, Ac_2O–$AlCl_3$; iii, OHC  OMe—NaOH; iv, SeO_2

Scheme 10

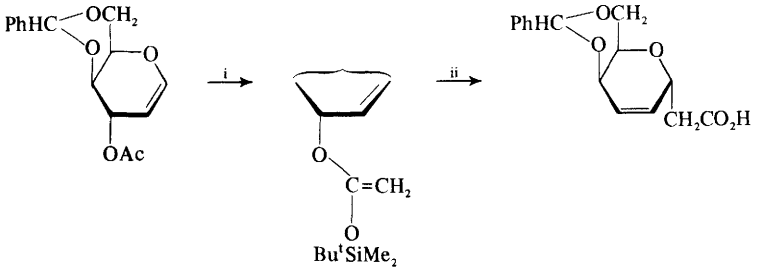
8-*C*-α-L-Arabinopyranosylapigenin has been isolated from *M. pentaphylla* together with two other components which were 6-*C*-arabinosyl-8-*C*-pentosylapigenins,[124] and 6-*C*-β-D-glucopyranosyl-5,4′-dihydroxy-7,3′-dimethoxyflavone has been obtained from *Achillea cretica*.[125] A further *C*-glucoside has an additional β-D-glucopyranosyl unit bonded to O-2 of the sugar,[126] and a di-*C*-glycosylflavone, 6-*C*-α-L-arabinopyranosyl-8-*C*-β-D-galactopyranosylapigenin was obtained from *Carlina corymbosa* roots.[127]

[124] J. Chopin, E. Basson, and A. G. Ramachandran Nair, *Phytochemistry*, 1979, **18**, 2059 (*Chem. Abstr.*, 1980, **92**, 2059).
[125] J. Chopin, *Phytochemistry*, 1980, **19**, 156 (*Chem. Abstr.*, 1980, **93**, 186 724).
[126] W. S. Woo, S. S. Kang, S. H. Shim, H. Wagner, V. M. Chari, O. Seligmann, and G. Obermeier, *Phytochemistry*, 1979, **18**, 353 (*Chem. Abstr.*, 1980, **92**, 6865).
[127] E. Besson, A. Dombris, J. Raynaud, and J. Chopin, *Phytochemistry*, 1979, **18**, 1899 (*Chem. Abstr.*, 1980, **92**, 198 701).



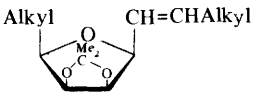
Reagents: i, DMF–H_2O; ii, $\bar{O}Me$

Scheme 11



Reagents: i, KH–Bu^tMe_2SiCl; ii, Δ

Scheme 12

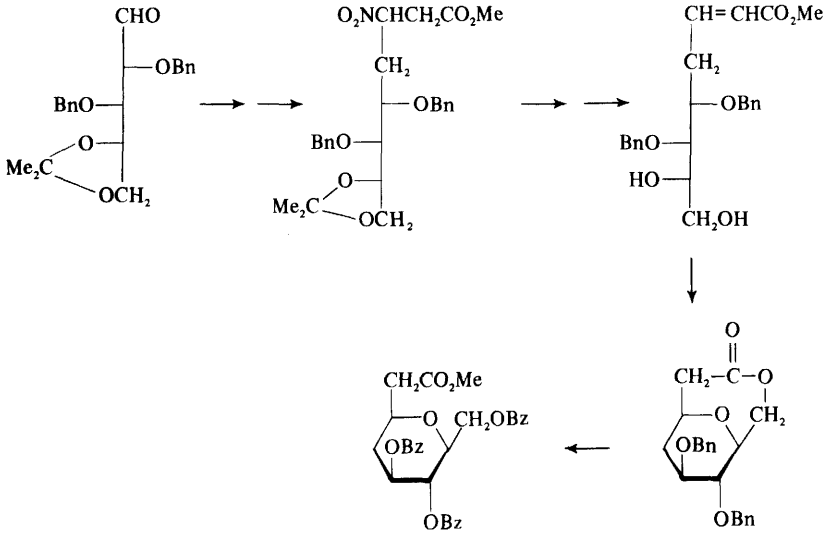


(37)

The flavonoid *C*-glycoside 5,7,4′-tri-*O*-methylvitexin has been prepared by the unusual procedure of building up the flavone system after the *C*-glycosidic bond had been formed (Scheme 10).[128]

2,5-Anhydroalditols are *C*-glycosides, and these derivatives of D-allitol and D-galactitol have been synthesized from 2,5-anhydro-1,6-di-*O*-benzoyl-D-glucitol as shown in Scheme 11. The former product does not complex with metal ions

[128] R. A. Eade and H.-P. Pham, *Aust. J. Chem.*, 1979, **32**, 2483.



(38)

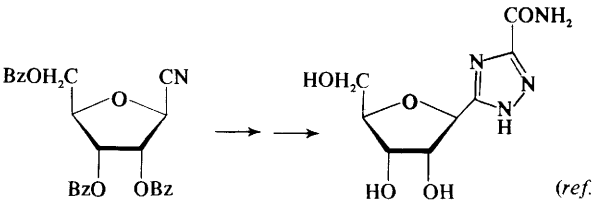
Scheme 13

while the latter does.[129] A further synthesis of simple *C*-glycosidic compounds is achievable by the Claisen rearrangement reaction (Scheme 12).[130]

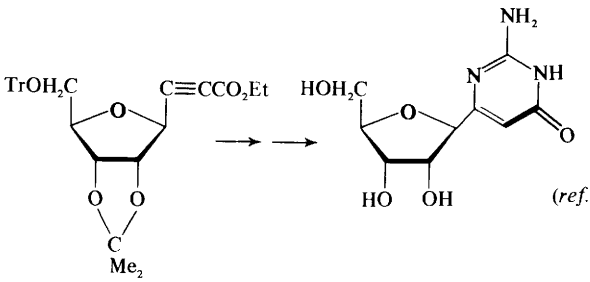
The *C*-vinyl unit (37) has been investigated as a component of the antibiotic aurodox and related compounds,[131] and the 2,6-anhydro-octose derivative (38), which is derived from the tetrahydropyranyl component of the antifungal agent ambruticin, has been made from L-arabinose by methods involving the use of methyl 3-nitropropanoate (Scheme 13), and thus its absolute stereochemistry is defined.[132]

Several further *C*-nucleosides have been obtained by elaboration of short carbon-bonded substituents on furanosyl rings.[133–136] Starting materials and products are shown in Scheme 14, and several isomers and related materials were described in the papers. The syntheses of D,L-showdomycin and its D,L-*arabino*-isomer from racemic starting materials have been reported, the former being outlined in Scheme 15.[137]

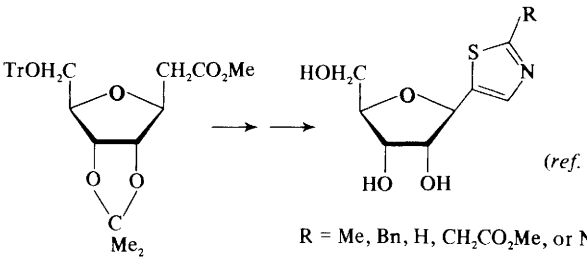
[129] S. J. Angyal and Y. Kondo, *Aust. J. Chem.*, 1980, **33**, 1013.
[130] R. E. Ireland, S. Thaisrivongs, N. Vanier, and C. S. Wilcox, *J. Org. Chem.*, 1980, **45**, 48.
[131] H. Maehr, M. Leach, T. H. Williams, and J. F. Blount, *Can. J. Chem.*, 1980, **58**, 501.
[132] G. Just and P. Potvin, *Can. J. Chem.*, 1980, **58**, 2173.
[133] M. S. Poonian and E. F. Nowoswiat, *J. Org. Chem.*, 1980, **45**, 203.
[134] S. Y.-K. Tam, R. S. Klein, F. G. de las Heras, and J. J. Fox, *J. Org. Chem.*, 1979, **44**, 4854.
[135] T. J. Cousineau and J. A. Secrist, *J. Org. Chem.*, 1979, **44**, 4351.
[136] T. Sato and R. Noyori, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1195.
[137] G. Just, T. J. Liak, M.-I. Lim, P. Potvin, and Y. S. Tsantrizos, *Can. J. Chem.*, 1980, **58**, 2024.



(ref. 134)

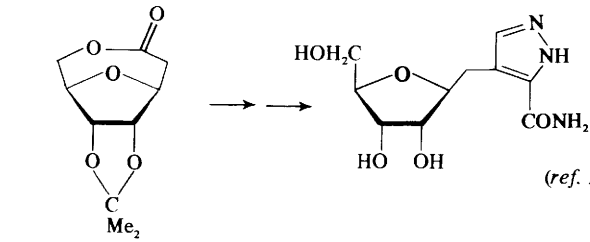


(ref. 135)



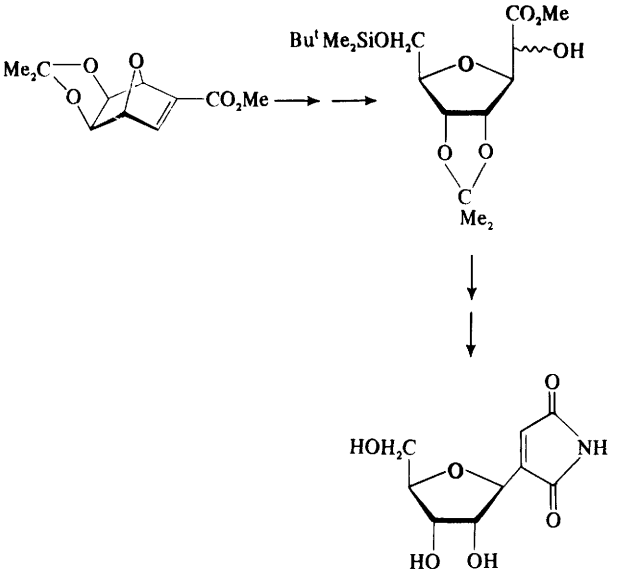
(ref. 136)

R = Me, Bn, H, CH_2CO_2Me, or NH_2



(ref. 137)

Scheme 14


Me2C
O
O
O
CO2Me
Bu^t Me2SiOH2C
O
CO2Me
OH
O
O
C
Me2
HOH2C
O
NH
O
O
HO
OH

Scheme 15

4

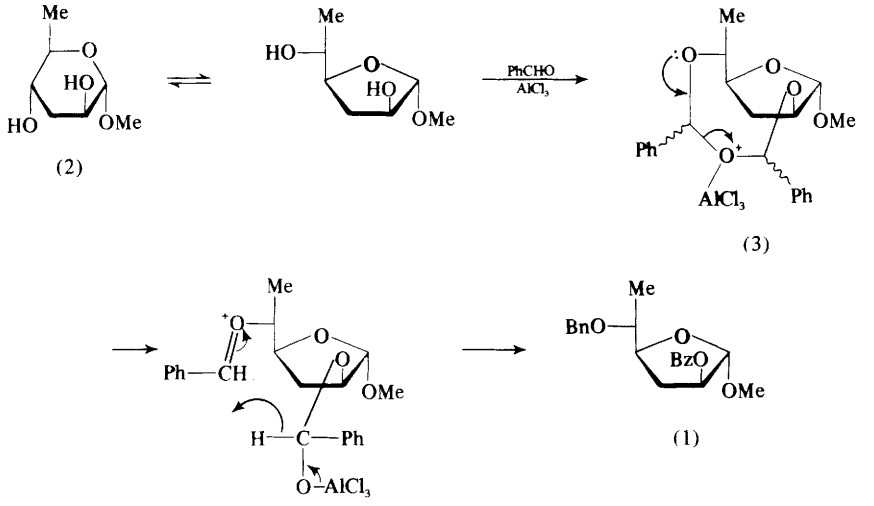
Ethers and Anhydro-sugars

1 Ethers

Alkyl Ethers. – Two variations of existing procedures for methylation have been described. The use of methyl trifluoromethanesulphonate for the methylation of oligo- and poly-saccharides is facilitated by employing trimethyl phosphate to aid solubility and 2,6-di-t-butylpyridine as acid acceptor.[1] Secondly, the use of potassium t-butoxide in conjunction with methyl iodide–dimethylsulphoxide is reported as an improvement on existing related methods.[2] The preparations of the 2,3-, 2,4-, and 3,4-di-*O*-methyl ethers of methyl α-L-fucopyranoside[3] and the 2- and 3-methyl ethers of methyl α-L-rhamnopyranoside[4] have been carried out by standard procedures, and an improved multistep synthesis of 2,3,6-tri-*O*-methyl-D-mannose has been described.[5] The application of standard reactions to D-erythrose and D-threose has afforded all the mono- and di-methyl ethers of their α- and β-methyl glycosides.[6] Methyl and benzyl ethers undergo cleavage with trimethylsilyl ethers of thiols, and selective de-*O*-methylation at the primary position was achieved when the reaction was applied to methyl 2,3,4,6-tetra-*O*-methyl-1-thio-α,β-D-glucopyranoside, the 2,3,4-tri-*O*-methyl ether being isolated in 70% yield. Prolonged exposure of the tetramethyl ether to the reagent afforded an uncharacterized dimethyl ether.[7] Several carbohydrate derivatives have been derivatized by the β-trimethylsilyloxyethoxymethyl (SEM) protecting group by reaction with the appropriate chloromethyl ether. The yields are all very high and the group may be removed by reaction with tetrabutylammonium fluoride in THF or, better, HMPT.[8] Some methylthiomethyl ethers of methyl α-L-rhamnopyranoside have been reported,[9] and Gigg has described the properties of the 3-methylbut-2-enyl (prenyl) ether group, which is not isomerized to the enol ether by rhodium tris(triphenylphosphine)chloride, allowing allyl and but-2-enyl groups to be removed while the prenyl group is left intact.[10] The synthesis of 6-*O*-[(*S*)-1′-carboxyethyl]-D-glucose and its (*R*)-isomer has been accomplished by alkylation of 1,2:3,5-di-*O*-isopropylidene-D-glucose with (*R*)- and (*S*)-2-chloropropionic acid, followed by mild acid hydrolysis.[11]

[1] P. Prehm, *Carbohydr. Res.*, 1980, **78**, 372.
[2] J. Finne, T. Krusius, and H. Rauvala, *Carbohydr. Res.*, 1980, **80**, 336.
[3] T. Takeda, S. Takabe, and Y. Ogihara, *Chem. Pharm. Bull.*, 1980, **28**, 632.
[4] V. Pozsgay and P. Nánási, *Carbohydr. Res.*, 1980, **81**, 184.
[5] A. S. Rao and N. Roy, *Indian J. Chem., Sect. B.*, 1980, **19**, 161 (*Chem. Abstr.*, 1980, **93**, 72 111).
[6] J. Jary and M. Marek, *Collect. Czech. Chem. Commun.*, 1980, **45**, 3571.
[7] S. Hanessian and Y. Guidon, *Tetrahedron Lett.*, 1980, **21**, 2305.
[8] B. H. Lipshutz and J. J. Pegram, *Tetrahedron Lett.*, 1980, **21**, 3343.
[9] R. Toman, V. Kováčik, and M. Kubačková, *Chem. Zvesti*, 1980, **34**, 223.
[10] R. Gigg, *J. Chem. Soc., Perkin Trans. 1*, 1980, 738.
[11] L. R. Orosko and O. S. Chizhov, *Bioorg. Khim.*, 1980, **6**, 1321 (*Chem. Abstr.*, 1980, **93**, 239 799).

Aralkyl Ethers. – Barton and his co-workers have reported a new method of *O*-benzylation by sequential treatment of the alcohol with Vilsmeier salt [$Me_2\overset{+}{N}$=C(Ph)Cl Cl^-] and sodium telluride. Examples in the carbohydrate field are given, but the method does not appear to have any outstanding advantages over the usual procedures.[12] Methyl 2-*O*-benzoyl-5-*O*-benzyl-3,6-dideoxy-α-D-*arabino*-hexofuranoside (1) has been prepared in high yield (90%) by a fascinating reaction involving the treatment of methyl 3,6-dideoxy-α-D-*arabino*-hexopyranoside (2) with benzaldehyde–aluminium chloride (or zinc chloride) (Scheme 1). This proceeds by isomerization of the pyranoside (2) to the furanoside, which leads to the trioxonane (3) that effectively undergoes an intramolecular Cannizaro reaction to give (1). The reason for the high regioselectivity of the reaction is not readily explained.[13]



Scheme 1

Further examples of the reductive ring-opening of benzylidene acetals to give benzyl ethers have been described leading to all possible di-*O*-benzyl ethers of methyl α-L-rhamnopyranoside.[14] This reaction has been employed in the synthesis of 4-hydroxy-3-methoxybenzyl and 4-hydroxy-3,5-dimethoxybenzyl ethers of methyl α-D-glucopyranoside by reduction of the 4,6-acetals derived from vanillin and syringealdehyde. These ethers were synthesized as models for the lignin–saccharide bond.[15] The regioselective benzylation of the dibutylstannate

[12] A. G. M. Barrett, R. G. Read, and D. H. R. Barton, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2184.
[13] J. C. Florent and C. Monneret, *Carbohydr. Res.*, 1980, **81**, 225.
[14] A. Lipták, P. Nánási, A. Neszmélyi, and H. Wagner, *Tetrahedron*, 1980, **36**, 1261.
[15] D. Joniak, B. Košiková, and L. Kosáková, *Collect. Czech. Chem. Commun.*, 1980, **45**, 1959.

of methyl α-L-rhamnopyranoside afforded the 2-*O*-benzyl ether in high yield, which on benzylation with benzyl bromide under phase-transfer conditions afforded the 2,3-dibenzyl ether in 52% yield.[16] In contrast it has been reported that the selective dibenzylation of benzyl α-D-rhamnopyranoside under conditions of phase transfer gives the 2,4-dibenzyl ether.[17] Benzyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside can be readily synthesized from the 2,3-dibenzyl ether by selective *O*-6-tosylation followed by benzyloxy-displacement. This reaction can also be used to make other 6-substituted glucose ethers, *e.g.* allyl ethers, but does not work satisfactorily for galactosides owing to participation by the 4-hydroxy-group.[18] Benzylation of benzyl 2-acetamido-3,6-di-*O*-acetyl-2-deoxy-α-D-glucopyranoside under various conditions gives either the 4-ether or the 4,6-diether.[19] Methyl 3-*O*-benzyl-β-D-xylopyranoside has been made by two methods, one involving the ring-opening of an epoxide ring by the benzyloxy-anion.[20a] The selective benzylation of methyl 2-*O*-benzyl-α-L-fucopyranoside and benzyl 2,6-di-*O*-benzyl-β-D-galactopyranoside under various conditions has been studied.[20b]

The *p*-chlorobenzyl group has several advantages over benzyl as a protecting group. It is readily introduced giving derivatives that are more readily crystalline than benzyl analogues, and it is readily removed by hydrogenolysis in acetic acid. The 2,3,4,6-tetra-*O*-(*p*-chlorobenzyl) ethers of mannose, glucose, and galactose have been described.[21]

A new procedure for *O*-debenzylation has been termed catalytic transfer hydrogenation, and involves reaction with palladium-on-charcoal in formic acid–methanol. Benzylidene acetals and trityl ether groups are also hydrogenolysed by this procedure.[22]

The *o*-, *m*- and *p*-vinylbenzyl ethers of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose have been polymerized, followed by deisopropylidenation, to give amphiphilic polymers which behave as a polysoap in aqueous solution.[23]

Tritylation of nucleosides may be conveniently accomplished in methylene chloride, using a 4 Å molecular sieve as acid acceptor.[24] Trityl and substituted trityl groups are easily removed by stirring briefly with finely powdered zinc bromide,[24] but the reaction is considerably less effective with trityl groups at secondary positions, so that 3′,5′-di-*O*-tritylnucleosides selectively give the 3′-*O*-trityl ether.[25] Similarly 3′,5′-di-*O*-tritylthymidine is selectively detritylated

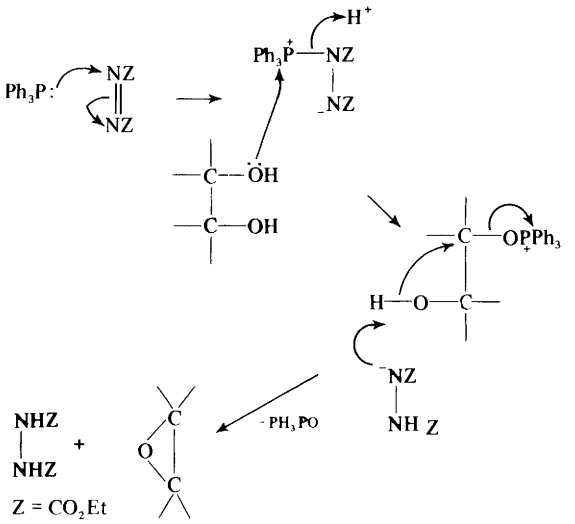
[16] S. S. Rana, J. J. Barlow, and K. L. Matta, *Carbohydr. Res.*, 1980, **85**, 313.
[17] V. Pozsgay and P. Nánási, *Proc. IUPAC Int. Symp. Chem. Nat. Prod., 11th*, 1978, **3**, 73 (*Chem. Abstr.*, 1980, **92**, 42 276).
[18] J. M. Petit, J. C. Jacquinet, and P. Sinaÿ, *Carbohydr. Res.*, 1980, **82**, 130.
[19] N. V. Bovin, S. E. Zurabyan, and A. Ya. Khorlin, *Izv. Akad. Nauk, SSSR, Ser. Khim.*, 1980, 199 (*Chem. Abstr.*, 1980, **92**, 215 673).
[20] (*a*) P. Kováč and J. Alföldi, *Chem. Zvesti*, 1979, **33**, 785; (*b*) S. S. Rana, C. F. Piskorz, J. J. Barlow, and K. L. Matta, *Carbohydr. Res.*, 1980, **83**, 170.
[21] S. Koto, S. Inada, N. Morishima, and S. Zew, *Carbohydr. Res.*, 1980, **87**, 294.
[22] V. S. Rao and A. S. Perlin, *Carbohydr. Res.*, 1980, **83**, 175.
[23] K. Kobayashi and H. Sumitomo, *Macromolecules*, 1980, **13**, 234 (*Chem. Abstr.*, 1980, **92**, 198 808).
[24] V. Kohli, H. Blöcker, and H. Kösler, *Tetrahedron Lett.*, 1980, **21**, 2683.
[25] M. D. Matteucci and M. H. Caruthers, *Tetrahedron Lett.*, 1980, **21**, 3243.

at the 5′-position by aqueous acetic acid to give the 3′-*O*-trityl ether.[26] A further method for detritylation involves boiling in an aprotic solvent such as benzene in the presence of either anhydrous Cu^{II}, Ni^{II}, Fe^{II}, Co^{II}, or Zn^{II} sulphates.[27]

Silyl Ethers. – A new procedure for the removal of t-butyldimethylsilyl groups involves reaction of the ether with *N*-bromosuccinimide in aqueous DMSO.[28]

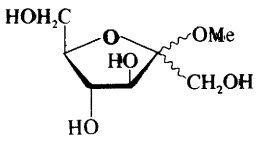
2 Intramolecular Ethers (Anhydro-sugars)

Oxirans. – The triphenylphosphine–diethyl azodicarboxylate reagent (TPP–DEAD) has been shown to be a useful reagent for the synthesis of oxirans directly from *trans-vic*-diols, the mechanism of which is outlined in Scheme 2.[29] For example, methyl β-D-rhamnopyranoside specifically affords the 3,4-anhydrotaloside, whereas 1,6-anhydro-β-D-glucose yielded a mixture of *allo*- and *galacto*-1,6;3,4-dianhydrides. However, the reaction only works satisfactorily if other hydroxy-groups, which could lead to the formation of larger and more stable anhydro-rings, are blocked. For example, methyl α-D-galactopyranoside is converted into the 3,6-anhydride by TPP–DEAD and it appears that in hexopyranosides with a 3,6-*cis* arrangement, blocking of the 6-hydroxy-group is essential for oxiran formation. Hence, Brandstetter and Zbiral have applied the TTP–DEAD reaction to a series of methyl glucopyranosides in which the 6-hydroxy

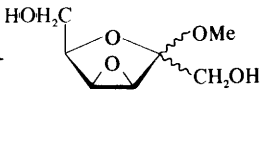


Scheme 2

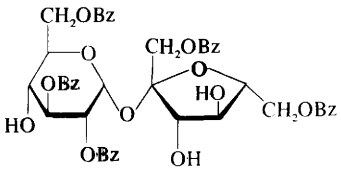
[26] L. C. Davies, P. B. Farmer, M. Jarman, and J. A. Stock, *Synthesis*, 1980, 75.
[27] G. Randazzo, R. Capasso, M. R. Cicala, and A. Evidente, *Carbohydr. Res.*, 1980, **85**, 298.
[28] R. J. Batten, A. J. Dixon, R. J. K. Taylor, and R. F. Newton, *Synthesis*, 1980, 234.
[29] G. Grynkiewicz, *Pol. J. Chem.*, 1979, **53**, 2501.



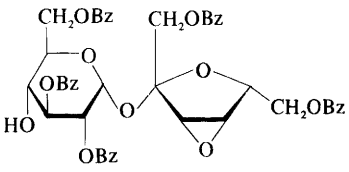
(4)



(5)



(6)



(7)

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

Scheme 3

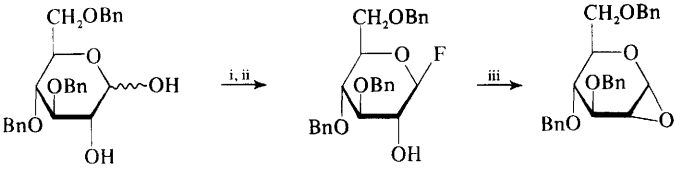
is blocked by a t-butyldimethylsilyl group.[30] Both the α- and β-glucopyranosides afforded mixtures of 2,3- and 3,4-epoxides of which the former predominated. In the β-glycoside both epoxides had the *allo*-configuration, whereas the α-anomer afforded the 2,3-*allo*- and 3,4-*galacto*-epoxides. With methyl 2,6-bis-*O*-t-butyldimethylsilyl-α- and -β-D-glucopyranosides, the 3,4-*galacto*-epoxide was the only product and a similar result was recorded for methyl 2-acetamido-6-*O*-t-butyldimethylsilyl-2-deoxy-α- and -β-D-glucopyranosides. Methyl 4,6-*O*-bis-t-butyldimethylsilyl-β-D-glucopyranoside afforded only the 2,3-*allo*-epoxide. Application of the TPP–DEAD reaction to methyl 4,6-*O*-benzylidene-α-D-galactopyranoside yielded only the 2,3-*gulo*-epoxide in 64% yield and methyl 4,6-dideoxy-α-D-*xylo*-hexopyranoside likewise gave only the 2,3-*ribo*-epoxide.[31] These results seem to suggest that the 3-hydroxy-group and to a lesser extent the 4-hydroxy-group are favoured for attack by TTP to form '$OP\overset{+}{P}h_3$'. Reaction of TPP–DEAD with methyl α- and β-D-fructofuranoside (4) afforded specifically the 3,4-*lyxo*-epoxides (5) in high overall yield without the need to protect the primary hydroxy-groups[32] and reaction of 1′,2,3,6,6′-penta-*O*-benzoyl-sucrose (6) with the reagent similarly afforded the 3′,4′-epoxide (7) in 26% overall yield from sucrose[33] (Scheme 3).

Details are provided for the reliable and reproducible conversion of methyl 4,6-*O*-benzylidene-2,3-di-*O*-tosyl-α-(and β-)D-galacopyranoside into 2,3-epoxides. The α-anomer gives the *gulo*- and *talo*-isomers in 38 and 25% yields, respectively,

[30] H. H. Brandstetter and E. Zbiral, *Helv. Chim. Acta*, 1980, **63**, 327.
[31] O. Mitsunobu, T. Kudo, M. Nishido, and N. Tsuda, *Chem. Lett.*, 1980, 1613.
[32] R. D. Guthrie, I. D. Jenkins, and R. Yamasaki, *J. Chem. Soc., Chem. Commun.*, 1980, 784.
[33] R. D. Guthrie, I. D. Jenkins, and R. Yamasaki, *Carbohydr. Res.*, 1980, **85**, C5.

by reaction with sodium methoxide in DMSO, whereas the β-anomer affords the *talo*-isomer in 66% yield by reaction in dioxan.[34]

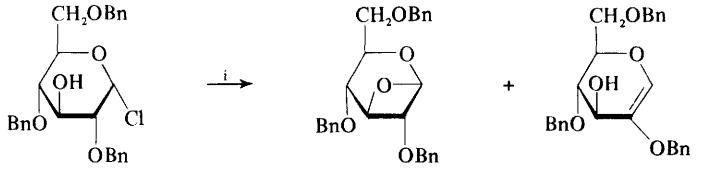
1,2-Anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose (8) has been synthesized from 3,4,6-tri-*O*-benzyl-D-glucose (9) and was isolated by gel permeation and h.p.l.c. (Scheme 4).[35] The conversion of *keto*-forms of ketoses into branched-chain epoxides by reaction with either diazomethane or dimethyloxosulphonium methylide have been studied.[36]



(9) (8)

Reagents: i, HCl–Et_2O–$CHCl_3$; ii, AgF; iii, $KOBu^t$

Scheme 4



(10) (11)

Reagent: i, $KOBu^t$ or NaH–dioxan

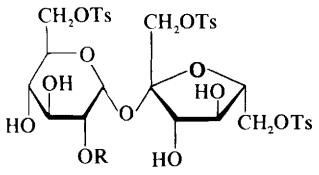
Scheme 5

Other Anhydrides. – The first synthesis of a 1,3-anhydro-hexose has been reported. 1,3-Anhydro-2,4,6-tri-*O*-benzyl-β-D-glucopyranose (10) was prepared from the corresponding α-glycosyl chloride by reaction with base (Scheme 5), although the corresponding 2-benzyloxyglycal (11) was also formed in substantial amount.[37]

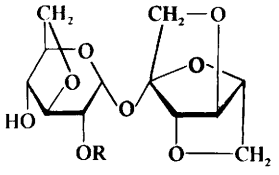
Treatment of 1′,2,6,6′-tetra-*O*-tosylsucrose (12) with base afforded the 1′4′;3′6′;3,6-trianhydro-2-*O*-tosylsucrose (13) showing that 3,6-anhydro-forma-

[34] J. L. Frahn, *Aust. J. Chem.*, 1980, **33**, 1021.
[35] H. Yamaguchi and C. Schuerch, *Carbohydr. Res.*, 1980, **81**, 192.
[36] T. Anthonsen, S. Hagen, and W. Lwande, *Acta Chem. Scand., Ser. B*, 1980, **34**, 41; S. Hagen, W. Lwande, L. Kilaas, and T. Anthonsen, *Tetrahedron*, 1980, **36**, 3101.
[37] H. Ito, R. Eby, S. Kramer, and C. Schuerch, *Carbohydr. Res.*, 1980, **86**, 193.

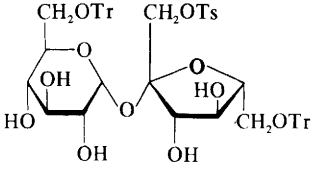
tion was faster than the formation of the 2,3-anhydro-ring.[38] The two sugar moieties of sucrose have now been spanned by an anhydro-linkage. Reaction of 1′-*O*-tosyl-6,6′-di-*O*-trityl sucrose (14) with base afforded the 1′,2-anhydride (15) in high yield after acetylation. This ring structure has not been encountered when related tosylates such as the 1′,2,6,6′-tetratosylate (12) and the 1′,6,6′-tritosylate (16) have been treated with base. In these cases, *O*-4′ displacement of the 1′-tosylate occurs to give the trianhydrides (13) and (17), respectively, in spite of the fact that the 1′,2-anhydro-ring is of the strainless *cis*-decalin type. The reason for this difference is that displacement of the 1′-tosylate group is rather slow since it is adjacent to the anomeric group, and consequently 3′,6′-anhydro-formation precedes its displacement and causes deformation of the fructofuranoside ring so that O-4′ and C-1′ are held in close proximity and lead inevitably to 1′,4′-anhydro-formation. In the absence of the 3′,6′-anhydro-ring, 1′,2-anhydro-formation becomes the favoured mode of displacement.[39]



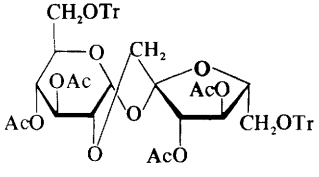
(12) R = Ts
(16) R = H



(13) R = Ts
(17) R = H



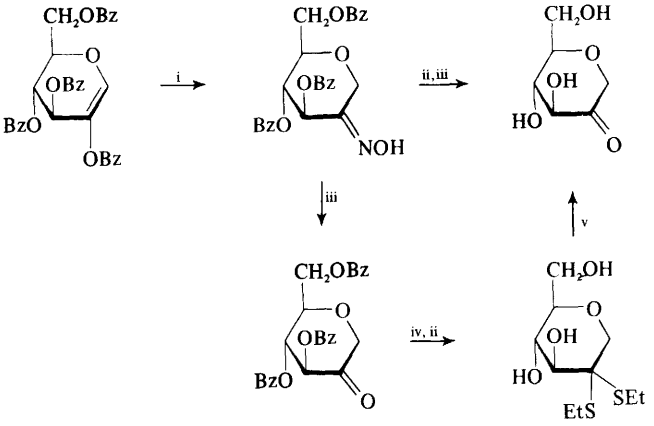
(14)



(15)

A convenient preparation of 1,5-anhydrohexuloses has been devised by Lichtenthaler *et al.* by conversion of the benzoylated 2-hydroxyglycal into the 2-oxime, followed by conversion into the *keto*-derivative (Scheme 6).[40]

[38] J. M. Ballard, L. Hough, S. P. Phadnis, and A. C. Richardson, *Carbohydr. Res.*, 1980, **83**, 138.
[39] M. K. Gurjar, L. Hough, and A. C. Richardson, *Carbohydr. Res.*, 1980, **78**, C21.
[40] F. W. Lichtenthaler, E. S. H. El Ashry, and V. H. Gockel, *Tetrahedron Lett.*, 1980, **21**, 1429.



Reagents: i, H_2NOH; ii, NaOMe; iii, MeCHO–H^+; iv, EtSH–BF_3; v, $HgCl_2$–$CdCO_3$

Scheme 6

5

Acetals

1 Introduction

Formation and migration of cyclic acetals of carbohydrates has been reviewed.[1]

Molecular mechanical calculations have been used to calculate the energies of various conformations of bicyclic acetals of C_4–C_6 alditols with formaldehyde. The thermodynamic stabilities of the [4.4.0] products were predicted to be higher than for the [5.3.0] products in the gas phase. Discrepancies with experimentally observed data were ascribed to solvent effects.[2]

A review of photoremovable protecting groups contains *inter alia* references to carbohydrate acetals.[3]

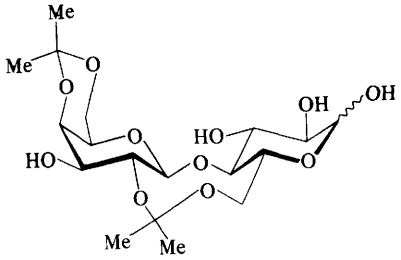
2 Isopropylidene Acetals

A very useful method for determining ring-size of cyclic isopropylidene acetals has been developed based on the chemical shift values of the acetalic carbon atom, and the difference in chemical shift for the two methyl groups.[4]

A continuous method for acid-catalysed acetonation of L-sorbose has been described, which gives the 2,3 : 4,6-diacetal in 80% yield.[5] A reinvestigation of the acetalation of D-glucitol with acetone under zinc chloride catalysis has been carried out by means of g.l.c. Mainly terminal acetals are produced in an initial kinetically-controlled reaction, followed by formation of about equal amounts of 1,2 : 3,4 : 5,6-tri- and 2,3 : 5,6-di-acetal under thermodynamic control. All acetals formed were identified including the hitherto unknown 1,2 : 3,5 : 4,6-tri-*O*-isopropylidene-D-glucitol.[6] Treatment of D-fructose with 2,2-dimethoxypropane in 1,2-dimethoxyethane containing tin(II) chloride gave the previously unknown 1,2-*O*-isopropylidene-β-D-fructofuranose characterized as its crystalline triacetate.[7] Isopropylidenation of D-mannitol using 2,2-dimethoxypropane in 1,2-dimethoxyethane under neutral conditions, *i.e.* no catalyst, gives the 1,2 : 5,6-diacetal as the main product, with the second product, 1,2 : 3,4 : 5,6-tri-*O*-isopropylidene-D-mannitol, deriving mainly from an initially formed 3,4-acetal. Under the neutral conditions employed no rearrangement of the first-formed

[1] D. M. Clode, *Chem. Rev.*, 1979, **79**, 491.
[2] U. Burkert, *J. Comput. Chem.*, 1980, **1**, 192 (*Chem. Abstr.*, 1980, **93**, 168 514).
[3] V. N. R. Pillai, *Synthesis*, 1980, 1.
[4] J. G. Buchanan, M. E. Chacón-Fuertes, A. R. Edgar, S. J. Moorhouse, D. I. Rawson, and R. H. Wightman, *Tetrahedron Lett.*, 1980, **21**, 1793.
[5] E. Pencheva, G. Spirov, Sh. S. Levi, M. I. Levi, and Kh. Ionchev, *Khim.-Farm. Zh.*, 1979, **13**, 102 (*Chem. Abstr.*, 1980, **92**, 76 812).
[6] J. Kuszmann, P. Sohár, G. Horváth, E. Tomori, and M. Idei, *Carbohydr. Res.*, 1980, **79**, 243.
[7] G. J. F. Chittenden, *J. Chem. Soc., Chem. Commun.*, 1980, 882.

products occurs. The 1,2-dimethoxyethane performs an active role in the reaction through a presumed hydrogen-bonded complex with the diol.[8] Exclusive kinetic control has been shown to operate in the reaction between ketoses or oligosaccharides and 2-methoxypropene in the presence of a trace of toluene-*p*-sulphonic acid at 0 °C. Using 2 molecular equivalents of 2-methoxypropene, L-sorbose and D-fructose gave the corresponding furanose 1,3-acetals in 35 and 55% yield, respectively, whereas D-tagatose gave the pyranose 1,3-acetal. Maltose gave the 4′,6′-acetal and sucrose gave mainly the 4,6-mono- and the 4,6 : 2,1′-di-acetals. Lactose gave the diacetal (1) characterized as its tetra-acetate.[9]



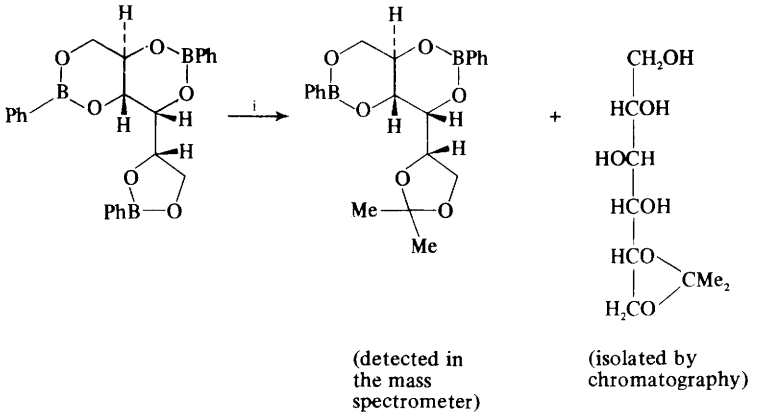
(1)

Using the ^{13}C n.m.r. method described above,[4] the isopropylidenations of D-ribose diethyldithioacetal and of D-erythritol have been re-examined. The former with acetone–sulphuric acid was shown to give the 2,5 : 3,4- and the 2,3 : 4,5-diacetals each in 40% yield and not the 2,4 : 3,5-diacetal as previously claimed. D-Erythritol gave mainly the 1,2,3,4-di-*O*-isopropylidene acetal with either acetone or 2,2-dimethoxypropane-toluene-*p*-sulphonic acid.[10]

Acetonolysis of 2-phenyl-1,3,2-dioxaborolanes of D-glucitol and D-mannitol gave the 1,2-*O*-isopropylidene-alditols as shown for D-glucitol in Scheme 1. A similar reaction with α-D-glucofuranose 1,2 : 3,5-bis(benzeneboronate) gave 1,2-*O*-isopropylidene-α-D-glucofuranose.[11]

Koenigs–Knorr conditions have been shown to cause acetal migration in the reaction of 1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose with tetra-*O*-acetyl-α-D-glucopyranosyl bromide at 45 °C. In addition to the expected disaccharide, 6-*O*-(tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2 : 3,5-di-*O*-isopropylidene-α-D-glucofuranose was obtained.[12] It was also reported that 1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose gives 6-chloro-1,2 : 3,5-di-*O*-isopropylidene-α-D-glucofuranose on treatment with phosphorus pentachloride.

[8] G. J. F. Chittenden, *Carbohydr. Res.*, 1980, **87**, 219.
[9] E. Fanton, J. Gelas, and D. Horton, *J. Chem. Soc., Chem. Commun.*, 1980, 21.
[10] G. Aslani-Shotorbani, J. G. Buchanan, A. R. Edgar, D. Henderson, and P. Shahidi, *Tetrahedron Lett.*, 1980, **21**, 1791.
[11] C. J. Griffiths and H. Weigel, *Carbohydr. Res.*, 1980, **81**, 17.
[12] A. Lipták, P. Nánasi, A. Neszmélyi, and H. Wagner, *Carbohydr. Res.*, 1980, **86**, 133.



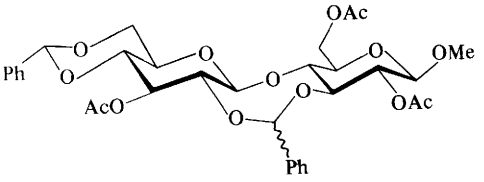
Reagent: i, $(CH_3)_2CO$–H_2SO_4(tr.)

Scheme 1

3 Benzylidene Acetals

An improved method for the preparation of methyl 4,6-*O*-benzylidene α- and β-D-glucopyranoside that can be accomplished within a day utilizes a preformed benzaldehyde–zinc chloride complex.[13]

Structural assignments based on ^1H and ^{13}C n.m.r. for the four benzylidene acetals derived from 1,6-dibromomannitol have been made.[14] Benzylidenation of 1,6-anhydro-β-D-galactopyranose and its 2-*O*-acetyl and 2-*O*-allyl derivatives under various conditions gave mixtures of 1,6-anhydro-*exo*- and *endo*-3,4-*O*-benzylidene-β-D-galactopyranose derivatives. Hydrogenolysis of both types of acetal with lithium aluminium hydride–aluminium chloride gave only the 3-*O*-benzyl derivative.[15] It has been shown that under the conditions of Frahn, methyl α-D-idopyranoside and its 2,3-di-*O*-methyl ether give only the 4,6-*O*-(*S*)-benzylidene acetals.[16] Reference to the conformations of these compounds is made in Chapter 20. The synthesis, crystal structure, and conformation of cellobiosides containing intersaccharide benzylidene bridges such as (2) has been reported.[17]

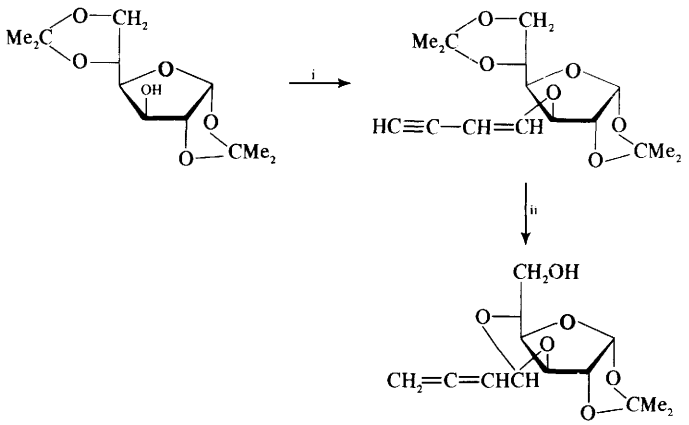


(2)

[13] D. M. Hall, *Carbohydr. Res.*, 1980, **86**, 158.
[14] P. Sohár, T. Horváth, and G. Ábrahám, *Acta Chim. Acad. Sci., Hung.*, 1980, **103**, 95.
[15] C. Subero, L. Fillol, and M. Martin-Lomas, *Carbohydr. Res.*, 1980, **86**, 27.
[16] S. J. Angyal and Y. Kondo, *Carbohydr. Res.*, 1980, **81**, 35.
[17] J. Thiem, K.-H. Klaska, and D. Jarchow, *J. Chem. Res.* (*S*), 1980, 190.

4 Other Acetals

The first preparation of an acetal of buta-2,3-dienal has been achieved (Scheme 2).[18] Monobutylidenation of 3-deoxy-D-*ribo*-hexitol using butyraldehyde and hydrochloric acid gave the 2,4-acetal as the sole product. A similar reaction with 3-deoxy-L-*xylo*-hexitol gave the 4,5-acetal as the kinetic product and the 4,6-acetal as the thermodynamic product.[19] Treatment of 2-acetamido-2-deoxy-D-glucose or its 2-benzyloxycarbonylamino-analogue with 2,2-dimethoxypropane or 2,2-dibenzyloxypropane in 1,4-dioxan gave the corresponding 3,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal or dibenzyl acetal in good yield.[20] The reaction of L-arabinitol with formaldehyde in the presence of hydrogen chloride gives the 2,4:3,5-acetal as the main product (39% yield), a compound not reported by Richtmeyer and Zissis in their study of this reaction.[21]

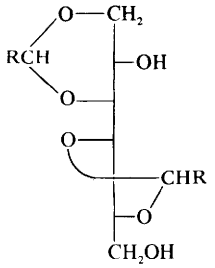


Reagents: i, $Me_2C(OH)(C{\equiv}C)_2C(OH)Me_2$; ii, $HOAc\text{-}H_2O$

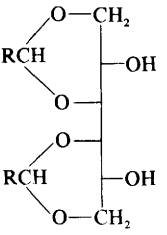
Scheme 2

Dialkoxyalkylphosphonates react with hexitols to yield phosphorylated acetals by transacetalation. Thus, with 2,2-diethoxy- and dimethoxy-ethylphosphonates, D-galactitol gave the 1,3:4,5-diacetals (3) as the major products and the 1,3:4,6-diacetals (4) as the minor. With 3,3-diethoxypropylphosphonate the 1,3:4,6-diacetal (5) predominated.[22] The former reagent with D-mannitol gave only the 1,3:4,6-diacetal, whereas D-glucitol gave two diacetals, only one of which was characterized (6), and a small amount of an uncharacterized monoacetal.[23] The reactions were catalysed by concentrated hydrochloric or hydrobromic acids or by anhydrous hydrogen chloride.

[18] C. Augé, S. David, and A. Lubineau, *J. Chem. Soc., Chem. Commun.*, 1980, 568.
[19] T. G. Bonner, D. Gibson, and D. Lewis, *Carbohydr. Res.*, 1980, **78**, 243.
[20] A. Hasegawa and M. Kiso, *Carbohydr. Res.*, 1980, **79**, 265.
[21] A. A. Othman and U. S. Al-Timari, *Tetrahedron*, 1980, **36**, 753.
[22] S. Yanai, M. Halmann, and D. Vofsi, *Carbohydr. Res.*, 1980, **83**, 243.
[23] S. Yanai, M. Halmann, and D. Vofsi, *Carbohydr. Res.*, 1980, **83**, 379.

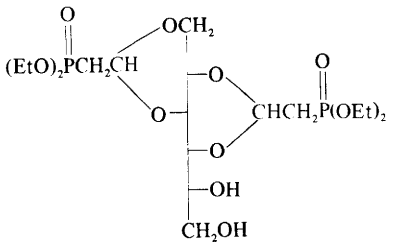


(3) R = $CH_2P(OEt)_2$ or $CH_2P(OMe)_2$



(4) R = $CH_2P(OEt)_2$ or $CH_2P(OMe)_2$

(5) R = $CH_2CH_2P(OEt)_2$



(6)

An efficient one-pot procedure for removal of 4,6-*O*-ethylidene groups from D-galactopyranose residues in hetero-oligosaccharides has been described, involving acetolysis, followed by hydrolysis and acetylation.[24]

Grignard reagents are reported to cleave acetals regioselectively. Thus 1,2 : 5,6-di-*O*-cyclohexylidene-α-D-glucofuranose yields 1,2-*O*-cyclohexylidene-6-*O*-(1-methylcyclohexyl)-α-D-glucofuranose with methyl magnesium iodide. With isopropyl magnesium iodide the 6-*O*-cyclohex-1-enyl ether is formed. Other examples are given.[25]

5 Chiral Reductions with Acetals

Reduction of ketones with sodium borohydride in the presence of a carboxylic acid and 1,2 : 5,6-di-*O*-cyclohexylidene-α-D-glucofuranose gave 35–50% enantiomeric enhancement values.[26] Another group has reported a similar reaction with the corresponding di-*O*-isopropylidene-glucose derivative and prochiral aromatic ketones. Optical yields of up to 64% were claimed. The chiral reagents appear to be sodium acyloxyborohydrides, which complex with the carbohydrate before reduction takes place.[27]

[24] M. V. Ovchinnikov, V. I. Betaneli, L. V. Backinowsky, and N. K. Kochetkov, *Bioorg. Khim.*, 1980, **6**, 306.
[25] M. Kawana and S. Emoto, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 230.
[26] J. D. Morrison, E. R. Grandbois, and S. I. Howard, *J. Org. Chem.*, 1980, **45**, 4229.
[27] A. Hirao, S. Nakahama, H. Mochizuki, S. Itsuno, and N. Yamazaki, *J. Org. Chem.*, 1980, **45**, 4231.

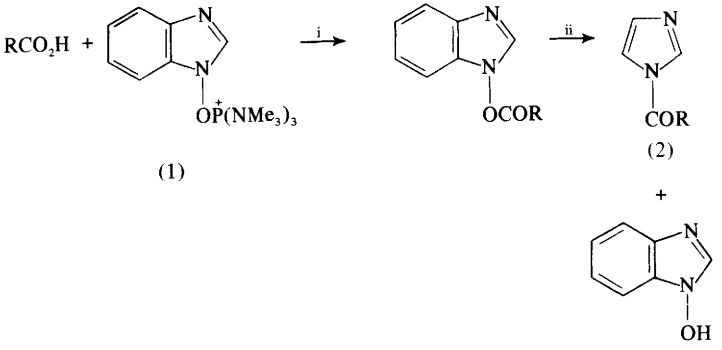
6

Esters

A review of photoremovable protecting groups, including many examples of esters of carbohydrates and nucleosides, has appeared.[1]

1 Carboxylic Esters

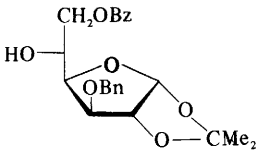
Selective acylation of primary hydroxy-groups occurs with acyl, benzoyl, and tosyl halides in a two-phase system consisting of dichloromethane–water containing sodium hydroxide and benzyltriethylammonium chloride.[2] Dibenzylidene-α,α-trehalose has been selectively acylated using a mixture of carboxylic acid, imidazole, triethylamine, and the phosphonium intermediate (1). The 2-mono-, 2,2′-di-, and 2,2′,3-tri-esters were obtained, from which the benzylidene groups were removed by acid hydrolysis. The acylating species appears to be the *N*-acylimidazole (2) generated as shown in Scheme 1.[3] The glucose derivative (3) reacts



(1) (2)

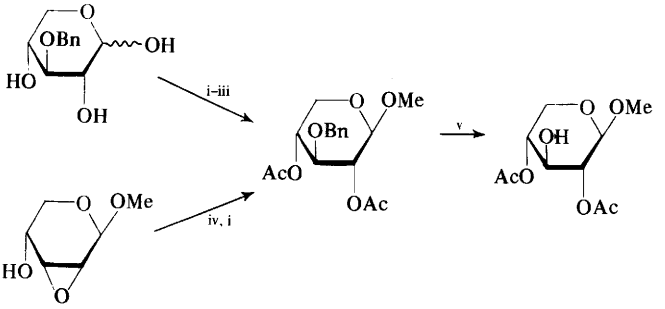
Reagents: i, NEt_3; ii, imidazole

Scheme 1



(3)

[1] V. N. R. Pillai, *Synthesis*, 1980, 1.
[2] W. Szeja, *Pol. J. Chem.*, 1980, **54**, 1301; *ibid.*, p. 1323.
[3] Y. Chapleur, B. Castro, and R. Troubiana, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1940.



Reagents: i, Ac_2O–C_5H_5N; ii, HBr–CH_2Cl_2; iii, MeOH–$Hg(CN)_2$; iv, BnO^-–BnOH; v, H_2–Pd

Scheme 2

with benzoic acid in the presence of diethyl azodicarboxylate and triphenylphosphine to give mainly the corresponding L-idose 5-benzoate with inversion of configuration, the expected glucose isomer being only a minor product. Methyl tosylate, used in place of benzoic acid, led to the inverted 5-*O*-tosyl ester. When the same reaction was attempted on 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, phosphonium salts were formed which afforded a good means of obtaining esters and ethers with the *gluco*-configuration.[4] The selective deacylation of enol esters to yield aldulose oximes is described in Chapter 9.

Fast acetylations have been achieved using acetic anhydride–iron(III) chloride. The reaction is exothermic and produces mainly α-acetates. With acetylations of glycosides prolonged reaction can lead to acetolysis of the glycoside. Many examples are given and the reaction is shown to be complete in most cases within minutes at 20 °C and to give high yields.[5] A study of the application of chloroacetyl groups for temporary protection in oligosaccharide synthesis has been carried out. The ester was shown to be stable under the conditions of the diphenylcyclopropenyl method of glycosidation. Using this method of protection, Lewis A blood-group determinant was synthesized.[6] Electrolytic methanolysis of acylated amino-sugars with a platinum or gold anode in methanol containing tetraethylammonium perchlorate has been studied. 2-Acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α- or -β-D-glucopyranose gave 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-α,β-D-glucopyranose in high yield, whereas methyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranoside gave 44% completely deacetylated glycoside and 40% of glycoside with the six position acetylated.[7] Methyl 2,4-di-*O*-acetyl-α-D-xylopyranoside has been synthesized by the two methods depicted in Scheme 2.[8] Partially acetylated methyl ethers of methyl α-L-rhamnopyranoside have been isolated by preparative g.l.c.[9] As models for behaviour in beverages and other foods, the stabilities of sugar

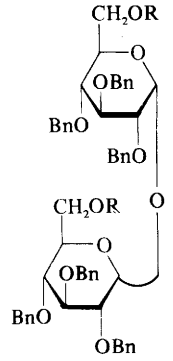
[4] H. Kunz and P. Schmidt, *Chem. Ber.*, 1979, **112**, 3886.
[5] F. Dasgupta, P. P. Singh, and H. C. Srivastava, *Carbohydr. Res.*, 1980, **80**, 346.
[6] N. V. Bovin, S. E. Zurabyan, and A. Ya. Khorlin, *Bioorg. Khim.*, 1980, **6**, 242.
[7] T. Imagawa, Y. Nakashima, and M. Kawanisi, *Chem. Lett.*, 1980, 1609.
[8] P. Kováč and J. Alföldi, *Chem. Zvesti*, 1979, **33**, 785.
[9] E. V. Evtushenko, N. M. Vakhrusheva, and Yu. S. Ovodov, *Khim. Prir. Soedin.*, 1979, 142 (*Chem. Abstr.*, 1980, **92**, 76 866).

acetates in citric acid solution have been studied. The rate depended markedly on pH, with primary acetates being hydrolysed faster than secondary. In 10% citric acid the 50%-hydrolysis time varied from 35 h for sucrose octa-acetate to 110 h for raffinose hendeca-acetate. The stability of the former was studied at various citric acid concentrations.[10]

The order of selective benzoylation of 1,5-anhydro-D-glucitol under standard conditions is $6 > 3 > 2 > 4$.[11] Partial benzoylations of methyl β-kojibioside and methyl β-sophoroside using seven molar equivalents of benzoyl chloride in pyridine at $-40\,^{\circ}C$ have been investigated. With the former the major product was the 4,6,2′,3′,4′,6′-hexabenzoate (92%) with 2% of the heptabenzoate, and with the latter, 37% heptabenzoate, 28% 4,6,2′,3′,4′,6′-hexabenzoate, and 27% 3,4,6,2′,3′,6′-hexabenzoate were obtained.[12] Hydroxyammonium acetate in pyridine is claimed to be superior to hydrazine hydrate for selective debenzoylation of acylated ribonucleosides. Thus adenosine 2′,3′,5′-tribenzoate and uridine 2′,3′,5′-tribenzoate gave high yields of the corresponding 3′,5′-dibenzoate. Many other examples are given.[13] Selective aroylations at C-6 of hexopyranosides have been achieved using triphenylphosphine–diethyl azodicarboxylate in the presence of the acid. If the acid is very weak, anhydro-sugar formation predominates.[14]

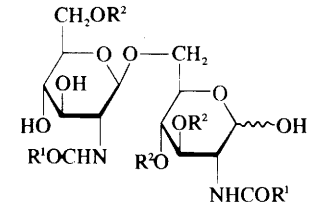
All the positional isomers of methyl mono-*O*-tetradecanoyl-α- and -β-D-glucopyranosides have been synthesized and their ^{1}H and ^{13}C n.m.r. spectra determined.[15] 1-*O*-Hexadecanoyl and 1-*O*-oleoyl esters of D-glucopyranose have been synthesized by reaction of the sodium salt of 4,6-*O*-benzylidene-D-glucopyranose with the acid chloride followed by hydrolysis of the acetal. Attempted preparation of 1-*O*-linolenoyl-D-glucopyranose by the same method led to 3-*O*-linolenoyl-D-glucopyranose.[16] Mono- and di-esters of sucrose prepared by transesterification with methyl esters of lauric, palmitic, and stearic acid have been investigated for their emulsifying properties on paraffin oil–water mixtures.[17] The α,α-trehalose 6,6′-diesters (4) and (5) have been prepared by a dimesylate displacement procedure.[18] Levulinyl esters are useful temporary blocking groups for oligosaccharide synthesis since they are readily removed in the presence of acetyl groups by hydrazine.[19] The lipodisaccharide (6) has been synthesized as part of an approach to the synthesis of Lipid A, which is the active centre of the bacterial endotoxin of *Salmonella*.[20,21] Transesterification of trehalose with

[10] E. B. Rathbone, C. K. Lee, and G. G. Birch, *Food Chem.*, 1980, **5**, 139 (*Chem. Abstr.*, 1980, **93**, 69 043).
[11] Y. Kondo, K. Yabuuchi, and S. Hirano, *Carbohydr. Res.*, 1980, **82**, 398.
[12] K. Takeo and T. Yasato, *Carbohydr. Res.*, 1980, **86**, 297.
[13] Y. Ishido, N. Sakairi, K. Okazaki, and N. Nakazaki, *J. Chem. Soc., Perkin Trans. 1*, 1980, 563.
[14] G. Grynkiewicz, *Pol. J. Chem.*, 1979, **53**, 2501.
[15] K. Yoshimoto, Y. Itatani, K. Shibata, and Y. Tsuda, *Chem. Pharm. Bull.*, 1980, **28**, 208.
[16] A. K. Tanaka, A. Kobayashi, and K. Yamashita, *Agric. Biol. Chem.*, 1979, **43**, 2537.
[17] J. Szymanowski, M. Wisniewski, and B. Atamanczuk, *Tluszcze, Srodki Piorace, Kosmet.*, 1979, **23**, 29 (*Chem. Abstr.*, 1980, **93**, 72 135).
[18] A. Liav and M. B. Goren, *Carbohydr. Res.*, 1980, **81**, C1.
[19] H. J. Koeners, J. Verhoeven, and J. H. van Boom, *Tetrahedron Lett.*, 1980, **21**, 381.
[20] M. Inage, H. Chaki, S. Kusumoto, and T. Shiba, *Tetrahedron Lett.*, 1980, **21**, 3889.
[21] M. Inage, H. Chaki, S. Kusumoto, T. Shiba, A. Tai, M. Nakahata, T. Harada, and Y. Izumi, *Chem. Lett.*, 1980, 1373.



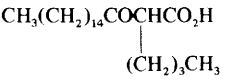
(4) R = $C_{16}H_{33}O$—C$_6$H$_4$—$(CH_2)_3C(=O)$—O—

(5) R = $C_{15}H_{31}$—C(H)(OH)—CH($C_{14}H_{29}$)—C(=O)—O—



(6) R^1 = $CH_3(CH_2)_{10}CHCH_2$ (OH)

R^2 = $CH_3(CH_2)_{12}CO$-



(7)

esters of the branched acid (7) in the presence of base gave the 6-palmitate *via* a *retro*-Claisen condensation from the 6′-ester. The reaction did not occur when the 6′-OH was etherified.[22] Selective pivaloylation of methyl α-D-glucopyranoside with 4.8 molar equivalents of pivaloyl chloride in ether for 1 h at 4 °C gave 89% 2,6-dipivaloate. Keeping the reaction mixture a further 24 h at 22 °C gave the 2,3,6-tripivaloate, the 2,4,6-tripivaloate, and the tetrapivaloate in a ratio of 1.2 : 1 : 1.5. When the ether was replaced by pyridine the two tripivaloates were obtained in 35 and 54%, respectively, after 1 h at 4 °C. Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with 2.2 molar equivalents of pivaloyl chloride in ether gave 77% of the corresponding 2-*O*-pivaloyl ester after 16 h at 22 °C, which fell to 54% after 48 h with concomitant production of the dipivaloate (27%).[23] Reaction of 9,10-dihydrolysergic acid with peracetylated α-D-glucopyranosyl bromide, α-D-galactopyranosyl bromide, α-D-xylopyranosyl bromide, and β-L-arabinopyranosyl bromide under Königs–Knorr conditions gave the corresponding esters. The esters of lysergic acid itself were obtained from α-D-xylopyranosyl and β-L-arabinopyranosyl bromides.[24]

[22] H. Aurelle and J. C. Promé, *Tetrahedron Lett.*, 1980, **21**, 3277.

[23] S. Tomić-Kulenović and D. Keglević, *Carbohydr. Res.*, 1980, **85**, 302.

[24] S. Johne and K. Seifert, *Symp. Pap. IUPAC Int. Symp. Chem. Nat. Prod., 11th*, 1978, **3**, 181 (*Chem. Abstr.*, 1980, **92**, 42 265).

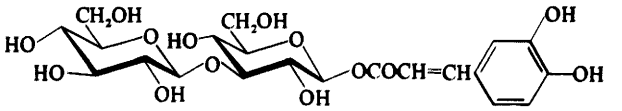
The pathway for *O*-acyl migration in D-glucose derivatives has been investigated by a systematic study, under various conditions, of methyl mono-*O*-myristoyl-α- and -β-D-glucopyranosides, and mono-*O*-myristoyl-D-glucopyranoses. The former show considerable migration on heating 5 min at 200 °C in a glass tube but are stable at 150 °C, whereas the latter are more labile, migration occurring at 130–150 °C. Migrations from *O*-1α to *O*-2 and *O*-4 to *O*-6 were facile; *trans*-migration from *O*-2 to *O*-3 were confirmed and were reversible, but *O*-3 to *O*-4 and *O*-1β to *O*-2 were not observed; *O*-3 to *O*-6 was shown to be a direct migration and not to pass through the *O*-4 myristoyl derivative, suggesting that the migrations occur through the $^1C_4(D)$ conformation.[25]

New carotenoid glycosyl esters have been obtained from galactose and maltose and the imidazolyl or 1,2,4-triazolyl derivative of the carotenoid acid in the presence of sodium hydride.[26]

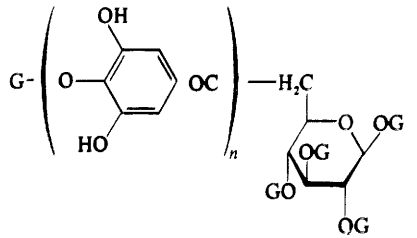
Summer leaves of *Spiraca thunbergii* contain 1-*O*-cinnamoyl-β-D-glucopyranose and its 6-*O*-(4-hydroxy-2-methylenebutanoyl) derivative, named spirarin.[27] A new hydroxycinnamic acid derivative, 1-caffeyllaminaribiose (8) has been isolated from *Asplenium adiantum-nigrum*.[28] 1,4-Di-*O*-*p*-coumaroyl-β-D-glucose occurs in the fronds of *Dennstaedtia scandens*.[29] The gallotannins (polygalloylglucoses) (9) of *Paconia albiflora* have been isolated by chromatography on Sephadex LH20. Homogeneous fractions containing (9) with $n = 0$–5 were obtained.[30] Eugeniin, a new ellagitannin, with the structure (10) has been obtained from cloves (flower buds of *Eugenia caryophyllata*).[31]

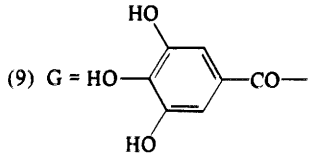
The synthesis of 6-esters of sucrose and naphthenic acids by acid-catalysed esterification with RCO_2Me ($R = C_{10}H_{19}$–$C_{16}H_{29}$) in 96–97% yield has been reported.[32] A novel aspirin pro-drug, 1-*O*-(2′-acetoxy)benzoyl-2-deoxy-α-D-glucopyranose has been prepared by standard procedures.[33] A report on the synthesis of α- and β-D-glucopyranosyl esters of L-serine has been published.[34] Irradiation of 1,6-di-*O*-*trans*-cinnamoyl-2,4:3,5-di-*O*-methylene-D-mannitol in solution gives rise, by stereoselective cycloaddition, to 1,2-diphenyl-cyclobutane-3,4-carboxylic acid dimethyl esters. The optical yield of the all-*trans*-isomer was 48%.[35a]

[25] Y. Tsuda and K. Yoshimoto, *Carbohydr. Res.*, 1980, **87**, C1.
[26] H. Pfander, R. Dumont, and M. Laederach, *Chimia*, 1980, **34**, 20 (*Chem. Abstr.*, 1980, **93**, 72 134).
[27] Y. Tanabe and A. Kita, *Yakugaku Zasshi*, 1980, **100**, 355 (*Chem. Abstr.*, 1980, **93**, 3911).
[28] F. Imperato, *Chem. Ind.* (*London*), 1979, 553.
[29] N. Tanaka, S. Nagase, K. Wachi, T. Murakami, Y. Saiki, and C. -M. Chen, *Chem. Pharm. Bull.*, 1980, **28**, 2843.
[30] M. Nishizawa, T. Yamagishi, G. -I. Nonaka, and I. Nishioka, *Chem. Pharm. Bull.*, 1980, **28**, 2850.
[31] G. -I. Nonaka, M. Harada, and I. Nishioka, *Chem. Pharm. Bull.*, 1980, **28**, 685.
[32] A. F. Artamonov, M. I. Goryaev, L. P. Petelina, and B. Bektursynov, *Vestn. Akad. Nauk Kaz. S.S.R.*, 1980, 70 (*Chem. Abstr.*, 1980, **93**, 239 801).
[33] J. E. Truelove, A. A. Hussain, and H. B. Kostenbauder, *J. Pharm. Sci.*, 1980, **69**, 231 (*Chem. Abstr.*, 1980, **93**, 95 498).
[34] S. Valentekovic and D. Keglevic, *Croat. Chem. Acta*, 1979, **52**, 375 (*Chem. Abstr.*, 1980, **93**, 168 565).
[35] (*a*) J. Bernstein, B. S. Green, and M. Rejto, *J. Am. Chem. Soc.*, 1980, **102**, 323; (*b*) L. E. Franzen and S. Svensson, *Carbohydr. Res.*, 1980, **79**, 147.

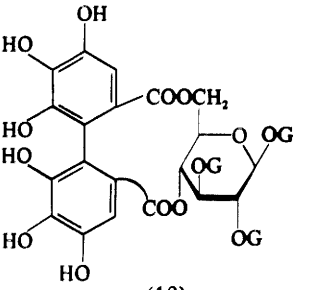


(8)





(9) G = HO—CO—



(10)

A study of the stability of partially methylated methyl α-D-xylopyranosides and D-xyloses towards trifluoroacetic acid–trifluoroacetic anhydride mixtures has shown that the compounds were stabilized most by formation of the 4-ester, less by formation of the 2-ester, and least by formation of the 3-ester. Methyl 2,3,4-tri-*O*-methyl-α-D-xylopyranoside was completely destroyed, compounds with one free hydroxy-group gave some unchanged glycoside, and compounds with two free hydroxy-groups were stable to 1 : 50 mixtures of TFA–TFAA. 2,3,4-Tri-*O*-methyl-D-xylose was completely degraded by mixtures of the two reagents in all proportions.[35b]

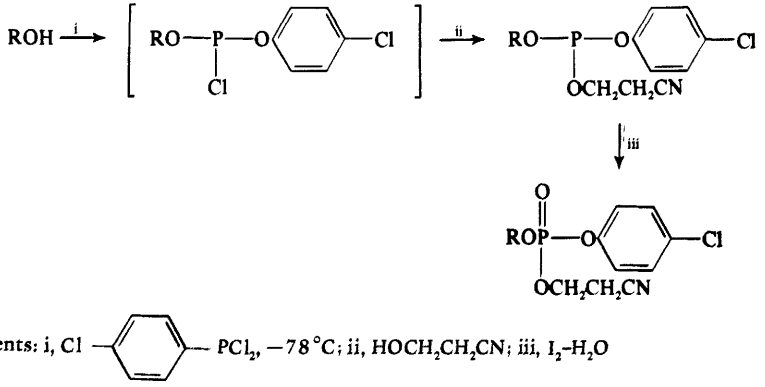
2 Phosphates and Relted Esters

A review of the mechanistic implications of the observed stereochemistry of bond-forming and bond-breaking processes at phosphorus in 5- and 6-membered cyclic phosphorus esters has been published.[36]

A useful method of introduction of protected phosphates prior to nucleotide formation is shown in Scheme 3.[37]

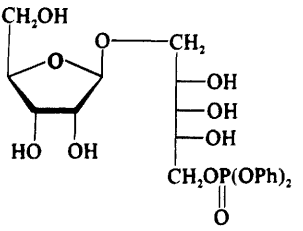
A fast micromethod (10–15 nmol scale) for the identification of glycosyl phosphate anomers based on spectrophotometric measurement of the rate of their acid-catalysed hydrolysis has been described.[38] The standard Gibbs free-energy change for hydrolysis of α-D-ribose 1-phosphate has been determined.

[36] C. R. Hall and T. D. Inch, *Tetrahedron*, 1980, **36**, 2059.
[37] D. Molko, R. B. Derbyshire, A. Guy, A. Roget, and R. Teoule, *Tetrahedron Lett.*, 1980, **21**, 2159.
[38] L. L. Danilov, N. S. Utkina, and V. N. Shibaev, *Bioorg. Khim.*, 1980, **6**, 780.



Reagents: i, Cl—C₆H₄—PCl_2, −78 °C; ii, $HOCH_2CH_2CN$; iii, I_2–H_2O

Scheme 3



(11)

The value of -22.6 ± 0.6 kJ mol^{-1} obtained is similar to that of other hemiacetal phosphoric esters.[39] Treatment of 4-*O*-acetyl-2,3-*O*-carbonyl-α-L-rhamnopyranosyl bromide with dibenzyl phosphate–triethylamine, followed by deprotection, yielded β-L-rhamnopyranosyl phosphate. The same paper contains a synthesis of thymidine 5′-(β-L-rhamnopyranosyl)pyrophosphate.[40] Long-chain (C_{10}–C_{16}) alkyl β-D-glucopyranosyl phosphates have been prepared *via* the orthoester method and described as novel anionic detergents.[41] The MacDonald procedure (anhydrous phosphoric acid *in vacuo* at 56–60 °C for 2 h) has been used to convert di- and tri-saccharides into their α-glycosyl phosphates.[42] The syntheses and ^{13}C n.m.r. of 2-acetamido-2-deoxy-D-glucose 1-, 3-, 4-, and 6-phosphates have been published. The ^{31}P chemical shifts were studied with respect to the position of the phosphate group.[43] D-Ribofuranosyl ribitol

[39] M. Camici, F. Sgarrella, P. L. Ipata, and U. Mura, *Arch. Biochem. Biophys.*, 1980, **205**, 191.

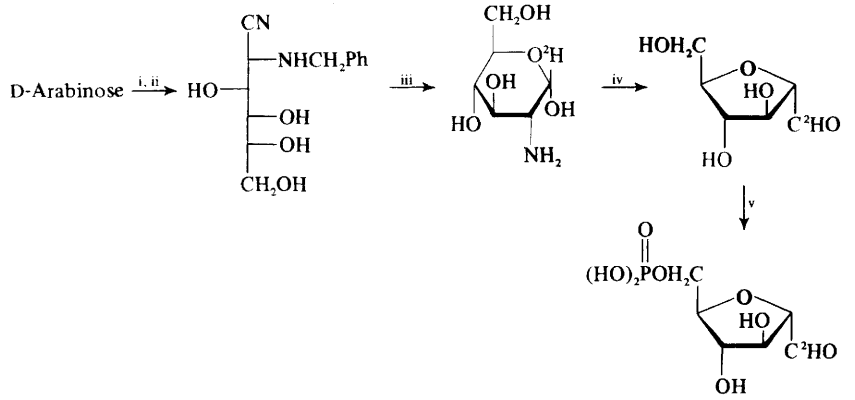
[40] V. N. Shibaev, N. S. Utkina, L. L. Danilov, and G. I. Eliseeva, *Bioorg. Khim.*, 1980, **6**, 1778.

[41] Yu. L. Sebyakin, L. V. Volkova, V. S. Markin, and R. P. Evstigneeva, *Bioorg. Khim.*, 1979, **5**, 1816 (*Chem. Abstr.*, 1980, **92**, 147 068).

[42] L. L. Danilov, M. F. Troitzky, N. S. Utkina, V. N. Shibaev, and N. K. Kochetkov, *Carbohydr. Res.*, 1980, **87**, 141.

[43] V. I. Gorbach, V. V. Isakov, Yn. G. Kulesh, P. A. Lukyanov, T. F. Solov'eva, and Yn. S. Ovodov, *Bioorg. Khim.*, 1980, **6**, 81.

5-phosphate (11) has been described.[44] *p*-Isothiocyanatophenyl α-D-mannopyranoside 6-phosphate has been coupled to albumin to give a model compound for study of the requirements of the fibroblast lysosomal enzyme-recognition systems.[45] Incubation of D-glucose or D-gluconic acid with sodium phosphate at various temperatures and pH values led to the formation of D-glucose 6-phosphate and D-gluconic acid 6-phosphate, respectively, in the absence of enzymes. Similar reactions were achieved with sodium arsenate, and the sugar arsenates were shown to be good analogues of the phosphates for various enzymes.[46] An inducible D-galactose 6-phosphate isomerase from *Staphylococcus aureus* catalyses the reversible isomerization of D-galactose 6-phosphate to D-tagatose 6-phosphate. An improvement of the hydrolysis step in the synthesis of D-tagatose 6-phosphate from D-galacturonic acid is also reported.[47] [1-^{2}H]Chitose 6-phosphate has been prepared using the Kuhn method followed by deamination as shown in Scheme 4.[48]



Reagents: i, $PhCH_2NH_2$–EtOH; ii, HCN; iii, Pd–$^2H_2$–^2HCl–^2H_2O, 30 p.s.i.; iv, HNO_2; v, ATP-hexokinase

Scheme 4

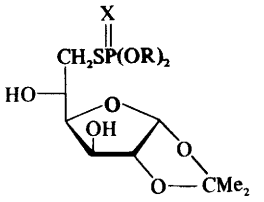
The ^{13}C n.m.r. spectra and anomeric compositions of ketohexose phosphates in solution are discussed in Chapter 20. A phosphoric ester having the properties of fructose 2,6-diphosphate was formed by mixing 85% phosphoric acid with 0.2 volumes of 1.8 M fructose 6-phosphate at 0 °C.[49] The syntheses of P^1-moraprenyl-P^2-(α-L-rhamnopyranosyl-(1 → 3)-α-D-galactopyranosyl)pyrophosphate and P^1-moraprenyl-P^2-(β-D-mannopyranosyl-(1 → 4)-α-L-rhamnopyranosyl-(1 → 3)-α-D-galactopyranosyl)pyrophosphate have been described. Moraprenyl

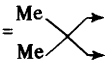
[44] P. J. Garegg and B. Samuelsson, *Carbohydr. Res.*, 1980, **86**, 293.
[45] G. N. Sando and E. M. Karson, *Biochemistry*, 1980, **19**, 3850.
[46] R. Lagunas, *Arch. Biochem. Biophys.*, 1980, **205**, 67.
[47] D. L. Bissett, W. C. Wenger, and R. L. Anderson, *J. Biol. Chem.*, 1980, **255**, 8740.
[48] R. E. Viola and W. W. Cleland, *Biochemistry*, 1980, **19**, 1861.
[49] E. van Schaftingen and H. -G. Hers, *Biochem. Biophys. Res. Commun.*, 1980, **96**, 1524.

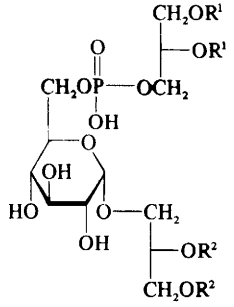
β-D-glucopyranosyl phosphate was also prepared from moraprenyl phosphate and α-D-glucopyranose t-butylorthoacetate. The compounds were required as intermediates for the biosynthesis of the *O*-antigen of *Salmonella senftenberg*.[50] Thio- and dithio-phosphates of the type (12) have been prepared by ring-opening of the 5,6-anhydro-D-glucofuranose derivative with the appropriate thio- or dithio-phosphate.[51] Stereospecific synthesis of α-D-galactopyranosyl phosphate and β-D-mannopyranosyl phosphate have been achieved by treatment of the appropriate 1,2-(isopropyl orthoacetate) with dry phosphoric acid for 1 h at 20 °C, followed by neutralization and chromatographic separation.[52]

Palmitic and oleic acid esters of glucosyl glycerol 6-phosphate of type (13) have been prepared.[53]

D-Glucose 6-[(*R*)-^{16}O, ^{17}O, ^{18}O] phosphate (14) was synthesized and converted into the 4,6-cyclic phosphates (15) and (16) as shown in Scheme 5. It was concluded that cyclization occurred with retention of configuration with better than 94% stereoselectivity.[54] Oxidation of the bicyclophosphite (17) with



(12) X = O or S; R = Et, Ph, or Me_3CCH_2; R, R = 

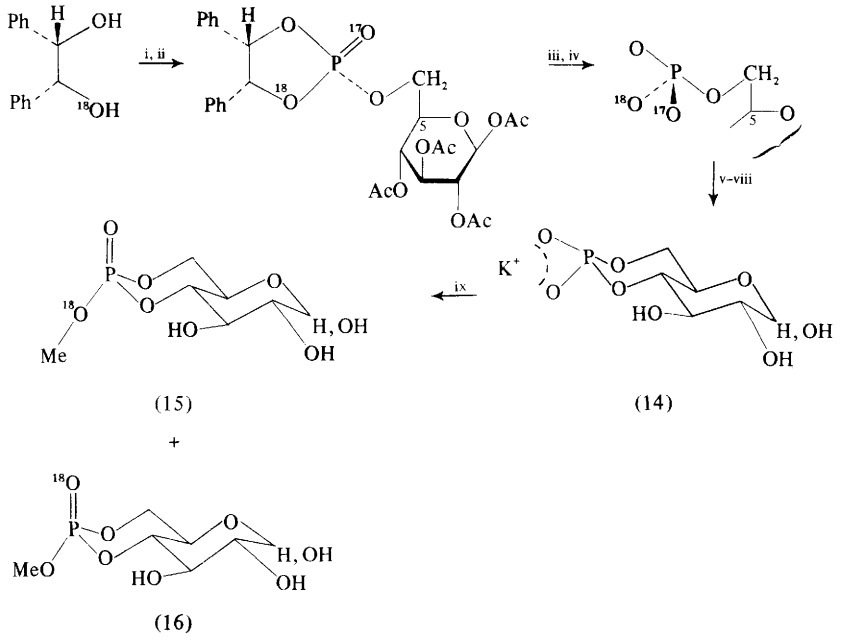


(13) R^1 = oleoyl
R^2 = palmitoyl

[50] L. L. Danilov, T. N. Druzhinina, V. N. Shibaev, and N. K. Kochetkov, *Bioorg. Khim.*, 1980, **6**, 468.
[51] W. Kudelska and M. Michalska, *Carbohydr. Res.*, 1980, **83**, 43.
[52] Yu. L. Sebyakin, L. V. Volkova, E. E. Rusanova, and R. P. Evstigneeva, *Zh. Org. Khim.*, 1979, **15**, 2228 (*Chem. Abstr.*, 1980, **92**, 111 237).
[53] C. A. A. van Boeckel and J. H. van Boom, *Tetrahedron Lett.*, 1980, **21**, 3705.
[54] R. L. Jarvest, G. Lowe, and V. V. L. Potter, *J. Chem. Soc., Chem. Commun.*, 1980, 1142.

25% hydrogen peroxide gave the 3,5-cyclic phosphate (18), whereas treatment of (17) with hydrochloric or hydrobromic acid gave the halogeno-3,5-cyclic phosphites (19).[55] The cyclic triesters of methyl β-D-ribopyranoside (20)–(22) have been prepared. *X*-Ray crystal structures of (20) and (21) were determined.[56]

The synthesis of 1,2 : 3,4-bis-*O*-(*N*-diethylamido)thiophosphates (23) and (24) has been achieved by heating the parent aldose with trisdiethylaminophosphine in dioxan and treating with sulphur.[57] Diastereoisomers of the phosphoramide (25) have been separated and their configurations at phosphorus determined.[58]



Reagents: i, $P^{17}OCl_3$–C_5H_5N; ii, tetra-*O*-acetyl-β-D-glc-*p*-; iii, H_2–Pd; iv, KOMe–MeOH; v, trioctylammonium hydroxide; vi, $(PhO)_2POCl$; vii, Bu^n_3N; viii, Bn^tOK; ix, 18-crown-6–MeI–DMSO

Scheme 5

3 Sulphonates

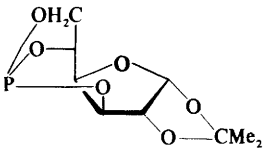
Several 1-*O*-sulphonyl derivatives of D-galactopyranose having a participating benzoyl or *p*-methoxybenzoyl group at *O*-2 were synthesized from the corresponding D-galactopyranosyl chloride derivatives by use of silver toluene-*p*-

[55] M. P. Koroteev and E. E. Nifant'ev, *Dokl. Akad. Nauk SSSR*, 1980, **250**, 1395 (*Chem. Abstr.*, 1980, **93**, 95 500).

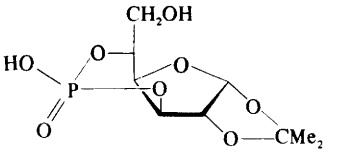
[56] A. C. Bellaart, D. van Aken, H. M. Buck, C. H. Stam, and A. van Herk, *Recl. Trav. Chim. Pays-Bas*, 1979, **98**, 523 (*Chem. Abstr.*, 1980, **92**, 129 255).

[57] V. N. Nabiullin, V. N. Zinin, and E. T. Mukmenev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1979, 2838 (*Chem. Abstr.*, 1980, **92**, 181 568).

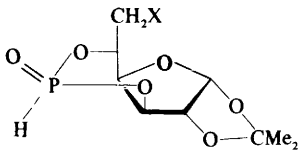
[58] J. A. Gerlt, S. Mehdi, J. A. Coderre, and W. O. Rogers, *Tetrahedron Lett.*, 1980, 2385.



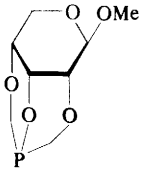
(17)



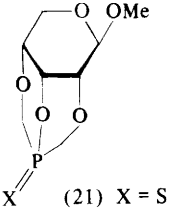
(18)



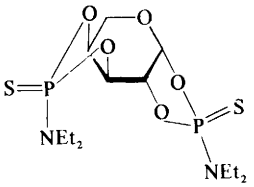
(19) X = Cl or Br



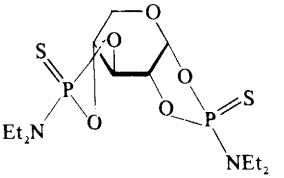
(20)



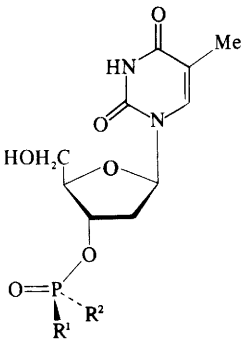
(21) X = S
(22) X = O



(23)



(24)



(25) R^1 = O—  —NO_2, R^2 = NHPh

sulphonate or trifluoroethane sulphonate in acetonitrile.[59] The use of these compounds in glycosidation is mentioned in Chapter 3.

Selective tosylation of methyl α-D-galactopyranoside with toluene-*p*-sulphonyl chloride (2 molar equivalents) in pyridine gave the 2,6-ditosylate (26.6%), the 2,3,6-tritosylate (17.2%), and the 3,6-ditosylate (2.2%).[60] Sucrose with 4 molar equivalents of toluene-*p*-sulphonyl chloride gave sucrose 6,1′,6′-tritosylate (33%) and 2,6,1′,6′-tetratosylate (32%); the latter was previously reported by Long but was here characterized for the first time.[61]

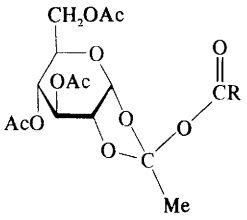
Attempted displacements of triflates by hydride ion are mentioned in Chapter 13.

4 Other Esters

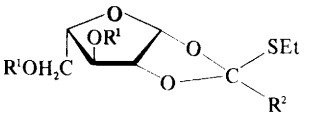
Reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with silver salts of fatty acids gives the reactive orthoanhydrides (26), which hydrolyse to mixed 1,3,4,6- and 2,3,4,6-tetra-*O*-acetyl-D-glucose and give orthoesters with alcohols. Rearrangement to C-1 esters can also be promoted.[62] 1,2-Methyl orthoacylates of D-glucose and higher fatty acids (C_9, C_{15}, C_{17}) have been prepared.[63]

Syntheses of four 1,2-thio-orthoesters of L-arabinose (27)–(30) have been described. They have been used in glycosidation reactions to give 1,2-*trans*-disaccharide derivatives.[64] Conversion of thio-orthoesters to *S*-glycosyl thio-orthoesters by reaction with monosaccharides with one free hydroxy-group and mercury(II) bromide catalysis has been reported.[65] Further examples of 1,2-*O*-(1-cyanoalkylidene) sugars have been prepared[66, 67] (see Vol. 13, p. 56). 1,2-Spiro-orthoesters of 3,4,6-tri-*O*-acetyl-α-D-glucopyranose (31) and (32) have been synthesized by the route shown in Scheme 6. Similarly prepared were the *endo*- and *exo*-phthalate orthoesters (33) and (34). Under various conditions (31) and (32) could not be induced to produce glycosides on heating with propan-2-ol. When tin(IV) chloride was added, however, good yields of the isopropyl α-D-glucoside were obtained, anomerization occurring that was enhanced by addition of carboxylic acids. The phthaloyl orthoester, by contrast, gave 2-*O*-phthaloyl α-D-glucopyranosyl chlorides with tin(IV) chloride.[68]

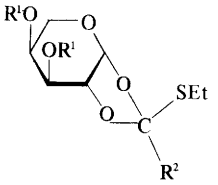
[59] H. F. Vernay, E. S. Rachaman, R. Eby, and C. Schuerch, *Carbohydr. Res.*, 1980, **78**, 267.
[60] B. Matsuhiro and A. B. Zanlungo, *Carbohydr. Res.*, 1980, **81**, 330.
[61] J. M. Ballard, L. Hough, S. P. Phadnis, and A. C. Richardson, *Carbohydr. Res.*, 1980, **83**, 138.
[62] G. Wulff and U. Schröder, *Chem. Ber.*, 1980, **113**, 2760.
[63] A. V. Voitenko, L. V. Volkova, and R. P. Evstigneeva, *Zh. Obshch. Khim.*, 1980, **50**, 162 (*Chem. Abstr.*, 1980, **93**, 8395).
[64] N. F. Balan, L. V. Backinowsky, and N. K. Kochetkov, *Bioorg. Khim.*, 1980, **6**, 1657.
[65] L. V. Backinowsky, Yu. E. Tsvetkov, N. E. Bairamova, N. F. Balan, and N. K. Kochetkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1980, 1905 (*Chem. Abstr.*, 1980, **93**, 220 988).
[66] V. I. Betaneli, M. V. Ovchinnikov, L. V. Backinowsky, and N. K. Kochetkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1979, 2751 (*Chem. Abstr.*, 1980, **92**, 147 070).
[67] M. Martin-Lomas, M. Bernabe, and M. E. Chacon-Fuertes, *An. Quim.*, 1979, **75**, 718 (*Chem. Abstr.*, 1980, **92**, 147 064).
[68] R. U. Lemieux and O. Hindsgaul, *Carbohydr. Res.*, 1980, **82**, 195.



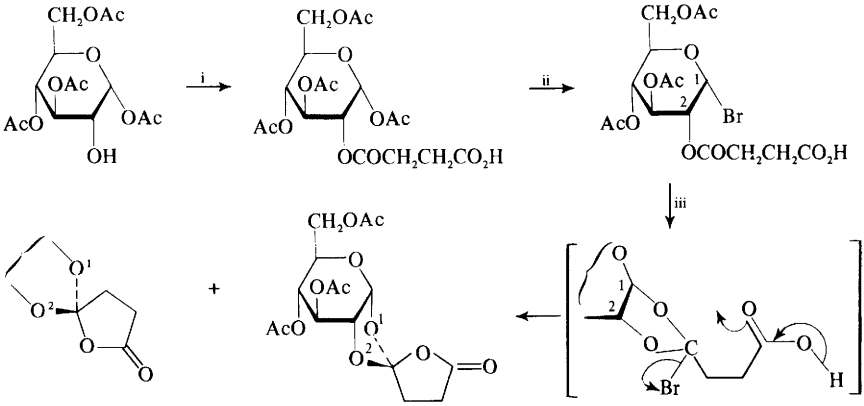
(26)



(27) R^1 = Ac, R^2 = Me
(28) R^1 = Bz, R^2 = Ph



(29) R^1 = Ac, R^2 = Me
(30) R^1 = Bz, R^2 = Ph



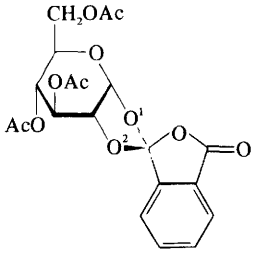
(32) *endo* (31) *exo*

Reagents: i, succinic anhydride–4-dimethylaminopyridine–py; ii, HBr–HOAc-Ac_2O–CH_2Cl_2; iii, Et_4NBr–CH_3CN–mol. sieve–lutidine

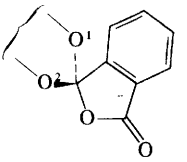
Scheme 6

Reaction of indoles with glycosyl halides in the presence of silver oxide and molecular sieve as catalysts gave orthoamides of the type shown in (35) and indole nucleosides (see Chapter 19).[69]

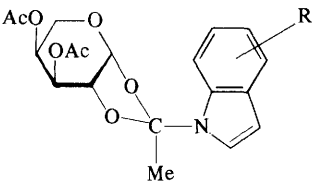
[69] T. N. Sokolova, V. E. Shevchenko, and M. N. Preobrazhenskaya, *Carbohydr. Res.*, 1980, **83**, 249.



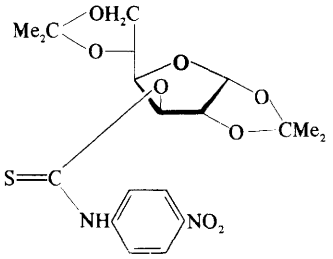
(33) *exo*



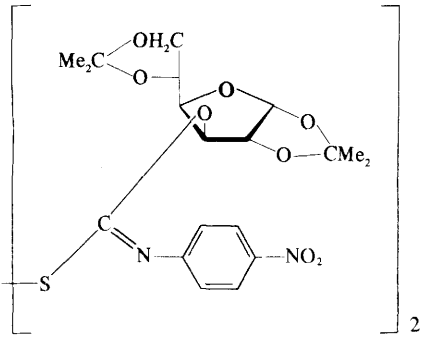
(34) *endo*



(35) R = H or NO_2



(36)



(37)

Sulphation of sucrose with pyridine–sulphur trioxide in dimethylformamide gave the octasulphate, which gave crystalline potassium, caesium, rubidium, and ammonium salts.[70] A new sulphated glycosphingolipid, *N*-acetylglucosamine 6-sulphate-β-(1 → 3)-Gal-β-(1 → 4)-Glc-β-(1 → 1)-ceramide, has been isolated from hog gastric mucosa.[71] Treatment of the aryl thiocarbamate (36) with triphenylbismuth carbonate gave the dimer (37) in 86% yield, although neither the thiocarbonyl groups of xanthates nor dialkylaminothiocarbamates were oxidized by this reagent.[72] A study of photolysis of mono- and di-xanthates of protected furanoid and pyranoid sugars has shown that isopropylidene acetals are unstable in methanol, particularly in the presence of air. 1,2-*O*-Isopropylidene acetals were much more stable to these conditions than the 5,6-acetals. Some de-xanthation also occurs.[73]

[70] K. Ochi, Y. Watanabe, K. Okui, and M. Shindo, *Chem. Pharm. Bull.*, 1980, **28**, 638.
[71] A. Slomiany, B. L. Slomiany, and C. Annese, *Eur. J. Biochem.*, 1980, **109**, 471.
[72] D. H. R. Barton, D. J. Lester, W. B. Motherwell, and M. T. Barros Papoula, *J. Chem. Soc., Chem. Commun.*, 1980, 246.
[73] G. Descotes, A. Faure, B. Kyrczka, and M. N. Bouchu, *Bull. Acad. Pol. Sci. Chim.*, 1979, **27**, 173 (*Chem. Abstr.*, 1980, **92**, 76 819).

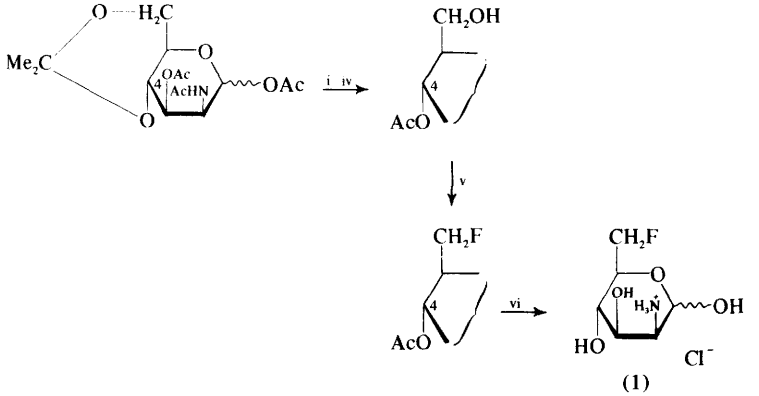
7

Halogeno-sugars

A review of hydrogenolysis of organic halides, including some carbohydrate examples, has appeared.[1] A detailed study of the solvolysis of anomeric glucopyranosyl fluorides in ethanol and 2,2,2-trifluoroethanol has been carried out.[2]

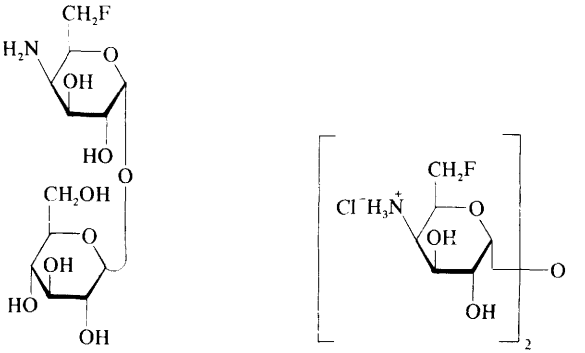
Xenon difluoride–boron trifluoride etherate has been used to obtain 2-deoxy-2-fluoro-glycosyl fluorides from glycals. 3,4,6-Tri-*O*-acetyl-D-glucal gave 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α- and -β-D-glucopyranosyl fluoride (73%) in a ratio of ~5:1, and the corresponding β-D-mannosyl fluoride in 5% yield. 2,3,6-Tri-*O*-acetyl-D-galactal gave corresponding stereoisomers in a similar ratio. Xenon difluoride has the advantage over other reagents previously used for this reaction in being an easily handled crystalline solid. The adducts are readily deacetylated without affecting the fluoro-groups.[3] Improved preparations of 2-deoxy-2-[^{18}F]fluoro-D-glucose and 2-deoxy-2-[^{131}I]iodo-D-glucose have been reported.[4] Treatment of methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-toluene-*p*-sulphonyl-α-D-glucopyranoside with tetra-n-butylammonium fluoride led to the corresponding 3-benzamido-2,3-dideoxy-2-fluoro-altroside, *via* the 2,3-epimino-alloside, thus illustrating the Fürst–Plattner diaxial ring-opening mode.[5] The synthesis and incorporation into animals of 3-deoxy-3-[^{18}F]fluoro-D-glucose has been reported. Displacement of the 3-*O*-triflate of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose by Cs^{18}F, followed by removal of the blocking groups, was employed.[6] The same compound has also been prepared using labelled tetraethylammonium fluoride.[7] Amberlyst A26(F^-) resin, previously dehydrated by azeotropy, displaces both primary and secondary tosyl groups to yield deoxy-fluoro-sugars. Thus 1,2:5,6-di-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-α-D-allofuranose gave the corresponding 3-deoxy-3-fluoro-glucose derivative in 72% yield, whereas 1,2:3,4-di-*O*-isopropylidene-6-*O*-toluene-*p*-sulphonyl-α-D-galactopyranose gave the 6-deoxy-6-fluoro-compound in 75% yield.[8] Methyl 4-deoxy-4-fluoro-α- and -β-D-galactopyranoside have been

[1] A. R. Pinder, *Synthesis*, 1980, 425.
[2] M. L. Sinnott and W. P. Jencks, *J. Am. Chem. Soc.*, 1980, **102**, 2026.
[3] W. Korytnyk and S. Valentekovic-Horvat, *Tetrahedron Lett.*, 1980, **21**, 1493.
[4] J. S. Fowler, R. E. Lade, R. R. MacGregor, C. Shiue, C. -N. Wan, and A. P. Wolf, *J. Labelled Compd. Radiopharm.*, 1979, **16**, 7 (1, Second Int. Symp. Radiopharm. Chem.) (*Chem. Abstr.*, 1980, **92**, 76 810).
[5] L. Hough, A. A. E. Penglis, and A. C. Richardson, *Carbohydr. Res.*, 1980, **83**, 142.
[6] T. J. Tewson, M. J. Welch, and M. E. Raichle, *J. Labelled Compd. Radiopharm.*, 1979, **16**, 10 (*Chem. Abstr.*, 1980, **92**, 59 125).
[7] S. J. Gatley and W. J. Shaughnessy, *Int. J. Appl. Radiat. Isot.*, 1980, **31**, 339 (*Chem. Abstr.*, 1980, **93**, 114 864).
[8] S. Colonna, A. Re, G. Gelbard, and E. Cesarotti, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2248.



Reagents: i, HOAc–H_2O; ii, TrCl–py; iii, Ac_2O–py; iv, H_2–Pd; v, Et_2NSF_3–diglyme; vi, 3 M-HCl

Scheme 1



(2) (3)

synthesized by standard methods and tested, with other 4-substituted galactosides, as substrates of β-D-galactosidase.[9] 2-Amino-2,6-dideoxy-6-fluoro-D-mannopyranose hydrochloride (1), synthesized by the route shown in Scheme 1, has been shown to exhibit anti-leukemia activity.[10] The 4-amino-4,6-dideoxy-6-fluoro-compounds (2) and (3) have been prepared by standard procedures.[11]

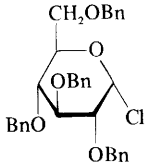
A method for introducing halogens by use of triflates and tetrabutylammonium halides has been published. Excellent yields were obtained for many primary chlorides, bromides, and iodides and for some secondary compounds. However, unfavoured displacements, for example, at C-3 of D-allofuranose compounds gave poorer yields, especially with the weaker nucleophiles bromide and chloride.[12] Synthesis of glycosyl chlorides has been achieved by sequential use of

[9] J. E. N. Shin, A. Maradufu, J. Marion, and A. S. Perlin, *Carbohydr. Res.*, 1980, **84**, 328.
[10] M. Sharma and W. Korytnyk, *Carbohydr. Res.*, 1980, **83**, 163.
[11] A. F. Hadfield, L. Hough, and A. C. Richardson, *Carbohydr. Res.*, 1980, **80**, 123.
[12] R. W. Binkley, M. G. Ambrose, and D. G. Hehemann, *J. Org. Chem.*, 1980, **45**, 4387.

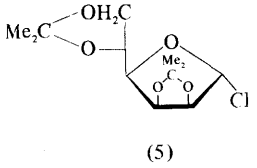
$$ROH \longrightarrow ROTl^{I} \xrightarrow{SOCl_2} ROSOCl \xrightarrow{TlCl} RCl + SO_2$$

R = glycosyl

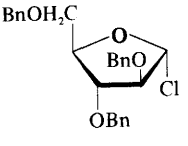
Scheme 2



(4)



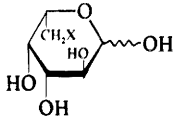
(5)



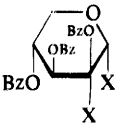
(6)

thallium ethoxide and thionyl chloride on aldoses blocked at all positions except the anomeric centre. The reaction was postulated to follow Scheme 2. By this means the glycosyl chlorides (4)–(6) were prepared.[13] Treatment of 1,2,3,4,6-penta-*O*-benzoyl-β-D-glucopyranose with titanium(IV) chloride gives instantaneously the β-glucosyl chloride, which is slowly anomerized by the $BzOTiCl_3$ formed in the reaction. The kinetics and Hammett factors were obtained for the reaction by monitoring at 1520 and 1110 cm^{-1} for the catalyst and C-1α-H, respectively. The reaction of the corresponding acetylated compound catalysed by $AcOTiCl_3$ was also studied.[14] Reaction of 3,4,6-tri-*O*-acetyl-D-glucal with iodine and zinc or mercury(II) chloride in the presence of silver salts in acetonitrile gave a 1:5 mixture of 3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-β-D-glucopyranosyl chloride and -α-D-mannopyranosyl chloride.[15] Addition of halogens to 3,4-di-*O*-acetyl-L-fucal followed by hydrolysis has been used to prepare 2-chloro-, 2-bromo-, and 2-iodo-2-deoxy-L-fucose. The 6-deoxy-6-halogeno-compounds (7)–(10) were prepared from 1,2:3,4-di-*O*-isopropylidene-α-L-galactose. Corresponding compounds in the D-series were also prepared. 6-Chloro-, 6-bromo, and 2-bromo-L-fucose inhibited incorporation of L-[^{3}H]fucose into macromolecular compounds of SW613 human mammary tumour cells. 6-Fluoro-L- and -D-fucose inhibited incorporation of D-[^{3}H]galactose and L-[^{3}H]fucose into human mammary tumour cells; both these fluoro-sugars were converted to nucleotides which led to incorporation into the macromolecular fraction of SW613 cells.[16] Further work on the addition of chlorine and bromine to 2,3,4-tri-*O*-benzoyl-D-xylal yielding the *cis*-halogenated products (11) and (12) has been carried out. Treatment of (11) and (12) with titanium(IV) chloride caused anomerization.[17] 2′,3′-Dichloro-2′,3′-dideoxy-uridine and its 3′-epimer have been synthesized by the routes shown in Schemes 3 and 4.[18]

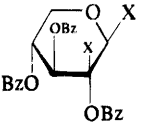
[13] A. Granata and A. S. Perlin, *Carbohydr. Res.*, 1980, **86**, 305.
[14] Z Csürös, G. Deák, L. Fenichel, P. Bakó, S. Holly, and I. Gyurkovics, *Carbohydr. Res.*, 1980, **82**, 273.
[15] P. J. Garegg and B. Samuelsson, *Carbohydr. Res.*, 1980, **84**, C1.
[16] J. R. Sufrin, R. J. Bernacki, M. J. Morin, and W. Korytnyk, *J. Med. Chem.*, 1980, **23**, 143.
[17] F. W. Lichtenthaler, T. Sakakibara, and E. Egert, *Chem. Ber.*, 1980, **113**, 471.
[18] S. David and G. De Sennyey, *Carbohydr. Res.*, 1980, **82**, 45.



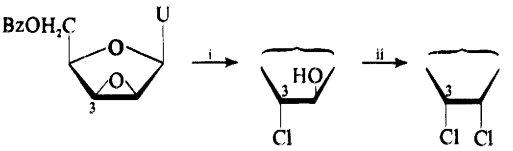
(7) X = F
(8) X = Cl
(9) X = Br
(10) X = I



(11) X = Cl or Br

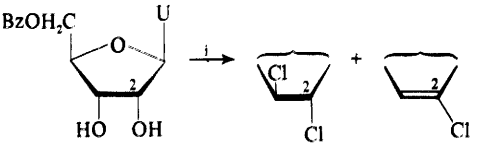


(12) X = Cl or Br



Reagents: i, HCl; ii, $(EtO)_3P{=}O{-}CCl_4{-}PPh_3$

Scheme 3

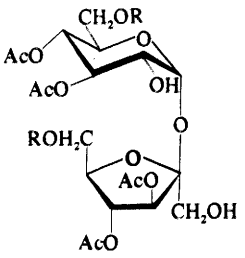


Reagent: i, $(EtO)_3P{=}O{-}CCl_4{-}PPh_3$

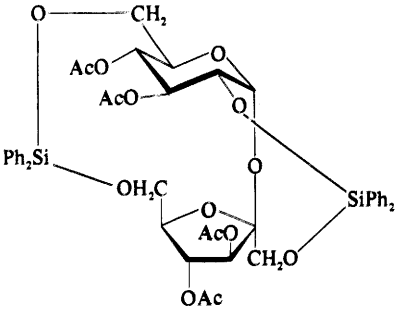
Scheme 4

1′-Chloro-1′-deoxy-sucrose has been prepared *via* 6,1′,6′-tri-*O*-(2,4,6-trimethylbenzenesulphonyl) sucrose and its rate of hydrolysis compared with those of sucrose and 1′-deoxy-sucrose.[19] The sucrose derivative (13), prepared *via* the 1′,2-*O*-diphenylsilylene derivative (14), gave 1-chloro-1-deoxy-β-D-fructofuranosyl 2-chloro-2-deoxy-α-D-mannopyranoside on treatment with sulphuryl chloride followed by lithium chloride. A similar reaction on the partial acetate (15) gave 1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl 2,6-dichloro-2,6-dideoxy-α-D-mannopyranoside.[20,21] Selective chlorination at C-1′ was achieved when 3,4,6,3′,4′,6′-hexa-*O*-acetyl-sucrose was treated with sulphuryl chloride in a mixture of pyridine and chloroform.[21] Reaction of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-(chlorosulphonyl)-α-D-glucopyranoside with lithium chloride in HMPT gave the corresponding 2-chloro-2-deoxy-mannoside, which was converted to the parent glycoside. When lithium bromide, sodium azide, sodium chloride, or sodium benzoate were used the 2-hydroxy-compound was obtained.[21] Sucrose

[19] R. D. Guthrie, I. D. Jenkins, and J. J. Watters, *Aust. J. Chem.*, 1980, **33**, 2487.
[20] M. R. Jenner and R. Khan, *J. Chem. Soc., Chem. Commun.*, 1980, 50.
[21] R. Khan, M. R. Jenner, and H. Lindseth, *Carbohydr. Res.*, 1980, **78**, 173.



(13) R = Ac
(15) R = H



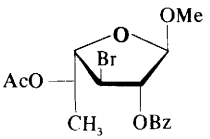
(14)

with methanesulphonyl chloride in DMF gives 6,6′-dichlorosucrose directly. The product was isolated without resort to column chromatography. The same product was obtained by using triphenylphosphine-*N*-chlorosuccinimide in DMF. 6,6′-Dibromosucrose was similarly prepared.[22] *allo*-Sucrose with sulphuryl chloride at −50 °C gave the 6,6′-dichloro-derivative.[23]

The syntheses of α-D-lyxofuranosyl bromide[24] and α-D-mannofuranosyl bromide[25] have been achieved *via* boronate esters (see Chapter 16).

The ring opening of benzylidene acetals with *N*-bromosuccinimide has been studied. 1,6-Anhydro-2,3-*O*-benzylidene-β-D-mannose gave 1,6-anhydro-2-*O*-benzoyl-3-bromo-3-deoxy-β-D-altrose and methyl 2,3 : 5,6-di-*O*-benzylidene-α-D-mannofuranose gave methyl 3,6-dibromo-2,5-di-*O*-benzoyl-3,6-dideoxy-α-D-altrofuranoside. The two products were easily converted to the corresponding deoxy-sugars. The 3-bromofucofuranoside (16) was obtained from the acetal (17). Methyl 2,3 : 3,5-di-*O*-benzylidene-α-D-mannopyranoside gave a mixture of the dibromides (18)–(20).[26] Selective reaction of partially silylated sugars by triphenylphosphine–diethyl azidodicarboxylate in the presence of hydrogen bromide or methyl iodide has led to the synthesis of bromo- or iodo-deoxy-sugars. Thus methyl 2,6-di-*O*-(t-butyldimethyl)silyl-β-D-glucopyranoside gave methyl 3-bromo(iodo)-3-deoxy-β-D-allopyranoside, whereas the α-anomer gave methyl 4-bromo(iodo)-4-deoxy-α-D-galactopyranoside. Further reactions of this type are mentioned in Chapter 4.[27] Photobromination of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose using either *N*-bromosuccinimide or bromine in carbon tetrachloride gave the various bromo- and bromo-deoxy-sugars shown in Scheme 5.[28] A similar reaction was carried out on 1,2,3,4,6-penta-*O*-benzoyl-β-D-glucopyranose to give the 5-bromo-sugar (21) in 77% yield. The α-anomer gave only 22% 5-bromo-derivative in a slow reaction.[29] Photobromination of aryl 2,3,4,6-

[22] R. Khan, C. L. Bhardwaj, K. S. Mufti, and M. R. Jenner, *Carbohydr. Res.*, 1980, **78**, 185.
[23] L. Hough and E. O'Brien, *Carbohydr. Res.*, 1980, **84**, 95.
[24] W. V. Dahlhoff and R. Köster, *Synthesis*, 1980, 936.
[25] W. V. Dahlhoff, A. Geisheimer, and R. Köster, *Synthesis*, 1980, 935.
[26] J.-C. Florent and C. Monneret, *Carbohydr. Res.*, 1980, **85**, 243.
[27] H. H. Brandstetter and E. Zbiral, *Helv. Chim. Acta*, 1980, **63**, 327.
[28] R. Blattner and R. J. Ferrier, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1523.
[29] R. J. Ferrier and P. C. Tyler, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1528.



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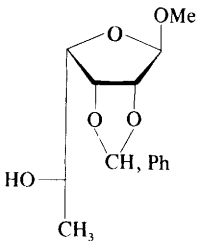

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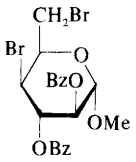

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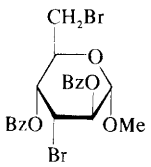

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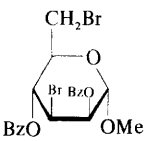

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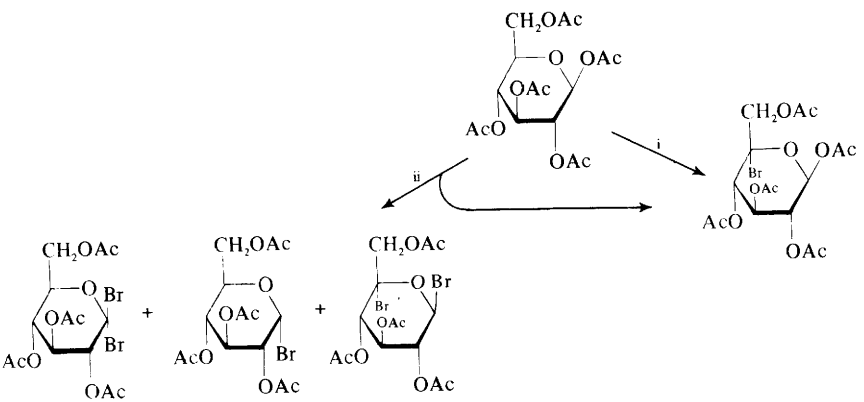
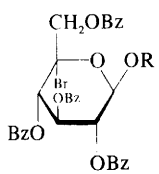
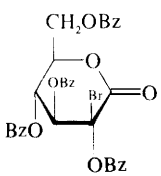


Reagents: i, NBS–CCl_4, $h\nu$; ii, Br_2–CCl_4, $h\nu$

Scheme 5



(21) R = Bz
(22) R = Ar



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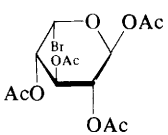
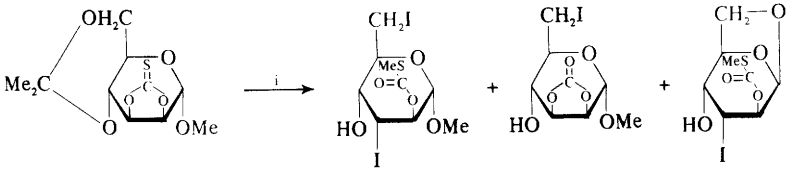


(24)

tetra-*O*-benzoyl-β-D-glucopyranoside also gave the 5-bromo-compound (22) useful for preparing idosides (see Chapter 3), whereas the corresponding methyl glucoside gave the 2-bromo-lactone (23) in 48% yield.[30] Further brominations under radical conditions of 1,2,3,4-tetra-*O*-acetyl-β-D-xylopyranose[31] and of 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-glucopyranose[32] have been carried out. The former gave the 5-bromo-pyranose (24) while the latter was brominated at C-6.

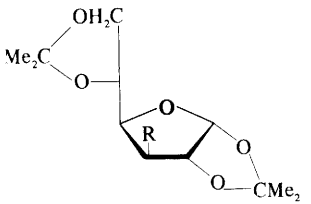
Displacements of the halogen of 6′-chloro-6′-deoxyraffinose by bromide, iodide, and azide ions have been carried out.[33]



Reagent: i, MeI, 80 °C

Scheme 6

The reactions of trimethylsilyl iodide with carbohydrate derivatives have been examined. Hexopyranose penta-acetates give the corresponding tetra-*O*-acetyl-glycosyl iodides as do acetylated glycosides. Glycosidic bond cleavage occurs in disaccharides to yield the corresponding glycosyl iodides. *trans*-Iodohydrins are obtained from epoxides. Trimethylsilyl bromide reacts in a similar fashion.[34] Isolated primary and secondary hydroxy-groups are converted to iodo-groups with inversion of configuration by treatment with triphenylphosphine–iodine–imidazole or triphenylphosphine–2,4,5-tri-iodoimidazole. Use of lower temperatures allows iodination of primary hydroxy-groups selectively. Compounds synthesized included methyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-α-D-manno-pyranoside, 3-deoxy-3-iodo-1,2:5,6-di-*O*-isoproplidene-α-D-allo-furanose, and methyl 5-deoxy-5-iodo-2,3,-*O*-isopropylidene-β-D-ribofuranoside.[35] The reaction



(25) R = $PO(NEt_2)_2$

[30] R. J. Ferrier and P. C. Tyler, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2762.
[31] R. J. Ferrier and P. C. Tyler, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2767.
[32] R. J. Ferrier and R. H. Furneaux, *Aust. J. Chem.*, 1980, **33**, 1025.
[33] L. Hough, A. C. Richardson, and M. A. Salam, *Carbohydr. Res.*, 1980, **80**, 117.
[34] J. Thiem and B. Meyer, *Chem. Ber.*, 1980, **113**, 3075.
[35] P. J. Garegg and B. Samuelsson, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2866.

of methyl 4,6-*O*-isopropylidene-2,3-thionocarbonyl-α-D-mannopyranoside with methyl iodide is shown in Scheme 6. Iodination at C-6 was believed to be caused by the hydrogen iodide liberated in the reaction.[36] The preparation of 3-deoxy-3-iodo-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose has been achieved by quaternization of the phosphondiamide (25) with methyl iodide, followed by thermal decomposition.[37]

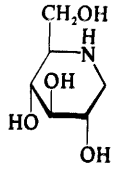
[36] J. J. Patroni, B. W. Skelton, R. V. Stick, and A. H. White, *Aust. J. Chem.*, 1980, **33**, 987.
[37] S. A. Lysenko, M. P. Koroteev, S. A. Ermishkina, A. S. Shashkov, E. E. Nifant'ev, and N. K. Kochetkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1979, 2391 (*Chem. Abstr.*, 1980, **92**, 129 205).

8

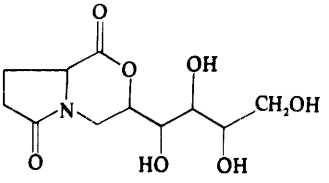
Amino-sugars

1 Introduction

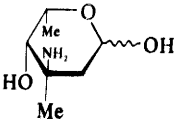
3-Amino-3-deoxy-α,α-trehalose has been identified as a fermentation product of *Nocardiopsis trehalosei* and like the other positional isomers (2- and 4-amino-trehaloses) it shows only weak antibiotic activity.[1] 1,5-Dideoxy-1,5-imino-D-glucitol (1) has been isolated from a *Streptomyces* species,[2] and is identical to 1-deoxynojirimycin obtained from the antibiotic nojirimycin (S. Inouye *et al.*, *Tetrahedron*, 1968, **23**, 2125), the *manno*-isomer was previously reported as being isolated from a legume (Vol. 13, p. 78). A polyol isolated from plant tumours has been termed agropine (2) and may be considered as a condensation product of a hexose and glutamic acid, but no stereochemical data have been given.[3] The C-3 epimer (3) of vancosamine has been found in a glycopeptide antibiotic,[4] and 2-amino-2-deoxy-L-gulose is a component of the antibiotic adenomycin.[5]



(1)



(2)



(3)

Whilst human erythrocytes contain *N*-acetyl-neuraminic acid as the only sialic acid, BALB/c mouse erythrocytes contain 9-*O*-acetyl-*N*-acetyl-neuraminic acid as their dominant sialic acid, which has not previously been encountered.[6] The mutarotation of *N*-acetyl-α-D-neuraminic acid was previously thought to be too fast to measure, but enzymic liberation of the free α-anomer in an n.m.r. tube has permitted this to be measured. Unexpectedly, at pH 5.4 mutarotation is quite slow, with a half-life of about 80 min for the α-anomer.[7] MO calculations

[1] L. A. Dolak, T. M. Castle, and A. L. Laborde, *J. Antibiot.*, 1980, **33**, 690.
[2] S. Murao and S. Miyata, *Agric. Biol. Chem.*, 1980, **44**, 219.
[3] D. T. Coxon, A. M. C. Davies, C. R. Fenwick, R. Self, J. L. Firmin, D. Lipkin, and N. F. Janes, *Tetrahedron Lett.*, 1980, **21**, 495.
[4] M. Debono and R. M. Molloy, *J. Org. Chem.*, 1980, **45**, 4685.
[5] T. Ogita, N. Otake, Y. Miyazaki, H. Yonehara, R. D. McFarlane, and C. J. McNeal, *Tetrahedron Lett.*, 1980, **21**, 3203.
[6] G. Reuter, J. F. G. Vliegenthart, M. Wember, R. Schauer, and R. J. Howard, *Biochem. Biophys. Res. Commun.*, 1980, **94**, 567.
[7] H. Friebolin, M. Supp, R. Brossmer, G. Keilich, and D. Ziegler, *Angew. Chem. Int. Ed. Engl.*, 1980, **19**, 208.

have been made on 2-amino-2-deoxy-β-D-galactopyranose and the H-bonds and weak interactions binding the most stable conformation were identified.[8]

2 Synthesis

The synthesis of several 2-amino-2-deoxy-heptoses has been achieved by ascent of the series by the aminonitrile method starting from D-glucose, D-mannose, and D-galactose.[9] The Wittig reaction has been employed for chain extension in the synthesis of a hikosamine derivative, methyl 4-acetamido-2,3,6,7,8,9,10,11-octa-*O*-acetyl-4-deoxy-α-D-*glycero*-D-*galacto*-D-*gluco*-undecapyranose (4). The crucial step in the synthesis was the condensation between the 6-*aldehydo*-derivative (5) and the Wittig reagent derived from 2,3 : 4,5-di-*O*-cyclohexylidene-1-deoxy-1-iodo-D-arabinitol (6). The derived product (7) was then further elaborated by standard reactions to give the undecapyranoside (4).[10] The use of the 1-ethoxyvinyl carbanion for the chain extension of 6-aldehyde derivatives has been described leading to the keto-azides (8), which are useful for the synthesis of lincosamine and its analogues.[11]

The introduction of an amino-group into carbohydrates has been achieved by displacement of a tosyloxy or similar leaving group by participation of a neighbouring *O*-carbamoyl group (—CONHR). Thus, 2-amino-1,6-anhydro-2-deoxy-β-D-mannose was prepared from 1,6 : 3,4-dianhydro-2-*O*-tosyl-β-D-glucopyranose as outlined in Scheme 1.[12] A similar reaction has been proposed by Barton and Motherwell.[13]

There has been a continuing interest in syntheses of 3-amino-2,3,6-trideoxy-hexoses such as daunosamine (9), acosamine (10), *etc.* In an interesting paper by Fronza *et al.*,[14] the two sugars have been synthesized from the non-carbohydrate compound (11), which was obtained in 25–30% yield from the incubation of cinnamaldehyde with acetaldehyde in the presence of bakers yeast (Scheme 2). The crucial amino-lactone (12) was also synthesized from L-threonine.[14] The same authors[15] have also completed their synthesis of *N*-benzoyl-L-ristosamine (3-benzamido-2,3,6-trideoxy-L-*ribo*-hexose) from 3-benzamido-2,3,6-trideoxy-L-*xylo*-hexono-1,5-lactone (Vol. 13, p. 79). An alternative synthesis of methyl *N*-acetyl-α-L-acosaminide (13) has been described by reduction of the appropriate acetylated oxime by diborane. The thioglycoside (14) was also prepared.[16]

[8] M. Cebe, *Fen. Fak. Derg. Seri A* (*Ege Univ.*), 1978, **2**, 235 (*Chem. Abstr.*, 1980, **93**, 114881).

[9] M. Gomez Guillen, J. A. Galbis Perez, and J. L. Jimenez Requejo, *An. Quim.*, 1979, **75**, 426 (*Chem. Abstr.*, 1980, **92**, 42288); J. A. Galbis Perez, R. M. Pinto Corraliza, E. Roman Galan, and M. Gomez Guillen, *An. Quim.*, 1979, **75**, 387 (*Chem. Abstr.*, 1980, **92**, 59138).

[10] J. A. Secrist and K. D. Barnes, *J. Org. Chem.*, 1980, **45**, 4526.

[11] I. Hoppe and U. Schöllkopf, *Liebigs Ann. Chem.*, 1980, 1474.

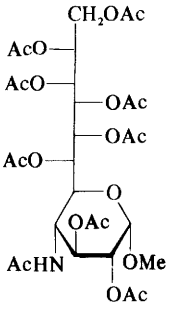
[12] M. Černý, H. Večerková, I. Černý, and J. Pacák, *Collect. Czech. Chem. Commun.*, 1980, **45**, 1837.

[13] D. H. R. Barton and W. B. Motherwell, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1124.

[14] G. Fronza, C. Fuganti, and P. Grasselli, *J. Chem. Soc., Chem. Commun.*, 1980, 442.

[15] G. Fronza, C. Fuganti, and P. Grasselli, *Tetrahedron Lett.*, 1980, **21**, 2999.

[16] I. Pelyvás and R. L. Whistler, *Carbohydr. Res.*, 1980, **84**, C5.



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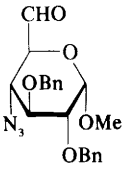

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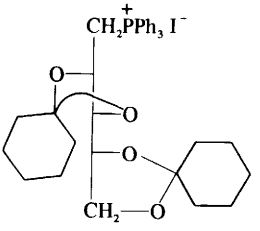

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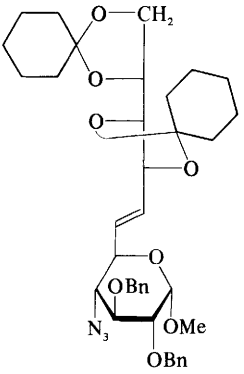

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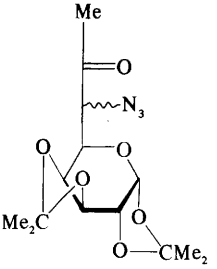

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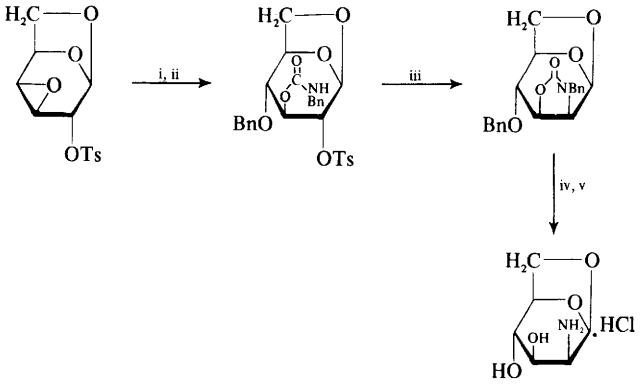
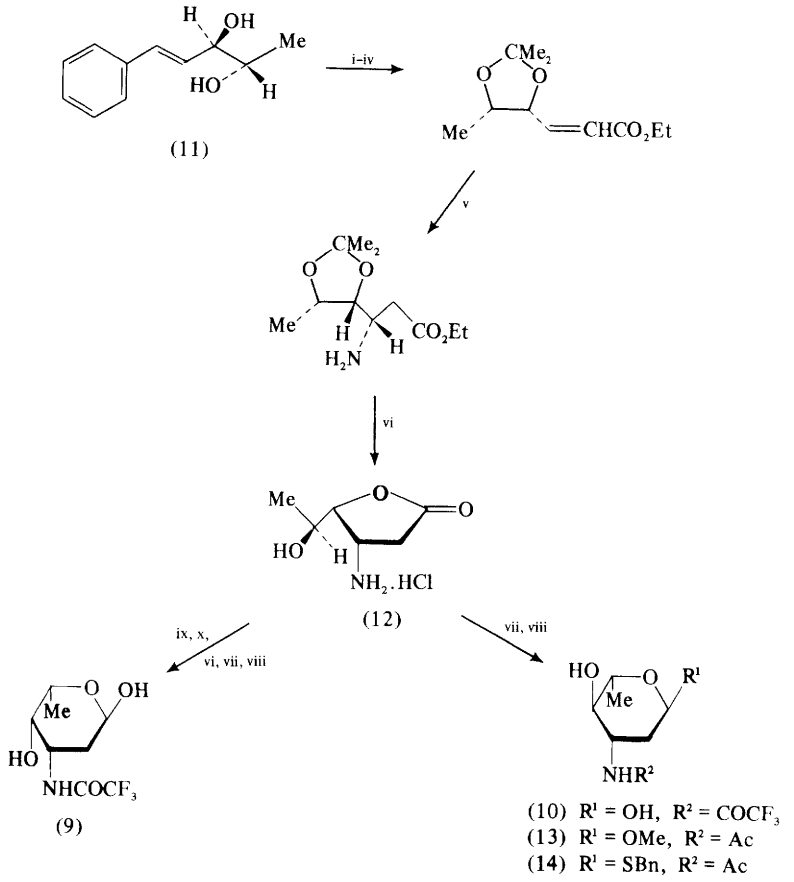


Reagents: i, NaOBn; ii, BnNCO; iii, KOBu^t; iv, NaOH; v, Pd–H_2–HCl

Scheme 1



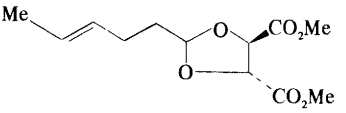
Reagents: i, $Me_2C(OMe)_2$-H^+; ii, O_3; iii, Ph_3P; iv, $Ph_3P{=}CHCO_2Et$; v, NH_3-MeOH; vi, H_3O^+; vii, $O(COCF_3)_2$; viii, DIBAL; ix, MsCl; x, NaOAc

Scheme 2

Asymmetric induction has been employed in the synthesis of methyl α-L-daunosaminide and its D-*xylo*-isomer from the non-chiral acetal 1,1-dimethoxyhex-4-ene. The first step is an acetal exchange reaction with diethyl (+)-tartrate to give the acetal (15), followed by functionalization of (15) by allylic tosylamination and hydroxylation of the double bond.[17]

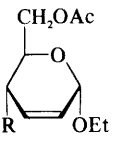
Full details of the synthesis of 2,3,4,6-tetradeoxy-3-trifluoroacetamido-L-*threo*- and -L-*erythro*-hexopyranoses (Vol. 13, p. 81) have been published[18] and the DL-*threo*-isomer has also been synthesized.[19]

[17] I. Dyong and R. Wiemann, *Chem. Ber.*, 1980, **113**, 2666; *ibid.*, p. 1592.
[18] H. H. Baer and H. R. Hanna, *Can. J. Chem.*, 1980, **58**, 1751.
[19] M. Chmielewski, *Pol. J. Chem.*, 1980, **54**, 1197.

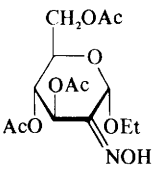


(15)

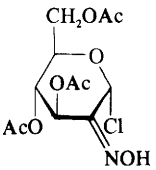
Allylic nucleophilic displacement reactions at C-4 of ethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (16) have been accomplished *via* a complex formed by reaction with $(Ph_3P)_4Pd$. The complex reacted with several amines to give a series of 4-amino-derivatives (17). The use of dibenzylamine resulted in the formation of a side product, the 2-dibenzylamino-3-ene.[20] Similarly, the 3-acetoxy-group of the 2-oxime (18) undergoes displacement by nucleophiles (N_3^-, potassium phthalimide, *etc.*) giving, ultimately, a variety of aminodeoxy-α-D-glycopyranosides.[21] 5-Amino-5-deoxy-D-galactose,[22] 3-amino-3-deoxy-D-glucose, and 3-amino-3-deoxy-D-gulose[23] have been made by reduction of the corresponding oximes and catalytic reduction (Pt) of (19), which exists as a dimer, gives 2-amino-1,5-anhydro-2-deoxy-D-glucitol in the absence of simple alcohols, but the corresponding 2-amino-2-deoxy-α-D-glucopyranosides in their presence.[24]



(16) R = OAc
(17) R = N <



(18)



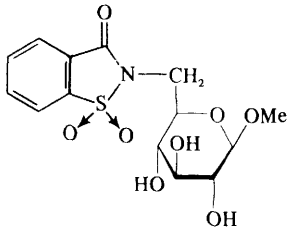
(19)

The syntheses of 3-amino-1,2-*O*-isopropylidene-α-L-erythrofuranose and -β-D-threofuranose are reported *via* azide displacement reactions[25] and the use of sodium saccharin as a nucleophilic agent has given the 6-substituted glucopyranoside (20).[26] The syntheses of several derivatives of 6-amino-6-deoxy-5-thio-D-glucofuranoses has been reported by ring-opening of an 5,6-episulphide[27] and 3,4-dideoxy-3-dimethylamino-D-*xylo*-hexose has been synthesized *via* 1,6 : 2,3-dianhydro-4-deoxy-β-D-*ribo*-hexopyranose.[28] Synthesis of *N*-acetyl-9-

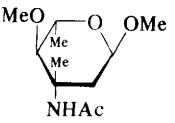
[20] H. H. Baer and Z. S. Hanna, *Carbohydr. Res.*, 1980, **78**, C11.
[21] R. U. Lemieux, F. F. Z. Georges, and Z. Smiatacz, *Heterocycles*, 1979, **13**, 169 (*Chem. Abstr.*, 1980, **93**, 26 685).
[22] H. Paulsen, Y. Hayauchi, and V. Sinnwell, *Chem. Ber.*, 1980, **113**, 2601.
[23] R. C. Tweit and H. W. Sause, *Carbohydr. Res.*, 1980, **84**, 175.
[24] T. L. Nagabhushan, *Can. J. Chem.*, 1980, **58**, 2720.
[25] J. Jarý, M. Masojidková, I. Kozák, M. Marek, and J. Stanek, jun., *Collect. Czech. Chem. Commun.*, 1980, **45**, 3378.
[26] C. K. Lee, *J. Chem. Soc. Pak.*, 1979, **1**, 133 (*Chem. Abstr.*, 1980, **93**, 168 545).
[27] Yu. A. Zhdanov and G. E. Levitan, *Zh. Obshch. Khim.*, 1979, **49**, 1665 (*Chem. Abstr.*, 1980, **92**, 6847).
[28] D. Miljkovic, N. Vukojevic, and J. Hranisavljevic, *Glas. Hem. Drus. Beograd.*, 1979, **44**, 167 (*Chem. Abstr.*, 1980, **92**, 42 286).

azido-9-deoxy-neuraminic acid[29] and *N*-acetyl-4-*O*-methyl-neuraminic acid[30] have been reported.

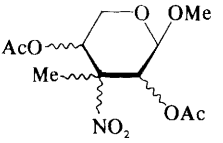
Brimacombe's group have accomplished syntheses of methyl 3-acetamido-2,3,6-trideoxy-3-*C*,4-*O*-dimethyl-α-D-*arabino*-hexopyranoside[31] and its L-enantiomer (21),[32] and since they have been previously oxidized to the corresponding 3-nitro-compounds, these represent syntheses of D- and L-evernitrose. The favoured route to the L-isomer (21) involved boron trifluoride-catalysed addition of methanol to 3-acetamido-4-*O*-acetyl-3,6-dideoxy-3-*C*-methyl-L-glucal, which gave an αβ mixture of glycosides; 2-deoxygenation of corresponding glucose or mannose derivatives by Barton and McCombie's procedure was a less satisfactory route.[32] A series of 3-deoxy-3-*C*-methyl-3-nitropentopyranosides (22) have been prepared by nitroethane condensation with periodate-oxidized methyl β-D-xylopyranoside; the D- and L-*xylo*-isomers predominated in the product mixture, with L-*lyxo*-, L- and D-*arabino*-isomers being minor components.[33]



(20)



(21)



(22)

A synthesis of methyl α-D-sibirosaminide (23) has been reported (Scheme 3), which starts from a 3-*C*-methylaltropyranoside derivative,[34] and Dyong and Schulte have described the synthesis of a closely related compound (24) from the 2-deoxy-3-ulose (25), which required introduction of the 2-hydroxy-group by means of a [2,3]-sigmatropic rearrangement (Scheme 4).[35] The addition of HCN to the *threo*-analogue of (25) in the presence of pyridine afforded the kinetic cyanohydrin (axial attack) in 74% yield, whereas in the presence of sodium bicarbonate the thermodynamic product with the opposite configuration was obtained. The two products were isolated as their mesylates, which were

[29] R. Brossmer, U. Rose, D. Kasper, T. L. Smith, H. Grasmuk, and F. M. Unger, *Biochem. Biophys. Res. Commun.*, 1980, **96**, 1282.

[30] J. M. Beau and R. Schauer, *Eur. J. Biochem.*, 1980, **106**, 531; J. M. Beau, R. Schauer, J. Haverkamp, L. Dorland, J. F. G. Vliegenthart, and P. Sinaÿ, *Carbohydr. Res.*, 1980, **82**, 125.

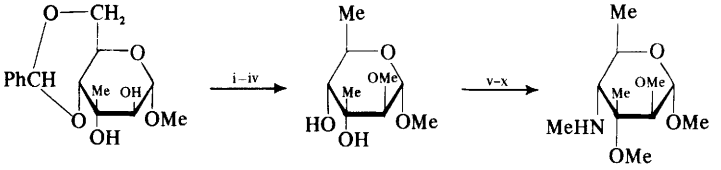
[31] J. S. Brimacombe, M. S. Saeed, and T. J. R. Weakley, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2061.

[32] J. S. Brimacombe and A. S. Mengech, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2054.

[33] M. M. Abuaan, J. S. Brimacombe, and J. N. Low, *J. Chem. Soc., Perkin Trans. 1*, 1980, 995.

[34] J. Yoshimura, N. Hong, A. ur Rahman, and K. I. Sato, *Chem. Lett.*, 1980, 777.

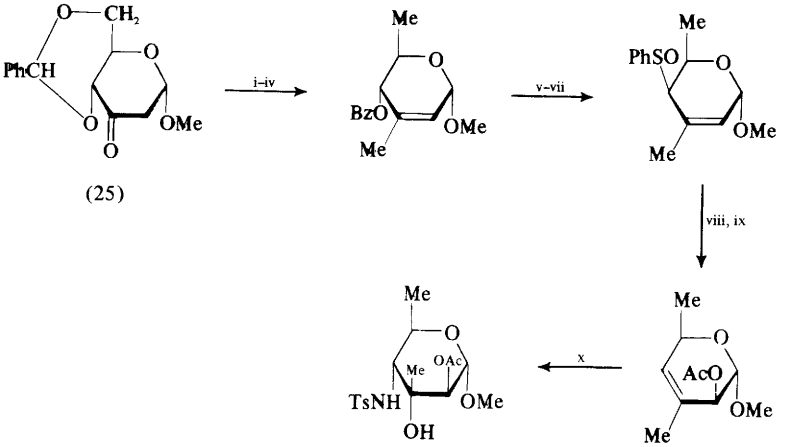
[35] I. Dyong and G. Schulte, *Tetrahedron Lett.*, 1980, **21**, 603.



(23)

Reagents: i, NaH–MeI; ii, NBS; iii, Bu_3SnH; iv, NaOMe; v, DMSO–$O(COCF_3)_2$; vi, H_2NOH; vii, H_2–PtO_2; viii, *p*-$NO_2C_6H_4OCHO$; ix, $LiAlH_4$; x, separation of altro isomer

Scheme 3



(25)

(24)

Reagents: i, MeMgI; ii, NBS; iii, Ni–H_2; iv, $SOCl_2$–py; v, NaOMe; vi, Bu_3P–$(CH_2CO)_2NSPh$; vii, *m*-CPBA; viii, $(MeO)_3P$; ix, Ac_2O–py; x, OsO_4–chloramine T

Scheme 4

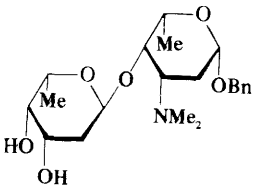
converted into the 3-amino-3-*C*-methyl derivatives by reduction *via* the epimine.[36] The branched-chain amino-sugars, methyl 3-deoxy-4-*C*-methyl-3-methylamino-α-L-arabinopyranosides,[37] and its de-*N*-methylated analogue[38] have been prepared by standard reactions.

Several aminodeoxydisaccharides have been prepared. For example, 6′-amino-6′-deoxy-raffinose,[39] 6,6′-diamino-6,6′-dideoxy-α,α-trehalose,[40] 6,6′-diamino-

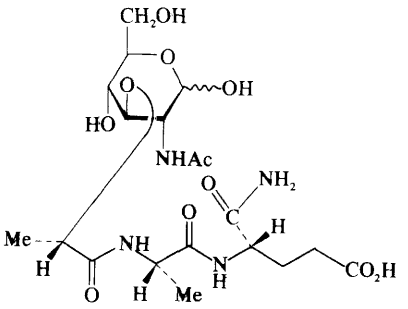
[36] T. T. Thang, F. Winternitz, A. Lagrange, A. Olesker, and G. Lukacs, *Tetrahedron Lett.*, 1980, **21**, 4495.
[37] H. W. Pauls and B. Fraser-Reid, *J. Am. Chem. Soc.*, 1980, **102**, 3956.
[38] H. Paulsen, H. Tietz, W. Koebernick, and V. Sinnwell, *Chem. Ber.*, 1980, **113**, 2616.
[39] L. Hough, A. C. Richardson, and M. A. Salam, *Carbohydr. Res.*, 1980, **80**, 117.
[40] H. Liav and M. B. Goren, *Carbohydr. Res.*, 1980, **87**, 153, 287.

6,6′-dideoxysucrose,[41] and 4-amino-4,6-dideoxy-6-fluoro-α-D-galactopyranosyl 4-amino-4,6-dideoxy-6-fluoro-α-D-galactopyranoside[42] or derivatives thereof have been made by modification of the parent disaccharides. 2-Amino-2-deoxysucrose has been synthesized from the appropriate monosaccharide moieties[43] and the disaccharide (26), which is a component of some anthracycline antibiotics, has been synthesized by standard methods.[44] A new synthesis of chitobiose has been described[45] as well as its 3-*O*-(α-L-fucosyl) derivative.[46]

The field of synthetic immunostimulants related to *N*-acetylmuramyl-L-alanyl-D-isoglutamine (MDP) (27) has been reviewed.[47] There has been a great deal of activity in the synthesis of analogues of (27) in which (*a*) the peptide group has been modified,[48–51] (*b*) the configuration of the sugar unit altered,[52,53] (*c*) functionality and/or substitution at C-6 varied,[48,49,51,53,54] (*d*) the position of the lactyl group changed,[52] and (*e*) an additional sugar unit was introduced at C-4.[54]



(26)



(27)

[41] J. H. Kim and E. J. Reist, *J. Carbohydr. Nucleosides, Nucleotides*, 1980, **7**, 257.
[42] A. F. Hadfield, L. Hough, and A. C. Richardson, *Carbohydr. Res.*, 1980, **80**, 123.
[43] S. Koto, S. Inada, and S. Zen, *Chem. Lett.*, 1980, 183.
[44] J. Boivin, C. Monneret, and M. Pais, *Tetrahedron Lett.*, 1980, **21**, 2413.
[45] S. Oguri and S. Tejima, *Chem. Pharm. Bull.*, 1980, **28**, 3184.
[46] S. Oguri, H. Ishihara, and S. Tejima, *Chem. Pharm. Bull.*, 1980, **28**, 3196.
[47] E. Lederer, *J. Med. Chem.*, 1980, **23**, 819.
[48] S. Kobayashi, T. Fukuda, I. Imada, M. Fujino, I. Azuma, and Y. Yamamura, *Chem. Pharm. Bull.*, 1979, **27**, 3193.
[49] A. Hasegawa, H. Okumura, M. Kiso, I. Azume, and Y. Yamamura, *Agric. Biol. Chem.*, 1980, **44**, 1309.
[50] S. Kobayashi, T. Fukuda, H. Yukimasa, M. Fujino, I. Azuma, and Y. Yamamura, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 2570.
[51] S. Kobayashi, T. Fukuda, H. Yukimasa, I. Imada, M. Fujino, I. Azuma, and Y. Yamamura, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 2917.
[52] M. Kiso, Y. Kaneda, Y. Goh, A. Hasegawa, and I. Azuma, *Agric. Biol. Chem.*, 1980, **44**, 1971.
[53] A. Hasegawa, H. Okumura, M. Kiso, I. Azuma, and Y. Yamamura, *Agric. Biol. Chem.*, 1980, **44**, 1301.
[54] M. Inage, M. Imoto, Y. Kambayashi, S. Kusumoto, and T. Shiba, *Tetrahedron Lett.*, 1980, **21**, 3767.

3 Reactions

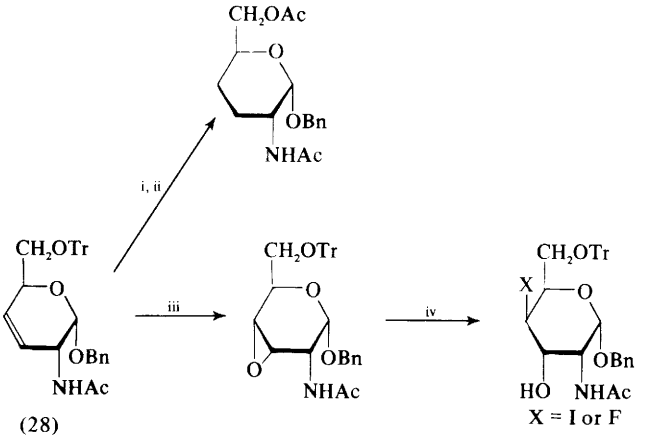
Deamination of benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-glucopyranosides afforded various products including 2,3-epoxides, 2-deoxy-3-uloses as well as products formed by migration of the benzyloxy-group from C-1 to C-2.[55] Nitrous acid deamination of methyl 4-amino-4-deoxy-β-L-arabinopyranoside followed by reduction with NaB^2H_4, hydrolysis with acid, reduction with $NaBH_4$, and acetylation afforded the acetates of xylitol, arabinitol, 4-deoxy-L-*threo*-pentitol, and 4-deoxy-D-*erythro*-pentitol in the ratio 1:tr.:3:4, with the last two labelled at C-3 with deuterium. These results indicated that the major route followed in the deamination reaction was the elimination of H-3 to give the 4-deoxy-3-ulose.[56] Nitrous acid deamination of per-*O*-methylated 2-amino-2-deoxy-D-glucitol and 2-amino-2-deoxy-3-*O*-β-D-galactopyranosyl-D-glucitol have been examined by g.l.c.–m.s. The major pathway involves a 1,2-hydride shift to give 2-deoxy-D-*arabino*-hexose derivatives, but lesser products arise from solvolytic displacement at C-2, 3 → 2 hydride shift, and C-4 to C-2 migration to give 2-deoxy-2-*C*-hydroxymethyl-D-ribose and -D-arabinose derivatives.[57] For a method of reductive deamination of amino-sugars see Chapter 11.

2-Acetamido-2-deoxy-D-mannose has been converted into its 6-deoxy-6-fluoro-analogue[58] and benzyl 2-acetamido-2,3,4-trideoxy-6-*O*-trityl-α-D-*erythro*-hex-3-enopyranoside (28) has been prepared by the Tipson–Cohen procedure and the double bond either reduced to give the 3,4-dideoxy-derivative or oxidized to the *allo*-epoxide, which underwent diaxial ring-opening with iodide and fluoride to give the corresponding 4-halogeno-gulopyranosides (Scheme 5).[59] The attempted displacement of the 3-tosyloxy-group by fluoride in (29) afforded the 2-fluoro-3-benzamido-derivative (30), a reaction that proceeded by way of the 2,3-epimine (Scheme 6).[60]

Reactions of the 2-acetamidoglycal (31) have led to several other deoxy- and unsaturated amino-sugars including the disaccharide (32).[61]

1-, 3-, 4-, and 6-phosphates of 2-acetamido-2-deoxy-D-glucose have been made by conventional methods[62] and *N*-t-alkyloxycarbonyl derivatives of amino-sugars are conveniently made by the use of di-t-alkyl pyrocarbonates.[63] It has been reported that the 2,2,2-trichloroethyl group can be cleaved selectively in the presence of a phthalimido-group, so that 2,2,2-trichloroethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside is readily converted into the compound with the anomeric hydroxy-group free by reaction with zinc dust at pH 4.5.[64]

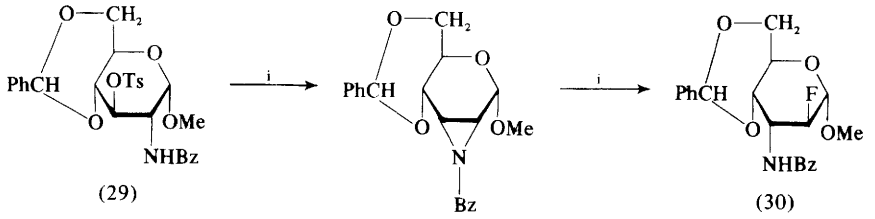
[55] W. P. Chan and P. H. Gross, *J. Org. Chem.*, 1980, **45**, 1369.
[56] J. Arnarp, A. Goos, and J. Lönngren, *Carbohydr. Res.*, 1980, **86**, 143.
[57] G. O. Aspinall, N. M. Gharia, and C. O. Wong, *Carbohydr. Res.*, 1980, **78**, 275.
[58] M. Sharma and W. Korytnyk, *Carbohydr. Res.*, 1980, **83**, 163.
[59] M. Sharma and W. Korytnyk, *Carbohydr. Res.*, 1980, **79**, 39.
[60] L. Hough, A. A. E. Penglis, and A. C. Richardson, *Carbohydr. Res.*, 1980, **83**, 142.
[61] A. Hasegawa, E. Tanahashi, and M. Kiso, *Carbohydr. Res.*, 1980, **79**, 255.
[62] V. I. Gorbach, V. V. Isakov, Yu. G. Kulesh, P. A. Luk'yanov, T. F. Solov'eva, and Yu. S. Ovodov, *Bioorg. Khim.*, 1980, **6**, 81 (*Chem. Abstr.*, 1980, **92**, 181 513).
[63] V. F. Pozdnev, *Khim. Prir. Soedin.*, 1980, 408 (*Chem. Abstr.*, 1980, **93**, 186 700).
[64] B. Y. Chung and Y. H. Kim, *Taehan Hwahakhoe Chi*, 1979, **23**, 175 (*Chem. Abstr.*, 1980, **92**, 164 237).



(28)

Reagents: i, H_2–Pd; ii, Ac_2O; iii, *m*-CPBA; iv, X^-

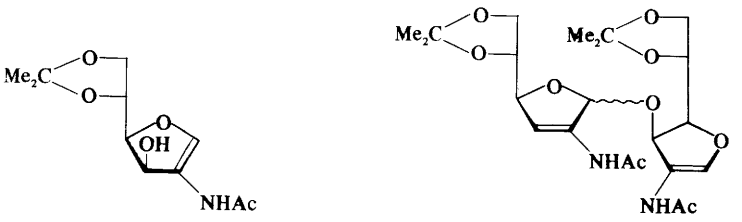
Scheme 5



(29) (30)

Reagent: i, Bu_4NF–MeCN or HMPT

Scheme 6



(31) (32)

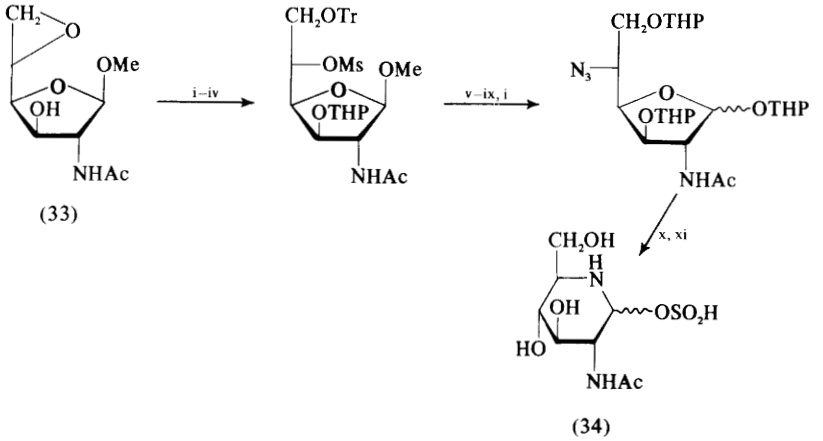
Contrary to previous reports Caroff and Szabo have shown that cleavage of permethylated oligo- and poly-saccharides containing amino-sugars, by either acid hydrolysis, acetolysis, or methanolysis, does not cause cleavage of *N*-methyl groups, but may result in some *O*-demethylation.[65]

[65] M. Caroff and L. Szabó, *Carbohydr. Res.*, 1980, **84**, 43.

For the formation of 2,4-DNP derivatives of amino-sugars, the optimum conditions have been found to be at pH 9.0 (carbonate buffer) in aqueous alcohol. Higher pHs and temperatures favour the formation of by-products.[66]

4 Diamino-sugars

Starting with benzyl 2-benzyloxycarbamido-2-deoxy-β-D-xylofuranoside, Hasegawa *et al.*[67] have synthesized 2,5-diacetamido-2,5-dideoxy-D-xylose and -D-ribose and 2,3,5-triacetamido-2,3,5-trideoxy-D-xylose and -D-ribose as *O*-acetylated derivatives by standard reactions and methyl 2,5-diacetamido-2,5-dideoxy-DL-ribofuranoside has been synthesized from non-carbohydrate materials.[68]



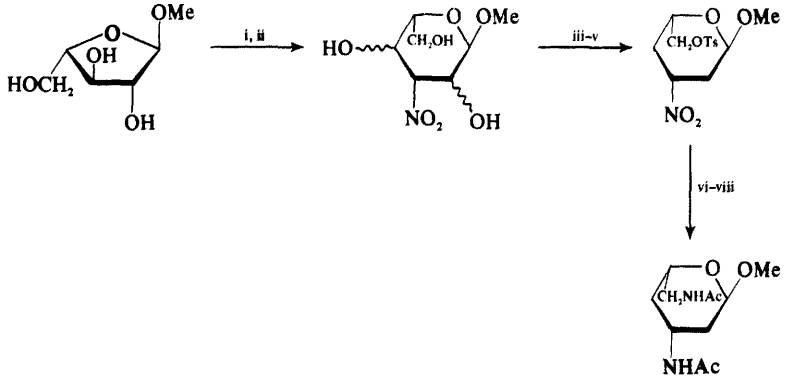
Reagents: i, dihydropyran–H^+; ii, NaOH; iii, TrCl; iv, MsCl; v, NaN_3–DMF; vi, HOAc; vii, Ac_2O; viii, H_3O^+; ix, NaOMe; x, Pd–H_2; xi, SO_2.

Scheme 7

Methyl 2-acetamido-5,6-anhydro-2-deoxy-α-L-idofuranoside (33) has been synthesized from 2-acetamido-2-deoxy-D-glucose and has been employed in the preparation of 2-acetamido-5-amino-2,5-dideoxy-D-glucopyranose as the sulphur dioxide adduct (34) (Scheme 7). Similarly the corresponding idopyranose was prepared in an analogous manner.[69]

The synthesis of 3,6-diacetamido-2,3,4,6-tetradeoxy-α-L-*threo*-hexopyranoside (35) has been accomplished from methyl α-L-arabinofuranoside by use of the cyclization of a dialdehyde with nitromethane. The arabinoside was first oxidized by periodate and the resulting dialdehyde ring-closed with nitromethane

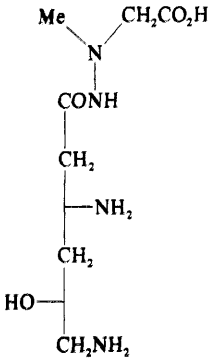
[66] M. J. Talieri and J. S. Thompson, *Carbohydr. Res.*, 1980, **86**, 1.
[67] A. Hasegawa, N. Aritake, and M. Kiso, *Carbohydr. Res.*, 1980, **81**, 23.
[68] R. R. Schmidt and R. Scheibe, *Liebigs Ann. Chem.*, 1980, 1307.
[69] A. Hasegawa, E. Tanahashi, and M. Kiso, *Carbohydr. Res.*, 1980, **81**, 249.



(35)

Reagents: i, $NaIO_4$; ii, $MeNO_2$–NaOMe; iii, TsCl (1 equiv.); iv, Ac_2O–BF_3; v, $NaBH_4$; vi, NaN_3; vii, Ni–H_2; viii, Ac_2O–MeOH

Scheme 8



(36)

to give a mixture of methyl 3-deoxy-3-nitrohexopyranosides, which were elaborated further to give (35) (Scheme 8).[70] The antibiotic negamycin (36) is a derivative of 3,6-diamino-2,3,4,6-tetradeoxy-L-*threo*-hexonic acid and the racemic form has been synthesized by two routes from non-carbohydrate starting materials.[71,72]

Syntheses are reported of methyl 3,6-diamino-2,3,6-trideoxy-D-*ribo*-hexopyranoside[73] and methyl 2-acetamido-4-amino-2,4,6-trideoxy-β-D-glucopyranoside.[74]

[70] W. Streicher and H. Reinshagen, *Carbohydr. Res.*, 1980, **83**, 383.
[71] G. Pasquet, D. Boucherot, W. R. Pilgrim, and B. Wright, *Tetrahedron Lett.*, 1980, **21**, 931.
[72] A. Pierdet, L. Nédélec, V. Delaroff, and A. Allais, *Tetrahedron*, 1980, **36**, 1763.
[73] I. Pelyrás and R. Bognar, *Acta Chim. Acad. Sci. Hung.*, 1980, **105**, 141.
[74] D. R. Bundle and S. Josephson, *Can. J. Chem.*, 1980, **58**, 2679.

9

Miscellaneous Nitrogen Derivatives

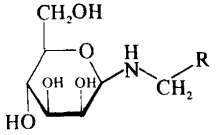
1 Glycosylamines

Several *N*-substituted β-mannopyranosylamines have been prepared by condensation of D-mannose with various benzylamines, and related heterocyclic amines. Their insulin-like activity was evaluated and derivatives (1) and (2) showed marked activity.[1] Additionally, several *N*-acyl derivatives of β-mannopyranosylamine were prepared incorporating a series of heterocyclic ring compounds.[2] A new synthesis of *N*-acylated glycosylamines involves the condensation of the appropriate glycosyl isothiocyanate with carboxylic acids in the presence of triethylamine, and this procedure has been utilized for the preparation of several 4-*N*-glycosyl-L-asparagine derivatives.[3] The glycosylamine of the trisaccharide α-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl-(1→6)-α-D-glucopyranose has been synthesized and coupled to asparagine in the usual manner,[4] and 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosylamine has been linked through nitrogen to several acyl substituents (*e.g.*, $ClCH_2CO$, CF_3CO, CF_3SO_2, *etc.*)[5] and also to the hexapeptide Asp-Ala-Thr-Leu-Ala-SerOH.[6]

A study of the hydrazinolysis of 4-*N*-glycosyl-L-asparagine derivatives has shown that the reaction does not proceed as previously suggested and it has been intimated that the results of past hydrazinolysis studies on glycopeptides may require careful reappraisal.[7] The synthesis of some *N*-(β-D-glucopyranosyl)-3-bromopyridinium and -isoquinolinium derivatives have been reported for studies of their cleavage by the crystalline A_3 isoenzyme of the extracellular β-glucosidases produced by the mould *Aspergillus wentii*.[8]

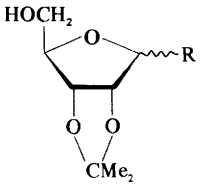
Condensation of 2,3-*O*-isopropylidine-β-D-ribofuranosylamine (3) with 2-cyanocyclohexanone afforded the enamines (4) with an α, β isolated yield ratio of 44 : 20. Photolysis of the α-anomer in acetonitrile resulted in rearrangement and cyclization to give the nucleoside analogue (5),[9] but when the photolysis was conducted in methanol, addition of the elements of methanol across the double bond of (4) occurred to give an adduct that underwent substantial anomerization.[10] The conformations and configurations of a series of *N*-glycosyl-

[1] M. M. Ponpipom, R. L. Bugianesi, and T. Y. Shen, *Carbohydr. Res.*, 1980, **82**, 135.
[2] M. M. Ponpipom, R. L. Bugianesi, and T. Y. Shen, *Carbohydr. Res.*, 1980, **82**, 141.
[3] A. Y. Khorlin, S. E. Zurabyan, and R. G. Macharadze, *Carbohydr. Res.*, 1980, **85**, 201.
[4] T. Ogawa, S. Nakabayashi, and S. Shibata, *Carbohydr. Res.*, 1980, **86**, C7.
[5] B. Paul, R. J. Bernacki, and W. Korytnyk, *Carbohydr. Res.*, 1980, **80**, 99.
[6] H. G. Garg and R. W. Jeanloz, *Carbohydr. Res.*, 1980, **86**, 59.
[7] M. S. Saeed and J. M. Williams, *Carbohydr. Res.*, 1980, **84**, 83.
[8] G. Legler, M. L. Sinnott, and S. G. Withers, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1376.
[9] J. P. Ferris, V. R. Rao, and T. A. Newton, *J. Org. Chem.*, 1979, **44**, 4378.
[10] J. P. Ferris, V. R. Rao, and T. A. Newton, *J. Org. Chem.*, 1979, **44**, 4381.

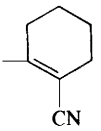


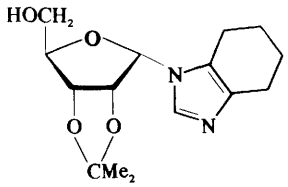
(1) R = 

(2) R = 



(3) R = NH_2

(4) R = 



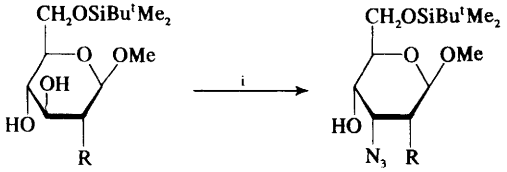
(5)

piperidines have been examined in which the sugar component was D-glucose, D-galactose, D-mannose, D- and L-arabinose, D-xylose, D-ribose, and cellobiose.[11]

2 Azido-sugars

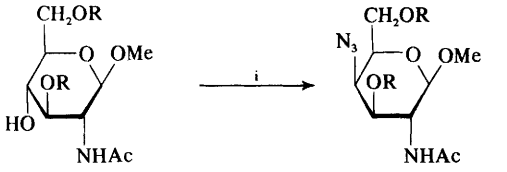
Several papers have dealt with the direct replacement of an hydroxy-group by azide. Thus, the use of a mixture of triphenylphosphine, carbon tetrabromide, and lithium azide resulted in the displacement of the primary hydroxy-group at C-5′ in various nucleosides. However, application of the same reagent combination to 2′-deoxy-5′-*O*-tritylnucleosides resulted in displacement of the 3′-hydroxy-group by azide with inversion of configuration.[12] The triphenylphosphine–diethyl azodicarboxylate reagent reacted with various glycosides in the presence of hydrazoic acid to give azides in which the azide group was introduced with inversion of configuration. Thus, methyl 6-*O*-t-butyldimethylsilyl-β-D-glucopyranoside (6) reacted with the reagent to give the 3-azido-allopyranoside (7) in good yield, and the corresponding 2-acetamido-2-deoxy-glycoside (8) reacted similarly to give the 3-azide (9) (Scheme 1). When the 3-hydroxy-group was blocked as in 3,6-bis(t-butyldimethylsilyl) ether (10), azidation took place at the 4-position to give the 4-azide (11). However, when the reaction was applied to the α-anomer of (10), only 16% of the 4-azide was obtained, the major product being the 4,6-bis(t-butyldimethylsilyl) ether arising from rearrangement of the 3-*O*-silyl group. The reagent was compatible with the presence of an oxiran ring, and reacted with the 2,3-epoxide (12) to give the 4-azide (13), which upon treatment with sodium azide in the presence of ammonium chloride afforded the 3,4-diazide (14) in 61% yield, along with 20% of the 2,4-diazide.[13] The same reagent was also employed for the synthesis of glycosyl azides.[14]

[11] B. N. Stepanenko, L. A. Abibullaeva, and V. D. Shcherbukhin, *Zh. Obshch. Khim.*, 1980, **50**, 1871 (*Chem. Abstr.*, 1980, **93**, 186737).
[12] I. Yamamoto, M. Sekine, and T. Hata, *J. Chem. Soc., Perkin Trans. 1*, 1980, 306.
[13] H. H. Brandstetter and E. Zbiral, *Helv. Chem. Acta*, 1980, **63**, 327.
[14] W. Schorkhuber and E. Zbiral, *Liebigs Ann. Chem.*, 1980, 1455.



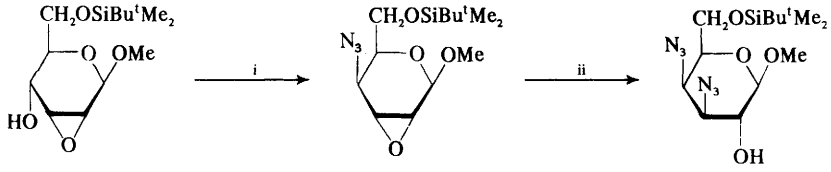
(6) R = OH
(8) R = NHAc

(7) R = OH
(9) R = NHAc



(10) R = $SiBu^tMe_2$

(11) R = $SiBu^tMe_2$



(12)

(13)

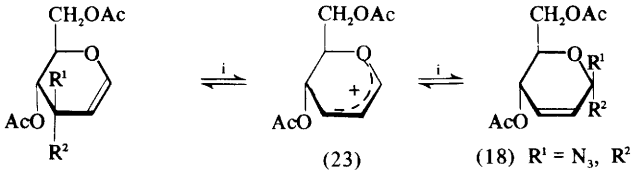
(14)

Reagents: i, $EtO_2C{-}N{=}N{-}CO_2Et$-Ph_3P-HN_3; ii, NaN_3-NH_4Cl

Scheme 1

Reaction of tri-*O*-acetylglucal (15) with sodium azide in acetonitrile containing boron trifluoride etherate afforded mixtures of the 3-azidoglycals (16) and (17) and the 2,3-dideoxyhex-2-enopyranosyl azides (18) and (19) (Scheme 2). The same mixture was obtained from either the ethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (20), tri-*O*-acetylglucal (15), tri-*O*-acetylallal (21), or 1,4,6-tri-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranoses (22) suggesting that the reaction proceeds through a common intermediate (23). The 3-azidoglycals could be reduced to the aminoglycals with $LiAlH_4$ and reaction of a mixture of the 3-azidoallal (17) and the α-azide (19) with triphenylphosphine in carbon disulphide afforded the 3-isothiocyanato-allal (24), and a mixture of (16) and (18) yielded the 3-isothiocyanato-glucal (25).[15] 3,4,6-Tri-*O*-benzyl-D-glucal reacted similarly with the reagent, but 3-*O*-acetyl-4,6-*O*-benzylidene-D-glucal, and the corresponding 3-*O*-methyl ether failed to react owing to their inability to achieve the $^5H_4$ conformation required to render the C-3 allylic substituent *quasi*-axial.[16]

[15] R. D. Guthrie and R. W. Irvine, *Carbohydr. Res.*, 1980, **82**, 207.
[16] R. D. Guthrie and R. W. Irvine, *Carbohydr. Res.*, 1980, **82**, 225.



(15) R^1 = OAc, R^2 = H
(16) R^1 = N_3, R^2 = H
(17) R^1 = H, R^2 = N_3
(21) R^1 = H, R^2 = OAc
(24) R^1 = H, R^2 = NCS
(25) R^1 = NCS, R^2 = H

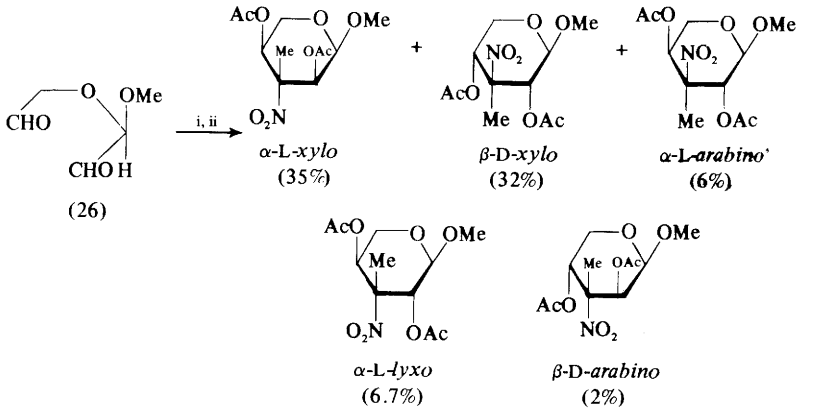
(23)

(18) R^1 = N_3, R^2 = H
(19) R^1 = H, R^2 = N_3
(20) R^1 = H, R^2 = OEt
(22) R^1, R^2 = H, OAc

Reagent: i, NaN_3–$BF_3 \cdot Et_2O$–MeCN

Scheme 2

Several papers have described the preparation of azido-sugars by S_N2 displacement reactions with azide anions. Starting from 1,2-*O*-isopropylidene-α-D-xylofuranose, Ozols *et al.*[17,18] have used this method for the prearation of 3′,5′-diazido-3′,5′-dideoxynucleosides and 3′-azido-3′-deoxynucleosides. As would be expected for an *exo*-sulphonyloxy-group at C-3, displacement was sluggish and afforded substantial amounts of the 3′-enofuranose. However, the use of trifluoromethanesulphonyl esters substantially improved yields. Similarly, 4-azido-4-deoxy-D-glucose[19] and methyl 4-azido-4-deoxy-α-D-galactopyranoside[20] have been made by displacement of the appropriate sulphonate esters.



(26)

α-L-*xylo* (35%)
β-D-*xylo* (32%)
α-L-*arabino* (6%)
α-L-*lyxo* (6.7%)
β-D-*arabino* (2%)

Reagents: i, $EtNO_2$–NaOMe; ii, Ac_2O

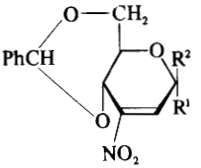
Scheme 3

[17] A. M. Ozols, A. V. Azhayev, N. B. Dyatkina, and A. A. Krayevsky, *Synthesis*, 1980, 557.
[18] A. M. Ozols, A. V. Azhayev, A. A. Krayevsky, A. S. Ushakov, N. V. Gnuchev, and B. P. Gottikh, *Synthesis*, 1980, 559.
[19] S. K. Sinha and K. Brew, *Carbohydr. Res.*, 1980, **81**, 239.
[20] J. E. N. Shin, A. Maradufu, J. Marion, and A. S. Perlin, *Carbohydr. Res.*, 1980, **84**, 328.

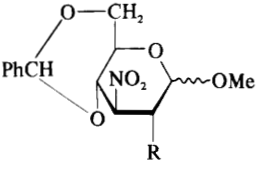
3 Nitro- and Cyano-sugars

Cyclization of the dialdehyde (26) with nitroethane afforded a mixture of five methyl 3-deoxy-3-*C*-methyl-3-nitropentopyranosides with the α-L-*xylo*-, β-D-*xylo*-, α-L-*arabino*-, α-L-*lyxo*-, and β-D-*arabino*-configurations in isolated yields of 35, 32, 6, 6.7, and 2% (as their di-*O*-acetyl derivatives), respectively (Scheme 3).[21]

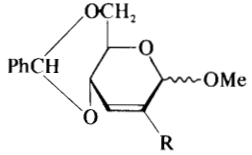
The 3-nitro-hex-2-enopyranoside (27) underwent addition of nitrous acid to give the 2,3-dinitro-glucopyranoside (28), but interestingly when (28) was treated with triethylamine and urea, loss of nitrous acid occurred to give the 2-nitro-hex-2-ene (29). The hex-2-ene (29) could be obtained directly from (27) by reaction with sodium nitrite in benzene–water using tributylhexadecylphosphonium bromide as phase-transfer reagent.[22] An analogous reaction occurred whrn the β-anomer (30) reacted with hydrocyanic acid in acetonitrile. The 2-cyano-derivative (31) formed initially, which underwent loss of nitrous acid to give the 2-cyano-hex-2-ene (32), then reacted further by addition of hydrogen cyanide giving a mixture of 2,3-dicyano-pyranosides (33) with the *allo*-, *altro*-, *gluco*-, and *manno*-configurations.[23]



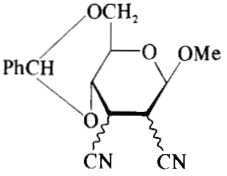
(27) R^1 = OMe, R^2 = H
(30) R^1 = H, R^2 = OMe



(28) R = NO_2 (α-anomer)
(31) R = CN (β-anomer)



(29) R = NO_2 (α-anomer)
(32) R = CN (β-anomer)



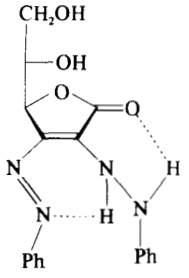
(33)

The epimerization of 1,2 : 5,6-di-*O*-isopropylidene-3-*C*-nitromethyl-α-D-allofuranose has been studied and was considered to occur by disproportionation into the 3-ulose and nitromethane followed by recombination.[24] A useful transformation of the nitromethyl branch chain to cyano has been accomplished by chlorination with hypochlorous acid to give the dichloronitromethyl branch chain followed by reaction with triphenylphosphine.[25]

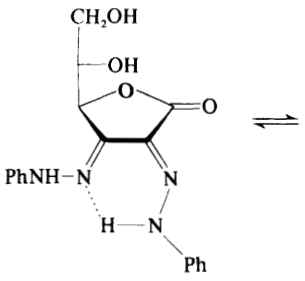
[21] M. M. Abuaan, J. S. Brimacombe, and J. N. Low, *J. Chem. Soc., Perkin Trans. 1*, 1980, 995.
[22] Y. Tachimori, T. Sakakibara, and R. Sudoh, *Carbohydr. Res.*, 1980, **82**, 51.
[23] T. Sakakibara and R. Sudoh, *Carbohydr. Res.*, 1980, **85**, 33.
[24] K. I. Sato, K. Koga, H. Hashimoto, and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 2639.
[25] R. H. Hall, A. Jordaan, and M. Malherbe, *J. Chem. Soc., Perkin Trans. 1*, 1980, 126.

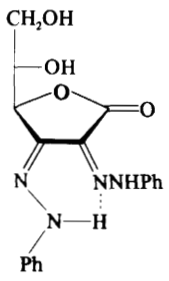
4 Hydrazones and Related Compounds

The structure of the osazone derived from dehydroascorbic acid remains in dispute. Recently (Vol. 13, p. 95) it was described as the phenylhydrazine-phenylazo-structure (34), but it is now claimed that the bis(hydrazone) formula (35) fits the n.m.r. and u.v. data more satisfactorily.[26] The structure of the bicyclic oxidation product of (35) has been shown to be a 3,6-anhydride (36) by n.m.r. and m.s.[27] A ^{13}C n.m.r. study of the formation of dehydroascorbic acid hydrazones revealed that the two 2-phenylhydrazides (37) were formed initially and subsequently underwent dehydration to give the two rotationally isomeric 2-phenylhydrazones.[28] Reaction of 6-bromo-6-deoxy-isoascorbic acid (D-*erythro*) with phenyl hydrazine afforded the cyclized bis(hydrazone) (38).[29] Treatment of D-*threo*-ascorbic acid bis(phenylhydrazone) with caustic soda afforded the cyclized product (39).[30] The corresponding D-*erythro*-[30] and L-*threo*-isomers[31] were also prepared and the side-chains have been modified in various ways.

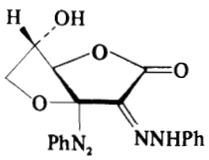


(34)

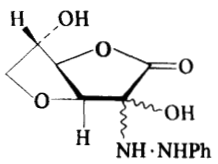




(35)



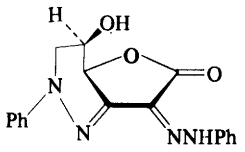
(36)



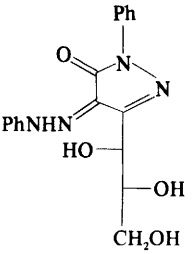
(37)

The dehydration of hexose, heptose, and octose phenylosazones in methanolic sulphuric acid has been studied. Each osazone gave rise to two 3,6-anhydrides epimeric at C-3 except 7-deoxy-D-*manno*-heptulose phenylosazone which afforded only the 3,6-anhydro-7-deoxy-L-*gulo*-heptulose phenylosazone with

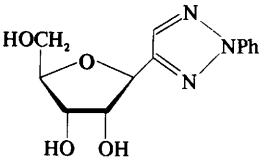
[26] P. Pollet and S. Gelin, *Tetrahedron*, 1980, **36**, 2955.
[27] H. S. El Khadem, E. S. H. El Ashry, D. L. Jaeger, G. P. Kreishman, and R. L. Foltz, *J. Heterocycl. Chem.*, 1980, **17**, 1181.
[28] B. Pederson, *Acta. Chem. Scand., Ser. B*, 1980, **34**, 429.
[29] E. S. H. El Ashry and Y. El Kilany, *Carbohydr. Res.*, 1980, **80**, C23.
[30] E. S. H. El Ashry, Y. El Kilany, and F. Singab, *Carbohydr. Res.*, 1980, **79**, 151.
[31] E. S. H. El Ashry, Y. El Kilany, and F. Singab, *Carbohydr. Res.*, 1980, **82**, 25.



(38)



(39)

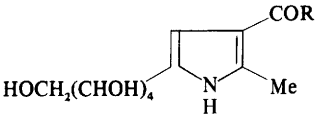


(40)

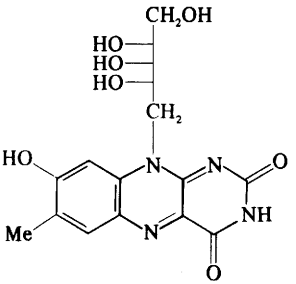
inversion of configuration at C-6.[32,33] Conversion of these anhydrides into their osotriazoles (*e.g.*, 40) afforded interesting nucleoside analogues.[34]

5 Heterocyclic Derivatives

Reaction of 2-amino-2-deoxypentoses with pentane-2,4-dione and 1-phenylbutane-1,3-dione afforded substituted pyrroles (*e.g.*, 41)[35] and the riboflavin analogue (42) was prepared by condensation of D-ribose with 5-amino-*o*-cresol, followed by cyclocondensation of the product with violuric acid.[36] Reaction of dehydroascorbic acid with *o*-phenylenediamine followed by aroylhydrazides afforded compounds of the type (43),[37] the side-chains of which have been further elaborated.[37–39] The acid derived by oxidation of 2,3:4,5-di-*O*-iso-



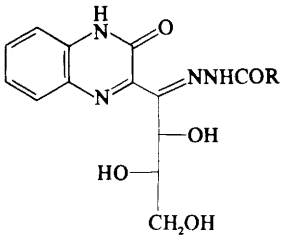
(41)



(42)

[32] M. A. E. Sallam, *Carbohydr. Res.*, 1980, **78**, C15; 1980, **85**, 93.
[33] M. A. E. Sallam, E. I. A. Hegazy, R. L. Whistler, and J. L. Markley, *Carbohydr. Res.*, 1980, **83**, C1.
[34] M. A. E. Sallam, *Tetrahedron Lett.*, 1980, **21**, 183.
[35] F. Garcia Gonzalez, M. Gomez Guillen, J. A. Galbis Perez, and P. Areces Bravo, *An. Quim.*, 1979, **75**, 756 (*Chem. Abstr.*, 1980, **92**, 111 246).
[36] G. D. Glebova, N. I. Kirillova, and V. M. Berezovskii, *Zh. Obshch. Khim.*, 1979, **49**, 1884 (*Chem. Abstr.*, 1980, **92**, 76 847).
[37] E. S. H. El Ashry, M. M. Nassr, and M. Shoukry, *Carbohydr. Res.*, 1980, **83**, 79.
[38] E. S. H. El Ashry, M. M. A. Abdel Rahman, Y. El Kilany, and A. Amer, *Carbohydr. Res.*, 1980, **87**, C5.
[39] M. A. E. Sallam, R. L. Whistler, and J. M. Markley, *Carbohydr. Res.*, 1980, **87**, 87.

propylidene-β-D-fructopyranose with permanganate, was condensed with *o*-phenylenediamine to give, in three steps, the *C*-nucleoside analogue (44), which existed in equilibrium with its α-anomer and the two furanose forms. Other related diamines were also used in these reactions.[40] The hydrazide (45) derived from galactaric acid underwent cyclization by thionyl chloride to give the product (46) and analogous compounds were prepared from other hydrazides.[41]



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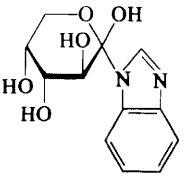

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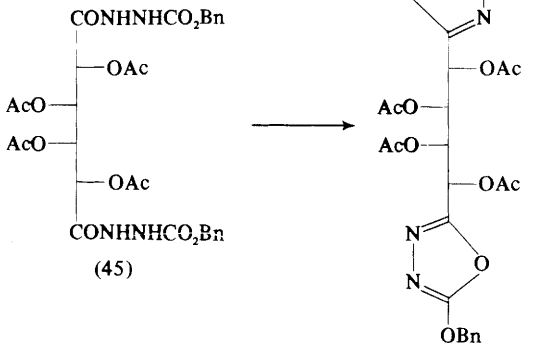
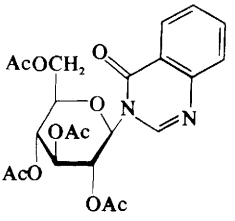


(45)

(46)



(47)

[40] Y. Chapleur and B. Castro, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2683.

[41] E. S. H. El Ashry, M. M. Nassr, M. M. A. Abdel Rahman, N. Rashed, and K. Mackawy, *Carbohydr. Res.*, 1980, **82**, 149.

Condensation of glycosyl isocyanides with amines in the presence of mercuric or silver chloride gave formamidines (Gly-N=CH—NR_2), but when methyl anthranilate was used with mercuric chloride, cyclization took place to give the nucleoside analogue (47). When silver chloride was used as catalyst only the intermediate formamidine was obtained.[42]

[42] D. Marmet, P. Boullanger, and G. Descotes, *Tetrahedron Lett.*, 1980, **21**, 1459.

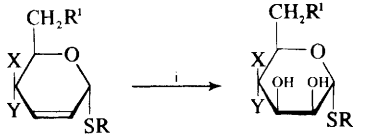
10

Thio-, Seleno-, and Phosphoro-sugars

A new method for the synthesis of 1-thioglycosides from glycosides uses Me_3SiSR–ZnI_2 in the presence of tetrabutylammonium iodide. Free hydroxy-groups require protection. By this means phenyl 1-thioglucopyranoside was prepared as an anomeric mixture (10 : 1, α:β) in 63% yield from methyl α-D-glycopyranoside. The reaction provides a useful alternative for the cleavage of glycosides resistant to standard acid hydrolysis, since thioglycosides are more readily hydrolysed. When methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside was treated with the methylthio-reagent (R = Me), the methyl α,β-thioglycosides obtained were partially de-*O*-methylated at the primary 6-position.[1]

2,4-Dinitrophenyl 2,3,4,6-tetra-*O*-benzyl-D-thioglucopyranoside has been synthesized in three steps from the corresponding glucosyl bromide *via* the amidinothio-derivative obtained by treatment with thiourea, followed by glycosylation with 1-chloro-2,4-dinitrobenzene.[2] Anomeric pairs of 1-thioglycosides have been prepared by anomerization with boron trifluoride followed by separation. The method was applied to alkyl 1-thioaldopyranosides of D-glucose, D-galactose, D-mannose, 2-acetamido-2-deoxy-D-glucose and -D-galactose, and L-fucose. The reaction was also applied to per-*O*-acetylated-1,2-*trans*-anomers of 6-(trifluoroacetamido)hexyl 1-thioaldopyranosides and 5-(methoxycarbonyl)-pentyl 1-thioaldopyranosides. Deblocking of these latter compounds and reacting with aminoacetaldehyde diethyl acetal led to derivatives suitable for coupling to proteins or solid matrices.[3]

cis-Hydroxylation of alkyl 2,3-dideoxy-1-thio-α-glyc-2-enopyranosides using osmium tetroxide has enabled the synthesis of some mannose derivatives



R = C_6H_{13}; R^1 = NHAc or NH-Cbz-L-prolyl; X = Y = H
R = Me; R^1 = Y = OAc; X = H
R = Me; R^1 = X = OAc; Y = H

Reagent: i, OsO_4

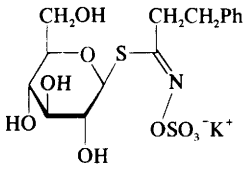
Scheme 1

[1] S. Hanessian and Y. Guindon, *Carbohydr. Res.*, 1980, **86**, C3.
[2] L. V. Volkova, N. G. Morozova, E. E. Loskutova, N. S. Tripol'skaya, and R. P. Evstigneeva, *Zh. Org. Khim.*, 1979, **15**, 1328 (*Chem. Abstr.*, 1980, **92**, 6867).
[3] D. T. Connolly, S. Roseman, and Y. C. Lee, *Carbohydr. Res.*, 1980, **87**, 227.

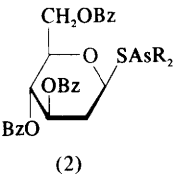
(Scheme 1).[4] The synthesis of ω-substituted alkyl 1-thio-α-D-mannopyranosides has been achieved using the appropriate ω-substituted bromo- or iodo-alkane in the presence of potassium carbonate on 1-thiomannose peracetate, which was either isolated or generated *in situ* by base cleavage of the amidino-group in 2-*S*-(tetra-*O*-acetyl-α-D-mannopyranosyl)2-thiopseudourea hydrobromide. In this way, heptyl, 6-(benzyloxycarbonylamino)hexyl, 6-hydroxyhexyl, and 5-carboxypentyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranosides were prepared.[5] A similar method was used to synthesize the 5-bromopentyl 1-thio-α-D-mannopyranosides, which was converted by displacement into the 5-nitrile and then reduced to the 6-aminohexyl thioglycoside. Using $Na^{14}CN$ the labelled aminohexyl thioglycoside was obtained.[6] Hexadecyl, 9-octadecenyl, adamantyl, 1,2-diphenyltetrafluoroethyl, hex-3-ynyl, and 3,6-dioxaoctylcholesteryl 1-thio-β-L-fucopyranosides have been synthesized as potential immunologic adjuvants.[7] Treatment of 1-thio-β-D-glucopyranose with acyl sulphenyl chlorides in acetonitrile in the presence of a crown ether gave acyl-glycosyl disulphides, required as cleavable detergents for use in isolation and purification of membrane proteins.[8] 1-Thio-oximino-sulphates of the type (1) have been prepared by reaction of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose with alkyl isocyanates to give oximes that were sulphated with sulphur trioxide in pyridine.[9]

Acid-catalysed reaction of thiols with glyc-1-enes (glycals) and glyc-2-enosides gives rise in both cases to a mixture of alkyl 1-thio-α-D-glyc-2-enosides and 3-alkylthio-3-deoxy-glycals, with the latter predominating.[10]

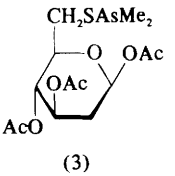
In continuation of work on dialkylarsinous acid derivatives (see Vol. 12, p. 96) compounds of types (2) and (3) have been prepared.[11] Similar derivatives of 1- and 6-thio- and 1- and 6-seleno-2-amino-2-deoxy-D-glucosamine have also been synthesized.[12] The compounds were used for cancer screening.



(1)



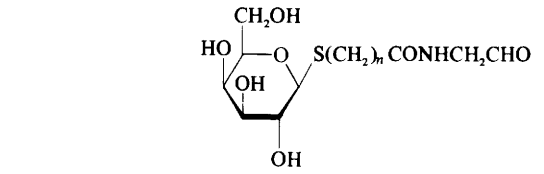
(2)



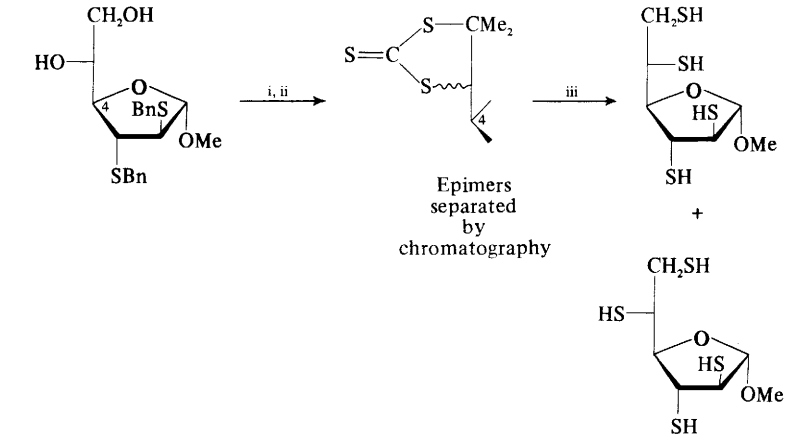
(3)

[4] W. Priebe and A. Zamojski, *Pol. J. Chem.*, 1980, **54**, 731.
[5] P. L. Durette and T. Y. Shen, *Carbohydr. Res.*, 1980, **83**, 178.
[6] P. L. Durette, R. L. Ellsworth, and T. Y. Shen, *J. Labelled Compd. Radiopharm.*, 1980, **17**, 129 (*Chem. Abstr.*, 1980, **93**, 72 192).
[7] M. M. Ponpipom, R. L. Bugianesi, T. Y. Shen, and A. Friedman, *J. Med. Chem.*, 1980, **23**, 1185.
[8] J. Cuomo, J. H. Merrifield, and J. F. W. Keana, *J. Org. Chem.*, 1980, **45**, 4216.
[9] V. Gill and A. J. McLeod, *Tetrahedron*, 1980, **36**, 779.
[10] W. Priebe and A. Zamojski, *Tetrahedron*, 1980, **36**, 287.
[11] M. V. Rosenthal and R. A. Zingaro, *Carbohydr. Res.*, 1980, **84**, 341.
[12] G. C. Chen, C. H. Banks, K. J. Irgolic, and R. A. Zingaro, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2287.

The thioglycosides of the amide derivatives (4) and (5) have been coupled with bovine serum albumin using sodium cyanide and borane as coupling agents at pH 6–7 and 37 °C.[13]



(4) $n = 1$
(5) $n = 5$

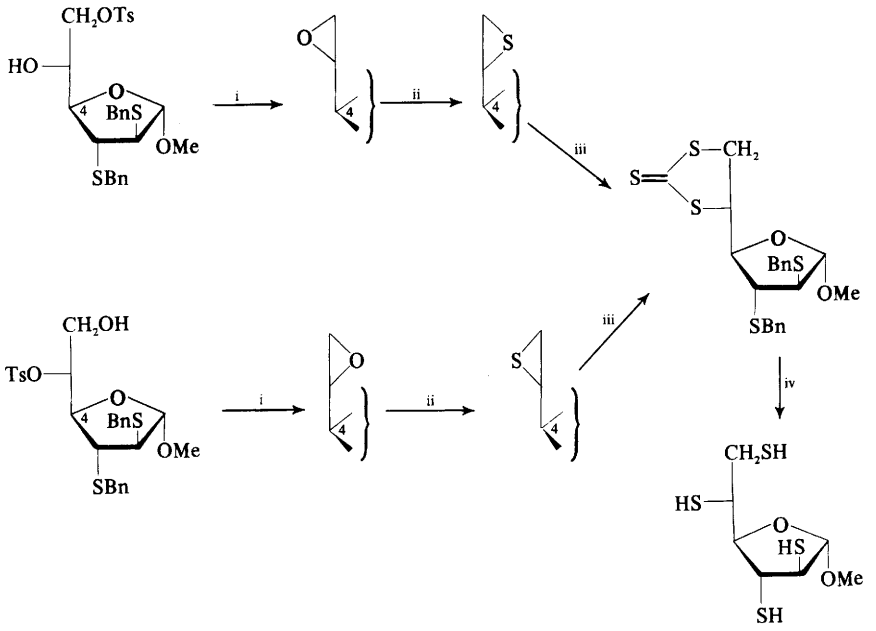


Reagents: i, MsCl–py; ii, Na_2CS_3; iii, $Na–NH_3$

Scheme 2

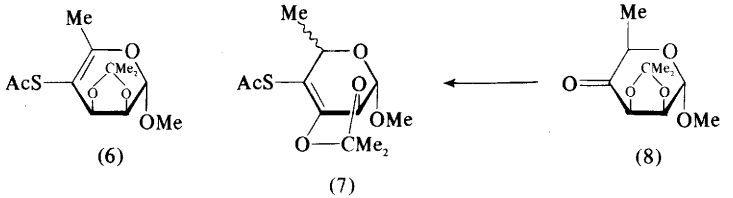
Methyl 2,3,5,6-tetradeoxy-2,3,5,6-tetrathio-β-L-galactofuranoside and -α-D-altropyranoside have been prepared[14] by the routes shown in Schemes 2 and 3. The syntheses of 6-deoxy-4-thio-α-D-talopyranose and -β-L-allopyranose have been achieved by applying to D-mannose the methods developed in the D-glucose series (see Vol. 12, p. 94). The unsaturated 4-thio-derivatives (6) and (7) were obtained from the 4-ulose (8) by treatment with phosphorus pentasulphide in pyridine followed by acetylation.[15]

[13] R. T. Lee and Y. C. Lee, *Biochemistry*, 1980, **19**, 156.
[14] T. Yamaguchi, M. Watanabe, T. Taguchi, and M. Kojima, *Chem. Pharm. Bull.*, 1980, **28**, 110.
[15] P. Simon, J.-C. Ziegler, and B. Gross, *J. Chem. Res.* (*S*), 1980, 352 [(*M*), 4337].



Reagents: i, NaOMe–MeOH; ii, $(NH_2)_2CS$; iii, $EtSCS_2K$; iv, $Na–NH_3$

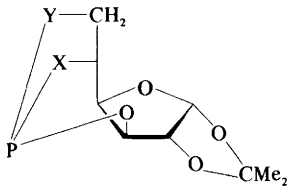
Scheme 3



Both the *endo*- and *exo*-diastereoisomers of methyl 2-*O*-benzyl-3-*O*,4-*S*-benzylidene-4,6-dideoxy-4-thio-α-D-galactopyranoside have been prepared. Reduction with lithium aluminium hydride–aluminium chloride of both diastereoisomers gave methyl 2-*O*-benzyl-4-*S*-benzyl-4,6-dideoxy-4-thio-α-D-galactopyranoside, the *endo*-isomer requiring only five minutes at room temperature, whereas the *exo*-isomer needed heating at reflux for 48 hours.[16]

The oxidation at sulphur of 6-*S*-benzyl-1,2-*O*-isopropylidene-3-*O*-methyl-6-thio-α-D-glucofuranose by *m*-chloroperbenzoic acid has been studied.[17]

[16] P. Fügedi and A. Liptak, *J. Chem. Soc., Chem. Commun.*, 1980, 1234.
[17] J. M. J. Tronchet and H. Eder, *Helv. Chim. Acta*, 1980, 63, 16.

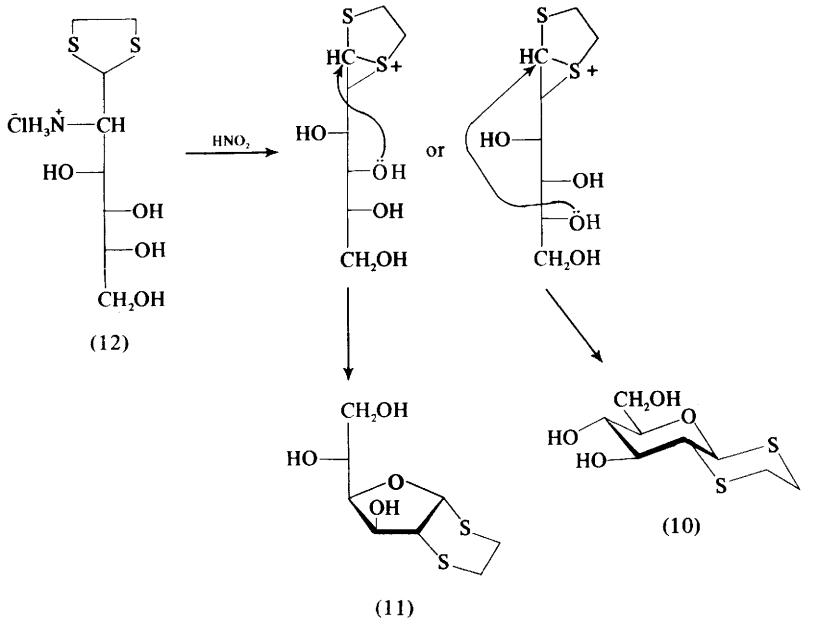


(9) X = O, Y = S or X = S, Y = O

Thiophosphates of the type shown in (9) have been synthesized by phosphorylation of the corresponding 1,2-*O*-isopropylidene-glucose with tris(dimethylamino)phosphite in absolute pyridine at 80–100 °C for two hours.[18]

Mention of episulphides formed by base treatment of thiophosphothionate esters has been made in Chapter 6.

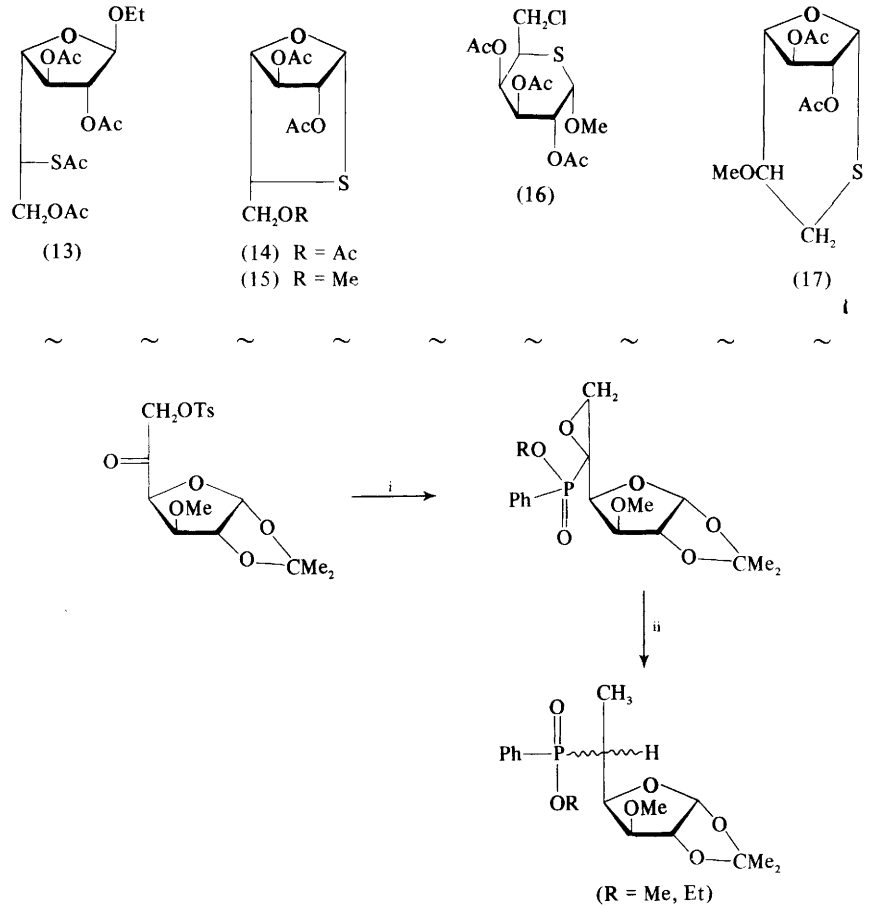
Formation of the 1,4-dithianes (10) and (11) in the nitrous acid deamination of mannosamine hydrochloride ethanedithioacetal (12) is thought to occur by the mechanism shown in Scheme 4.[19]



Scheme 4

[18] E. E. Nifant'ev, M. P. Koroteev, S. A. Lysenko, and N. K. Kochetkov, *Izv. Akad. Nauk, SSSR, Ser. Khim.*, 1980, 1441 (*Chem. Abstr.*, 1980, **93**, 220 985).

[19] P. Angibeaud and J. Defaye, *Carbohydr. Res.*, 1980, **82**, 385.



Reagents: i, DBU–PhPO(OR); ii, RaneyNi–EtOH

Scheme 5

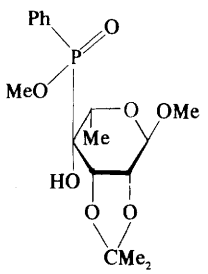
Application of the Grenacher reaction (condensation of aldehydes with rhodanine) to di-*O*-isopropylidene derivatives of *aldehydo*-L-arabinose, -D-arabinose, and -L-xylose followed by base-catalysed hydrolysis gave sugar derivatives of the type $RCH{=}CH(SH)CO_2H$ where R = glycosyl.[20,21] Photoirradiation of phenyl 2,3,5-tri-*O*-acetyl-1-seleno-α,β-ribofuranose results in migration of the sugar residue to the *ortho*-position with concomitant formation of the diselenide dimer.[22]

[20] Yu. A. Zhdanov, A. V. Kir'yanov, and G. A. Korol'chenko, *Dokl. Akad. Nauk, SSSR*, 1979, **249**, 367 (*Chem. Abstr.*, 1980, **92**, 147066).

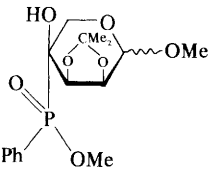
[21] Yu. A. Zhdanov, A. V. Kir'yanov, and G. A. Korol'chenko, *Zh. Obshch. Khim.*, 1979, **49**, 2159 (*Chem. Abstr.*, 1980, **92**, 129204).

[22] J.-L. Fourrey, G. Henry, and P. Jowin, *Tetrahedron Lett.*, 1980, **21**, 455.

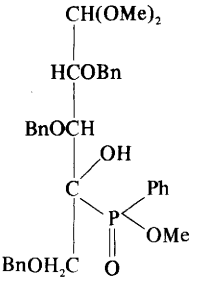
The by-products in the syntheses using 5-thio-D-galactose previously reported (see Vol. 13, p. 102) have been investigated. In the methanolysis of the ethyl furanoside (13) with methanol–hydrogen chloride, the thio-derivatives (14), (15), and the sulphur-ring derivative (16) were identified. The 1,5-thiane derivative (14) was also a by-product in the acetolysis of (13). A by-product in the hydrobrominolysis of methyl 2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-galactopyranoside was found to be the cyclic thioacetal (17). Mechanisms for the formation of (13)–(17) are suggested.[23]



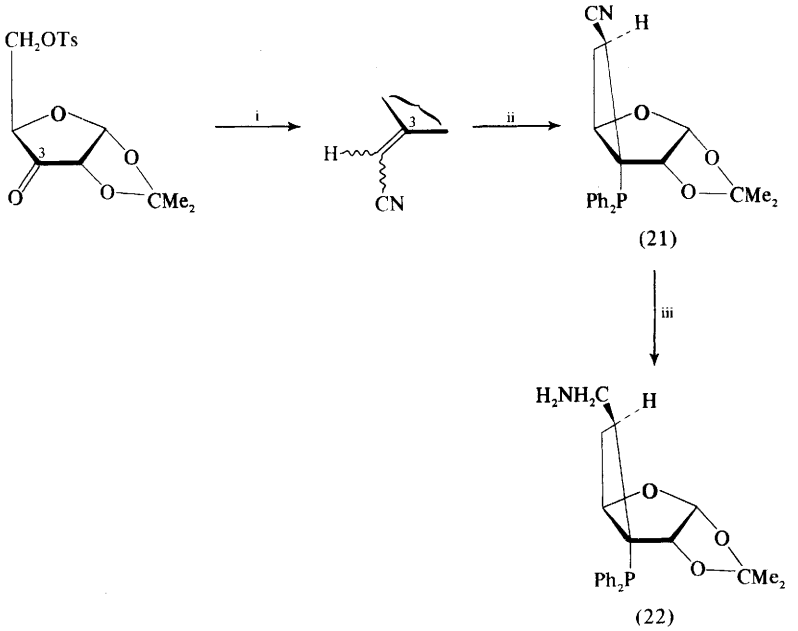
(18)



(19)



(20)



Reagents: i, $Ph_3P{=}CHCN$; ii, Ph_2PNa–THF; iii, $LiAlH_4$

Scheme 6

[23] J. E. N. Shin and A. S. Perlin, *Carbohydr. Res.*, 1980, **84**, 315.

Additions of phosphinates to glycosuloses have been utilized to synthesize 5,6-dideoxy-5-*C*-phosphinyl-D-*xylo*-hexose derivatives (Scheme 5).[24] A similar reaction was used to prepare the α-hydroxyphosphinates (18)–(20).[25] 4-Deoxy-D-*erythro*-tetrose 4-phosphonate and 4,5-dideoxy-D-*erythro*-pentose 5-phosphonate have been obtained by lead tetra-acetate oxidation of D-glucose 6-phosphonate and the 6-homophosphonate.[26] Sugar phosphine derivatives (21) and (22) prepared by the route shown in Scheme 6 have been used in conjunction with $Ru(C_8H_{14})_2Cl$ complex to provide a chiral hydrogenation catalyst. The cyano-compound (21) gave optical yields of up to 91.6% *S*-isomer in reductions of methyl (*Z*)-2-acetamide-3-phenylpropenoate.[27] Some phosphorus derivatives of D-glucose, D-xylose, and D-mannitol for use in asymmetric catalysis are mentioned in Chapter 6.

[24] S. Inokawa, K. Yamamoto, Y. Kawata, H. Kawamoto, H. Yamamoto, K. Takagi, and M. Yamashita, *Carbohydr. Res.*, 1980, **86**, C11.

[25] M. Yamashita, P. T. Long, M. Shibata, and S. Inokawa, *Carbohydr. Res.*, 1980, **84**, 35.

[26] P. LeMaréchal, C. Froussios, M. Level, and R. Azerad, *Biochem. Biophys. Res. Commun.*, 1980, **92**, 1097.

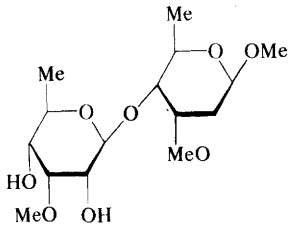
[27] Y. Nakamura, S. Saito, and Y. Morita, *Chem. Lett.*, 1980, 7.

11

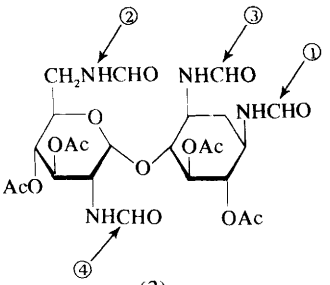
Deoxy-sugars

A new trideoxy disaccharide (1) has been isolated from *Marsdenia tenacissima*,[1] which is composed of 6-deoxy-3-*O*-methyl-D-allose and its 2-deoxy derivative, cymarose. Full details are now published of the identity of variose (from the antibiotic variamycin) and D-cymarose (Vol. 13, p. 107).[2]

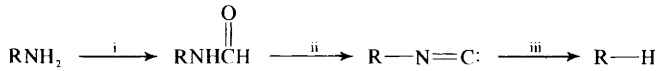
Full details of the reductive deamination of amino-sugars by the sequence shown in Scheme 1 have been reported. It is usually necessary to have hydroxy-groups protected by acetylation and in this way 2-deoxy-α- and -β-D-*arabino*-hexose tetra-acetates can be made in high overall yields.[3] The reaction has been applied to the neamine derivative (2) with which the reaction proceeds in a stepwise fashion allowing mono-, di-, tri-, and tetra-deoxy derivatives to be isolated. The order of reduction is indicated on the structure (2).[4]



(1)



(2)



Reagents: i, *p*-$NO_2C_6H_4OCHO$; ii, $POCl_3$–Et_3N; iii, Bu_3SnH

Scheme 1

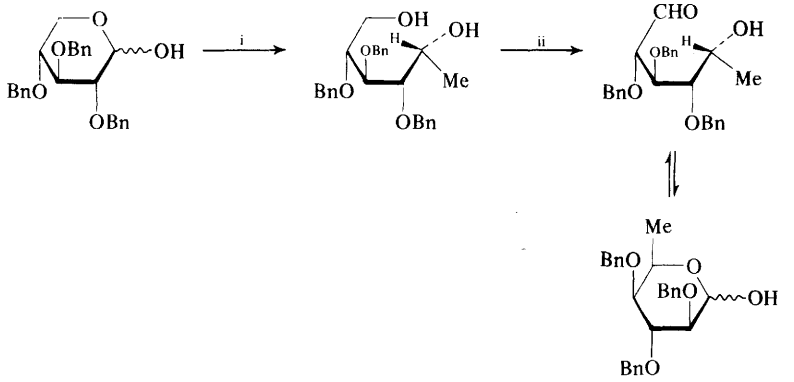
[1] S. Singhal, M. P. Khare, and A. Khare, *Indian J. Chem., Sect. B*, 1980, **19**, 425 (*Chem. Abstr.*, 1980, **93**, 105 577c).

[2] J. S. Brimacombe, Z. Al-Hasan, and A. S. Mengech, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1800.

[3] D. H. R. Barton, G. Bringmann, G. Lamotte, W. B. Motherwell, R. S. Hay Motherwell, and A. A. E. Porter, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2657.

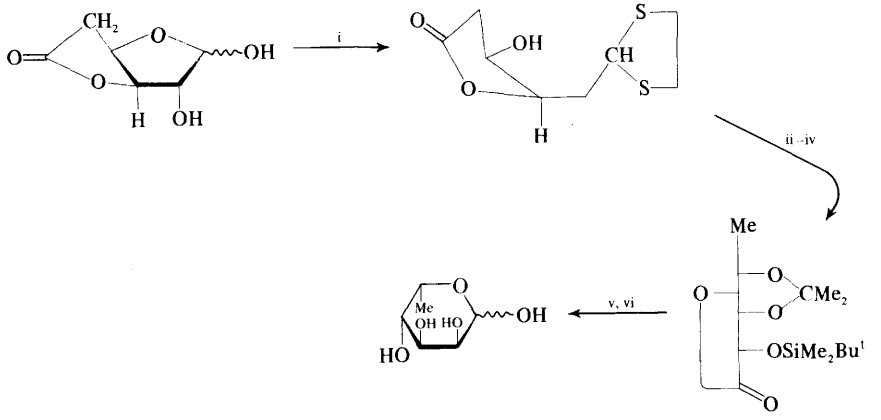
[4] D. H. R. Barton, G. Bringmann, and W. B. Motherwell, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2665.

A novel and simple synthesis of 2,3,4-tri-*O*-benzyl-6-deoxy-D-idopyranose has been accomplished by ascent of the series *via* a Grignard reagent (Scheme 2). Methyl magnesium iodide reacted stereospecifically with 2,3,4-tri-*O*-benzyl-D-xylopyranose to give the 6-deoxy-D-iditol derivative, which on oxidation was converted to the 6-deoxyhexose derivative. Ethyl magnesium bromide showed a similar high stereoselectivity.[5] An efficient synthesis of 6-deoxy-L-gulose has been reported from D-glucurono-1,5-lactone, by conversion of the reducing group to a deoxy-function *via* a thioacetal and partial reduction of the lactone group to aldehyde (Scheme 3).[6]



Reagents: i, MeMgBr; ii, NCS-Me_2S

Scheme 2



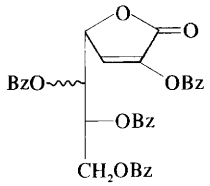
Reagents: i, $(HSCH_2)_2$-H^+; ii, $(MeO)_2CMe_2$-H^+; iii, Ni; iv, Bu^tMe_2SiCl; v, Bu^i_2AlH; vi, H^+

Scheme 3

[5] Y. Tsuda, T. Nunozawa, and K. Yoshimoto, *Chem. Pharm. Bull.*, 1980, **28**, 3223.
[6] R. E. Ireland and C. S. Wilcox, *J. Org. Chem.*, 1980, **45**, 197.

Photolytic decarbonylation of several 6-deoxy-α-L-*lyxo*-hex-4-ulopyranosides, and related *C*-glycosides, yielded mainly the 5-deoxy-β-D-ribofuranosides.[7]

A rapid procedure for the synthesis of 2-deoxy-D-[1-^{14}C]*arabino*-hexose has been reported from D-arabinitol by a five-step procedure. The label is introduced by nucleophilic displacement of a 1-iodo-function and the nitrile subjected to hemihydrogenation. The speed with which the final two steps can be accomplished makes it suitable for the labelling of the sugar with ^{11}C with a half-life of only 20 min.[8] The preparation of 2-deoxy-D-*arabino*- and -D-*lyxo*-hexoses has been achieved from the diethyl dithioacetals of D-glucose and D-galactose, respectively, by an extension of a previously described procedure[9] (Vol. 11, p. 103). Benzoylation of D-*glycero*-D-*gulo*- and D-*glycero*-L-*manno*-heptono-1,4-lactones afforded the products of β-elimination (3), which upon catalytic hydrogenation afforded the 3-deoxy-D-*gluco*- and -D-*manno*-heptono-1,4-lactones which in turn on debenzylation and Wöhl degradation (with Ce^{IV} sulphate) afforded the 2-deoxyhexoses.[10] The synthesis of 2-deoxy-DL-pentoses[11] and some chlorinated derivatives[12] thereof are reported.

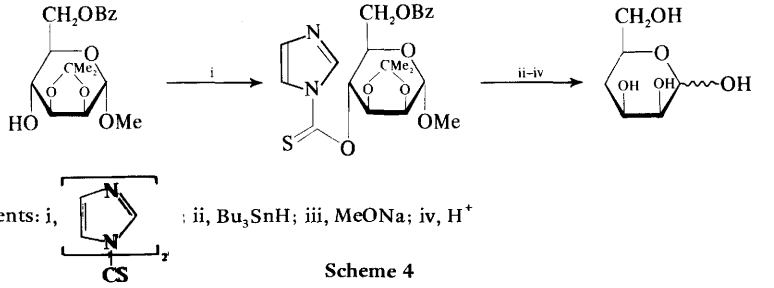


(3)

When epoxides with a *trans*-related sulphonyloxy-group are reduced with Raney nickel and other reducing agents, deoxy-products are formed resulting from the participation of the sulphonyloxy-group in epoxide ring formation. However, this can be avoided by the use of diborane in the presence of borohydride ion, and consequently reduction of methyl 2,3-anhydro-4-*O*-tosyl-β-L-lyxopyranoside afforded the 2- and 3-deoxy-derivatives with the tosyl group intact in 65 and 23% yields, respectively.[13]

A new and apparently convenient synthesis of 4-deoxy-D-*lyxo*-hexose involves reaction of methyl 6-*O*-benzoyl-2,3-*O*-isopropylidene-α-D-mannopyranoside with the adduct formed from imidazole and thiophosgene followed by reduction of the resulting thiocarbamate with tributylstannane (Scheme 4.)[14] Reduction of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(methylthio)thiocarbonyl-β-D-altrofuranose

[7] P. M. Collins and A. S. Travis, *J. Chem. Soc., Perkin Trans. 1*, 1980, 779.
[8] G. Mestelan, F. Aubert, J. P. Beaucourt, D. Comar, and L. Pichat, *J. Labelled Compd. Radiopharm.*, 1979, **16**, 179, *ibid.*, p. 661 (*Chem. Abstr.*, 1980, **92**, 76 809, *ibid.*, 198 648).
[9] M. Y. H. Wong and G. R. Gray, *Carbohydr. Res.*, 1980, **80**, 87.
[10] L. F. Sala, A. F. Cirelli, and R. M. de Lederkremer, *Carbohydr. Res.*, 1980, **78**, 61.
[11] S. M. Makin, Yu. E. Raifel'd, and O. V. Limanova, *Zh. Org. Khim.*, 1979, **15**, 1843 (*Chem. Abstr.*, 1980, **92**, 111 234).
[12] N. Mitsuo, Y. Abe, T. Takizawa, and T. Kunieda, *Chem. Pharm. Bull.*, 1980, **28**, 1327.
[13] Y. L. Fu and M. Bobek, *J. Org. Chem.*, 1980, **45**, 3836.
[14] J. R. Rasmussen, *J. Org. Chem.*, 1980, **45**, 2725.



Reagents: i, ; ii, Bu_3SnH; iii, MeONa; iv, H^+

Scheme 4

and -mannofuranose with tributyltin deuteride indicated that the reaction occurred with retention of configuration. However, similar reduction of epimeric 4-xanthates in the pyranose series gave the same mixture of epimeric deuteriated products indicating a common radical intermediate.[15]

Methyl glycosides and the 1,2-*O*-isopropylidene derivative of 4-deoxy-DL-*threo*-pentose have been prepared by standard reactions.[16]

Durette has reported an expeditious synthesis of methyl 2,6-dideoxy-α-D-*arabino*-hexopyranoside from the 2-deoxyglycoside by specific iodination at C-6 using imidazole, iodine, and triphenylphosphine, followed by reductive dehalogenation.[17] The 4-*O*-benzyl ether of the corresponding benzyl glycoside has also been prepared by standard procedures, along with the β-glycoside.[18] Methyl 2,6-dideoxy-α-D-*xylo*- and -α-D-*lyxo*-hexopyranosides have been synthesized from methyl 3,4-anhydro-6-deoxy-α-D-galactopyranoside and triacetylgalactal, respectively, by standard reactions.[19] 2,6-Dideoxy-DL-hexoses as acetals and methyl ethers have been synthesized from the stereospecific hydroxylation of *trans*-4,6,6-trimethoxyhex-2-ene and *trans*-6,6-dimethoxy-hex-3-en-2-ol.[20]

A synthesis of ascarylose (3,6-dideoxy-L-*arabino*-hexose) from 3,6-dideoxy-L-*erythro*-hexos-2-ulose is reported by base-catalysed rearrangement of the 2-ulose to 3,6-dideoxy-L-*arabino*-hexono-1,4-lactone followed by reduction with sodium bis(2-methoxyethoxy)aluminium hydride.[21]

The total synthesis of all four 3,6-dideoxy-DL-hexoses and all four 3-deoxy-DL-hexoses has been achieved by stereospecific hydroxylations of butyl 2-acetoxy-*trans*-hex-4-enoate and butyl 2-acetoxy-6-hydroxy-*trans*-hex-4-enoate, respectively.[22] In an alternative synthesis 3,6-dideoxy-DL-*arabino*- and -DL-*ribo*-hexopyranoses were prepared from the Diels–Alder adduct derived from methyl

[15] T. S. Fuller and R. V. Stick, *Aust. J. Chem.*, 1980, **33**, 2509.
[16] C. Gagnieu and A. Grouiller, *Carbohydr. Res.*, 1980, **84**, 61.
[17] P. L. Durette, *Synthesis*, 1980, 1037.
[18] J. Thiem, J. Elvers, and J. P. Lorentzen, *Chem. Ber.*, 1980, **113**, 2827.
[19] M. Marek and J. Jary, *Collect. Czech. Chem. Commun.*, 1980, **45**, 2979.
[20] S. M. Makin, Yu. E. Raifel'd, O. V. Limanova, and B. M. Arshava, *Zh. Org. Khim.*, 1980, **16**, 1179 (*Chem. Abstr.*, 1980, **93**, 168 502).
[21] V. N. Shibaev, V. A. Petrenko, L. L. Danilov, N. S. Utkina, M. I. Struchkova, and N. K. Kochetkov, *Izv. Akad. Nauk, SSSR, Ser. Khim.*, 1980, 158 (*Chem. Abstr.*, 1980, **92**, 215 658).
[22] M. Chmielewski, *Tetrahedron*, 1980, **36**, 2345.

vinyl ketone and isobutyl vinyl ether by a sequence of hydroboration, oxidation, acetylation, and elimination.[23] 3,4-Dideoxy-DL-*threo*- and -DL-*erythro*-hexoses and 3,4,6-trideoxy-DL-*threo*- and -DL-*erythro*-hexoses have been made as glycosides starting from dihydropyran derivatives.[24]

Alkylation of 2-deoxy-3,4 : 5,6-di-*O*-isopropylidene-D-*arabino*-hexose diethyl dithioacetal at C-1 with butyl lithium–methyl iodide afforded the corresponding derivative of 1,3-dideoxy-D-*arabino*-heptulose.[25]

[23] G. Berti, G. Catelani, S. Magi, and L. Monti, *Gazz. Chim. Ital.*, 1980, **110**, 173 (*Chem. Abstr.*, 1980, **93**, 168 504).

[24] A. Saroli, D. Descours, G. Carret, D. Anker, and H. Pacheco, *Carbohydr. Res.*, 1980, **84**, 71.

[25] D. Horton and R. A. Markovs, *Carbohydr. Res.*, 1980, **78**, 295.

12

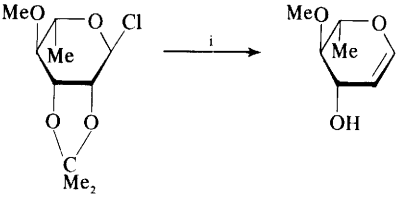
Unsaturated Derivatives

A new review on the reactions of unsaturated sugars and their derivatives has appeared in two parts.[1]

1 Glycals

^{13}C Spectral data on 24 derivatives of D-glucal and D-allal have been published, and the chemical shifts were discussed in terms of atomic charge densities.[2]

Ireland and his co-workers have amplified their studies on the synthesis of furanoid and pyranoid glycals (Scheme 1) and their use in the synthesis of 2,3-unsaturated C-glycosides (see Chapter 3).[3]



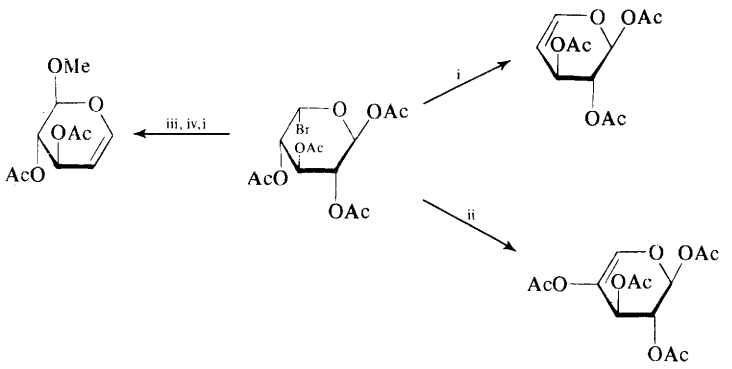
Reagent: i, Li–NH_3

Scheme 1

Unusual types of pyranoid glycal derivatives with electronegative substituents at C-5 have been encountered during studies of 5-bromo-D-xylopyranose tetra-acetate (Scheme 2).[4] In the course of related work a 5-bromo-D-glucopyranosyl bromide ester was obtained which gave a diene having a glycal structure with an additional exocylic double bond (see Chapter 7).

The allylic rearrangement undergone by glycal derivatives has received further attention. Tri-*O*-acetyl-D-glucal or -allal, on treatment with sodium azide in acetonitrile in the presence of boron trifluoride, give the allylic glycosyl carbonium ion and then a mixture of the α- and β-2,3-unsaturated glycosyl azides and 3-azido-2-deoxy-D-allal and -glucal diacetates. In similar fashion, 2,3-unsaturated starting materials (glycosides or glycosyl acetates) also gave these four compounds. The azides, on treatment with carbon disulphide in the presence of triphenylphosphine, gave 4,6-di-*O*-acetyl-3-deoxy-3-isothiocyanato-D-allal and

[1] K. Heyns and J. Feldmann, *Staerke*, 1980, **32**, 40, *ibid.*, p. 92 (*Chem. Abstr.*, 1980, **93**, 26 662).
[2] R. D. Guthrie and R. W. Irvine, *Aust. J. Chem.*, 1980, **33**, 1037.
[3] R. E. Ireland, S. Thaisrivongs, N. Vanier, and C. S. Wilcox, *J. Org. Chem.*, 1980, **45**, 48.
[4] R. J. Ferrier and P. C. Tyler, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2767.



Reagents: i, Zn–HOAc; ii, DBU; iii, MeOH–Ag_2O; iv, HBr–HOAc

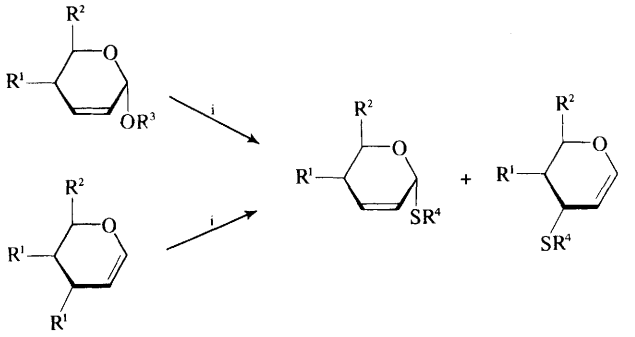
Scheme 2

-D-glucal.[5] In related fashion, tri-*O*-benzoyl-D-glucal and -D-allal treated with azide in HMPT afforded analogues of the same four products, but the 4,6-*O*-benzylidene-3-*O*-benzoylglycals gave the 3-azidoglycal isomers exclusively. The mechanisms of these reactions are discussed in detail.[6] Similar processes occur with benzyl-protected compounds, and mixtures of 3-azidoglycals and 2,3-unsaturated glycosyl azides are obtained from 3,4,6-tri-*O*-benzyl-D-glucal and benzyl 4,6-di-*O*-benzyl-2,3-dideoxy-hex-2-enopyranosides. Again, however, 4,6-*O*-benzylidene compounds resulted in 3-azidoglycal products exclusively. Contrary to an earlier report (*Ber.*, 1978, **111**, 1632) the 2,3-unsaturated glycosyl azides do isomerize to 3-azidoglycals.[7] Related studies on the reaction of glycal esters with thiols showed that both types of allylic products were obtained either by use of protonic catalysts or with tin(IV) chloride (Scheme 3). Under equilibrating conditions the 3-thioglycals predominated.[8]

A 2-acetoxyglycal derivative is illustrated in Scheme 2 above, and related compounds were prepared from fully acylated 5-bromo-D-glucose (Scheme 4). Exocyclic alkenes were also produced, and were the main isomers derived by use of zinc and acetic acid.[9]

Other examples of C-1 substituted glycals are compounds (1) and (2) which have been obtained, respectively, by eliminations from tri-*O*-benzoyl-L-rhamnopyranosyl nitrile and 2,3:4,5-di-*O*-benzylidene-L-sorbofuranose. The former product, on debenzoylation, gave a diol which could be oxidized to the conjugated enone or the γ-pyrone;[10] compound (2) was derived by use of butyllithium.[11]

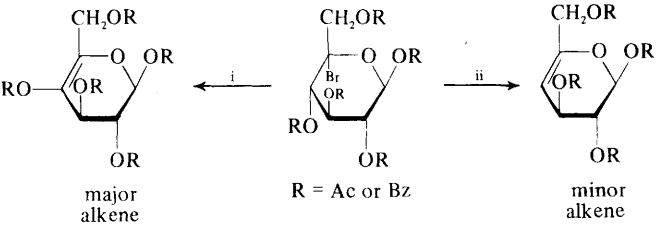
[5] R. D. Guthrie and R. W. Irvine, *Carbohydr. Res.*, 1980, **82**, 207.
[6] R. D. Guthrie, R. W. Irvine, and I. D. Jenkins, *Aust. J. Chem.*, 1980, **33**, 2499.
[7] R. D. Guthrie and R. W. Irvine, *Carbohydr. Res.*, 1980, **82**, 225.
[8] W. Priebe and A. Zamojski, *Tetrahedron*, 1980, **36**, 287.
[9] R. Blattner, R. J. Ferrier, and P. C. Tyler, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1535.
[10] T. Huynh-Dinh, C. Gouyette, and J. Igolen, *Tetrahedron Lett.*, 1980, **21**, 4499.
[11] A. Klemer, G. Jung, and E. Meissner, *Chem. Ber.*, 1980, **113**, 1761.



R^1 = H or OAc; R^2 = CH_2OAc or CH_2NHAc; R^3 = Me or C_6H_{13}; R^4 = alkyl

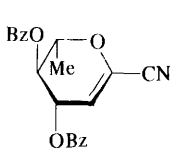
Reagent: i, R^4SH–H^+ or $SnCl_4$

Scheme 3

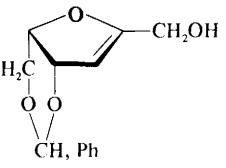


Reagents: i, DBU; ii, Zn–HOAc

Scheme 4



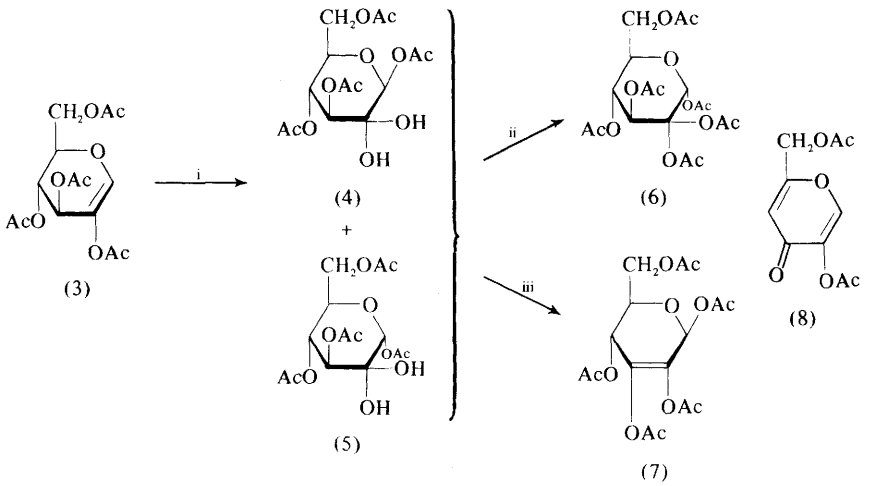
(1)

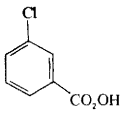


(2)

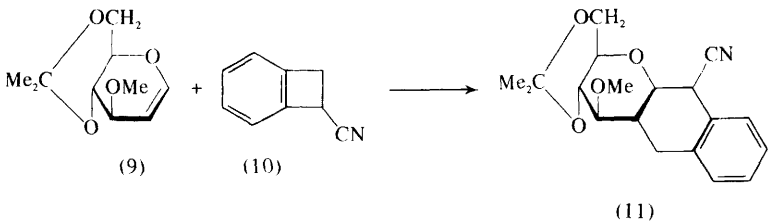
Oxidation of the 2-hydroxyglycal ester (3) with *m*-chloroperbenzoic acid gave the anomeric hexos-2-ulose acetates (4) and (5) which, on acetylation under acidic conditions, gave the α-hexa-acetate (6). Alternatively, acetyl chloride in pyridine led to the β-enediol penta-acetate (7); further elimination gave the γ-pyrone (8). The chemistry of these and several other reactions has been described in a lengthy paper and is outlined in Scheme 5.[12] The chlorination of 2-hydroxyxylal esters is described in Chapter 7.

[12] F. W. Lichtenthaler and P. Jarglis, *Chem. Ber.*, 1980, **113**, 489.



Reagents: i,  ; ii, Ac_2O–H^+; iii, AcCl–py

Scheme 5



Scheme 6

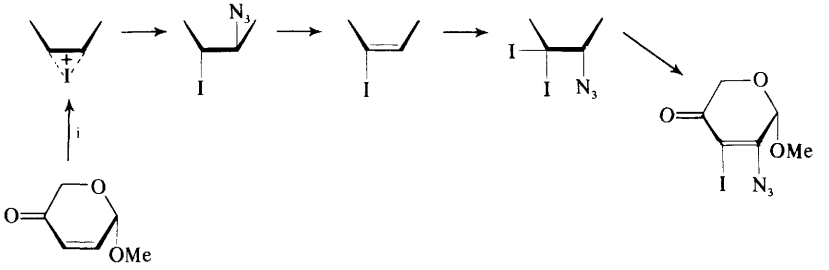
The glycal derivative (9), on heating with the cyclobutane (10), gave the adduct (11) (Scheme 6) which was used[13] to prepare a model of the aglycone of aureolic acid (Chapter 23).

2 Other Unsaturated Derivatives

New methods of introducing double bonds into sugar rings continue to appear, and this year 3-methyl-2-selenoxo-1,3-benzothiazole applied to epoxides is advocated. In dichloromethane and in the presence of trifluoroacetic acid it gives the alkenes in high yield.[14] Otherwise, potassium iodide, zinc, and phosphorus pentoxide in DMF at 90 °C can be used effectively, methyl 2,3-

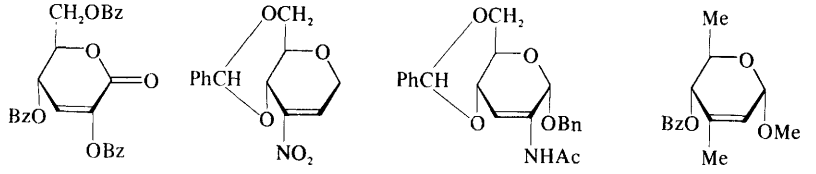
[13] R. W. Franck and T. V. John, *J. Org. Chem.*, 1980, 45, 1170.
[14] H. Paulsen, F. R. Heiker, J. Feldmann, and K. Heyns, *Synthesis*, 1980, 636.

anhydro-4,6-*O*-benzylidene-α-D-manno- and -allo-pyranoside giving methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside in 83 and 86% yield, respectively.[15] The same product has been obtained in similar yield from methyl 4,6-*O*-benzylidene-2-*O*-toluene-*p*-sulphonyl-α-D-glucopyranoside by treatment with sodium iodide and a zinc–copper couple in refluxing DMF–dimethoxyethane which, at least applied to this compound, were more effective than the similar Tipson–Cohen procedures.[16]



Reagent: i, ICl–NaN_3, −30 °C

Scheme 7

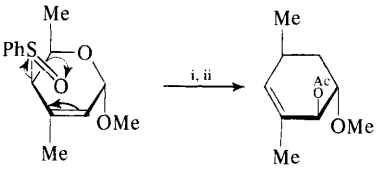


(12) (13) (14) (15)

By a set of addition–elimination reactions the iodo- and azido-groups can be introduced on to the double bond of enones (Scheme 7), and this could be useful in carbohydrate synthesis.[17] Several compounds have been reported which have 2,3-double bonds carrying other substituents. Reaction of tetra-*O*-benzoyl-2-bromo-D-glucono-1,5-lactone (Chapter 7) with sodium iodide in acetone gave the enone (12).[18] The 3-nitroalkene (13) was obtained from 1,5-anhydro-D-glucitol by periodate cleavage and nitromethane cyclization, and its additions with nucleophiles were studied.[19] The 2-acetamidoalkene (14) was produced, together with the 3-deoxy-3-ene and the 3-azide, on treatment of benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-methanesulphonyl-α-D-allopyranoside with sodium azide,[20] and the 3-methylalkene (15) has been isolated after treat-

[15] P. J. Garegg, D. Papadimas, and B. Samuelsson, *Carbohydr. Res.*, 1980, **80**, 354.
[16] B. K. Radatus and I. S. Clarke, *Synthesis*, 1980, 47.
[17] G. Kuświk and G. Grynkiewicz, *Pol. J. Chem.*, 1980, **54**, 1319.
[18] R. J. Ferrier and P. C. Tyler, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2762.
[19] T. Sakakibara, Y. Nomura, and R. Sudoh, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1642.
[20] W. Meyer zu Reckendorf and H. Hehenberger, *Chem. Ber.*, 1980, **113**, 3089.

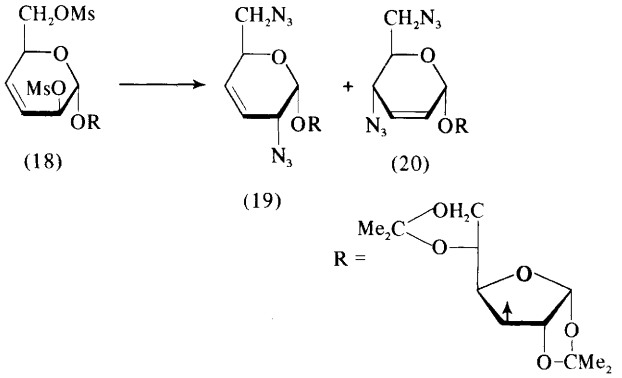
ment of a 2-deoxy-3-*C*-methylhexose derivative with a chlorinating agent.[21] Hydroboration of compound (14) and the 3-ene mentioned above afforded the corresponding 2-acetamido-2-deoxy-D-glucose derivative. Debenzoylation of the branched-chain compound (15) and treatment with *N*-(thiophenyl)succinimide and tributylphosphine gave an allylic phenylthio-compound. The derived sulphoxide (16) on heating in trimethyl phosphite followed by acetylation gave the rearranged acetate (17) (Scheme 8) from which a 4-amino-sugar derivative was obtained.



(16) (17)

Reagents: i, $(MeO)_3P$; ii, Ac_2O–py

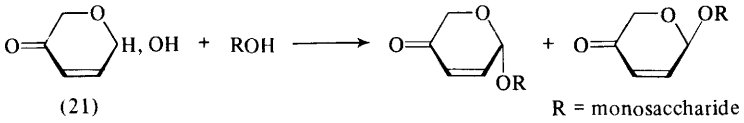
Scheme 8



Scheme 9

Treatment of the disaccharide allylic mesylate (18) with sodium azide gave the product of S_N2 displacement (19) (30%) and also the rearranged isomer (20) (42%) (Scheme 9). The former, after reduction, gave a disaccharide derivative of purpurosamine.[22] A further report on unsaturated disaccharide derivatives describes the condensation between 1,2 : 3,4-di-*O*-isopropylidene-α-D-galactose, 1,2 : 5,6-di-*O*-isopropylidene-α-D-glucose, and benzyl and methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside and the enone (21) brought about by the use of diethyl azodicarboxylate and triphenylphosphine in the presence of mercury(II) bromide. Enone products were formed as shown (Scheme 10), and

[21] I. Dyong and G. Schulte, *Tetrahedron Lett.*, 1980, **21**, 603.
[22] S. David, A. Lubineau, and S. D. Gero, *J. Org. Chem.*, 1979, **44**, 4986.

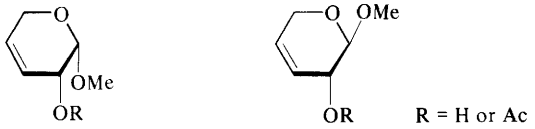


(21)

Scheme 10

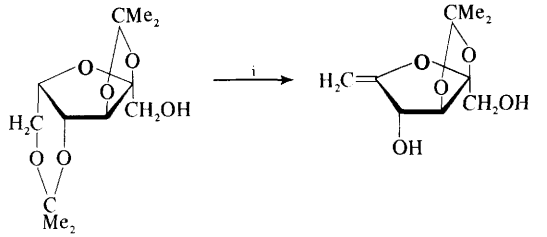
these on reduction gave dideoxypentosyl-disaccharides and 2,3-unsaturated derivatives thereof, which were structurally characterized.[23]

^{13}C Spectra of 22 racemic methyl 3,4-dideoxyald-3-enopyranosides have been recorded, and from the data acquired conformational equilibria were estimated. For the pentose members (22) and (23) of the series the preferred conformations are the half-chairs with the anomeric groups held axial by the anomeric effect.[24]



(22) (23)

In Chapter 19 reference is made to a 2′,3′-unsaturated nucleoside being hydroxylated to a ribofuranosyl compound which then, *via* the 5′-deoxy-5′-iodo-analogue was converted into the 5′-deoxy-4-enofuranosyl nucleoside. A compound with a related alkene system has been obtained from an L-sorbofuranose acetal (Scheme 11).[11] [*cf.* Compound (2) above.]

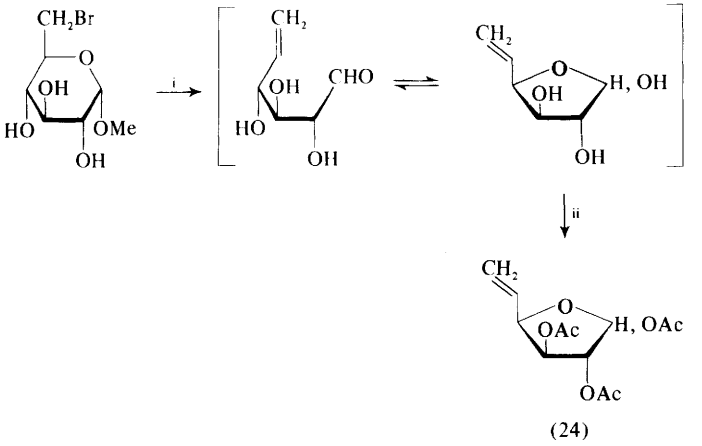


Reagent: i, BuLi

Scheme 11

An extension of the reaction of Bernet and Vasella (see Vol. 13, p. 122) by which fully protected 6-bromo-6-deoxyhexopyranosides are converted into acyclic aldehydic 5,6-dideoxyhex-5-enoses involves conversion of unsubstituted methyl 6-bromo-6-deoxyhexopyranosides into the corresponding 5,6-unsatur-

[23] G. Grynkiewicz, *Carbohydr. Res.*, 1980, **80**, 53.
[24] M. Chmielewski, A. Banaszek, A. Zamojski, and H. Adamowicz, *Carbohydr. Res.*, 1980, **83**, 3.

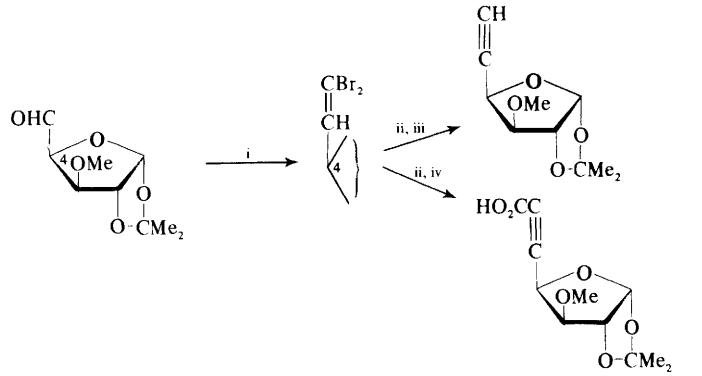


(24)

Reagent: i, 'active' Zn–MeOH; ii, Ac_2O–py

Scheme 12

ated furanosyl acetates [*e.g.*, (24), Scheme 12]. Several examples of conversion at about 70% efficiency were recorded; by-products were formed by reductive C—Br bond cleavage.[25] Compounds with 6-substituted double bonds are obtainable from dialdofuranose derivatives by application of the Wittig reaction, and Tronchet and colleagues have described 5,6-dideoxyhex-5-enofuranoses with fluorine, chlorine, bromine, and cyanide groups in pairs at C-6.[26–28] The geminal dibromides could be converted to terminal alkynes or hept-5-ynofuranose uronic acids (Scheme 13).[28]

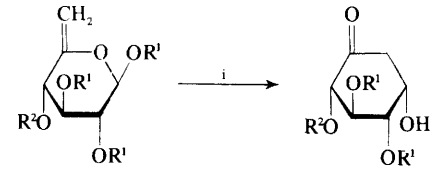


Reagents: i, $Ph_3P = CBr_2$; ii, BuLi; iii, H_2O; iv, CO_2

Scheme 13

[25] M. Nakane, C. R. Hutchinson, and H. Gollman, *Tetrahedron Lett.*, 1980, **21**, 1213.
[26] J. M. J. Tronchet and O. R. Martin, *Carbohydr. Res.*, 1980, **85**, 187.
[27] J. M. J. Tronchet and A.-P. Bonenfant, *Helv. Chim. Acta*, 1980, **63**, 1644.
[28] J. M. J. Tronchet, A.-P. Bonenfant, F. Pervet, A. Golzalez, J.-B. Zumwald, E. M. Martinez, and B. Baehler, *Helv. Chim. Acta*, 1980, **63**, 1181.

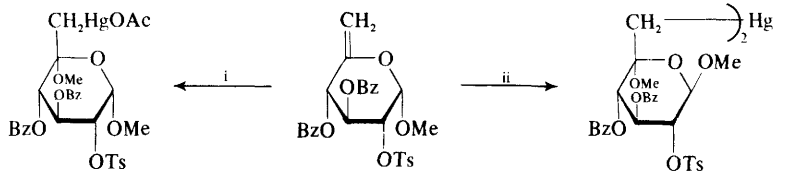
Treatment of 6-deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-α-D-galactose with potassium phthalimide led to small amounts of the terminal alkene,[29] and related 6-deoxyhex-5-enopyranoses are produced, as main products, on treatment of 5-bromo-penta-*O*-acetyl- and -*O*-benzoyl-β-D-glucopyranose with zinc and acetic acid (*cf.* Scheme 4); the exocyclic alkenes derived by loss of hydrogen bromide were formed when the bromides were treated with sodium iodide in acetone.[9] The 6-deoxyalkenes can be converted in good yield into inosose derivatives by treatment with mercury(II) salts in the presence of water. An α-glucosylated inosose was also made in this manner (Scheme 14).[30] Methoxymercuration of these alkenes give stable adducts containing one or two sugar units bonded to the metal; in the latter case reaction occurs with anomeric inversion (Scheme 15). The chemistry of the adducts was described.[31]



R^1 = Ac or Bz
R^2 = Ac, Bz, or tetra-*O*-acetyl-α-D-glucopyranosyl

Reagent: i, $Hg(OAc)_2$–H_2O

Scheme 14



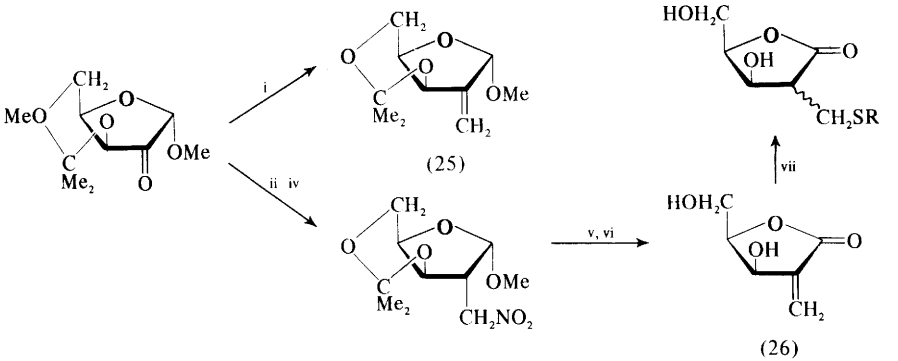
Reagents: i, $Hg(OAc)_2$–MeOH; ii, PhHgOAc–MeOH

Scheme 15

Other examples have been given of the preparation of branched-chain and extended-chain alkenes by application of Wittig reagents to sugar aldehydes and ketones,[32] and the mass spectra of alkenes derived from 1,2:5,6-di-*O*-isopropylidene-D-*ribo*-hexos-3-ulose have been described.[33] Compound (25) was

[29] B. Coxon and R. C. Reynolds, *Carbohydr. Res.*, 1980, **78**, 1.
[30] R. Blattner, R. J. Ferrier, and P. Prasit, *J. Chem. Soc., Chem. Commun.*, 1980, 944.
[31] R. J. Ferrier and P. Prasit, *Carbohydr. Res.*, 1980, **82**, 263.
[32] E. Martinez, J. Usov, and M. Perez de Eulate, *Carbohydr. Res.*, 1980, **85**, 307.
[33] A. Glangetas, F. O. Gülacar, J. M. J. Tronchet, and A. Buchs, *Helv. Chim. Acta*, 1980, **63**, 1740.

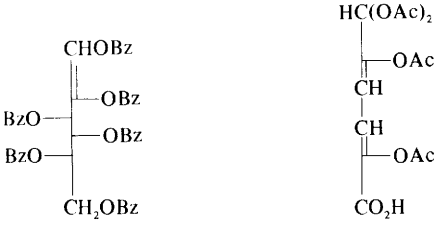
made by a standard Wittig synthesis, but on acid hydrolysis it gave a furan rather than an α-methylene-γ-butyrolactone (such compounds are potent cytotoxic compounds). The desired compound (26) was, however, made by nitromethane addition to the initial 2-ulose and subsequent elimination (Scheme 16), and it reacted with thiols as indicated.[34]



Reagents: i, $Ph_3P{=}CH_2$; ii, $\bar{C}H_2NO_2$; iii, Ac_2O–DMSO; iv, $NaBH_4$; v, H^+; vi, Br_2–HOAc; vii, RSH

Scheme 16

The acyclic alkene (27) was produced amongst the compounds formed by benzoylation of L-sorbose at room temperature with benzoyl chloride in pyridine; on ozonolysis it gave 2,3,4,5-tetra-*O*-benzoyl-L-xylonic acid.[35] The diene (28) is a product of base-catalysed acetylation of D-mannuronolactone.[36]



[34] V. Nair and A. K. Sinhababu, *J. Org. Chem.*, 1980, **45**, 1893.
[35] M. E. Gelpi, M. C. Teglia, and R. A. Cadenas, *Carbohydr. Res.*, 1980, **83**, 73.
[36] K. Tajima, H. Itoh, and H. Marooka, *Chem. Lett.*, 1980, 1465.

13

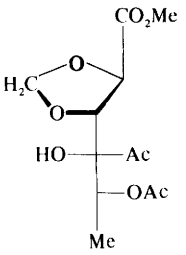
Branched-chain Sugars

1 Natural Products

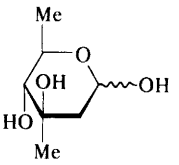
The branched-chain aldonic acids, 2-*C*-methyl-D-erythronic acid and a 2-*C*-hydroxymethylpentonic acid have been isolated from *Phaseolus vulgaris*,[1] and the former has also been isolated from the plants *Trifolium incarnatum*[1] and *Astragulus lusitanicus*.[2] Methyl *O*-acetyleurekanate, a degradation product of flambamycin and avilamycin has been shown to be methyl 4-*C*-acetyl-5-*O*-acetyl-6-deoxy-2,3-*O*-methylene-D-galactonate (1) by *X*-ray crystallography and by degradation.[3]

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

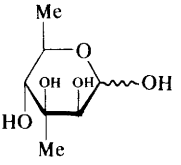
Yoshimura's group have reported the synthesis of a number of branched-chain sugars which occur as components of the oligosaccharide antibiotics evernino-micin B, C, and D, to wit, D-evermicose (2), D-evalose (3), and 6-deoxy-4-*C*-hydroxymethyl-5-*O*-methyl-2,3-*O*-methylene-L-idono-1,4′-lactone (4) as well as L-evernitrose (see Chapter 9). Compounds (2) and (3) were prepared from the corresponding glycos-3-ulosides by standard reactions,[4] and the lactone (4) was synthesized from benzyl 2,3-di-*O*-benzoyl-β-L-arabinopyranoside (Scheme 1).[4,5] Compound (4) is closely related to methyl eurekanate (1) obtained from related antibiotics. The methyl α-pyranoside of D-virenose (6-deoxy-3-*C*-methyl-D-gulose),



(1)

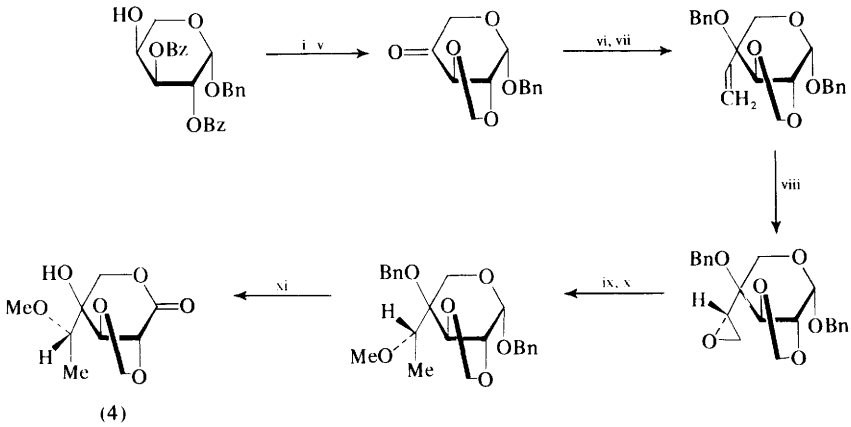


(2)



(3)

[1] R. W. Schramm, B. Tomaszewska, and G. Petersson, *Phytochemistry*, 1979, **18**, 1393.
[2] J. de Pascual Teresa, J. C. Hernández Aubanell, A. San Feliciano, and J. M. Miguel del Corral, *Tetrahedron Lett.*, 1980, **21**, 1359.
[3] E. Kupfer, K. Neupert-Laves, M. Dobler, and W. Keller-Schierlein, *Helv. Chim. Acta*, 1980, **63**, 1141.
[4] M. Matsuzawa, N. Hong, and J. Yoshimura, *Koen Yoshishu-Tennen Yuki Kagoliutsu Toronkai*, 1979, 485 (*Chem. Abstr.*, 1980, **92**, 215 656).
[5] M. Matsuzawa and J. Yoshimura, *Carbohydr. Res.*, 1980, **81**, C5.



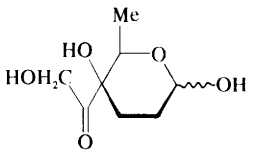
(4)

Reagents: i, AcOH–DMSO–Ac_2O; ii, NaOMe; iii, CH_2Cl_2–NaH; iv, Hg_2Cl_2–$CaCO_3$; v, DMSO–$(F_3CCO)_2O$; vi, CH_2=$CHCH_2MgBr$; vii, BnBr–NaH; viii, *m*-CPBA; ix, $LiAlH_4$; x, MeI–Ag_2O; xi, Br_2–MeOH–H_2O

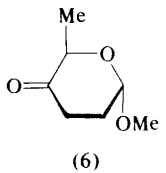
Scheme 1

a diastereomer of (3), has been similarly synthesized from the 3-uloside derived from oxidation of methyl 4,6-*O*-benzylidene-2-*O*-benzyl-α-D-galactopyranoside. Reaction of the 3-uloside with methyl magnesium iodide afforded only the 3-*C*-methylgulopyranoside, which was deoxygenated at C-6 in the customary way to give methyl α-D-virenoside.[6]

The introduction of functionalized two-carbon side-chains, as found in (1) and (4) has received some attention. The usual way is by reaction of a suitable keto-derivative with a vinyl Grignard reagent, followed by functionalization of the vinyl group by way of epoxidation. In this way Fraser-Reid and Walker[7] achieved a synthesis of pillarose (2,3,6-trideoxy-4-*C*-hydroxyacetyl-D-*threo*-hexose) (5) from the 4-uloside (6). As an alternative method, Brimacombe's group have published details of the use of 1-methoxyvinyl lithium, which reacts with keto-compounds to give a 1-methoxyvinyl side-chain capable of functionalization in various ways. For example, Scheme 2 shows its application to 1,2 : 5,6-di-*O*-isopropylidene-α-D-*ribo*-hex-3-ulose.[8] Reaction of this reagent with methyl

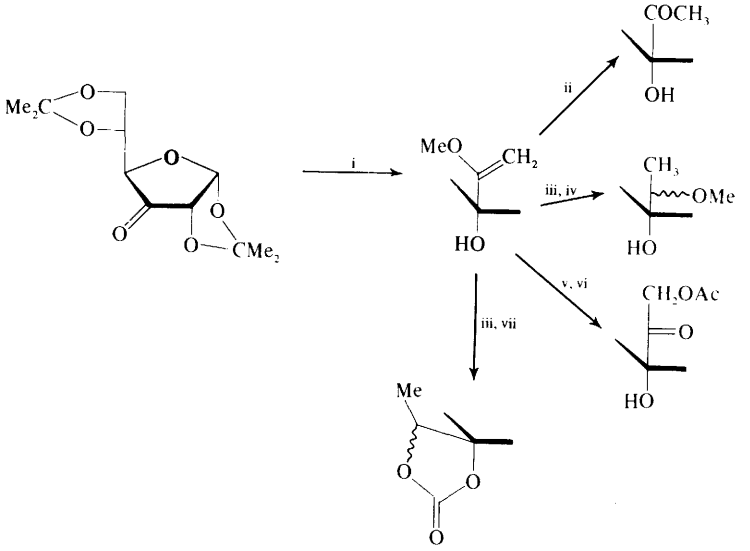


(5)



(6)

[6] J. Yoshimura, N. Hong, and K. I. Sata, *Chem. Lett.*, 1980, 1131.
[7] B. Fraser-Reid and D. L. Walker, *Can. J. Chem.*, 1980, **58**, 2694.
[8] J. S. Brimacombe and A. M. Mather, *J. Chem. Soc., Perkin Trans. 1*, 1980, 269.



Reagents: i, $LiC(OMe)=CH_2$; ii, H_3O^+; iii, H_2–Pd; iv, MeI–NaH–DMF; v, *m*-CPBA; vi, Ac_2O-py; vii, $COCl_2$–py

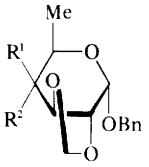
Scheme 2

4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hex-3-ulopyranoside, the corresponding 2-ulopyranoside and benzyl 2,3-*O*-isopropylidene-β-L-*erythro*-pent-4-ulopyranoside afforded a series of 2-, 3-, and 4-branched-chain sugars. Additionally, application of the reagent to the enantiomer of (6) afforded a derivative of L-pillarose [enantiomer of (5)].[9]

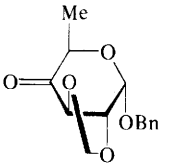
The synthesis of benzyl 4-*C*-acetyl-6-deoxy-2,3-*O*-methylene-α-D-glucopyranoside (7) and -galactopyranoside (8) have been achieved from the 4-uloside (9) by reaction with vinyl magnesium bromide, followed by epoxidation, reduction, and oxidation to the *C*-acetyl derivative. The *gluco*-isomer is the favoured product in the Grignard reaction, but when 2-lithio-2-methyl-1,3-dithian was reacted with (9), the *galacto*-isomer was formed exclusively, from which (8) was obtained by reaction with mercuric salts in the usual way.[10]

The use of 4,5-dihydro-2-lithio-5-methyl-1,3,5-dithiazine rather than 2-lithio-1,3-dithians for the synthesis of branched-chain and chain-extended sugars is reported to give better results. The dithiazine is more reactive and the products more readily desulphurized. The reagent reacted with primary halides, epoxides, and keto-compounds, but secondary halides underwent elimination.[11]

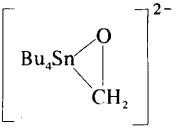
[9] J. S. Brimacombe, R. Hanna, A. M. Mather, and T. J. R. Weakley, *J. Chem. Soc., Perkin Trans. 1*, 1980, 273.
[10] J. Yoshimura and M. Matsuzawa, *Carbohydr. Res.*, 1980, **85**, C1.
[11] H. Paulsen, M. Stubbe, and F. R. Heiker, *Liebigs Ann. Chem.*, 1980, 825.



(7) R^1 = Ac, R^2 = OH
(8) R^1 = OH, R^2 = Ac

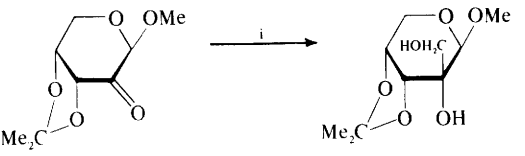


(9)

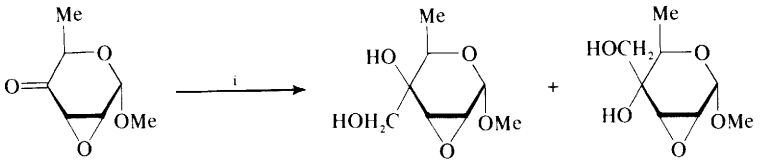


(10)

A useful reagent has been introduced by Paulsen *et al.*[12] for the introduction of hydroxymethyl side chains. The dianion (10) formed by reactions of tributylstannyl-methanol with two equivalents of butyl lithium reacts with keto-groups, even in the presence of epoxide functions, to give the hydroxymethyl branch. For example, it reacted with the ulosides (11) and (12) to give the indicated products (Scheme 3).



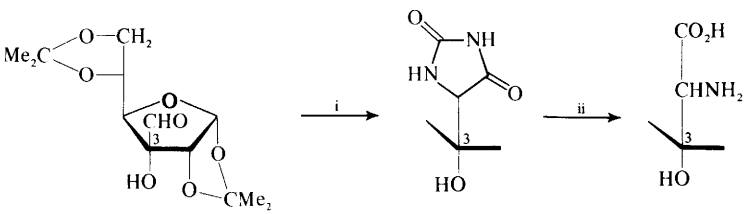
(11)



(12)

Reagent: i, $[Bu_4SnCH_2O]^{2-}Li_2^+$

Scheme 3



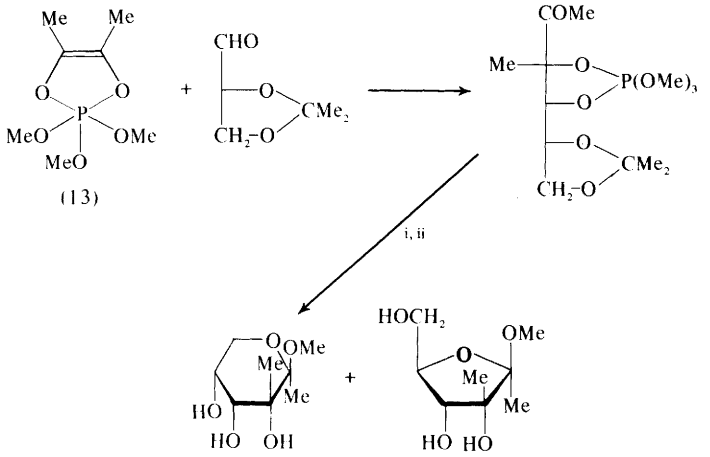
Reagents: i, $NaCN-CO_2-(NH_3)_2CO_3$; ii, $Ba(OH)_2$

Scheme 4

[12] H. Paulsen, E. Sumfleth, V. Sinnwell, N. Meyer, and D. Seebach, *Chem. Ber.*, 1980, **113**, 2055.

Introduction of a *C*-glycyl [$-CH(NH_2)CO_2H$] side-chain has been accomplished in the case of the 3-ulose in Scheme 2, by either reaction with methyl 2-nitroacetate, followed by reduction and hydrolysis,[13] or by reaction of the corresponding *C*-formyl derivative with sodium cyanide, ammonium carbonate, and carbon dioxide, followed by hydrolysis (Bucherer hydantoin procedure) (Scheme 4).[14] A *C*-formyl side-chain can be established from a nitromethyl side-chain by oxidation of the sodium acinitronate salt by Ti^{III} chloride at pH 1. Several *C*-formyl branched-chain sugars have been synthesized in this way.[15]

The Ramirez dioxaphosphole condensation has been successfully applied to the synthesis of branched-chain 1-deoxyhexuloses. The dioxaphosphole (13) and 2,3-*O*-isopropylidene-D-glyceraldehyde afforded, after hydrolysis and methanolysis, a mixture of methyl 1-deoxy-3-*C*-methyl-β-D-*ribo*-hexulopyranoside and the corresponding furanoside (Scheme 5). The nature of the product obtained could be varied by the use of different dioxaphospholes.[16]

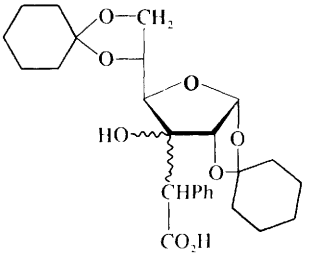


Reagents: i, H_2O; ii, $MeOH–H^+$

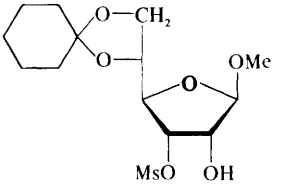
Scheme 5

Russian authors[17] have applied the Ivanov reaction to 1,2:5,6-di-*O*-cyclohexylidene-α-D-*ribo*-hexos-3-ulofuranose, which involves reacting phenylacetic acid, magnesium, and isopropyl bromide in tetrahydrofuran. The 3-ulose is then added to this preformed complex, when the addition of the phenylacetic acid side-chain occurs to give (14).

[13] A. Rosenthal and B. L. Cliff, *Carbohydr. Res.*, 1980, **79**, 63.
[14] A. Rosenthal and R. H. Dodd, *J. Carbohydr., Nucleosides, Nucleotides*, 1979, **6**, 467.
[15] J. J. Nieuwenhuis and J. H. Jordaan, *Carbohydr. Res.*, 1980, **86**, 185.
[16] S. David and M. C. Lépine, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1262.
[17] Yu. A. Zhdanov, O. V. Doron'kina, and G. V. Bogdanova, *Dokl. Akad. Nauk., SSSR*, 1980, **253**, 618 (*Chem. Abstr.*, 1980, **93**, 220 990).



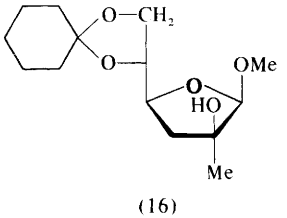
(14)



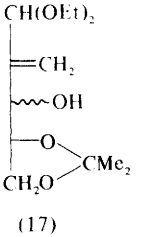
(15)

3′-*C*-Ethyl(and butyl)-uridine have been synthesized by standard reactions, involving a Grignard addition,[18] and the transformation of methyl 5,6-*O*-cyclohexylidene-3-*O*-mesyl-β-D-allofuranoside (15) into the 3-deoxy-2-*C*-methyl derivative (16) has been detailed, a process thought to involve the elimination of methanesulphonic acid leading to the 2-uloside, followed by a highly selective addition of excess of the Grignard reagent, only 4% of the 2-epimer of (16) being isolated.[19]

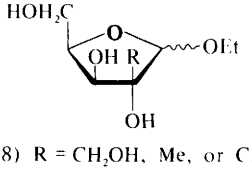
Tetrosides and pentosides with variously functionalized one-carbon branches at C-2 (CH_2OH, CH_3, CH_2NH_2) have been prepared from 2-methylene derivatives such as (17) (for preparation, see the following Section). Epoxidation of (17) by the Sharpless procedure [Bu^tO_2H, diacetylacetonatovanadium(IV) oxide] was highly selective, giving only one product. Opening of the epoxide ring with lithium dimethyl cuprate, sodium hydroxide, sodium azide, and lithium aluminium hydride, led to the appropriate branched-chain derivatives (18).[20]



(16)



(17)



(18) R = CH_2OH, Me, or CH_2N_3

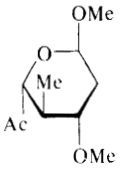
3 Compounds with a H–C–OR Branch

The 2-*C*-methylene derivatives (17) are available by condensation of 1,1-dimethoxyprop-2-en-2-yl-lithium with 2,3-*O*-isopropylidene-D-glyceraldehyde, with the *erythro*-isomer predominating over the *threo*-isomer (7 : 3). Methanolysis of (17) afforded methyl 2-deoxy-2-*C*-methylene-β-D-*erythro*-pentopyranoside and methyl 2-deoxy-2-*C*-methylene-α-L-*threo*-pentopyranoside from the *erythro*-

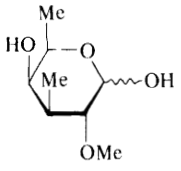
[18] A. Rosenthal and S. N. Mikhailov, *Carbohydr. Res.*, 1980, **79**, 235.
[19] M. Kawana and S. Emoto, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 222.
[20] J. C. Depezay, A. Duréault, and M. Sanière, *Carbohydr. Res.*, 1980, **83**, 273.

and *threo*-isomers, respectively. Catalytic hydrogenation of each then afforded mixtures of the corresponding 2-deoxy-2-*C*-methyl-pentopyranosides.[21]

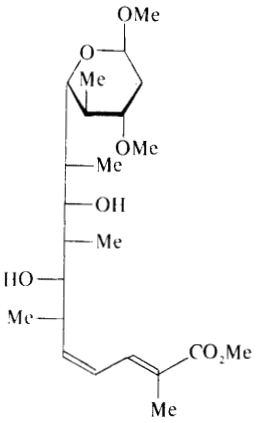
All eight isomers of methyl 2,4-dideoxy-2,4-di-*C*-methyl-6-*O*-t-butyldimethylsilyl-α-D-hexopyranosides have been prepared by standard methods, providing chiral intermediates for the synthesis of macrolide antibiotics,[22] and 1,6-anhydro-2,4-dideoxy-2,4-di-*C*-methyl-D-glucopyranose has been synthesized for the same purpose.[23] The 4-*C*-methyl-heptos-6-ulopyranoside (19) has been prepared by chain extension through C-1 of (20), followed by oxidation at C-6. Methods of extending the chain further through C-6 were investigated as a preliminary to the anticipated synthesis of (21), a degradation product of rifamycin.[24]



(19)



(20)

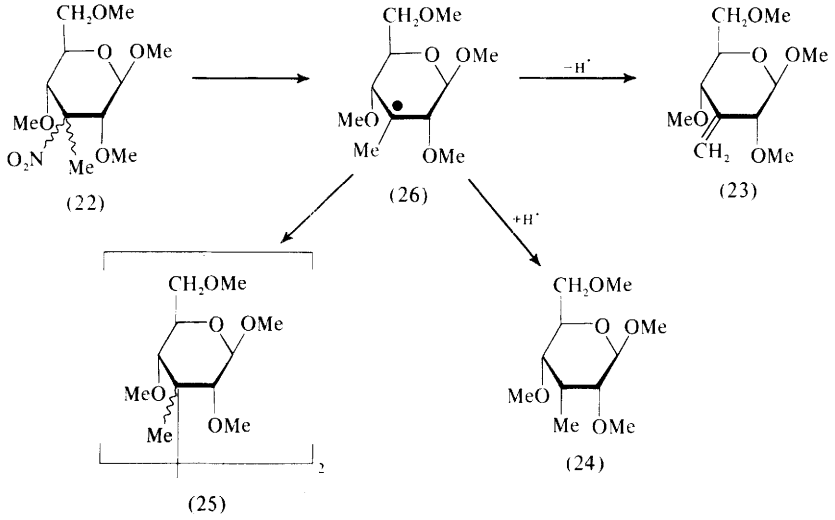


(21)

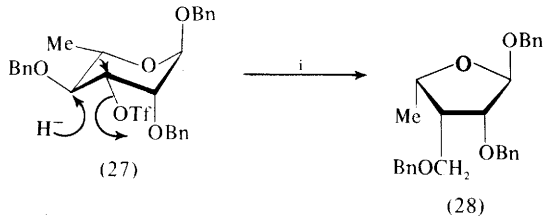
In connection with the modification of Everninomicin D, the electrochemical reduction of the 3-*C*-methyl-3-nitropyranoside (22) has been studied. In an acetonitrile solution of tetraethylammonium tetrafluoroborate as the supporting electrolyte, it afforded a mixture of the 3-*C*-methylene (23) and 3-*C*-methyl (24) derivatives and a dimer (25), resulting presumably from the C-3 radical (26), in 36%, 14%, and 2% yield, respectively (Scheme 6). The reaction was then carried out with the intact antibiotic to give three new analogues.[25]

Additions of carbon nucleophiles to 3-nitro-hex-2-enopyranosides have resulted in the preparation of several 2,3-dideoxy-3-nitrohexopyranosides with

[21] J. C. Depezay and Y. Le Merrer, *Carbohydr. Res.*, 1980, **83**, 51.
[22] S. S. Costa, A. Lagrange, A. Olesker, G. Lukacs, and T. T. Thang, *J. Chem. Soc., Chem. Commun.*, 1980, 721.
[23] A. F. Sviridov, A. Ya Shmyrina, O. S. Chizhov, A. S. Shashkov, and N. K. Kochetkov, *Bioorg. Khim.*, 1980, **6**, 1647.
[24] M. Nakata, Y. Ikeyama, H. Takao, and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 3252.
[25] A. K. Ganguly, P. Kabasakalian, J. Morton, O. Sarre, A. Westcott, S. Kalliney, P. Mangiaracina, and A. Papaphilippou, *J. Chem. Soc., Chem. Commun.*, 1980, 56.



Scheme 6



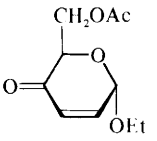
Reagent: i, $LiBEt_3H$

Scheme 7

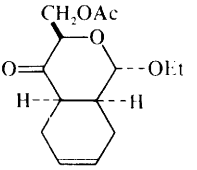
a 2-*C*-branch, the stereochemistry of which is dependent upon the reagent used and the conditions employed.[26,27]

Attempted displacement of the triflate group of benzyl 2,4-di-*O*-benzyl-3-*O*-triflyl-α-L-rhamnoside (27) by hydride ion using lithium triethylborohydride resulted in an unexpected ring-contraction (Scheme 7), which yielded benzyl-2-*O*-benzyl-3-*C*-benzyloxymethyl-3,5-dideoxy-α-L-lyxofuranoside (28).[28] This reaction is formally analogous to similar solvolytic reactions which give rise, after a proton loss, to *C*-formyl derivatives.

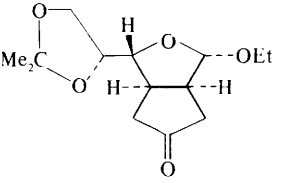
[26] T. Sakakibara, A. Seta, Y. Tachimori, and R. Sudoh, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 2322.
[27] H. H. Baer and Z. S. Hanna, *Carbohydr. Res.*, 1980, **85**, 136.
[28] V. Pozsgay and A. Neszmélyi, *Tetrahedron Lett.*, 1980, **21**, 211.



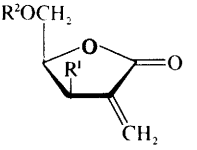
(29)



(30)



(31)



(32) $R^1 = OH$, $R^2 = H$
(33) $R^1 = CH_2OMe$, $R^2 = Bn$

The enone (29) functions as a dienophile and undergoes a Diels–Alder reaction with butadiene to give the *lyxo*-adduct (30) exclusively. The adduct was elaborated into the bicyclic lactone (31) by standard reactions.[29]

The fact that the α-methylene-γ-butyrolactone group is present in certain terpenoid antineoplastic agents has resulted in synthetic efforts directed at analogues derived from carbohydrates, such as (32) and (33).[30,31]

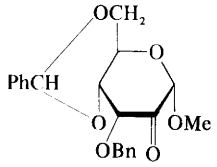
[29] J. L. Primeau, R. C. Anderson, and B. Fraser-Reid, *J. Chem. Soc., Chem. Commun.*, 1980, 6,
[30] V. Nair and A. K. Sinhababu, *J. Org. Chem.*, 1980, **45**, 1893.
[31] T. F. Tam and B. Fraser-Reid, *J. Chem. Soc., Chem. Commun.*, 1980, 556.

14

Dicarbonyl Compounds and their Derivatives

An h.p.l.c. method has been developed for the analysis of glucosone (D-*arabino*-hexos-2-ulose).[1]

The wood rotting fungus *Oudemansiella mucida* oxidizes aldohexoses to aldohexos-2-uloses and converts L-sorbose into the corresponding 2,5-diulose.[2] Chemical oxidations of carbohydrate secondary alcohol groups continue to attract attention, and pyridinium chlorochromate has been found to effect satisfactory oxidation without causing epimerization at neighbouring centres. Compound (1) has been prepared in this manner as have analogous 3- and 4-uloside derivatives.[3] Oxidation with this reagent can be catalysed by addition of molecular sieves, 1,2:5,6-di-*O*-isopropylidene-α-D-glucose giving the 3-ulose derivative in 85% yield under these conditions; a theophylline nucleoside derivative was likewise efficiently oxidized.[4]

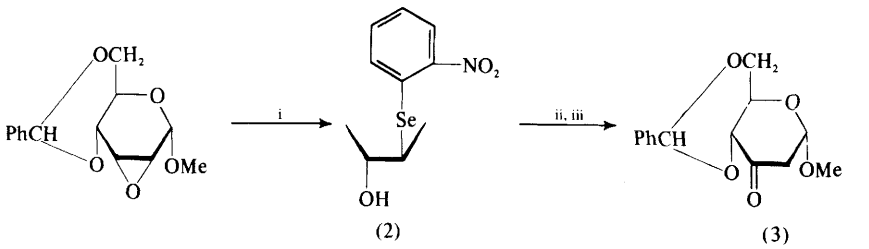


(1)

A study has been made of the oxidation of the hydroxy-group of various derivatives of 1,2-*O*-isopropylidene-α-D-glucofuranose with a ruthenium triphenylphosphine complex and benzalacetophenone as hydrogen acceptor. The 3- and the 6-monomethyl ethers gave the 5-uloses in modest yields, whereas derivatives with an unsubstituted primary position yielded uronic acids (again with modest efficiency), which were isolated as 6,3-lactones. Some degree of epimerization occurred at C-5.[5] A related investigation of the selective oxidation of 1,2-*O*-isopropylidene-α-D-glucofuranose and of sucrose with bromine water at pH 7 showed that the former was oxidized to some degree at C-3, but mainly at C-5. With sucrose, reaction occurred at C-2 and C-4 and to a lesser extent at C-3′. The 2,3′-dicarbonyl compound was also produced in small proportions.[6]

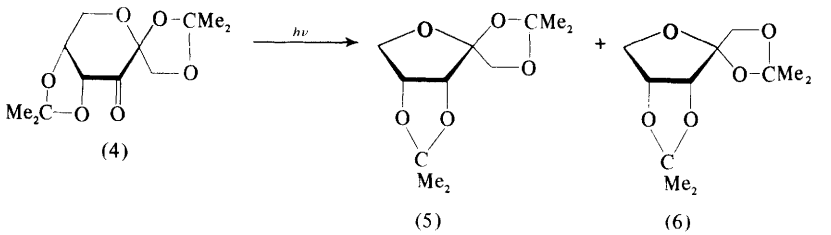
A one-step synthesis of deoxycarbonyl derivatives from epoxides uses *o*-nitroselenoxides as intermediates (Scheme 1). The reaction is, however, considerably

[1] J. Geigert, D. S. Hirano, and S. L. Neidleman, *J. Chromatogr.*, 1980, **202**, 319.
[2] J. Volc, P. Sedmera, and V. Musílek, *Collect. Czech. Chem. Commun.*, 1980, **45**, 950.
[3] B. B. Bissember and R. H. Wightman, *Carbohydr. Res.*, 1980, **81**, 187.
[4] J. Herscovici and K. Antonakis, *J. Chem. Soc., Chem. Commun.*, 1980, 561.
[5] G. Descotes, D. Sinov, and J. -P. Praly, *Carbohydr. Res.*, 1980, **78**, 25.
[6] R. Anderson, O. Larm, E. Scholander, and O. Theander, *Carbohydr. Res.*, 1980, **78**, 257.

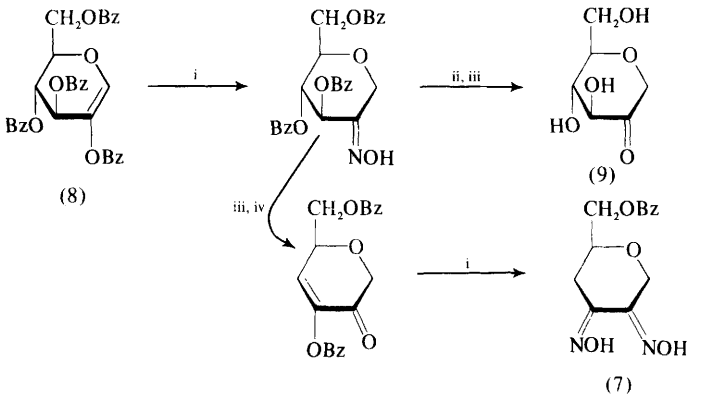


Reagents: i, *o*-nitroselenocyanate–$NaBH_4$; ii, H_2O_2; iii, Δ

Scheme 1



Scheme 2



Reagents: i, NH_2OH; ii, NaOMe; iii, $MeCHO–H^+$; iv, py

Scheme 3

restricted since the isomeric 2,3-anhydro-D-mannoside derivative did not react, and by-products were formed by oxidation at C-1. The acetate of compound (2) gave, as main product, the enol acetate of the ketone (3) together with 2,3-unsaturated aldonic acid derivatives.[7]

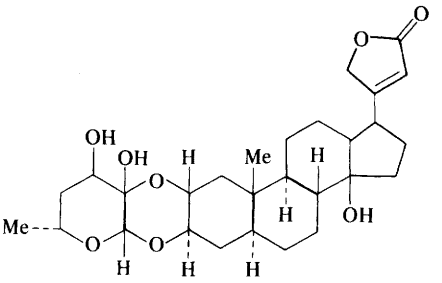
[7] K. Furuichi, S. Yogai, and T. Miwa, *J. Chem. Soc., Chem. Commun.*, 1980, 66.

The diulose derivative (4) on photolysis gives the pentulose derivatives (5) and (6) as main products in the ratio 1.2 : 1 (Scheme 2), affording a synthesis of D-*erythro*-pentulose from fructose.[8] See Chapter 3 for related work.

The 2,3-diulose derivative (7) can be obtained from the hydroxyglycal (8) as outlined in Scheme 3; these studies led to a useful synthesis of the anhydroketose (9).[9]

4,6-Dideoxy-D-*erythro*-hexos-2-ulose has been found to occur in the cardenolide (10) of the *Asclepiadaceae*.[10]

Bromination at C-5 of hexopyranose derivatives gives access to aldos-5-ulose derivatives (see Chapter 7).



(10)

[8] P. M. Collins, P. Gupta, and A. S. Travis, *J. Chem. Soc., Perkin Trans. 1*, 1980, 277.

[9] F. W. Lichtenthaler, E. S. H. El Ashry, and V. H. Göckel, *Tetrahedron Lett.*, 1980, **21**, 1429.

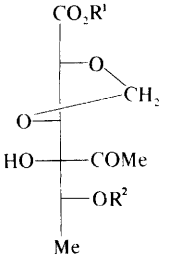
[10] H. T. A. Cheung and T. R. Watson, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2162.

15

Sugar Acids and Lactones

1 Aldonic Acids

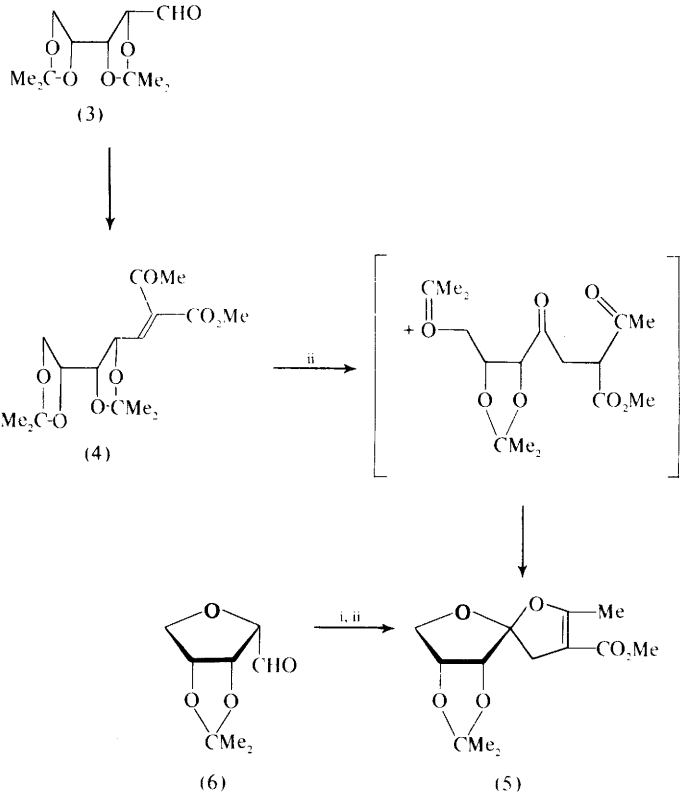
The branched-chain aldonic acid derivative (1) has been shown to be a component of avilamycin by isolation of the product (2) of mild methanolysis and acetylation; the latter compound was structurally characterized by *X*-ray analysis.[1]



(1) $R^1 = H$, $R^2 = H$
(2) $R^1 = Me$, $R^2 = Ac$

Several oxidation reactions that give aldonic acids or their lactones from free sugar derivatives have been investigated. 2,3 : 5,6-Di-*O*-isopropylidene-D-mannofuranose with the complex $RuH_2(PPh_3)_4$ and a hydrogen acceptor gave the corresponding lactone in high yield. Without the hydrogen acceptor, the alditol was produced as well as the lactone.[2] A kinetic study has been carried out on the electro-oxidation of D-glucose in phosphate buffer; the lactone was the primary product.[3] Similar oxidation of maltose, cellobiose, and higher oligosaccharides gave the corresponding aldonolactones, calcium carbonate being added to maintain the neutrality of the solutions.[4] Oxidation of D-galactose with variable valency metal salts has been studied and, whereas mercury(II) and silver(I) salts gave the hexonic acid, copper(II), iron(III), and cerium(IV) salts led to acids produced by C—C bond cleavage.[5] Specific loss of C-1 occurs on treatment of aldonic acid salts or aldonolactones with cerium(IV) sulphate in dilute sulphuric acid solution, D-lyxose, D-erythrose, and D-threose being produced in excellent yields from D-galactono-1,4-lactone, potassium D-arabinonate, and calcium

[1] E. Kupfer, K. Neupert-Laves, M. Dobler, and W. Keller-Schierlein, *Helv. Chim. Acta*, 1980, **63**, 1141.
[2] G. Descotes, J. P. Praly, and D. Sinov, *J. Mol. Catal.*, 1979, **6**, 421 (*Chem. Abstr.*, 1980, **92**, 147095).
[3] S. Ernst, J. Heitbaum, and C. H. Hamann, *Ber. Bunsenges. Phys. Chem.*, 1980, **84**, 50 (*Chem. Abstr.*, 1980, **92**, 198649).
[4] W. N. Emmerling and B. Pfannemüller, *Carbohydr. Res.*, 1980, **86**, 321.
[5] V. I. Krupenskii, *Zh. Prikl. Khim. (Leningrad)*, 1979, **52**, 2362 (*Chem. Abstr.*, 1980, **92**, 94652).



Reagents: i, $MeCOCH_2CO_2Me$; ii, CF_3COOH

Scheme 1

D-xylonate, respectively.[6] Degradation of the chain also occurs to some degree when 2-deoxy-D-*arabino*-hexose is treated with alkaline hydrogen peroxide, and D-arabinitol is produced together with 2-deoxy-D-*arabino*-hexonic acid. A secondary process leads to the production of formic acid.[7]

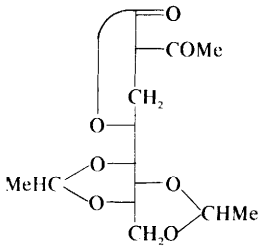
Further examples have been reported of the synthesis of aldonic acids by carbon–carbon bond-forming reactions. 2,3:4,5-Di-*O*-isopropylidene-D-arabinose (3) with methyl acetoacetate gave the Knoevenagel product (4), which is a branched-chain, unsaturated heptonic acid derivative. This rearranged on treatment with trifluoroacetic acid to afford the spiro-product (5) (Scheme 1). This same compound was obtainable from the 2,5-anhydroaldose derivative (6) by similar treatment.[8] The synthesis of destomic acid, 6-amino-6-deoxy-L-*glycero*-

[6] L. F. Sala, A. Fernandez Cirelli, and R. M. de Lederkremer, *An. Asoc. Quim. Argent.*, 1978, **66**, 57 (*Chem. Abstr.*, 1980, **92**, 76 838).
[7] H. S. Isbell, H. L. Frush, and P. Soontracharden, *Carbohydr. Res.*, 1980, **78**, C7.
[8] F. J. Lopez Herrera, *Tetrahedron Lett.*, 1980, **21**, 4963.

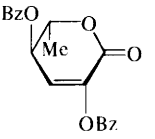
D-*manno*-heptonic acid, and its 6-epimer has been effected from the cyanohydrins of 1,2:3,4-di-*O*-isopropylidene-D-*galacto*-dialdose (see Chapter 8), and treatment of 5,6-anhydro-1,3:2,4-di-*O*-ethylidene-D-glucitol with the anion of ethyl acetoacetate led to the octonic acid-γ-lactones (7). Ethyl cyanoacetate afforded related products that dimerized on hydrolysis.[9]

A continuous electrochemical procedure for the reduction of D-ribono-γ-lactone which uses a membrane separation has been developed and applied on a pilot plant scale.[10,11]

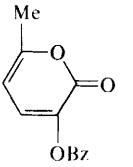
Benzoylation of L-rhamnono-δ-lactone can, under mild conditions, give the triester, but more forcing reaction conditions can be used to produce either the 3-deoxy-2-ene (8) or the pyranone derivative (9) in good yields.[12] The unsaturated aldonic acid derivatives (10) and (11) were produced each in about 20% yield on heating of the selenoxide (12); the main product was formed by direct elimination between C-2 and C-3.[13]



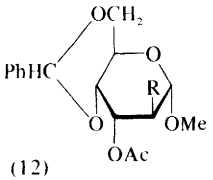
(7)



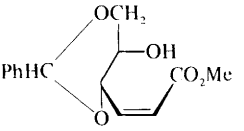
(8)



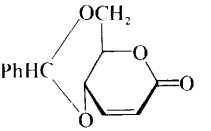
(9)



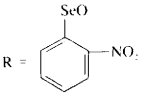
(12)



(10)



(11)



[9] V. I. Kornilov, Yu. A. Zhdanov, and S. V. Turik, *Zh. Obshch. Khim.*, 1979, **49**, 1917 (*Chem. Abstr.*, 1980, **92**, 76 813).

[10] A. Korczynski, L. Piszczek, J. Swiderski, and A. Doniec, *Przem. Chem.*, 1979, **58**, 487 (*Chem. Abstr.*, 1980, **92**, 22 734).

[11] A. Korczynski, L. Piszczek, J. Swiderski, and A. Doniec, *Zesz. Nauk. Politech. Slask., Chem.*, 1979, **631**, 85 (*Chem. Abstr.*, 1980, **93**, 114 855).

[12] O. J. Varela, A. F. Cirelli, and R. M. de Lederkremer, *Carbohydr. Res.*, 1980, **79**, 219.

[13] K. Furuichi, S. Yokai, and T. Miwa, *J. Chem. Soc., Chem. Commun.*, 1980, 66.

A report has appeared on the ^{1}H n.m.r. spectra of D-arabinonic acid and D-galactonic acid confirming that the lactone rings are retained up to pH 7. Complexing of the former with iron(III) ions causes lactone ring-opening.[14] A study of the iron-binding capacities of D-gluconamides and lactonamides has also been reported.[15]

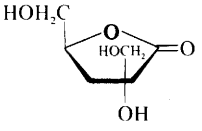
2 Aldaric Acids

Cerheptaric acid (3-deoxy-*manno*-heptaric acid) has been found to be widely distributed in the *Cereus* and *Trichocereus* genera of the cactacean family.[16]

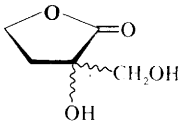
3 Saccharinic Acids

A review (in Russian) has been published by Gakhokidze,[17] and the same author has reported on the conversion of 3,4,6-tri-*O*-acetyl-D-mannose into 2-deoxy-D-*arabino*-hexonic acid (orthosaccharinic acid) by use of aqueous lead hydroxide.[18]

The first naturally occurring branched-chain saccharinic acid, 2-*C*-methyl-D-erythronolactone, has been isolated from milk vetch (*Astragalus lusitanicus*).[19] Reduction of the isosaccharinic acids (13) and (14) with sodium borohydride gave mixtures of the corresponding free sugars and branched-chain alditols.[20,21]



(13)



(14)

4 Ulosonic Acids

The isomeric forms of hexulosonic acids present in aqueous and other solutions have been studied by ^{13}C n.m.r. methods. L-*xylo*-Hexulosonic acid and its methyl ester exist predominantly in the α-pyranose form, whereas the D-*arabino*-isomers show α- and β-pyranose and α- and β-furanose forms. The methyl ester favours the pyranoses in water and the furanoses in DMSO. D-*xylo*-Hex-5-ulosonic acid showed both furanoses and the acyclic form, while this latter

[14] L. N. Odilavadze, L. O. Kashiya, M. E. Shishniashvili, and N. A. Kostromina, *Izv. Akad. Nauk Gruz. SSR, Ser. Khim.*, 1980, **6**, 159 (*Chem. Abstr.*, 1980, **93**, 221 002).

[15] F. Scholnick and P. E. Pfeffer, *J. Dairy Sci.*, 1980, **63**, 471 (*Chem. Abstr.*, 1980, **93**, 72 167).

[16] R. Kringstad, *Carbohydr. Res.*, 1980, **80**, 285.

[17] R. A. Gakhokidze, *Usp. Khim.*, 1980, **49**, 420 (*Chem. Abstr.*, 1980, **93**, 47 015).

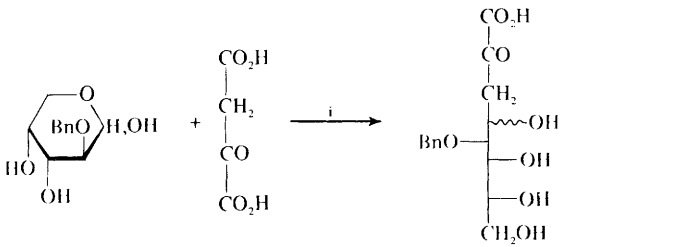
[18] R. A. Gakhokidze and N. N. Sidamonidze, *Soobshch. Akad. Nauk Gruz. SSR*, 1980, **97**, 97 (*Chem. Abstr.*, 1980, **93**, 95 531).

[19] J. de Pascual Teresa, J. C. Hernández Aubanell, A. San Feliciano, and J. M. Miguel del Corral, *Tetrahedron Lett.*, 1980, **21**, 1359.

[20] R. Alén and E. Sjöström, *Acta Chem. Scand., Ser. B*, 1979, **33**, 693.

[21] R. Alén and E. Sjöström, *Acta Chem. Scand., Ser. B*, 1980, **34**, 387.

modification was absent from the D-*lyxo*-hex-5-ulosonic acid equilibrium. The sodium salt of D-*threo*-hex-2,5-diulosonic acid exists in pyranose forms with the carbonyl group at C-5 hydrated.[22] The reduction of this last compound with sodium borohydride gave L-*xylo*- and D-*arabino*-hexulosonic acids in the ratio 6:1 and, as the former is readily converted into L-ascorbic acid, this represents an efficient route to the vitamin from glucose (57% overall yield).[23] In connection with the commercial synthesis of ascorbic acid the electrochemical oxidation of 2,3:4,6-di-*O*-isopropylidene-L-sorbose has been further studied by two groups.[24,25]



(15) D-*gluco*-isomer
(16) D-*manno*-isomer

Reagent: i, NaH_3BO_4–Ni^{2+}

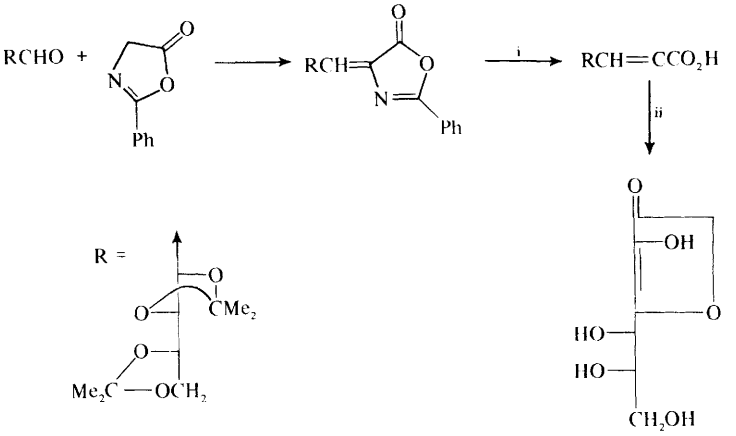
Scheme 2

Continuing his work on 3-deoxyald-2-ulosonic acids Szabo has shown that 2-*O*-benzyl-D-glyceraldehyde condensed with oxaloacetic acid gives 5-*O*-benzyl-3-deoxy-D-*erythro*- and -D-*threo*-hexulosonic acids in the proportions 4:1 and, extending this reaction, has produced the octulosonic acid ethers (15) and (16) (Scheme 2). Various derivatives of the methyl ester, methyl α-pyranoside of the latter were studied to determine factors affecting the acid sensitivity of the glycosidic bonds. Esterification of the carboxylic acid group and the presence of the benzyl ether group at O-5 both had stabilizing effects.[26] The 3-deoxy-D-*manno*-oct-2-ulosonic acid present in bacterial cell walls has been examined by physical methods. Lactonization was shown to occur on acidification, although circular dichroism measurements suggested that the product was not a previously

[22] T. C. Crawford, G. C. Andrews, H. Faubl, and G. N. Chmurny, *J. Am. Chem. Soc.*, 1980, **102**, 2220.
[23] G. C. Andrews and T. C. Crawford, *Ventron Alembic*, 1980, **18**, 1 (*Chem. Abstr.*, 1980, **93**, 95 489).
[24] N. S. Lidorenko, M. Ya. Fioshin, G. F. Muchnik, V. T. Serebryanskii, I. A. Avrutskaya, M. A. Khrizolitova, and N. A. Rodionova, *Elektrokhimiya*, 1980, **16**, 750 (*Chem. Abstr.*, 1980, **93**, 56 663).
[25] M. Levi, I. Pesheva, A. Shterev, Kh. Chapkunov, M. Dolapchieva, B. Asenov, and D. Merdzhanova, *Tr. Nauchnoizsled. Khim. -Farm. Inst.*, 1978, **10**, 95 (*Chem. Abstr.*, 1980, **93**, 175 954).
[26] D. Charon and L. Szabo, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1971.

identified lactone made under acid conditions.[27] A new synthetic route to 3-deoxyulosonic acids is outlined in Scheme 3.[28]

Glycosides of 5-*N*-acetyl-D-neuraminic acid can be synthesized using glycosyl halide derivatives with silver salts of polymeric carboxylic acids, *e.g.* polymaleic acid, as catalysts.[29]



Reagents: i, $\bar{O}H$; ii, H^+

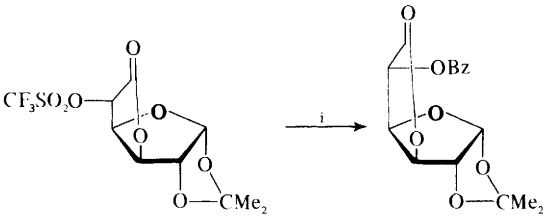
Scheme 3

5 Uronic Acids

Oxidation of various 1,2-cyclic acetals of α-D-glucofuranose by hydrogen transfer in the presence of benzalbenzophenone as acceptor and the complex $RuH_2(PPh_3)_4$ as catalyst leads to 6,3-lactones; considerable epimerization occurs at C-5.[30] Chromium trioxide in acetic anhydride also gives rise to 6,3-lactones from acetylated methyl 3,6-anhydro-D-galactopyranosides,[31] and the 6,6′-dicarboxylic acid has been prepared from α,α-trehalose by oxidation with oxygen over platinum as catalyst in sodium hydrogen carbonate solution. The dimethyl ester and the acetylated diacid dichloride were then used for the attachment of lipid components.[32]

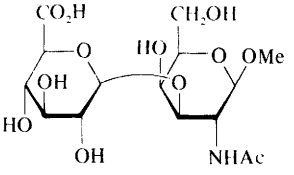
[27] L. D. Melton, E. R. Morris, D. A. Rees, D. Thom, and S. M. Bociek, *Carbohydr. Res.*, 1980, **81**, 295.
[28] Yu. A. Zhdanov, A. V. Kir'yanov, and G. A. Korol'chenko, *Zh. Obshch. Khim.*, 1979, **49**, 2618 (*Chem. Abstr.*, 1980, **92**, 129 220).
[29] V. Eschenfelder and R. Brossmer, *Carbohydr. Res.*, 1980, **78**, 190.
[30] G. Descotes, D. Sinov, and J. -P. Praly, *Carbohydr. Res.*, 1980, **78**, 25.
[31] A. I. Usov and V. V. Deryabin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1980, 394 (*Chem. Abstr.*, 1980, **93**, 26 724).
[32] M. B. Goren and K. -S. Jiang, *Carbohydr. Res.*, 1980, **79**, 225.

The key step of a simple synthesis of 1,2-*O*-isopropylidene-β-L-idofururono-6,3-lactone is outlined in Scheme 4.[33] A similar objective was achieved in the same laboratory by use of the tosyl analogue of the initial triflate, but the procedure was more lengthy involving reduction of the lactone, benzoylation of the resultant hemiacetal and treatment of the diester with acetate anion which entered at C-6 following the establishment of the 5,6-benzoxonium ion. A subsequent oxidation step was involved to recover the carbonyl group at C-6.[34]



Reagent: i, BzONa

Scheme 4

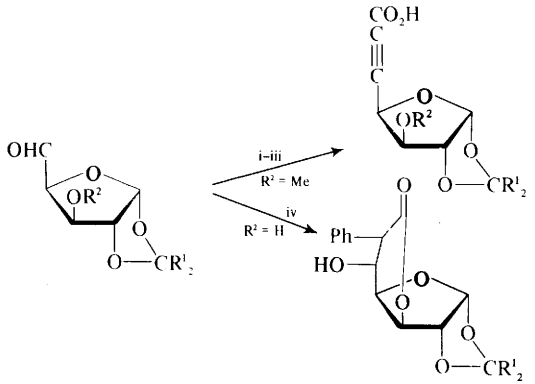


(17)

Methods have been reported for the isolation in gram quantities of L-guluronic and D-mannuronic acids as their brucine salts from the hydrolysate of alginic acid.[35] Alternatively, treatment of chondroitin 4- or 6-sulphate pyridinium salts with DMSO containing 10% of methanol at 95 °C afforded mainly the methyl glycoside (17) of *N*-acetylchondrosine. Dermatan sulphate and hyaluronic acid were also depolymerized to give methyl glycosides of di- and higher saccharides.[36]

Uronic acid derivatives have been produced by elaboration of the aldehydic side-chain of dialdofuranose compounds by application of the Wittig reaction[37] or the Ivanov reaction[38] (Scheme 5).

[33] R. Csuk, H. Honig, J. Nimpf, and H. Weidmann, *Tetrahedron Lett.*, 1980, **21**, 2135.
[34] I. Macher, K. Dax, E. Wanek, and H. Weidman, *Carbohydr. Res.*, 1980, **80**, 45.
[35] I. R. Siddiqui, *Carbohydr. Res.*, 1980, **80**, 343.
[36] Y. Inoue and K. Nagasawa, *Carbohydr. Res.*, 1980, **85**, 107.
[37] J. M. J. Tronchet, A. P. Bonenfant, F. Pervet, A. Gonzalez, J. -B. Zumwald, E. M. Martinez, and B. Baehler, *Helv, Chim. Acta*, 1980, **63**, 1181.
[38] Yu. A. Zhdanov, G. V. Bogdanova, and O. V. Doron'kina, *Dokl. Akad. Nauk SSSR*, 1980, **251**, 118 (*Chem. Abstr.*, 1980, **93**, 95 532).



Reagents: i, $Ph_3P{=}CBr_2$; ii, BuLi; iii, CO_2; iv, Mg–$BuCO_2H$

Scheme 5

Epimerization of D-glucuronic acid catalysed by molybdate ions gives about 15% of D-mannuronic acid and small amounts of the corresponding keto-compound, *i.e.* D-*lyxo*-hex-5-ulosonic acid. The work was carried out with uniformly ^{14}C-labelled starting material and the products are therefore similarly labelled.[39] Degradation of the acetates of hexofururono-6,3-lactones under acetylating conditions has been shown to give either a pyranose compound or a derivative of a hexa-2,6-dienoic acid.[40]

The synthesis of 1-*O*-acyl-D-glucuronic acid derivatives has been achieved from the benzyl β-pyranoside *via* its 2,3,4,6-tetra-*O*-(α-ethoxyethyl) derivative.[41] The 1-*O*-methanesulphonyl ester of D-glucuronic acid was used to prepare acyl derivatives involving the attachment of biliverdin and bilirubin. In model experiments the sulphonate also afforded glucuronosides.[42] D-Glucuronosides have also been prepared by standard Koenigs–Knorr glycosylation from various bile acids[43] and Δ^8-tetrahydrocannabinol.[44]

L-Iduronic acid glycosides are more readily hydrolysed by acid than the analogous neutral glycosides or the isomeric D-*gluco*-acids, a difference that has been utilized in their isolation from glycosaminoglycans, *e.g.* heparin. Rate studies were carried out on several neutral and acidic glycosides and on *N*-acetyl-2-amino-2-deoxy-D-glucosides.[45]

6 Ascorbic Acids

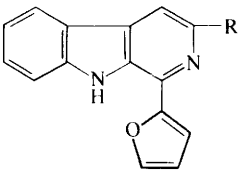
A detailed review of the chemical methods of synthesis of L-ascorbic acid has appeared.[46] A new synthesis involves oxidation of 1,3 : 2,4-di-*O*-methylene-L-

[39] V. Bilik, R. Sandtnerova, Z. Ktatky, and L. Petrus, *Chem. Zvesti*, 1980, **34**, 518.
[40] K. Tajima, H. Itoh, and H. Marooka, *Chem. Lett.*, 1980, 1465.
[41] F. Compernolle, *Carbohydr. Res.*, 1980, **83**, 135.
[42] F. Compernolle, *Biochem. J.*, 1980, **187**, 857.
[43] J. Goto, K. Suzaki, and T. Nambara, *Chem. Pharm. Bull.*, 1980, **28**, 1258.
[44] K. Watanabe, K. Oguri, and H. Yoshimura, *Chem. Pharm. Bull.*, 1979, **27**, 3009.
[45] H. E. Conrad, *Biochem. J.*, 1980, **191**, 355.
[46] T. C. Crawford and S. A. Crawford, *Adv. Carbohydr. Chem. Biochem.*, 1980, **37**, 79.

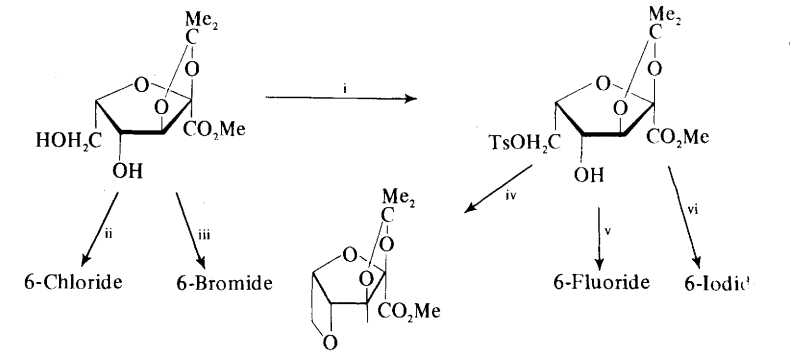
arabinitol to 2,4 : 3,5-di-*O*-methylene-L-lyxose, which was converted to a 2-keto-hexonic acid derivative *via* cyanohydrin intermediates, the keto-acid finally affording the vitamin on hydrolysis.[47]

Heating an aqueous solution of L-ascorbic acid containing pyridine and boric acid causes decarboxylation and the formation of lyxose and xylose,[48] and reaction of the acid with L-tryptophan at pH 7 for extended periods led to several products including compounds (18) and (19), which were mutagenic to a bacterium.[49]

The 6-bromo- and 6-chloro-6-deoxy-derivatives of L-ascorbic acid can be made directly by reaction with hydrogen bromide or hydrogen chloride in



(18) R = H
(19) R = CO_2H



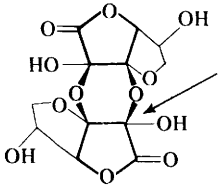
Reagents: i, TsCl–py; ii, Ph_3P–$(EtO)_3PO$–CCl_4; iii, Ph_3P–$(EtO)_3PO$–Br_2; iv, NaOMe; v, NaF–DMF; vi, PrCOMe–NaI

Scheme 6

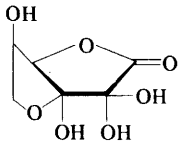
[47] A. A. Othman and V. S. Al-Timari, *Tetrahedron*, 1980, **36**, 753.
[48] A. Ichikawa and M. Yamate, *Hiroshima Jogakuin Daigaku Ronshu*, 1979, **29**, 173 (*Chem. Abstr.*, 1980, **93**, 8415).
[49] H. Kanamori, K. Morimoto, N. Kinae, and J. Tomita, *Chem. Pharm. Bull.*, 1980, **28**, 3143.

formic acid. Indirectly the four 6-halogeno-compounds were made as indicated in Scheme 6, which also illustrates an unusual oxetan derivative.[50]

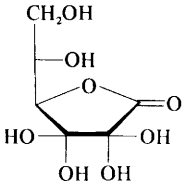
Crystalline dehydroascorbic acid exists as the symmetrical dimer (20), but in DMF or DMSO solution an epimerization occurs at the centre indicated and an isomer is established as a component of an equilibrium. Hydrolysis gives the hemiacetal (21), which undergoes ring-opening to afford the hydrated species (22).[51] The same starting material, on dissolving in boiling methanol, gives a mixture of isomeric bicyclic hemiacetals, *e.g.* (23) (^{13}C n.m.r. study).[52]



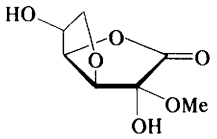
(20)



(21)



(22)



(23)

Diffusion coefficients of L-ascorbic acid and its anion have been measured in aqueous solution; that of the anion is less than that of the acid at zero concentration indicating that it interacts more strongly with the solvent.[53] The separation of the acid from its C-5 epimer has been effected by use of h.p.l.c.[54]

The oxidations of L-ascorbic acid in the presence of copper(II)-poly(4-vinylpyridine)complex[55] and by molecular oxygen in the presence of iron(II) ions[56]

[50] J. Kiss, K. P. Berg, A. Dirscherl, W. E. Oberhänsli, and W. Arnold, *Helv. Chim. Acta*, 1980, **63**, 1728.

[51] J. Hvoslef and B. Pedersen, *Acta Chem. Scand., Ser. B*, 1979, **33**, 503.

[52] J. Hvoslef and B. Pedersen, *Acta Chem. Scand., Ser. B*, 1980, **34**, 285.

[53] M. Samim and S. M. A. Baki, *Aust. J. Chem.*, 1980, **33**, 1857.

[54] M. H. Bui-Nguyen, *J. Chromatogr.*, 1980, **196**, 163.

[55] Yu. I. Skurlatov, V. Ya. Kovner, S. O. Travin, Yu. E. Kirsh, A. P. Purmal, and V. A. Kabanov, *Eur. Polym. J.*, 1979, **15**, 811 (*Chem. Abstr.*, 1980, **92**, 94 660).

[56] A. N. Astanina, N. A. Larina, T. V. Barinov, E. D. Damianidis, A. N. Karavanov, and A. N. Rudenko, *Vestn. Mosk. Univ., Ser. 2: Khim.*, 1980, **21**, 202 (*Chem. Abstr.*, 1980, **93**, 47 053).

have been examined, and the electron transfer to *N*-alkylphenothiazine radical cations has been studied within the pH range 0–7.2.[57]

The electrochemical reduction of dehydroascorbic acid monophenylhydrazone gave 'scorbaminic acid' more easily than did chemical methods, and electro-oxidation was found to be an efficient method of converting ascorbic acid to its dehydro-derivative.[58] A further electrochemical study examined the redox reaction of tris(2-deoxy-2-L-ascorbyl)amine.[59]

[57] E. Pelizzetti, D. Meisel, W. A. Mulac, and P. Neta, *J. Am. Chem. Soc.*, 1979, **101**, 6954.

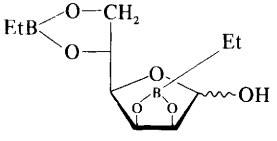
[58] O. Manousek, J. Volke, and J. Hlavaty, *Electrochim. Acta*, 1980, **25**, 515 (*Chem. Abstr.*, 1980, **93**, 186 703).

[59] K. Tsuji, T. Hayashi, and M. Namiki, *Electrochim. Acta*, 1980, **25**, 605 (*Chem. Abstr.*, 1980, **93**, 132 720).

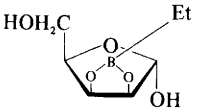
16

Inorganic Derivatives

A comparative study of the chelation of 2-deoxy-D-ribose with boric, germanic, telluric, and arsenious acids using potentiometry has shown that only 1:1 complexes are formed. Values of the chelation constants were compared with those of the pentoses.[1] A similar study on mannitol and glucose with boric acid demonstrated that the former was about 740 times more effective a complexant than glucose, but that the conclusions were complicated by the degree of association of boric acid in solution.[2] Reactions at the anomeric centre of mannofuranose have been carried out by means of the 2,3 : 5,6-ethylboronate (1) formed by treatment of D-mannose with limited triethyl boroxine.[3] By the same means D-lyxose gave the 2,3-blocked lyxofuranose (2) also useful for



(1)

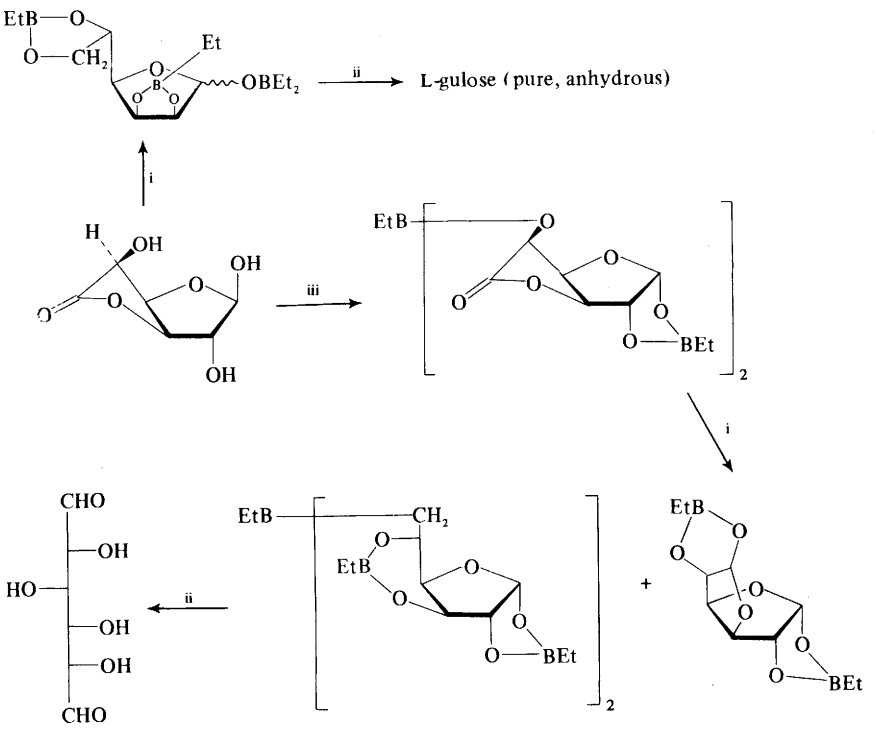


(2)

chemical reaction at C-1.[4] Useful conversions of D-glucuronolactone carried out *via* boronates are shown in Scheme 1,[5] and those of D-gulono-1,4-lactone in Scheme 2.[6] 2-Deoxy-hexoses react with ethyl(dimethoxy)borane to give open-chain derivatives. Thus 2-deoxy-D-glucose gives a mixture of 3,4 : 5,6-di(ethylboronate) (85%) and the 3,5 : 4,6-isomer (15%); with 2-deoxy-D-galactose the ratio of diboronates is reversed.[7] A study of the mixed bis(benzeneboronates) obtained from benzeneboronic anhydride with D-ribitol, D-arabinitol, D-xylitol, 1-deoxy-D-glucitol, 1-deoxy-L-gulitol, 1-deoxy-L-mannitol, and 1-deoxy-D-talitol using methylation and e.i–m.s. has shown that all contain mixtures of the three types shown in formulae (3)–(5).[8]

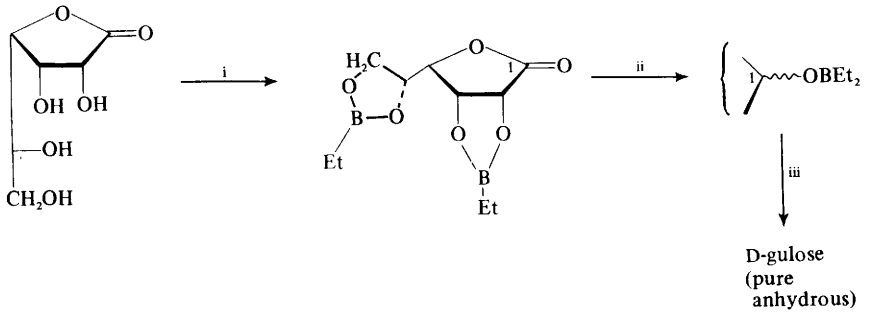
The ^{13}C n.m.r. of aldoses complexed to molybdate shows that ribose, talose, and allose behave as tridentate donors using hydroxy-groups at positions 2, 3,

[1] E. Huttunen, *Finn. Chem. Lett.*, 1979, 236 (*Chem. Abstr.*, 1980, **92**, 147 072).
[2] H. B. Davis and C. J. B. Mott, *J. Chem. Soc., Faraday Trans. 1*, 1980, **76**, 1991.
[3] W. V. Dahlhoff, A. Geisheimer, and R. Köster, *Synthesis*, 1980, 935.
[4] W. V. Dahlhoff and R. Köster, *Synthesis*, 1980, 936.
[5] W. V. Dahlholff, P. Idelmann, and R. Köster, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 546.
[6] R. Köster, P. Idelmann, and W. V. Dahlhoff, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 547.
[7] W. V. Dahlhoff and R. Köster, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 548.
[8] C. J. Griffiths and H. Weigel, *Carbohydr. Res.*, 1980, **81**, 7.



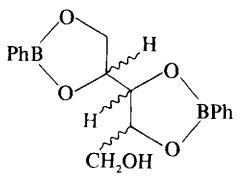
Reagents: i, Et_2BH; ii, $MeOH-(CH_2OH)_2$; iii, $(EtBO)_3$

Scheme 1

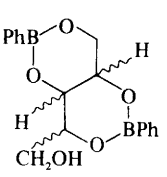


Reagents: i, $(EtBO)_3$; ii, Et_2BH; iii, $MeOH-(CH_2OH)_2$

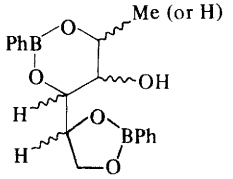
Scheme 2



(3)



(4)



(5)

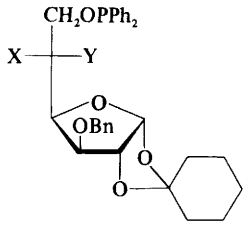
and 4, whereas lyxose and mannose use the hydroxy-groups at positions 1, 2, and 3.[9] Electrophoresis has been used to study vanadate–polyol interactions. Jobs method was used to study the vanadium–polyol ratio for D-glucitol, D-mannitol, D-galactitol, 3-*O*-α-D-glucopyranosyl-L-gulitol, D-ribose, and maltose. It was suggested that in the range pH 5–9.5 metavanadate $[(VO)_n^{n-}]$ is the complexing agent.[10]

Derivatives of carbohydrates that have been used to complex with rhodium catalysts to promote asymmetric hydrogenation include the phosphorus derivatives (6) and (7),[11] and (8)–(12)[12] synthesized[13] by esterification of the hydroxy-compounds with the appropriate phosphonyl chloride. Treatment of π-allylpalladium chloride with the phosphite ester (13) gave a complex that was an enantioselective catalyst for hydrogenation of unsaturated acids and esters.[14]

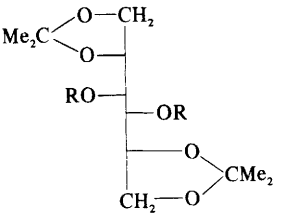
The ^1H and ^{13}C n.m.r. of the Ca^{2+} complex of *N*-glycolylneuraminic acid at pH 7 showed that a 1:1 complex is formed. Analysis of electric field shifts gave the approximate position of the ion shown in formula (14).[15] The interactions of Na^+, Ca^{2+}, and La^{3+} with methyl glycofuranosides in methanol have been studied by measurement of the rate of acid-catalysed methanolysis in the presence of chlorides. Rates decreased with increasing ionic charge. The conclusion was reached that steric requirements for complex formation with metal ions differ even when the ionic radius is approximately the same and that the main factor is charge, to which is related the ability to deform the furanoside.[16]

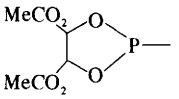
The gold thio-glucose (15), synthesized *via* the sodium salt of 1-thioglucose with gold iodide, induces diabetes in experimental animals.[17] An extended *X*-ray absorption fine structure (EXAFS) study of gold co-ordination in the anti-arthritic drug thioglucopyranosyl-*S*-gold ('Solganol') showed that the gold(I) atom is bonded to two bridging sulphur atoms thus forming a polymeric

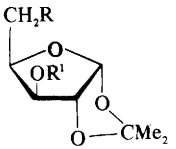
[9] J. Alföldi, V. Bilik, and L. Petruš, *Collect. Czech. Chem. Commun.*, 1980, **45**, 123.
[10] F. Searle and H. Weigel, *Carbohydr. Res.*, 1980, **85**, 51.
[11] T. H. Johnson and G. Rangarajan, *J. Org. Chem.*, 1980, **45**, 62.
[12] H. Brunner and W. Pieronczyk, *J. Chem. Res.* (*S*), 1980, 76.
[13] H. Brunner and W. Pieronczyk, *J. Chem. Res.* (*S*), 1980, 74.
[14] E. E. Nifant'ev, T. S. Kukhareva, L. S. Gorshkova, V. A. Pavlov, and E. I. Klabunovskii, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1979, 1915 (*Chem. Abstr.*, 1980, **93**, 47 017).
[15] L. W. Jaques, B. F. Riesco, and W. Weltner, *Carbohydr. Res.*, 1980, **83**, 21.
[16] H. Lönnberg, A. Vesala, and R. Käppi, *Carbohydr. Res.*, 1980, **86**, 137.
[17] Y.-S. Chang and T.-F. Tsui, *Sheng Wu Hua Hsueh Yu Sheng Wu Wu Li Chin Chan*, 1979, **30**, 56 (*Chem. Abstr.*, 1980, **93**, 95 510).



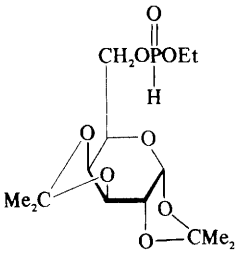
(6) X = H, Y = $OPPh_2$
(7) X = $OPPh_2$, Y = H



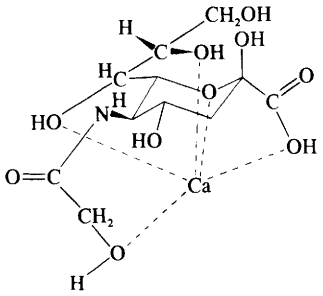
(8) R = PPh_2
(9) R = 
(10) R = 



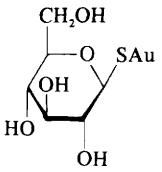
(11) R = PPh_2, R^1 = H
(12) R = $OPPh_2$, R^1 = PPh_2



(13)



(14)



(15)

species.[18] Cadoxen (an aqueous solution of cadmium oxide–ethylene diamine), which is a good solvent for cellulose and other sugars, has been complexed with D-glucose, cellobiose, methyl α-D-glucopyranoside, and cellulose for study by ^1H, ^{13}C, and ^{113}Cd n.m.r. The ^{13}C and ^{113}Cd n.m.r. results were not consistent

[18] M. A. Mazid, M. T. Razi, P. J. Sadler, G. N. Greaves, S. J. Gurman, M. H. J. Koch, and J. C. Phillips, *J. Chem. Soc., Chem. Commun.*, 1980, 1261.

with formation of chelate alcoholates involving OH-2 and OH-3 as previously suggested. More probably H-bonding is the solubilizing interaction with the Cd^{2+} ion holding the two amino-groups of the diamine in a favourable orientation for H-bonding with the hydroxy-groups. The ion also strengthens these bonds by decreasing the pK_a of the amino-groups.[19]

An extensive range of ferrocene–sugar derivatives has been reported and studied by ^1H n.m.r.[20]

Gel chromatographic analysis has been carried out on silatranyl and alkoxysilyl derivatives of sugars.[21]

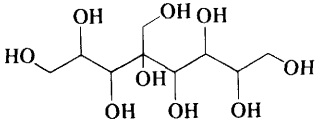
[19] A. D. Bain, D. R. Eaton, R. A. Hux, and J. P. K. Tong, *Carbohydr. Res.*, 1980, **84**, 1.
[20] M. J. Adam and L. D. Hall, *Can. J. Chem.*, 1980, **58**, 1188.
[21] L. M. Antipin, V. M. Kilesso, V. I. Kopkov, A. P. Luzin, and B. N. Stepanenko, *Uchebn. Zaved., Khim. Khim. Tekhnol.*, 1979, **22**, 1010 (*Chem. Abstr.*, 1979, **91**, 222 057).

17

Alditols and Cyclitols

1 Alditols

A new branched-chain nonitol, calditol, assigned the structure (1), has been isolated as a component of the lipids in *Calderella* thermoacidophile bacteria, in which it provides the hydrophilic tail; the stereochemistry was not determined.[1] The effects of pH, solvent, and catalyst treatment on the Raney nickel-catalysed hydrogenation of xylose to xylitol has been studied,[2] and the factors governing this process have been reviewed.[3] The yields of D-mannitol obtained by



(1)

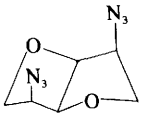
hydrogenation of mixtures of D-glucose and D-fructose over platinum have been improved by adding an immobilized bio-catalyst (glucose isomerase) to the sugar mixture.[4] The selective formation of branched-chain sugar alcohols in the formose reaction has been studied; if most of the calcium ions are removed at the end of the induction period, 2-*C*-hydroxymethylglycerol, 2,4-di-*O*-hydroxymethylpentitol and a mixture of 3-*C*-hydroxymethylpentitols appear to be formed selectively; magnesium and iron salts showed a similar selectivity, but a different pattern emerged with added lead hydroxide.[5] Using *N*,*N*-diethylaminoethanol as the catalyst, only pentaerythritol was obtained from formaldehyde, whereas if fructose was added as a co-catalyst, 2-hydroxymethylglycerol was formed together with three other products, but no pentaerythritol could be detected.[6] A chromatographic study of the reaction of xylitol with concentrated hydrochloric acid or dilute sulphuric acid under various conditions has shown that 1,4-anhydropentitol is the first major product formed, but prolonged treatment with hydrochloric acid gave mainly 5-chloro-5-deoxy-1,4-anhydropentitol together with some dichlorodideoxypentitol.[7]

[1] M. De Rosa, S. De Rosa, A. Gambacorta, and J. D. Bu'Lock, *Phytochemistry*, 1980, **19**, 249.
[2] M. Harkonen and P. Nuojua, *Kem.-Kemi*, 1979, **6**, 531 (*Chem. Abstr.*, 1980, **92**, 42 284).
[3] M. Harkonen and P. Nuojua, *Kem.-Kemi*, 1979, **6**, 445 (*Chem. Abstr.*, 1980, **92**, 147 051).
[4] M. Makkee, A. P. G. Kieboom, H. Van Bekkum, and J. A. Roels, *J. Chem. Soc., Chem. Commun.*, 1980, 930.
[5] Y. Shigemasa, M. Kawahara, C. Sakazawa, R. Nakashima, and T. Matsuura, *J. Catal.*, 1980, **62**, 107 (*Chem. Abstr.*, 1980, **93**, 72 151).
[6] T. Matsumoto, M. Komiyama, and S. Inoue, *Chem. Lett.*, 1980, 839.
[7] J. Szafranek and A. Wisniewski, *J. Chromatogr.*, 1980, **187**, 131.

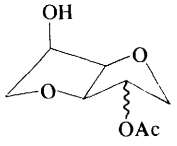
2,5-Diazido-2,5-dideoxy derivatives of 1,4;3,6-dianhydrohexitols have been prepared in a further study of the reactivity of 2,5-disulphonyl esters of the latter with nucleophilic reagents (see Vol. 12, p. 141). Standard displacements yielded the di-*exo*-L-*ido* and *exo*, *endo*-D-*gluco* isomers from 1,4;3,6-dianhydro-D-mannitol and -D-glucitol, respectively, the latter showing significant hypnotic activity; D- and L-*manno* derivatives (di-*endo*-azides) were prepared from diazidodideoxyhexitol precursors, since the di-*exo*-dimesylate of 1,4;3,6-dianhydro-L-iditol was unreactive to S_N2 substitution by azide ion; the L-*manno* derivative (2) showed useful hypnotic activity, whereas its antipode was inactive. The 1(4),3(6)-dithio-L-*manno* analogue of (2) was also prepared, but this was also inactive.[8] Heating D-glucitol and D-mannitol in dioxan–ethyl acetate in presence of acid resin yielded the corresponding 1,4;3,6-dianhydrides; prolonged reaction gave 2-*O*-acetyl derivatives (3), which could be converted to *exo*-5-chloro-5-deoxy-1,4;3,6-dianhydrohexitols by a standard sulphonate–chloride displacement sequence. These chloro-derivatives were predictably inert to base treatment.[9] 1,2;5,6-Dianhydro-3,4-dideoxy-D-*erythro*- and -D-*threo*-hexitols (4) and the corresponding *E*-3-ene derivatives have been prepared from 1,2;5,6-di-*O*-isopropylidene-D-glucitol and -D-mannitol respectively by standard transformations.[10] As expected from the Bertrand–Hudson rule, D-arabinitol is oxidized by *Acetobacter pasteurianus* BS1775 whereas [4-^{2}H]-D-arabinitol is completely inert. [4-^{2}H]-D-Ribitol is similarly resistant, and [2-^{2}H]-D-mannitol is only oxidized at C-5 and not at C-2; this appears to be the first example of deuterium blocking a biochemical reaction completely.[11] The kinetics of the oxidation of dulcitol by chloramine T have been explored, and a mechanism for the formation of galactose proposed.[12]

2,5- and 3,4-Di-*O*-acyl-D-mannitol derivatives have been prepared conventionally using standard saturated fatty acids in a study of their surfactant properties.[13]

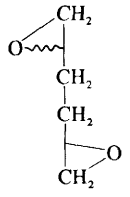
The *X*-ray irradiation of xylitol, sorbitol, and dulcitol single crystals has been studied.[14]



(2)



(3)



(4)

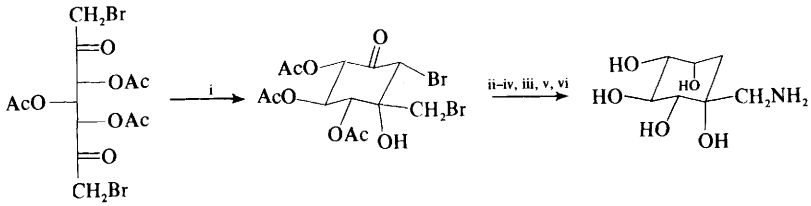
[8] J. Kuszmann and G. Medgyes, *Carbohydr. Res.*, 1980, **85**, 259.
[9] J. C. Goodwin, J. E. Hodge, and W. Weisleder, *Carbohydr. Res.*, 1980, **79**, 133.
[10] J. Kuszmann and P. Sohár, *Carbohydr. Res.*, 1980, **83**, 63.
[11] L. Stankovič, V. Bílik, L. Petruš, and V. Kováčik, *Chem. Zvesti*, 1980, **34**, 695.
[12] S. P. Madnawat, V. Singh, and D. R. Singh, *J. Indian Chem. Soc.*, 1980, **57**, 318 (*Chem. Abstr.*, 1980, **93**, 150 516).
[13] J. Fernandez-Bolanos, F. Collantes de Teran Palacios, R. Sanchez-Lopez, and N. Bueno Iborra, *An. Quim.*, 1979, **75**, 1013 (*Chem. Abstr.*, 1980, **93**, 26 680).
[14] E. E. Budzinski, W. R. Potter, and H. C. Box, *J. Chem. Phys.*, 1980, **72**, 972.

1-Amino-1-deoxy-alditol derivatives of ursolic and 18β-glycyrrhetinic acid have been prepared by condensation of D-glucose and D-ribose with 3-amino-derivatives of the acids followed by sodium cyanoborohydride reduction.[15] 1-Deoxy-1-methylamino-D-glucitol has been *N*-alkylated with long-chain alkyl halides to give corresponding tertiary amines, which were further quaternized to give ammonium salts that were effective antimicrobial agents against Gram-positive bacteria.[16] D-Glucose and D-mannose react with ethyl acetoacetate to give ethyl 2-methyl-5-(D-*arabino*-tetrahydroxybutyl)furan-3-carboxylate.[17] The structure of the heterocyclic aminohexitol derivative agropine is mentioned in Chapter 8.

2 Cyclitols

The synthesis of phosphoinositides has been reviewed,[18] and the synthesis of branched-chain *epi*-configuration deoxyhalogeno- and deoxyamino-cyclitols by cyclization of hepto-2,6-diuloses described, for example as shown in Scheme 1.[19]

1-D-5-*O*-(α-D-Galactopyranosyl)-4-*O*-methyl-*myo*-inositol has been identified as a new galactosyl cyclitol in seeds of *Vigna angularis* (adzuki bean).[20]



Reagents: i, NaOAc; ii, $NaBH_4$; iii, Ac_2O; iv, NaN_3; v, NaOMe; vi, H_2–Pt

Scheme 1

2-Deoxy-*scyllo*-inosamine (5) has been found to accumulate in an idiotroph of *Micromonospora sagamensis*, which normally produces sagamycin from 2-deoxystreptamine (6); this suggests the biosynthetic sequence to give (6) outlined in Scheme 2.[21] The same inosamine (5), or its enantiomer, has also been isolated from a mutant strain of *Bacillus circulans*.[22]

[15] C. H. Brieskorn and H. Eschelbach, *Arch. Pharm. (Weinheim, Ger.)*, 1979, **312**, 852 (*Chem. Abstr.*, 1980, **92**, 129 125).

[16] V. I. Veksler, V. E. Deeva, L. N. Kovalenko, A. V. Markovich, E. A. Lysenko, B. V. Sokolov, V. D. Sokolov, N. A. Solov'yan, Z. Ya. Khavin, *et al.*, *Zh. Obshch. Khim*, 1979, **49**, 2731 (*Chem. Abstr.*, 1980, **92**, 181 509).

[17] R. Imura and K. Ishimoto, *Kumamoto Joshi Daigaku Gakujutsu Kiyo*, 1977, **29**, 55 (*Chem. Abstr.*, 1980, **92**, 111 239).

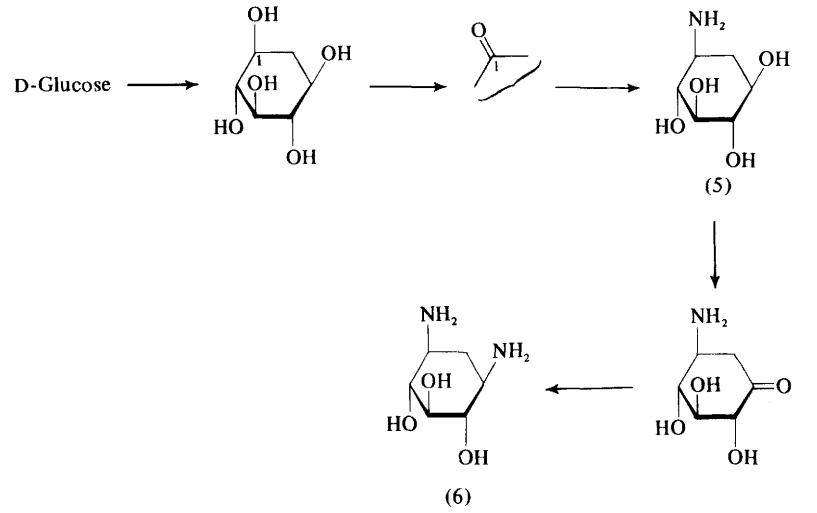
[18] A. E. Stepanov and V. I. Shvets, *Chem. Phys. Lipids*, 1979, **25**, 247 (*Chem. Abstr.*, 1980, **92**, 147 055).

[19] D. E. Kiely and J. M. Riordan, *Am. Chem. Soc., Symp. Ser.*, 1980, **125** (Aminocyclitol Antibiotics), 95 (*Chem. Abstr.*, 1980, **93**, 132 696).

[20] T. Yasui, *Agric. Biol. Chem.*, 1980, **44**, 2253.

[21] H. Kase, T. Iida, Y. Odakura, K. Shirahata, and K. Nayayama, *J. Antibiotics*, 1980, **33**, 1212.

[22] F. Fujiwara, Y. Takahashi, K. Matsumoto, and E. Kondo, *J. Antibiotics*, 1980, **33**, 824.



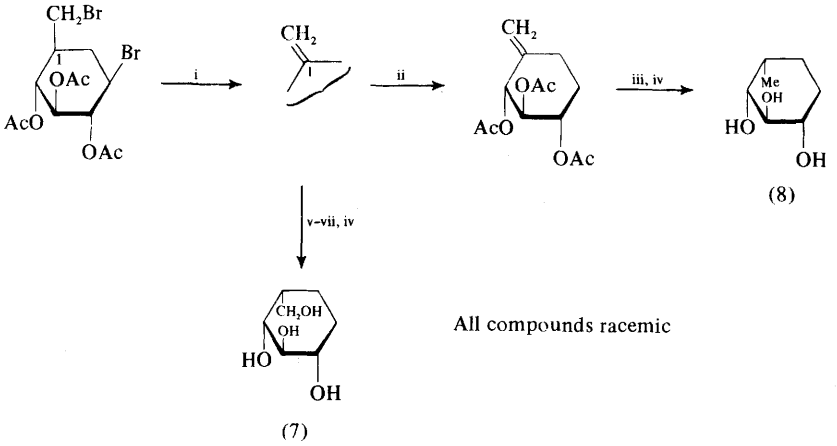
Scheme 2

An easy conversion of naturally occurring quebrachitol (2-*O*-methyl-L-*chiro*-inositol) to *muco*-inositol has been described, involving oxidative removal of the methyl group from the perbenzoyl derivative and inversion at C-2 by solvolysis of the corresponding tosylate with concomitant benzoate neighbouring-group participation.[23]

Racemic validatol (7) and deoxyvalidatol (8) have been synthesized by the procedure outlined in Scheme 3.[24] Racemic cyclitols have also been prepared from cyclohexene by repeated sequential allylic bromination and treatment with sodium benzyloxide to give a mixture of di(benzyloxy)cyclohexenes; the 3,4-diether (9) then being hydroxylated by standard procedures leading to the tetraol derivatives (10) (the 1,2,4/3-, 1,3/2,4-, and 1,4/2,3-isomers), from which racemic dihydroconduritols could be obtained.[25]

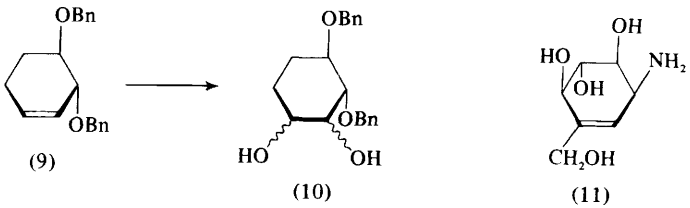
Many syntheses of amino-cyclitols have been reported in the past year, reflecting the great interest in these compounds as components of antibiotics. Paulsen's group has outlined a multistep synthesis of valienamine (11) from quebrachitol,[26] and a long paper describes the synthesis of an extensive range of selectively-substituted derivatives of 2-deoxystreptamine and analogues, including tri- and tetra-amino-compounds.[27] A synthesis of peracetylated racemic valienamine (12) together with its 3-epimer (13), 1′-amino-regioisomer (14),

[23] S. J. Angyal and L. Odier, *Carbohydr. Res.*, 1980, **80**, 203.
[24] S. Ogawa, T. Toyokuni, M. Omata, N. Chida, and T. Suami, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 455.
[25] A. Hasegawa, T. Kobayashi, and M. Kiso, *Agric. Biol. Chem.*, 1980, **44**, 165.
[26] H. Paulsen and F. R. Heiker, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 904.
[27] H. Paulsen and E. Sumfleth, *Chem. Ber.*, 1980, **113**, 1723.



Reagents: i, AgF–py; ii, Bu_3SnH; iii, H_2–Pt; iv, NaOMe; v, $NaBH_4$–BF_3; vi, H_2O_2; vii, Ac_2O–py

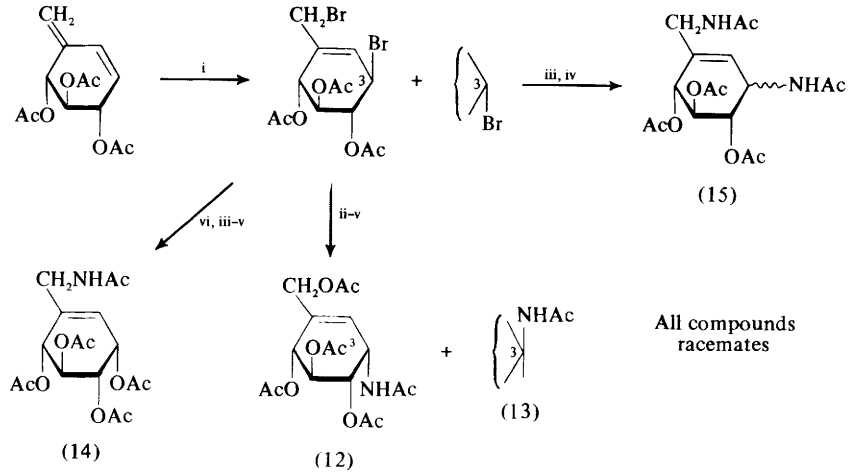
Scheme 3



and 1′,3-diamino analogues (15) is summarized in Scheme 4; either epimer predominated in the bromination step depending on the conditions.[28]

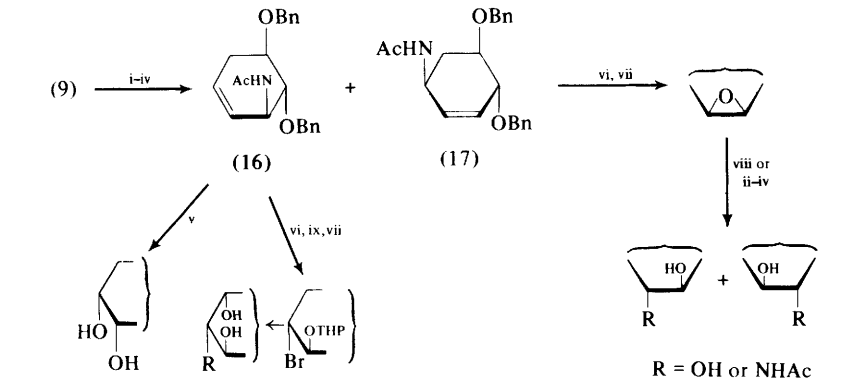
The di(benzyloxy)cyclohexene (9) mentioned above has also been used to synthesize racemic deoxyinosamine, deoxyinosadiamine, and inosamine derivatives *via* the unsaturated inosamine derivatives (16) and (17); Scheme 5 illustrates the basic sequences that were applied to both isomers.[29] The same group has similarly prepared racemic amino-cyclitols from 3-benzyloxycyclohexene,[30] and 3-methoxycyclohexene was used for a synthesis of the peracetylated DL-2,5-diamino-2,3,5-trideoxy-4-*O*-5-*N*-dimethyl-*chiro*-inositol (18).[31] Base-catalysed cyclization of the substituted diones (19) gave the corresponding cyclitols (20), which were then used to prepare other 2,1′-substituted cyclitols including mono- and di-amino-cyclitols, *e.g.*, (21).[32]

[28] S. Ogawa, T. Toyokuni, and T. Suami, *Chem. Lett.*, 1980, 713.
[29] M. Kiso, T. Kobayashi, and A. Hasegawa, *Agric. Biol. Chem.*, 1980, **44**, 419.
[30] M. Kiso, T. Kobayashi, and A. Hasegawa, *Agric. Biol. Chem.*, 1980, **44**, 169.
[31] M. Kiso, H. Hibino, M. Tanaka, and A. Hasegawa, *Agric. Biol. Chem.*, 1980, **44**, 1717.
[32] J. M. Riordan, D. E. Kiely, L. J. De Lucas, H. M. Einspahr, and C. E. Bugg, *Carbohydr. Res.*, 1980, **82**, 303.



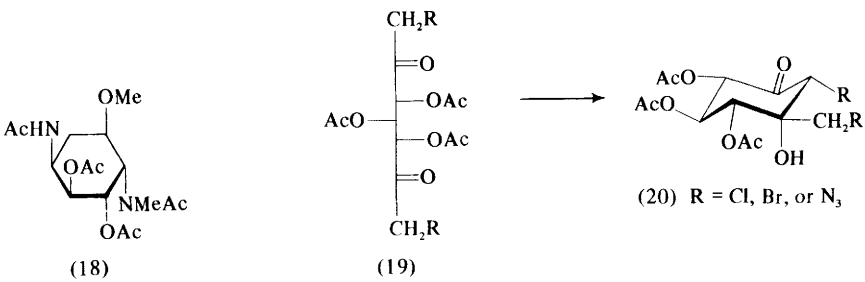
Reagents: i, Br_2; ii, KOAc–18-crown-6; iii, NaN_3; iv, H_2S–py or $NaBH_4$; v, Ac_2O; vi, AgOAc

Scheme 4

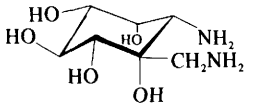


Reagents: i, Br_2; ii, NaN_3; iii, LAH; iv, Ac_2O–MeOH; v, OsO_4; Br_2–H_2O; vii, NaOMe; viii, H_2SO_4; ix, dihydropyran

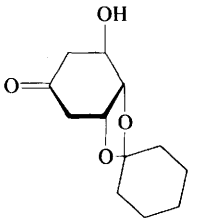
Scheme 5



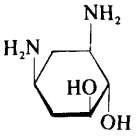
L-Quinic acid has been converted to the trihydroxycyclohexanone derivative (22), which was then used to synthesize a range of aminocyclitols including 2,6-dideoxystreptamine (23), 2,5,6-trideoxystreptamine, 5-amino-2,5,6-trideoxystreptamine, and 3,5-dideoxyfortamine (24), by standard transformations, especially sulphonate → azide sequences.[33]



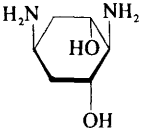
(21)



(22)

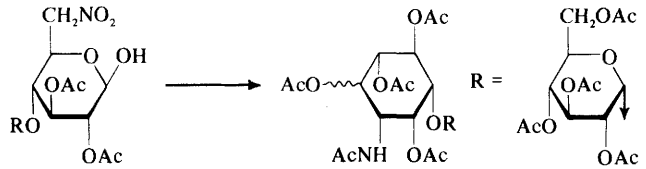


(23)

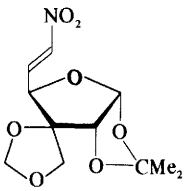


(24)

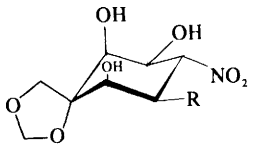
1,6-Anhydromaltose has been converted to the pseudo-disaccharides (25) containing 3-amino-3-deoxy-*epi*-inositol or 1-amino-1-deoxy-1-L-*myo*-inositol *via* the 6-deoxy-6-nitromaltose derivative (26).[34] The branched-chain unsaturated 6-nitro-sugar (27), prepared conventionally from D-glucose, yielded isomeric dithianyl adducts which were similarly cyclized to give the nitro-cyclitols (28) and (29), of interest as potential intermediates for the synthesis of tetrodo-



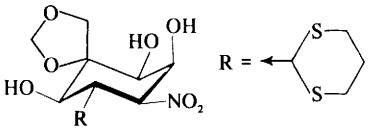
(26) (25)



(27)



(28)



(29)

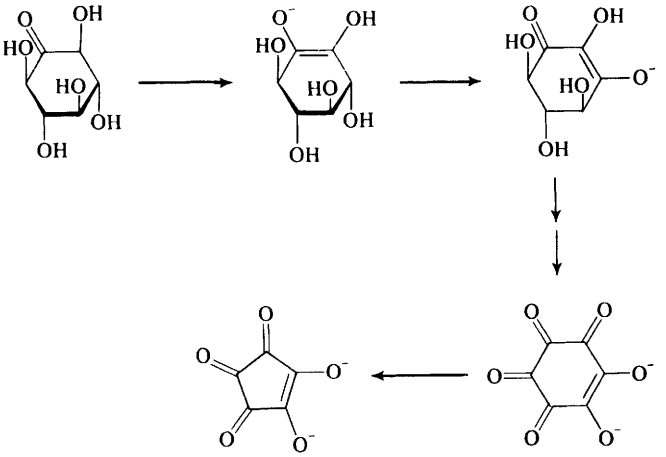
[33] L. Castellanos, J. Cléophax, C. Colas, S. D. Gero, J. Leboul, D. Mercier, A. Olesker, A. Rolland, B. Quiclet-Sire, and A.-M. Sepulchre, *Carbohydr. Res.*, 1980, **82**, 283.

[34] I. Fujimaki and H. Kuzuhara, *Agric. Biol. Chem.*, 1980, **44**, 2055.

loxin.[35] The synthesis of a racemic validamine derivative is mentioned in Chapter 8.

Variously derivatized 2-deoxy- and 2,5-dideoxy-streptamines have been synthesized; 2,5-dideoxystreptamine was prepared from kanamycin by a simple procedure,[36] and 5-*O*-(2,3-dideoxy-α-D-*erythro*-hexopyranosyl)-2-deoxy-streptamine dihydrochloride was obtained by glycosidation of a 2-deoxystreptamine derivative with tri-*O*-acetyl-D-glucal and hydrogenation.[37] The preparation of a 5-aminocyclohexanetetrol from kanamycin A is mentioned in Chapter 18.

Changes in the u.v. absorption of 2,4,6/3,5-pentahydroxycyclohexanone in alkaline phosphate buffer under anaerobic conditions have been ascribed to phosphate-catalysed enolization; on exposure to oxygen, further changes occurred which were interpreted by formation of polyone compounds *via* enediolate intermediates, as outlined in Scheme 6.[38] There have been further reports on the synthesis of mono- and di-phosphate esters of asymmetrically substituted *myo*-inositol, *e.g.*, (30),[39,40] and the mannopyranosyl ortho-ester



Scheme 6

[35] M. Funabashi, H. Wakai, K. Sato, and J. Yoshimura, *J. Chem. Soc., Perkin Trans. 1*, 1980, 14.

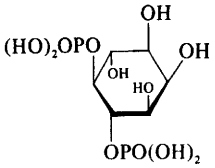
[36] A. Canas-Rodriguez, S. Galan Ruiz-Poveda, and A. Martinez-Tobed, *An. Quim.*, 1979, 75, 692 (*Chem. Abstr.*, 1980, 92, 129 218).

[37] A. Canas-Rodriguez and A. Martinez-Tobed, *An. Quim.*, 1979, 75, 697 (*Chem. Abstr.*, 1980, 92, 129 219).

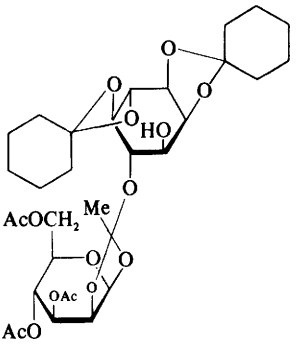
[38] D. R. Liljegren and M. E. Tate, *Carbohydr. Res.*, 1980, 82, 378.

[39] V. N. Krylova, N. I. Kobel'kova, and G. F. Oleinik. *Zh. Org. Khim.*, 1980, 16, 62 (*Chem. Abstr.*, 1980, 93, 72 148).

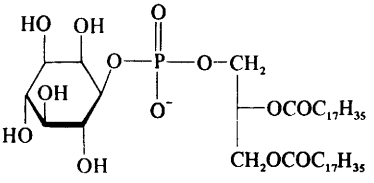
[40] V. N. Krylova, N. P. Gornaeva, G. F. Oleinik, and V. I. Shvets, *Zh. Org. Khim.*, 1980, 16, 315 (*Chem. Abstr.*, 1980, 93, 95 518).



(30)



(31)



(32)

derivative (31) has been used to prepare the monophosphoinositide (32) by coupling with an appropriately substituted glyceryl phosphate followed by deprotection with aqueous acetic acid.[41]

Semi-empirical MO calculations have been made on the chair conformations of inositols. The EHT method gives results that fit experimental observations, predicting destabilizing 1,3-non-bonded interactions between oxygen, and suggesting that hydrogen-bond interactions between the hydroxy-group and oxygen are a major factor determining conformational preferences, whereas the CNDO-2 method overestimates such stabilization energies and cannot predict the destabilizing effect of lone-pair interactions.[42]

[41] V. N. Krylova, A. I. Lyutik, A. E. Kosaeva, and V. I. Shvets, *Zh. Org. Khim.*, 1979, **15**, 2323 (*Chem. Abstr.*, 1980, **92**, 147 084).

[42] I. Lee, J. H. Sohn, S. C. Kim, and Y. K. Jeon, *Taehan Hwahak Hoechi*, 1979, **23**, 271 (*Chem. Abstr.*, 1980, **92**, 129 213).

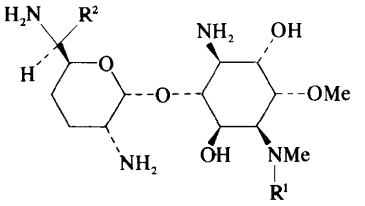
18

Antibiotics

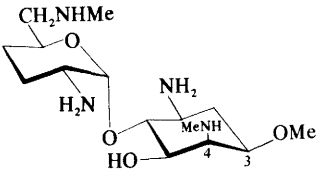
1 Aminoglycoside Antibiotics

The papers given at a symposium on aminocyclitol antibiotics have been published; most are reports of the synthesis of naturally occurring compounds or their conversion to modified analogues in search of improved antibiotic activity.[1] A review has also appeared covering the structure, physicochemical and biological properties, structure–activity relationships, and mode of action of aminoglycoside antibiotics.[2]

New fortimicin antibiotics have been reported. Fortimicins C, D, and KE have been identified as the forticimicin derivatives (1), (2), and (3), respectively.[3] *N*-Formylfortimicin A (4) has been isolated from *Micromonospora olivoasterospora*,[4] and a new fortimicin antibiotic (5), containing an unusual iminoformyl group, has been obtained from the actinomycete *Dactylosporangium matsuzakiense*.[5] Sannamycin C (6), isolated from *S. sannanensis* KC-7038, is also a fortimicin analogue, being a 6-*N*-methylpurpurosamine C derivative of 2-deoxy-3-*epi*-fortamine;[6] its 4-*N*-glycyl derivative was found to inhibit Gram positive and negative bacteria resistant to other aminoglycoside antibiotics. The structures of many minor components of the fortimicin complex have also been reported.[7]



C (1) $R^1 = COCH_2NHCONH_2$, $R^2 = Me$
D (2) $R^1 = COCH_2NH_2$, $R^2 = H$
KE (3) $R^1 = R^2 = H$
(4) $R^1 = COCH_2NHCHO$, $R^2 = Me$
(5) $R^1 = COCH_2NHCH{=}NH$, $R^2 = Me$



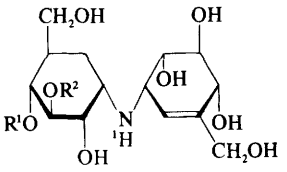
(6)

[1] *Am. Chem. Soc. Symp. Ser.*, 1980, **125** (Aminocyclitol Antibiot.)
[2] J. Reden and W. Duerckheimer, *Top. Curr. Chem.*, 1979, **83**, 105.
[3] T. Ida, M. Sato, I. Matsubara, Y. Mori, and K. Shirahata, *J. Antibiot.*, 1979, **32**, 1273.
[4] S. Inouye, T. Shomura, K. Ohba, H. Watanabe, S. Omoto, T. Tsuruoka, M. Kojima, and T. Niida, *J. Antibiot.*, 1980, **33**, 510.
[5] S. Inouye, K. Ohba, T. Shomura, M. Kojima, T. Tsuruoka, J. Yoshida, N. Kato, M. Ito, S. Amano, S. Omoto, *et al.*, *J. Antibiot.*, 1979, **32**, 1354.
[6] T. Deushi, T. Yamaguchi, K. Kamuja, A. Iwasaki, T. Mizoguchi, M. Nakayama, I. Watanabe, H. Itoh, and T. Mori, *J. Antibiot.*, 1980, **23**, 1274.
[7] J. B. McAlpine, R. S. Egan, R. S. Stanaszek, M. Cirovic, S. L. Mueller, R. E. Carney, P. Collum, E. E. Fager, A. W. Goldstein, *et al.*, in ref. 1, p. 295.

A new antibiotic, S-11-A, obtained from a mutant strain of *Bacillus circulans*, has been shown to be 1-deamino-1-hydroxy-xylostasin; this contains a known biosynthetic precursor of the 2-deoxy-streptamine present in xylostasin.[8]

Degradation of the antibiotic sporaviridin has yielded two further pentasaccharides, viridopentaose A and C, which are closely related to viridopentaose B mentioned in last year's report (see Vol. 13, p. 158) viosamine is replaced by the corresponding simple sugars 6-deoxy-D-glucose and -D-glucose, respectively.[9] N.m.r. evidence indicates that the acidic antitumour antibiotic neocarzinostatin contains 2,6-dideoxy-2-methylamino-galactose as a component of a chromophor attached to protein.[10]

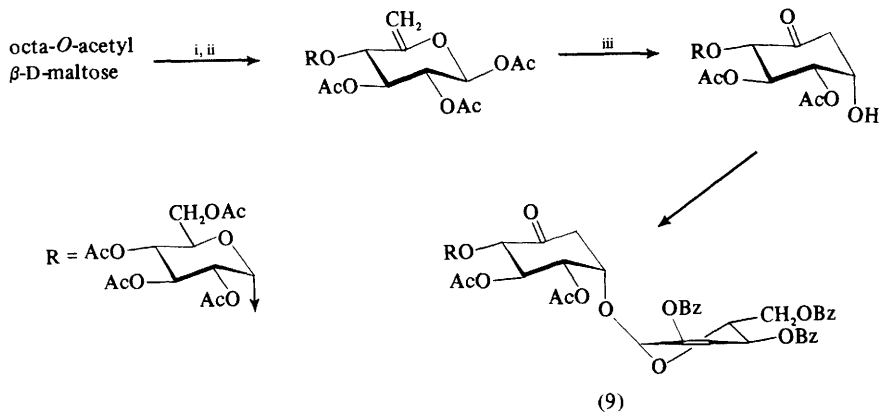
Synthetic studies have shown that validamycin A has the structure (7)[11–13] and not the isomeric structure (8) previously proposed (see Vol. 6, p. 134). Glucosylation of validoxylamine A (7, $R^1=R^2=H$) by *Rhodotorula lactosa* gave a mixture of α- and β-D-glucosyl derivatives; of these, the 4-β-isomer was shown to be identical with validamycin A, the 4-α-isomer being validamycin D.[14]



(7) R^1 = β-D-Glc*p*, R^2 = H
(8) R^1 = H, R^2 = β-D-Glc*p*

Ferrier's group has described a new approach to the synthesis of aminoglycoside antibiotics, which utilizes their hex-5-enose–inosose conversion procedure; Scheme 1 outlines the conversion of octa-acetyl-β-D-maltose to a pseudotrisaccharide possessing a di-*O*-α-D-hexopyranosylcyclohexane structure closely related to that present in many antibiotics.[15] More conventional reactions have been used in the conversion of a ribostamycin derivative to neomycin C, being the first reported synthesis of a pseudotetrasaccharide,[16] and in a new synthesis of neamine (4-*O*-neosaminyl-2-deoxy-streptamine) and its 6-glycosylated-streptamine isomer.[17] Quinic acid has been used to prepare 2,5,6-

[8] T. Fujiwara, Y. Takahashi, K. Matsumoto, and E. Kondo, *J. Antibiot.*, 1980, **33**, 836.
[9] K. Harada, S. Ito, T. Murase, and M. Suzuki, *Heterocycles*, 1979, **13**, 145 (*Chem. Abstr.*, 1980, **93**, 47046).
[10] G. Albers-Schönberg, R. S. Dewey, O. D. Hensens, J. M. Liesch, M. A. Napier, and I. H. Goldberg, *Biochim. Biophys. Res. Commun.*, 1980, **95**, 1351.
[11] S. Ogawa, Y. Shibata, N. Chida, and T. Suami, *Chem. Lett.*, 1980, 135.
[12] S. Ogawa, N. Chida, and T. Suami, *Chem. Lett.*, 1980, 139.
[13] T. Suami, S. Ogawa, and N. Chida, *J. Antibiot.*, 1980, **33**, 98.
[14] Y. Kameda, N. Asano, O. Wakae, and T. Iwasa, *J. Antibiot.*, 1980, **33**, 764.
[15] R. Blattner, R. J. Ferrier, and P. Prasit, *J. Chem. Soc., Chem. Commun.*, 1980, 944.
[16] S. Umezawa, A. Harayama, and Y. Nishimura, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 3259.
[17] A. Harayama, T. Tsuchiya, and S. Umezawa, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 3626.



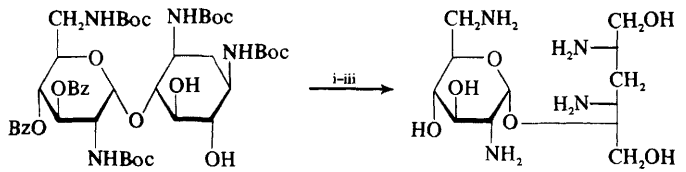
Reagents: i, NBS, *hν*; ii, Zn–HOAc; iii, $Hg(OAc)_2$–HOAc

Scheme 1

trideoxy-streptamine, and from this 5,6-dideoxy-neamine was obtained biosynthetically using *Streptomyces*; the same group also prepared 3′,5,6-trideoxy-neamine by a glycal coupling procedure.[18] Syntheses of Sorbisitin A_1 and of fortimicin B are mentioned in Chapter 8.

Selective periodate oxidation of neamine derivatives can lead to novel amino-glycosides, which are analogues of sorbistin antibiotics, as shown in Scheme 2; likewise cleavage of the C-3,C-4 bond of the neosamine unit led to the acetalated glycoside (10) of 2-deoxy-streptamine.[19]

Numerous reports describe the modification of natural amino-glycoside antibiotics or products derived from them by conventional methods. 1-*N*-Alkylated kanamycins can be prepared very efficiently by utilizing an O → N acyl migration to protect the sugar amino-groups selectively, leaving the deoxy-streptamine amino-groups free; a formylation–deformylation sequence then



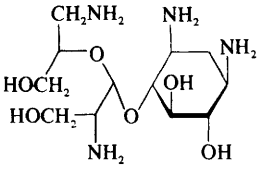
Boc = t-butoxycarbonyl

Reagents: i, IO_4^-; ii, BH_4^-; iii, CF_3CO_2H

Scheme 2

[18] C. Colas, B. Quiclet-Sire, J. Cléphax, J.-M. Delaumény, A.-M. Sepulchre, and S. D. Gero, *J. Am. Chem. Soc.*, 1980, **102**, 857.

[19] S. Tohma, T. Yoneta, and S. Fukatsu, *J. Antibiot.*, 1980, **33**, 671.



(10)

leaves the 1-amino-group free for selective alkylation.[20] Kanamycin analogues prepared include 6′-*C*-alkyl derivatives of 3′,4′-dideoxy-kanamycin B,[21] 3′-deoxyamikacin from 3′-deoxy-kanamycin A,[22] 6″-deoxy- and 4″,6″-dideoxy-derivatives of kanamycin B,[23] 2′,3′-epimino- and 2″,3″-epimino-derivatives of kanamycin B, ribostamycin, and neamine,[24] 3′-*epi*-4′-deoxy-kanamycin B,[25] and 1-*N*-(1,3-dihydroxy-2-propyl)kanamycin B.[26] 1-*N*-(3-Amino-2-hydroxypropionyl) derivatives of kanamycin A, gentamicin B, gentamicin C_{1a}, 5-epigentamicin B, and 5-episisomicin have been prepared, showing similar or improved potency compared to the parent antibiotics, the sisomicin derivatives being claimed as the most potent, broadest spectrum antibiotics prepared to date.[27–29] Other reports describe the synthesis of 1‴-deoxo-derivatives of butirosin and some of its deoxy- and amino-analogues (*i.e.*, a 1-*N*-acyl to 1-*N*-alkyl modification, using borane),[30] the conversion of paromomycin and paromamine to 4′-deoxy-analogues,[31] the preparation of mono-*N*-acetyl derivatives of tobramycin, using immobilized aminoglycoside acetyl transferase,[32] and the conversion of validamycin A to a glucosamine-containing analogue, in which the glucose was replaced by glucosamine by partial hydrolysis followed by reglycosidation, both the α- and β-anomers being obtained.[33]

2-*O*-Mesyl-fortimicin B has been used to synthesize 2-deoxy-fortimicin A and B, and also 1-deamino-2-deoxy-2-*epi*-amino-fortimicin A and B; 2-deoxy-forti-

[20] M. B. Thomas and M. T. Williams, *Tetrahedron Lett.*, 1980, **21**, 4981.
[21] H. Umezawa, D. Ikeda, T. Miyasaka, and S. Kondo, *J. Antibiot.*, 1979, **32**, 1363.
[22] T. Tsuchiya, T. Jikihara, T. Mijake, S. Umezawa, M. Hamada, and H. Umezawa, *J. Antibiot.*, 1979, **32**, 1351.
[23] T. Miyasaka, D. Ikeda, S. Kondo, and H. Umezawa, *J. Antibiot.*, 1980, **33**, 527.
[24] V. Kumar, G. S. Jones, I. Blacksberg, W. A. Remers, M. Misiek, and T. A. Pursiano, *J. Med. Chem.*, 1980, **23**, 42.
[25] E. Akita, Y. Moriuchi, and T. Miyazawa, *Heterocycles*, 1979, **13**, 157 (*Chem. Abstr.*, 1980, **93**, 26 684).
[26] K. Richardson, K. W. Brammer, and S. Jevons, *Curr. Chemother. Infect. Dis., Proc. Int. Congr. Chemother., 11th*, 1979, (Publ. 1980), **1**, 390 (*Chem. Abstr.*, 1980, **93**, 150 531).
[27] A. K. Mallams, P. Reichert, and J. B. Morton, in ref. 26, p. 406.
[28] T. L. Nagabhushan, A. B. Cooper, and G. H. Miller, in ref. 26, p. 411.
[29] D. F. Rane and P. J. L. Daniels, in ref. 26, p. 408.
[30] T. Hayashi, H. Saeki, N. Takeda, and E. Ohki, *J. Antibiot.*, 1979, **32**, 1280.
[31] S. Hanessian and J.-M. Vatele, *J. Antibiot.*, 1980, **33**, 675.
[32] F. Le Goffic, J. F. Le Bigot, S. Sicsic, and C. Vincent, *Nouv. J. Chim.*, 1980, **4**, 53 (*Chem. Abstr.*, 1980, **92**, 196 368).
[33] A. Hasegawa, T. Kobayashi, H. Hibino, and M. Kiso, *Agric. Biol. Chem.*, 1980, **44**, 143.

micin A was more antibiotically active than fortimicin A, whereas the 2-*epi*-amino-analogue was inactive.[34] Another paper describes the preparation of 2-deoxy-fortimicin A and the 1-epimers of both fortimicin A and 2-deoxy-fortimicin A; epimerization at C-1 had little antibiotic effect.[35] Base-catalysed rearrangement of 3-*O*-demethyl-fortimicin A produced 1-*N*-glycyl-3-*O*-demethyl-fortimicin B and 3-*O*-demethyl-isofortimicin.[36] Treatment of 1,4,2′,6′-tetra-*N*-benzyloxycarbonyl fortimicin A with triphenylphosphine and carbon tetrachloride at 50 °C yielded the 2-monochloro-analogue, whereas at 80 °C a mixture of the 2,5-dichloro-derivative and the corresponding 2-chloro-4,5-unsaturated compound was obtained.[37] Acylation of 1,2′,6′-tri-*N*-benzyloxy-carbonyl-fortimicin B followed by hydrogenolysis allowed the preparation of a wide range of 4-*N*-acyl analogues of fortimicin A for antibacterial assessment.[38]

Istamycin A[39] and demethyl analogues of istamycin A[40] have been prepared from 3′,4′-dideoxy-neamine; studies with the latter compounds established that the 4-*N*-methyl group was essential for antibiotic activity, whereas 6′-*N*-3-*O*-didemethyl-istamycin A was still active. 3′- And 4′-amino analogues of neamine have been prepared, together with a number of their 3′- and 4′-epimers, but none were found to be as active as neamine itself.[41] Gentamine C_{1a} has been converted into gentamine C_2 and its 6′-epimer, both of which showed weak antibiotic activity.[42] Gentamycin C has been used to prepare a garamine derivative by partial hydrolysis, which was then acylated to give a range of 4-*O*-amino-acid esters and 4-*O*-urethanes of garamine.[43] 6′-Hydroxy-spectinomycin has been synthesized by an adaptation of the procedure previously described by these workers for spectinomycin itself, using a 3-methoxy-sugar to prevent C-3 acetyl migration and concomitant elimination of the C-6 acetoxy-group; 6′-bromo- and 6′-chloro-spectinomycin were also prepared.[44]

Bioconversions of aminoglycoside antibiotics have been discussed.[45] Further studies in the biosynthesis of streptomycin have shown that only streptidine-6-phosphate acts as an acceptor for dihydrostreptose in the synthesis of *O*-α-L-dihydrostreptose(1 → 4)streptidine-6-phosphate using a purified enzyme preparation from *S. griseus*,[46] and that this pseudodisaccharide could be

[34] J. R. Martin, P. Johnson, J. Tadanier, and A. W. Goldstein, *J. Antibiot.*, 1980, **33**, 810.
[35] R. E. Carney and J. B. McAlpine, in ref. 26, p. 397.
[36] P. A. Lartey and D. J. Grampovnik, *J. Antibiot.*, 1980, **33**, 1071.
[37] T. Suami, K.-I. Tadano, and K. Matsuzawa, *J. Antibiot.*, 1980, **33**, 1289..
[38] J. Tadanier, J. R. Martin, P. Kurath, A. W. Goldstein, and P. Johnson, *Carbohydr. Res.*, 1980, **79**, 91.
[39] D. Ikeda, T. Miyasaka, M. Yoshida, Y. Horiuchi, S. Kondo, and H. Umezawa, *J. Antibiot.*, 1979, **32**, 1365.
[40] D. Ikeda, Y. Horiuchi, S. Kondo, and H. Umezawa, *J. Antibiot.*, 1980, **23**, 1281.
[41] R. D. Sitrin, F. R. Pfeiffer, J. R. Rosenbloom, D. J. Cooper, S. J. Schmidt, D. Peterson, G. Wellman, J. R. E. Hoover, and J. A. Weisbach, *J. Antibiot.*, 1980, **33**, 383.
[42] D. Ikeda, T. Miyasaka, K. Yoshida, K. Iinuma, S. Kondo, and H. Umezawa, *J. Antibiot.*, 1979, **32**, 1357.
[43] H. Paulsen and H. Böttcher, *Chem. Ber.*, 1979, **112**, 3864.
[44] C. J. Maring and D. R. White, *Tetrahedron Lett.*, 1980, **21**, 4065.
[45] A.-M. Sepulchre, B. Quiclet, and S. D. Gero, *Bull. Soc. Chim. Fr.*, 1980, 56.
[46] B. Kniep and H. Grisebach, *Eur. J. Biochem.*, 1980, **105**, 139.

converted to dihydrostreptomycin 6-phosphate using another cell-free enzyme preparation from this micro-organism in presence of nucleotide-bound *N*-methyl-L-glucosamine.[47] The biosynthesis of spectinomycin from glucose utilizes the enzyme *myo*-inositol 1-phosphate synthase, and the 4,6-dideoxyhexose is produced by hydride transfer from C-4 to C-6.[48] The 5-aminocyclohexanetetrol involved in the biosynthesis of 2-deoxystreptamine has been shown to possess the 1L-1,3,5/2,4-configuration by comparison with an authentic specimen synthesized from kanamycin A.[49] A cell-free extract of *Bacillus brevis* converted xylostasin into its 4′-*O*-monoadenylyl derivative.[50]

The structure of gentamicin A has been confirmed by methanolysis, yielding derivatives which gave rotations corresponding to paromamine derivatives containing a 4-linked glucosamine unit, but not to derivatives of its 6-linked diastereoisomer.[51]

A study of the degradation of fortimicin A and 4-*N*-acyl fortimicin B as free bases in water has suggested that either simple cleavage of the 4-*N*-acyl residue occurs, giving fortimicin B, or inter-ring acyl migration takes place leading to 2′-*N*-acyl fortimicin B (isofortimicin rearrangement).[52]

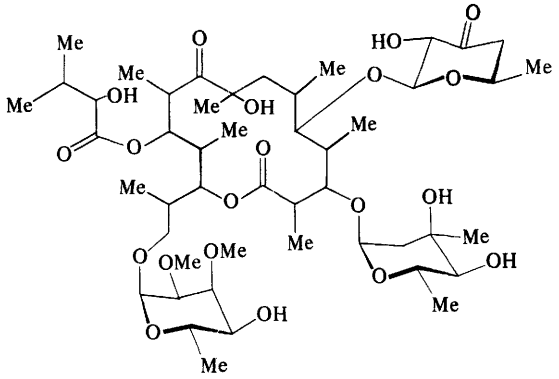
A study of streptomycin using ^{15}N and ^{13}C n.m.r. indicates that the streptose formyl group does not cyclize with either methylamino- or guanidino-groups in the other rings giving a four-ring structure, but is probably hydrated.[53]

A sensitive method for the identification of aminoglycoside antibiotics has been described; components are detected on thin-layer chromatograms by applying an agar medium inoculated with a *Bacillus subtilis* test organism, and quantitative assays can be made.[54]

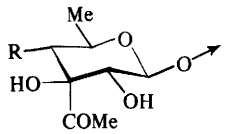
2 Macrolide Antibiotics

Single-crystal *X*-ray analysis has established that the novel macrolide antibiotic isolated from *S. chryseus* has the structure (11), containing mycarose, 4,6-dideoxy-D-*erythro*-hexos-3-ulose, and 6-deoxy-2,3-di-*O*-methyl-L-allose as separate sugar units.[55] Similarly *X*-ray analysis has shown that rosaramicin obtained from *Micromonospora rosaria* contains desosamine β-linked to a macrolide ring.[56] Mycinamycins, a new family of basic 16-membered macrolide antibiotics from *Micromonospora sp.* A-11725, also contain desosamine along

[47] B. Kniep and H. Grisebach, *J. Antibiot.*, 1980, **33**, 416.
[48] H. Otsuka, O. A. Mascaretti, L. H. Hurley, and H. G. Floss, *J. Am. Chem. Soc.*, 1980, **102**, 6817.
[49] K. Igarashi, T. Honma, T. Fujiwara, and E. Kondo, *J. Antibiot.*, 1980, **33**, 830.
[50] H. Shirafuji, M. Kida, T. Asako, and M. Yoneda, *Agric. Biol. Chem.*, 1979, **43**, 2579.
[51] H. Maeher, J. Smallheer, and C. P. Schaffner, *J. Antibiot.*, 1980, **23**, 1380.
[52] J. Tadanier, J. R. Martin, P. Johnson, A. W. Goldstein, and R. Hallas, *Carbohydr. Res.*, 1980, **85**, 61.
[53] W. E. Hull and H. R. Kricheldorf, *Liebigs Ann. Chem.*, 1980, 158.
[54] J. K. Pauncz and I. Harsanyi, *J. Chromatogr.*, 1980, **195**, 251.
[55] B. Arnoux, C. Pascard, and J. Lunel, *Symp. Pap. IUPAC Int. Symp. Chem. Nat. Prod., 11th*, 1978, **2**, 247 (*Chem. Abstr.*, 1980, **92**, 22 767).
[56] A. K. Ganguly, Y.-T. Liu, O. Sarre, R. S. Jaret, A. T. McPhail, and K. K. Onan, *Tetrahedron Lett.*, 1980, **21**, 4699.



(11)



(12) R = H
(13) R = OH

with mycinose (6-deoxy-2,3-di-*O*-methyl-D-allose) as separate units.[57] Staphcoccomycin, a new basic macrolide isolated from the fermentation broth of *Streptomyces sp.* AS-NG-16, has been characterized as the desmycarosyl derivative of angolamycin.[58] Shunt metabolites of turimycin biosynthesis occurring in *S. hygroscopicus* have been isolated and identified as platenolide glycosides containing mycarose or 3-demethyl-mycarose (L-digitoxose)[59] or alternatively the novel 3-*C*-acetyl branched-chain sugars 3-*C*-acetyl-4,6-dideoxy-D-*xylo*-hexopyranose (12) or 3-*C*-acetyl-6-deoxy-D-glucopyranose (13)[60] as the sugar components. An intermediate in the biosynthesis of tylosin by *S. fraidiae*, isolated from the culture broth of a mutant, has been shown to be mycarosyl protylonolide;[61] the mutant could also convert mycaminosyl tylonolide into tylosin by attaching the necessary mycarose and mycinose units. The absolute configuration of tylosin follows from an *X*-ray study on protylonolide.[62] Mass

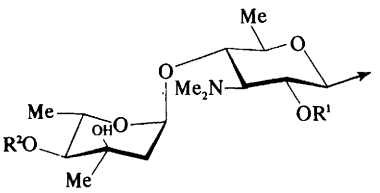
[57] M. Hayashi, M. Ohno, and S. Satoi, *J. Chem. Soc., Chem. Commun.*, 1980, 119.
[58] I. R. Shimi, S. Shoukry, and F. T. Ali, *J. Antibiot.*, 1979, **32**, 1249.
[59] U. Gräfe, W. Schade, W. Ihn, G. Reinhardt, K. Dornberger, H. Thrum, and L. Radics, *J. Antibiot.*, 1980, **33**, 574.
[60] U. Gräfe, W. Schade, W. Ihn, G. Reinhardt, K. Dornberger, H. Thrum, and L. Radics, *J. Antibiot.*, 1980, **33**, 566.
[61] S. Omura, N. Sadakane, C. Kitao, H. Matsubara, and A. Nakagawa, *J. Antibiot.*, 1980, **33**, 913.
[62] S. Omura, H. Matsubara, A. Nakagawa, A. Furusaki, and T. Matsumoto, *J. Antibiot.*, 1980, **33**, 915.

spectral studies have been extensively used in establishing the structures of the polyene macrolide antibiotics partricin A and B, which contain mycosamine,[63] and the structure of a new pentaene macrolide antitumour antibiotic containing L-rhamnose, produced by an *Actinomyces* strain.[64] A new macrolide complex A6888 isolated from *S. flocculus* yielded four major components; factors A and F were identified as cirramycin B and cirramycin A, respectively, whereas factors C and X were considered to be new compounds, which contain the same 4-*O*-(2,3,6-trideoxyhexosyl)-3,4,6-trideoxy-3-dimethylaminohexose disaccharide side-chain.[65]

The total synthesis of carbomycin B and josamycin is referred to in Chapter 23.

The oxidation of midecamycin with dimethyl sulphoxide–acetic anhydride has been studied: the macrolide allylic alcohol function was oxidized to the corresponding ketone, whereas the 2′-hydroxy-group on the mycaminose moiety was acetylated rather than oxidized, while the mycarose unit was simultaneously converted to its 3″-*O*-methylthiomethyl ether derivative.[66]

The disaccharide unit (14) in 4″-*O*-deacyldeltamycin can be selectively acetylated with acetic anhydride to give the corresponding 2′-*O*-acetyl derivative (15); this could then be further acylated with acyl chlorides to give 2′-*O*-acetyl-4″-*O*-acyl derivatives, which were selectively deacetylated to 4″-*O*-acyl deltamycin analogues (16) on boiling in methanol: 4″-*O*-acyl deltamycin also yields these analogues directly by treatment with acyl chlorides.[67] This same transformation has been achieved biochemically in the conversion of tylosin to 4″-*O*-acyl tylosin derivatives using a strain of *S. thermotolerans*.[68] Maridomycin III is transformed into 18-dihydro- and 4″-dipropionyl derivatives by marido-



(14) $R^1 = R^2 = H$
(15) $R^1 = Ac$, $R^2 = H$
(16) $R^1 = H$, $R^2 = COR$

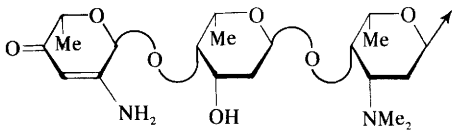
[63] J. Golik, J. Zieliński, and E. Borowski, *J. Antibiot.*, 1980, **33**, 904.
[64] J. Pawlak, J. Zieliński, J. Golik, J. Gumieniak, and E. Borowski, *J. Antibiot.*, 1980, **33**, 989.
[65] S. M. Nash, L. O. Boek, P. W. Ensminger, M. M. Hoehn, and K. F. Koch, *Curr. Chemother. Infect. Dis. Proc. Int. Congr. Chemother., 11th*, 1979 (Publ. 1980), **1**, 462 (*Chem. Abstr.*, 1980, **93**, 166021).
[66] S. Inouye, S. Omoto, K. Iwamatsu, and T. Niida, *J. Antibiot.*, 1980, **33**, 61.
[67] Y. Shimauchi, K. Hori, M. Sakamoto, Y. Mutoh, Y. Fukagawa, S. Hori, and T. Ishikura, *J. Antibiot.*, 1980, **33**, 284.
[68] R. Okamoto, T. Fukumoto, H. Nomura, K. Kiyoshima, K. Nakamura, A. Takamatsu, H. Naganawa, T. Takeuchi, and H. Umezawa, *J. Antibiot.*, 1980, **23**, 1300.

mycin III-insensitive streptomyces, the reduction of the C-18 formyl unit in the macrolactone being considered to provide the detoxification mechanism in these insensitive strains.[69]

The application of CI mass spectrometry to the structural assignment of basic macrolide antibiotics has been investigated; major ions arise by glycosidic bond cleavage, and amino-sugars and neutral sugars are clearly distinguished.[70] FD mass spectra of some polyene antibiotic derivatives have also been reported.[71]

3 Anthracycline Antibiotics

The structures of several new anthracycline antibiotics have been elucidated including rudolphomycin, which possesses the trisaccharide unit (17) containing a novel unsaturated amino-glycosulose.[72] Disaccharide fragments obtained from carminomycin II and III by catalytic hydrogenation were found to contain daunosamine and an acyclic hemiacetal of 2,4-dideoxy-tetrose.[73] Fermentation broths have yielded a number of daunorubicin analogues (modified in the tetracycline unit).[74]



(17)

Synthetic approaches to anthracycline antibiotics have been reviewed.[75] Several papers report syntheses of daunorubicin analogues by the glycosidation of daunomycinone derivatives with amino-sugars: glycosides of daunomycinone have been prepared from 3-*epi*-L-daunosamine, D-acosamine, D-daunosamine, D-ristosamine, and 3-*epi*-D-daunosamine,[76] and 4-demethoxy-9-deoxy-9-methyl

[69] M. Uyeda, K. Nakamichi, K. Shigemi, and M. Shibata, *Agric. Biol. Chem.*, 1980, **44**, 1399.

[70] M. Suzuki, K. I. Harada, N. Takeda, A. Tatematsu, M. Ohno, S. Satoi, and M. Hayashi, *Koen-Yoshishu-Tennen Yuki Kagobutsu Toronkai, 22nd*, 1979, 354 (*Chem. Abstr.*, 1980, **93**, 72 163, 95 523).

[71] L. Falkowski, J. Golik, A. Jarzebski, B. Stefanska, and E. Borowski, *Symp. Pap. – IUPAC Int. Symp. Chem. Nat. Prod., 11th*, 1978, **2**, 258 (*Chem. Abstr.*, 1980, **92**, 59 147).

[72] T. W. Doyle, D. E. Nettleton, R. E. Grulich, D. M. Balitz, D. L. Johnson, and A. L. Vulcano, *J. Am. Chem. Soc.*, 1979, **101**, 7041.

[73] I. A. Spiridonova, N. N. Lomakina, and T. F. Vlasova, *Antibiotiki* (*Moscow*), 1980, **25**, 563 (*Chem. Abstr.*, 1980, **93**, 239 832).

[74] F. Arcamone, G. Cassinelli, F. Dimatteo, S. Forenza, M. C. Ripamonti, G. Rivola, A. Vigevani, J. Clardy, and T. McCabe, *J. Am. Chem. Soc.*, 1980, **102**, 1462.

[75] T. R. Kelly, *Annu. Rep. Med. Chem.*, 1979, **14**, 288.

[76] J. Boivin, A. Montagnac, C. Monneret, and M. Pais, *Carbohydr. Res.*, 1980, **85**, 223.

daunorubicin,[77] 4-demethoxy-daunorubicin and 4′-epidoxorubicin[78] have been synthesized, the latter two showing an improved pharmacological profile over the parent antibiotics. 4′-*epi*- And 3′,4′-*epi*-daunorubicins have also been prepared by glycosidation of daunomycinone with 3-amino-1,5-anhydro-2,3,6-trideoxy-L-*arabino*- and -L-*ribo*-hex-1-enitol.[79] A blocked mutant of *S. coeruleorubidus* has been used to convert ε-pyrromycinone to ε-isorhodomycinone and hence to 1-hydroxy-13-dihydro-daunomycin and its *N*-formyl derivative, although the products were less effective antibiotics than daunomycin.[80] Acyl derivatives of carminomycin and rubomycin have been prepared from appropriate derivatives of L-alanine and D-phenylalanine.[81]

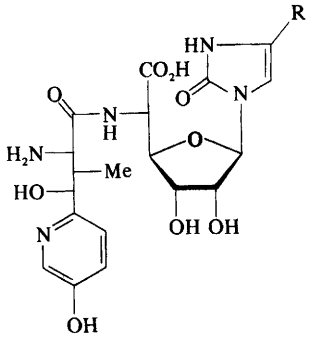
An extended conformational analysis of doxorubicin suggests a different conformation from that found in the crystal; the calculated conformation contains a bifurcated hydrogen bond bridging the 5-oxygen and 6-hydroxy-group of the anthraquinone ring with the 5′-oxygen of the sugar ring. This conformation allows doxorubicin to intercalate with the bases of double helical DNA, the protonated sugar amino nitrogen being close to a phosphate group.[82]

FD mass spectra of some anthracycline antibiotics have been recorded,[83] and an h.p.l.c. procedure for their analysis described.[84]

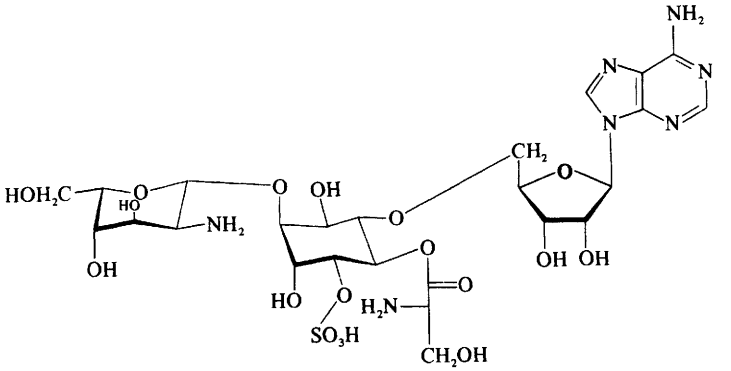
4 Nucleoside Antibiotics

The chemistry and biochemistry of polyoxins has been discussed.[85] The structure of the neopolyoxins A, B, and C, which are potent inhibitors of fungal cell-wall chitin synthetase, has been established; neopolyoxins A and B are the imidazole nucleosides (18) and (19), respectively, whereas neopolyoxin C is the corresponding uracil-1-yl nucleoside; the structure of polyoxin N was also revised, the amino-acid side-chain of (18) being replaced by 2-amino-5-*O*-carbamoyl-2-deoxy-L-xylonic acid.[86] The new antibiotic nikkomycin B also has the structure of (18), although its stereochemistry has not been fully established.[87] Adenomycin has

[77] P. Giardino, A. Vigevani, L. Bernardi, and F. Arcamone, *Gazz. Chim. Ital.*, 1980, **110**, 101 (*Chem. Abstr.*, 1980, **93**, 186 698).
[78] S. Penco, *Process Biochem.*, 1980, **15**, 12 (*Chem. Abstr.*, 1980, **93**, 239 831).
[79] J. Boivin, M. Pais, and C. Monneret, *Carbohydr. Res.*, 1980, **79**, 193.
[80] A. Yoshimoto, Y. Matsuzawa, T. Oki, H. Naganawa, T. Takeuchi, and H. Umezawa, *J. Antibiot.*, 1980, **33**, 1150.
[81] E. N. Olsuf'eva and L. S. Povarov, *Antibiotiki* (*Moscow*) 1980, **25**, 333 (*Chem. Abstr.*, 1980, **93**, 95 528).
[82] Y. Nakata and A. J. Hopfinger, *FEBS Lett.*, 1980, **117**, 259.
[83] K. Fukushima and T. Arai, *Shitsurgo Bunseki*, 1979, **27**, 97 (*Chem. Abstr.*, 1980, **93**, 114 889).
[84] R. C. Pandey and M. W. Toussaint, *J. Chromatogr.*, 1980, **198**, 407.
[85] K. Isono and S. Suzuki, *Heterocycles*, 1979, **13** (Spec. Issue), 333 (*Chem. Abstr.*, 1980, **93**, 47 120).
[86] M. Uramoto, K. Kobinata, K. Isono, T. Higashijima, T. Miyazawa, E. E. Jenkins, and J. A. McCloskey, *Tetrahedron Lett.*, 1980, **21**, 3395.
[87] W. A. König, W. Hass, W. Dehler, H. -P. Fiedler, and H. Zähner, *Liebigs Ann. Chem.*, 1980, 622.



(18) R = CHO
(19) R = CO_2H



(20)

been shown to be the unusual pseudo-disaccharide derivative (20) of adenosine,[88] which is a cross between an amino-glycoside and a nucleoside antibiotic, containing 2-amino-2-deoxy-L-gulose, (—)-*chiro*-inositol, and L-serine. Tunicamycin has been shown to be a mixture of at least 10 homologous antibiotics, possessing the same sugar skeleton but which differing $\alpha\beta$-unsaturated (and one saturated) C_{13}–C_{17} acyl side-chains attached at N-20′ (see Vol. 11, p. 165).[89]

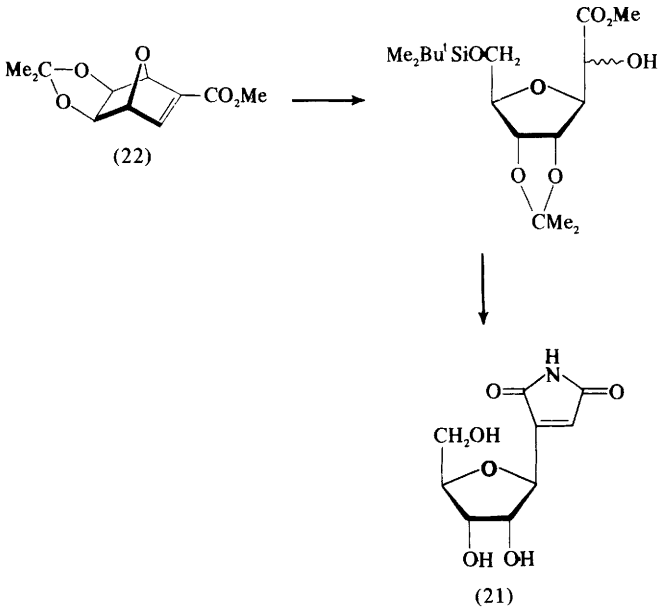
Formycin has been prepared by constructing the pyrimidine ring from a 4-nitro-pyrazole-*C*-nucleoside precursor.[90] Diels–Alder reactions have been used in a synthesis of DL-showdomycin (21) *via* the adduct (22) outlined in Scheme

[88] T. Ogita, N. Otake, Y. Miyazaki, H. Yonehara, R. D. Mcfarlane, and C. J. McNeal, *Tetrahedron Lett.*, 1980, **21**, 3203.
[89] T. Ito, A. Takatsuki, K. Kawamura, K. Sato, and G. Tamura, *Agric. Biol. Chem.*, 1980, **44**, 695.
[90] J. G. Buchanan, A. Stobie, and R. H. Wightman, *Can. J. Chem.*, 1980, **58**, 2624.

3,[91] and in a synthesis of DL-aristeromycin (23) summarized in Scheme 4.[92] The α-anomer of tubercidin and some other isomeric and dihydro-analogues have been prepared by standard procedures; whereas tubercidin and its α-anomer show pronounced cytotoxic activity, dihydrogenated derivatives did not.[93] The ^{13}C n.m.r. spectrum of gougerotin has been interpreted.[94]

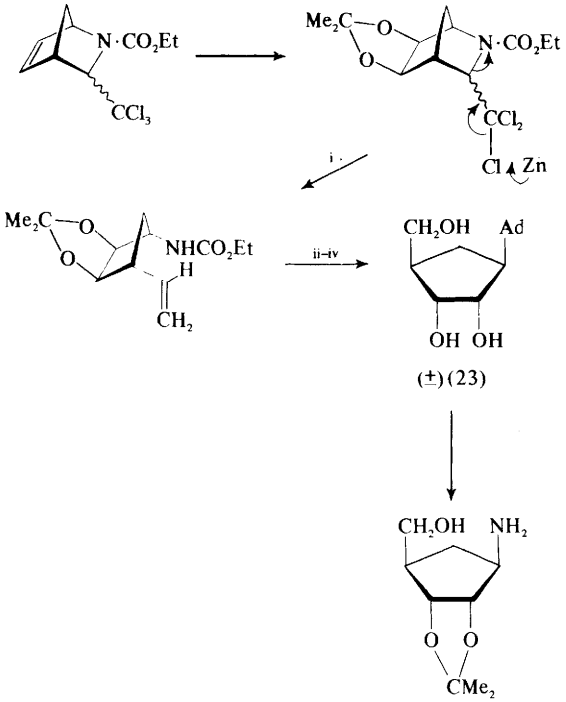
5 Miscellaneous Antibiotics

New carbohydrate-containing antibiotics continue to be isolated from micro-organisms. The papulacandins are a group of antifungal compounds obtained from *Papularia sphaerosperma*; papulacandin A has the pseudo-disaccharide structure (24), and papulacandins B and C are the analogous hydroxy-trienoic acid derivative (25) and the corresponding all-*trans*-isomer, respectively; populacandin D lacks the galactose unit of these compounds.[95]



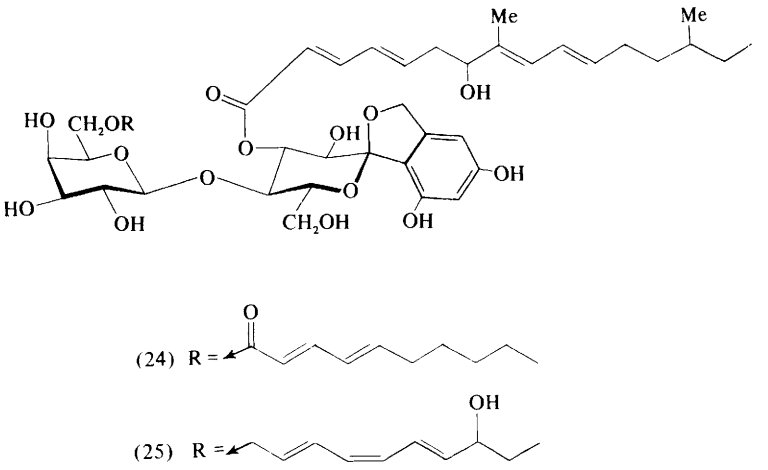
Scheme 3

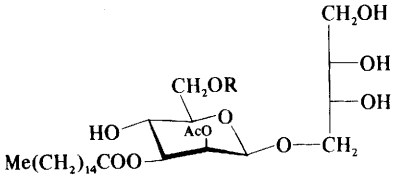
[91] G. Just, T. J. Liak, M.-I. Lim, P. Potvin, and Y. S. Isantrizos, *Can. J. Chem.*, 1980, **58**, 2024.
[92] A. K. Saksena, *Tetrahedron Lett.*, 1980, **21**, 133.
[93] L. V. Ektova, V. N. Tolkachev, N. L. Radyukina, T. P. Ivanova, Ya. V. Dobrynin, and M. N. Preobrazhenskaya, *Bioorg. Khim.*, 1979, **5**, 1369 (*Chem. Abstr.*, 1980, **92**, 111 256).
[94] L. Dolak, *J. Antibiot.*, 1979, **32**, 1346.
[95] P. Traxler, H. Fritz, H. Fuhrer, and W. J. Richter, *J. Antibiot.*, 1980, **33**, 967.



Reagents: i, Zn; ii, O_3; iii, $NaBH_4$; iv, NaOH

Scheme 4





(26) R = H
(27) R = Ac

Schizonellin A and B are the erythritol D-mannosyl glycosides (26) and (27), respectively, which are antibacterial and antifungal glycolipids obtained from *Basidomycetes*.[96]

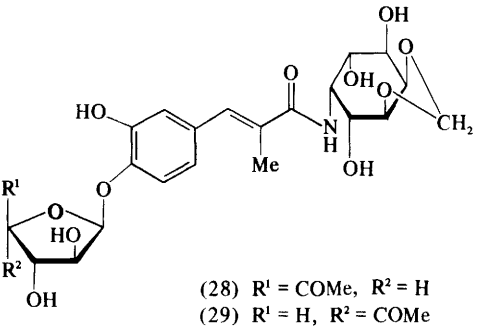
Hygromycin (28) and epihygromycin (29) have been isolated from *Corynebacterium equi*, a newly isolated bacterium; the two isomers could be equilibrated in alkaline solution.[97] Trichoviridin has been shown by chemical and *X*-ray studies to be the unusual isocyanide diepoxide (30) derived from a cyclopentanepolyol.[98] A new antibiotic (Bu-2545) isolated from a *Streptomyces* strain (H230-5) has been shown to be the lincomycin relative (31).[99] Rubiflavin is a mixture of antibiotics whose main components, rubiflavin A and B, have been identified as desacetylpluramycin (32) and kidamycin (33).[100]

The remaining uncertainties in the structure of the carbohydrate portion of ristocetin A have been resolved by ^{13}C n.m.r. studies, which suggest the pattern (34).[101,102]

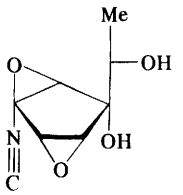
(+)-Furanomycin has been shown to have the structure (35) by a synthesis from 2,5-anhydro-L-idose, which is summarized in Scheme 5.[103] The quinoglycosides (36), which are bacteriocides and fungicides, have been synthesized by condensation of 2-methyl quinolinuim salts with peracetylated aldoses.[104] The synthesis of the aminohexonhydrazide antibiotic negamycin is covered in Chapter 8.

Analogues of the polycyclic aromatic glycoside chartrensin have been synthesized by hydrolytic cleavage of the parent difucosyl disaccharide sidechain and reglycosidation with D-fucose, D-glucose, and D-maltose by standard Koenigs–Knorr condensation (the fucose derivative was also prepared by partial

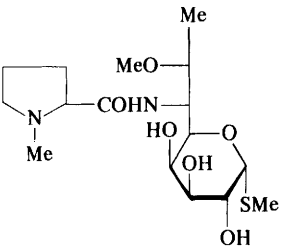
[96] G. Deml. T. Anke, F. Oberwinkler, B. M. Giannetti, and W. Steglich, *Phytochemistry*, 1980, **19**, 83.
[97] Y. Wakisaka, K. Koizumi, Y. Nishimoto, M. Kobayashi, and N. Tsuji, *J. Antibiot.*, 1980, **33**, 695.
[98] W. D. Ollis, M. Rey, W. O. Godtfredsen, N. Rastrup-Andersen, S. Vangedal, and T. J. King, *Tetrahedron*, 1980, **36**, 515.
[99] M. Hanada, M. Tsunakawa, K. Tomita, H. Tsukiura, and H. Kawaguchi, *J. Antibiot.*, 1980, **33**, 751.
[100] H. Nadig and U. Séquin, *Helv. Chim. Acta*, 1980, **63**, 2446.
[101] F. Sztaricskai, A. Neszmélyi, and R. Bognar, *Tetrahedron Lett.*, 1980, **21**, 2983.
[102] M. P. Williamson and D. H. Williams, *Tetrahedron Lett.*, 1980, 4187.
[103] M. M. Joullie, P. C. Wang, and J. E. Semple, *J. Am. Chem. Soc.*, 1980, **102**, 587.
[104] L. E. Zhivoglazova, N. A. Volyanskaya, V. E. Pridan, V. V. Mikhasyuta, and Yu. L. Volyanskii, *Khim.-Farm. Zh.*, 1980, **14**, 48 (*Chem. Abstr.*, 1980, **93**, 239 838).



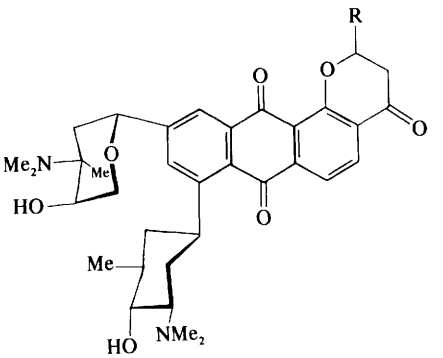
(28) R^1 = COMe, R^2 = H
(29) R^1 = H, R^2 = COMe



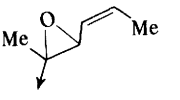
(30)



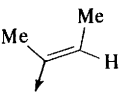
(31)

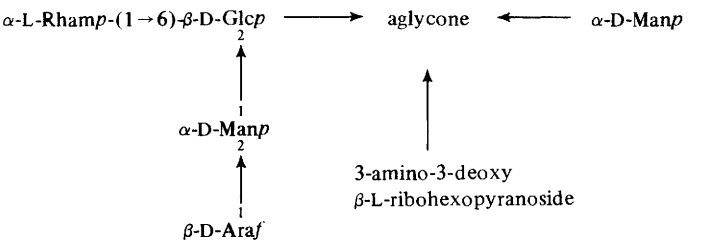


(32) R =

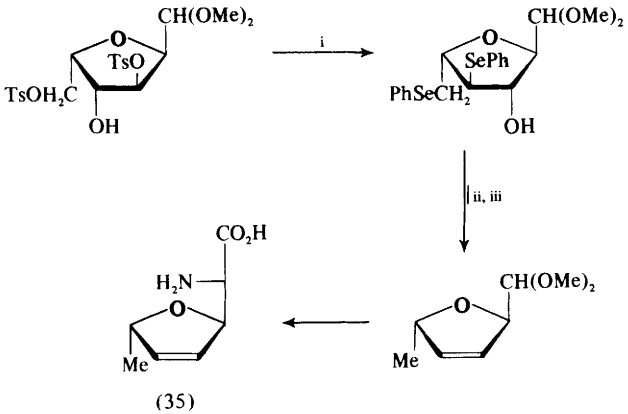


(33) R =





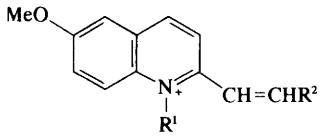
(34)



(35)

Reagents: i, NaSePh–DMF; ii, Ni; iii, TsCl–py

Scheme 5



(36) R^1 = Ar, CHR^2 = peracetylated *aldehydo*-Glc, Gal, Maltose, or Lactose

hydrolysis of chartrensin); these analogues were just as effective cytotoxic agents as the parent antibiotic.[105] The antibiotic mycophenolic acid has been glucosylated in the presence of *S. aureofaciens* to yield an antitumour 7-*O*-β-D-glucopyranosyl derivative.[106] *N*-Acyl derivatives of 2-amino-2-deoxy-D-glucose have been prepared from mustards derived from aminophenylcarboxylic acids such as *p*-(*N*,*N*-di-2-chloroethylamino)phenylacetic acid; the resulting compounds were shown to be antitumour agents of high activity and low toxicity in tests with a plasmacytoma.[107] The *N*-nitrosoureides chlorozotocin and streptozotocin have been synthesized from glucosamine by *N*-acylation using *N*-nitrosocarbamic esters of *p*-nitrosophenol.[108] A similar reaction has been used to convert 3-amino-3-deoxy-D-glucose (D-kanosamine) or its methyl glycoside to the corresponding *N*-2-chloroethyl-*N*-nitrosocarbamate.[109] The ^{13}C n.m.r.

[105] M. Takai, Y. Uehara, and J. A. Beisler, *J. Med. Chem.*, 1980, **23**, 549.
[106] B. J. Abbott, D. R. Horton, and J. G. Whitney, *J. Antibiot.*, 1980, **33**, 506.
[107] E. N. Shkodinskaya, V. I. Trusheikina, O. S. Vasina, O. V. Goryunova, V. S. Martynov, and S. A. Degteva, *Vopr. Onkol.*, 1979, **25**, 29 (*Chem. Abstr.*, 1980, **92**, 147 094).
[108] J. Martinez, J. Oiry, J. L. Imbach, and F. Winternitz, *Eur. J. Med. Chem. – Chim. Ther.*, 1980, **15**, 211 (*Chem. Abstr.*, 1980, **93**, 239 805).
[109] K. Sasaki, S. Aizawa, T. Satomi, H. Akutsu, S. Kawabata, and Y. Momoki, *J. Antibiot.*, 1980, **33**, 517.

spectrum of the glycosylated polyamide antibiotic tallysomycin has been assigned using data from bleomycin A_2 and model compounds, and the assignments were utilized in a study of the interaction of the antibiotic with zinc(II).[110] U.v. irradiation of a bleomycin-producing strain has yielded a new antibiotic of the bleomycin–phleomycin group, cleomycin; cleomycin A_2 differs from bleomycin A_2 by having threonine in a peptide unit replaced by an α-amino-acid residue containing a 1-hydroxy-cyclopropyl side-chain.[111]

Eurekanic acid, a degradation product of flambamycin and avilamycin, is referrred to in Chapter 15.

[110] F. T. Greenaway, J. C. Dabrowiak, R. Grulich, and S. T. Crooke, *Org. Magn Res.*, 1980, **13**, 270.

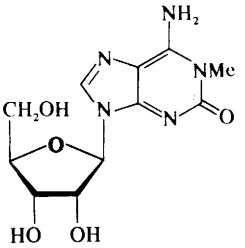
[111] H. Umezawa, Y. Muraoka, A. Fujii, H. Naganawa, and T. Takita, *J. Antibiot.*, 1980, **33**, 1079.

19

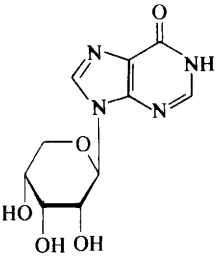
Nucleosides

1 Isolation from Natural Products

The pharmacologically active nucleoside 1-methylisoguanosine (1) has been isolated from an ethanol extract of a marine sponge, and its structure was confirmed by synthesis from a ribofuranosyl-imidazole precursor.[1] Synthesis has also established the structure of 9-β-D-ribopyranosyl hypoxanthine (2), which has been detected as a minor component in fermentation broths of *S. antibioticus*.[2] The nucleoside derivative 6-(*o*-hydroxybenzylamino)-9-(β-D-ribofuranosyl)purine has been isolated from *Zantedeschia aethiopica*, and shown to be responsible for regreening of the spathe during fruitification.[3] The structure of the antibiotic adenosine derivative adenomycin is referred to in Chapter 18.



(1)

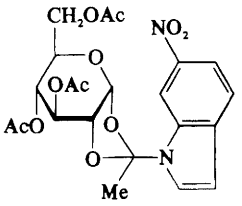


(2)

2 Synthesis

The condensation of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose with silylated pyrimidines has been shown to be conveniently catalysed by iodotrimethylsilane, leading to high yields of uridine and cytosine derivatives; chloromercuri-*N*-benzoyl purine gave less pure product in poorer yield.[4] The reaction of indoles with glycosyl halides in the presence of silver oxide and molecular sieves has been studied; mixtures of 1- and 3-glycosyl-indoles were generally obtained together with corresponding sugar orthoamide derivatives, the latter predominating with 5- or 6-nitro-indoles, *e.g.*, the 6-nitro-indolyl derivative (3).[5] The

[1] A. F. Cook, R. T. Bartlett, R. P. Gregson, and R. J. Quinn, *J. Org. Chem.*, 1980, **45**, 4020.
[2] D. L. Kern, P. D. Cook, and J. C. French, *J. Heterocycl. Chem.*, 1980, **17**, 461.
[3] H. J. Chaves des Neves and M. S. S. Pais, *Biochem. Biophys. Res. Commun.*, 1980, **95**, 1387.
[4] Z. Točik, R. A. Earl, and J. Beránek, *Nucleic Acid Res.*, 1980, **8**, 4755.
[5] T. N. Sokolova, V. E. Shevchenko, and M. N. Preobrazhenskaya, *Carbohydr. Res.*, 1980, **83**, 249.



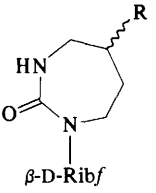
(3)

regio- and stereo-selectivity of glycosylation of 6-benzylaminopurine under different conditions using either glycosyl halides or sugar acetates has been systematically investigated,[6] and other reports from Imbach's laboratory describe similar studies of the ribosylation of indazole,[7] which suggested that some regioselectivity between the heterocyclic nitrogens can be achieved by a judicious choice of conditions, only β-ribosides being formed in either case, and studies using different aldopentofuranoses,[8] where no marked influences were detected. Enzymic trans-arabinosylation of uracil arabinoside using *Acetobacter aerogenes* in presence of the appropriate purine base has been used to prepare adenine arabinoside[9] and 9-β-D-arabinofuranosyl-2-chloro-hypoxanthine,[10] the latter being converted chemically to the corresponding guanine arabinoside.

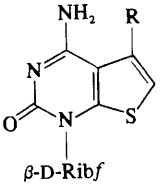
Conventional methods have been used to prepare ribonucleoside analogues from 2-(1*H*)pyrazinone,[11] 3,5-disubstituted pyridines (including α-anomers),[12] 6-methyl-1,3-oxazine-2,4-dione and 6-methyluracil,[13] 2-alkyl-4,5-dicarboxamidoimidazoles,[14] 7-membered ring analogues (4) and (5) of uracil and tetrahydrouracil [one diastereomer of (4) being the most potent inhibitor of cytidine deaminase yet discovered],[15] 2-alkylthioadenine,[16] 8-aza-3-deaza-guanine,[17]

[6] J. L. Barascut, I. Couret, and J. L. Imbach, *J. Carbohydr. Nucleosides, Nucleotides*, 1979, **6**, 477.
[7] J. L. Barascut, D. Molko, and J. L. Imbach, *J. Carbohydr. Nucleosides, Nucleotides*, 1980, **7**, 185.
[8] B. L. Kam, J. L. Barascut, and J. L. Imbach, *Carbohydr. Res.*, 1980, **78**, 285.
[9] T. Utagawa, H. Morisawa, T. Miyoshi, F. Yoshinaga, A. Yamazaki, and K. Mitsugi, *FEBS Lett.*, 1980, **109**, 261.
[10] H. Morisawa, T. Utagawa, T. Miyoshi, F. Yoshinaga, A. Yamazaki, and K. Mitsugi, *Tetrahedron Lett.*, 1980, **21**, 479.
[11] M. Mano, T. Seo, T. Hattori, T. Kaneko, and K.-I. Imai, *Chem. Pharm. Bull.*, 1980, **28**, 2734.
[12] E. J. Freyne, E. L. Esmans, J. A. Lepoivre, and F. C. Alderweireldt, *Carbohydr. Res.*, 1980, **78**, 235.
[13] A. A. Akhrem, N. E. Pupeiko, E. I. Kvasyuk, I. A. Mikhailopulo, V. P. Reshchikov, N. M. Fertukova, N. A. Nikolaeva, and T. P. Grishina, *Vestsi Akad. Navuk, BSSR, Ser. Khim. Navuk*, 1979, 103 (*Chem. Abstr.*, 1980, **92**, 147110).
[14] P. C. Wyss, P. Schonholzer, and W. Arnold, *Helv. Chim. Acta*, 1980, **63**, 1353.
[15] V. E. Marquez, P. S. Liu, J. A. Kelley, J. S. Driscoll, and J. J. McCormack, *J. Med. Chem.*, 1980, **23**, 715.
[16] N. K. Saxena and D. S. Bhakuni, *Indian J. Chem., Sect. B*, 1979, **18**, 248 (*Chem. Abstr.*, 1980, **92**, 42 318).
[17] R. B. Meyer, jun., G. R. Revenkar, P. D. Cook, K. W. Ehlen, M. P. Schweizer, and R. K. Robins, *J. Heterocycl. Chem.*, 1980, **17**, 159.

thieno[2,3-*d*]pyrimidine (6) (including *arabino*-analogues),[18] *N*- and *O*-substituted lumazines,[19,20] 5-methylthio-6*H*-pyrazolo[4,3-d]pyrimidin-7-one,[21] 3-cyano-4,6-dimethylthiopyrazolo[3,4-d]pyrimidine,[22] and other 4- or 4,6-substituted derivatives of the latter heterocycle, including 8-aza-7-deaza-adenosine.[23] Syntheses of arabino-nucleoside analogues have included Ara-tubercidin (9-β-D-arabinofuranosyl-7-deaza-adenine),[24] and derivatives of 4-amino-imidazole and hypoxanthine,[25] benzimidazole and some 5- and 6-halo-substituted benzimida-



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



(6) R = H or Me

zoles (nucleosides that are more resistant to acid hydrolysis than purine analogues),[26] and Ara-A (9-β-D-arabinofuranosyl-adenine), by the most convenient practical procedure yet described starting from adenosine.[27] 1-α-L-Arabinopyranosyl derivatives of indole and 7-azaindole have also been prepared.[28]

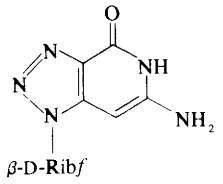
D-Lyxofuranosyl imidazoles have been prepared by standard periodate–borohydride chain shortening of corresponding mannofuranosyl derivatives; elaboration of the heterocyclic ring from a D-lyxosylamine precursor only gave pyranosyl derivatives.[29] Ribofuranosyl azides have been used to synthesize triazole α- and β-nucleoside analogues by cycloaddition with propynol and 3-chloropropyne,[30,31] or with methyl 4-hydroxybut-2-ynoate leading to the

[18] V. D. Patil, D. S. Wise, and L. B. Townsend, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1853.
[19] G. Ritzmann, L. Kiriasis, and W. Pfleiderer, *Chem. Ber.*, 1980, **113**, 1524.
[20] G. Ritzmann, K. Ienaga, L. Kiriasis, and W. Pfleiderer, *Chem. Ber.*, 1980, **113**, 1535.
[21] O. V. Goryunova, I. A. Korbukh, M. N. Preobrazhenskaya, and A. I. Chernyshev, *Bioorg. Khim.*, 1979, **5**, 1361 (*Chem. Abstr.*, 1980, **92**, 76 849).
[22] I. A. Korbukh, Yu. N. Bulychev, and M. N. Preobrazhenskaya, *Khim. Geteroksikl. Soedin.*, 1979, 1687 (*Chem. Abstr.*, 1980, **92**, 147 111).
[23] I. A. Korbukh, N. G. Yakunina, and M. N. Preobrazhenskaya, *Bioorg. Khim.*, 1980, **6**, 1632.
[24] H.-D. Winkeler and F. Seela, *Chem. Ber.*, 1980, **113**, 2069.
[25] K. Kadir, G. Mackenzie, and G. Shaw, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2304.
[26] Z. Kazimierczuk, L. Dudycz, R. Stolarski, and D. Shugar, *Z. Naturforsch., Teil C*, 1980, **35**, 30 (*Chem. Abstr.*, 1980, **93**, 95 536).
[27] K. J. Divakar and C. B. Reese, *J. Chem. Soc., Chem. Commun.*, 1980, 1191.
[28] V. I. Mukhanov, T. N. Sokolova, T. G. Nikolaeva, Ya. V. Dobrynin, and M. N. Preobrazhenskaya, *Khim. – Farm. Zh.*, 1979, **13**, 47 (*Chem. Abstr.*, 1980, **92**, 6855).
[29] G. Mackenzie and G. Shaw, *J. Chem. Res. (S)*, 1980, 254.
[30] M. J. Camarasa, R. Alonso, and F. G. De Las Heras, *Carbohydr. Res.*, 1980, **83**, 152.
[31] R. Alonso, M. J. Camarasa, G. Alonso, and F. G. De Las Heras, *Eur. J. Med. Chem., Chim. Ther.*, 1980, **15**, 105 (*Chem. Abstr.*, 1980, **93**, 114 916).

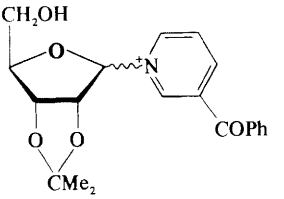
guanosine analogue (7).[32] Other syntheses of triazole nucleosides from glycosyl azides are referred to in Chapter 9. Peracetylglycosyl isothiocyanates have been converted to glycosyl-1,2,4-triazole derivatives by cyclization of the thiosemicarbazides prepared from them with substituted hydrazines; an alternative procedure led to *sym*-triazine derivatives as well.[33]

Reaction of 2,3-isopropylidene-β-D-ribofuranosylamine with *N*-2,4-dinitrophenyl-3-benzoyl-pyridinium chloride yielded the pyridinium nucleoside analogue (8).[34] Glycosyl isocyanides yield formamidines with amines, which can be cyclized to nucleoside analogues in appropriate cases; thus, methyl anthranilate in presence of mercuric chloride yields the benz-pyrimidine derivative (9).[35]

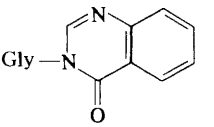
Standard methods have been used to prepare 1-(6-deoxy-β-D-allo- and -α-L-talo-furanosyl) uracil[36] and 9-α-L-rhamnopyranosyl-2-alkylthio-adenines.[37]



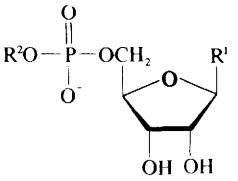
(7)



(8)

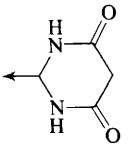


(9)



(10) R^1 = OH, R^2 = R
(11) R^1 = R^2 = R
(12) R^1 = R, R^2 = H

R =



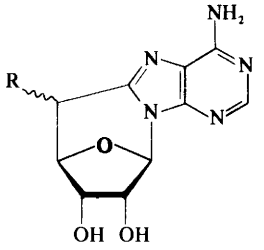
D-Ribose-5-phosphate and barbituric acid react in aqueous solution at pH 5.5 giving initially the barbituryl phosphate (10), but on further standing the barbituryl nucleoside (11) and probably the corresponding barbituryl phosphate (12) were formed; the initial product was considered to undergo intramolecular rearrangement to give the nucleotide.[38]

[32] R. A. Earl and L. B. Townsend, *Can. J. Chem.*, 1980, **58**, 2550.
[33] H. Ogura, H. Takahashi, and O. Sato, *Nucleic Acids Symp. Ser.*, 1979, **6** (Symp. Nucleic Acids Chem., 7th) S13 – S16 (*Chem. Abstr.*, 1980, **92**, 198 664).
[34] C. R. Winne, J. A. Lepoivre, and F. C. Alderweireldt, *Bull. Soc. Chim. Belg.*, 1980, **89**, 67 (*Chem. Abstr.*, 1980, **93**, 26 711).
[35] D. Marmet, P. Boullanger, and G. Descotes, *Tetrahedron Lett.*, 1980, **21**, 1459.
[36] N. Sh. Padyukova and J. Smrt, *Collect. Czech., Chem. Commun.*, 1980, **45**, 2550.
[37] N. K. Saxena and D. S. Bhakuni, *Indian J. Chem., Sect. B*, 1979, **18**, 348 (*Chem. Abstr.*, 1980, **92**, 129 234).
[38] H. Komura, K. Nakanishi, B. W. Potvin, H. J. Stern, and R. S. Krooth, *J. Am. Chem. Soc.*, 1980, **102**, 1208.

3 Anhydro- and Cyclo-nucleosides

A study of 2,2′-anhydronucleosides has been reported, in which a range of pyrimidine derivatives were prepared and their hydrolyses to β-D-arabino-furanosyl compounds investigated.[39] Treatment of 5-iodopyrimidine nucleosides with sodium methoxide yielded 6,2′-, 6,5′-, and novel 6,3′-anhydropyrimidine nucleosides, and their rates of cyclization and ring-opening were compared.[40]

Irradiation of 5′-deoxy-2′,3-*O*-isopropylidene-8-phenylthio-adenosine under anaerobic conditions in presence of t-butylhydroperoxide yielded 5′-deoxy-5′,8-cycloadenosine in good yield, providing an *in vitro* analogy for functionalization of this methyl group involved in many coenzyme B_{12}-controlled rearrangement reactions.[41] Another synthesis of this cycloadenosine utilized a 5′-deoxy-5′-iodo-adenosine derivative in a zinc-mediated reaction involving a 5′-methylene radical intermediate.[42] 5′-Hydroxyalkyl 5′-deoxy-5′-8-(*R* + *S*)-cycloadenosines (13) have been prepared from the corresponding 5′-keto-cyclonucleoside by reactions with either sulphur or phosphorus ylides and appropriate further transformations.[43]



(13) R = CH_2OH or CH_2CH_2OH

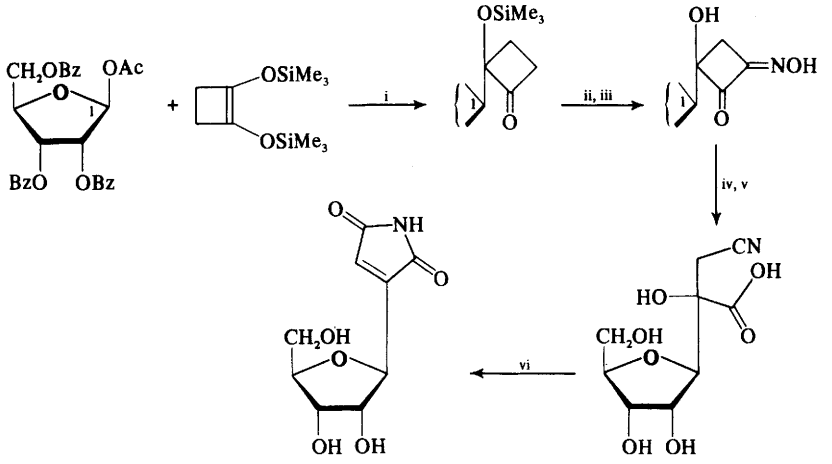
4 *C*-Nucleosides

The synthesis of *C*-nucleosides has been reviewed.[44]

There has been a surge of interest in the synthesis of *C*-nucleosides, doubtless inspired by the antimetabolite and antibiotic properties of several representatives.

A new high-yielding synthesis of showdomycin (14) utilizes the reaction of 1,2-bis(trimethylsilyloxy)cyclobutene with a ribofuranosyl acetate derivative as outlined in Scheme 1.[45] A synthesis of (3*R*, *S*)-3,4-dihydroshowdomycin (15)

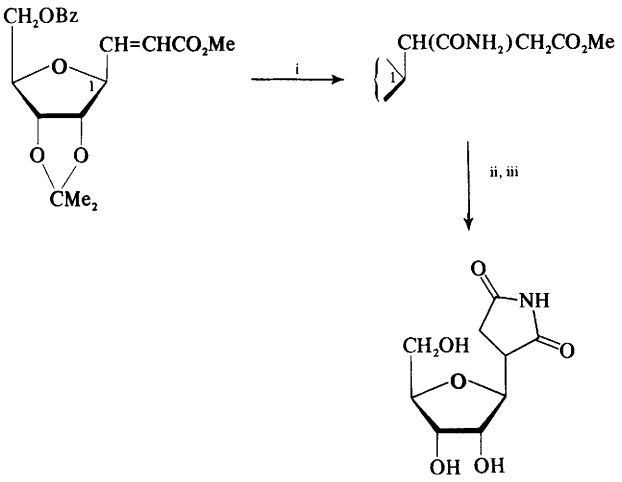
[39] K. Kondo and I. Inoue, *J. Org. Chem.*, 1980, **45**, 1577.
[40] T. Maruyama and M. Honjo, *Nucleic Acids Symp. Ser.*, 1979, **6** (Symp. Nucleic Acids Chem., 7th), S7–S10 (*Chem. Abstr.*, 1980, **92**, 198 663).
[41] D. Gani, A. W. Johnson, and M. F. Lappert, *J. Chem. Soc., Chem. Commun.*, 1980, 1244.
[42] J. Zylber, R. Pontikis, A. Merrien, C. Merrien, M. Baran-Marszak, and A. Gaudemer, *Tetrahedron*, 1980, **36**, 1579.
[43] A. Matsuda, K. Niizuma, and T. Ueda, *Chem. Pharm. Bull.*, 1980, **28**, 876.
[44] S. R. James, *J. Carbohydr., Nucleosides, Nucleotides*, 1979, **6**, 417.
[45] T. Inoue and I. Kuwajima, *J. Chem. Soc., Chem. Commun.*, 1980, 251.



(14)

Reagents: i, $SnCl_4$; ii, $(Me_3Si)_2NLi$–Me_3SiCl; iii, NOCl–CH_2Cl_2, −40 °C; iv, r.t., 2d; v, NH_3–MeOH; vi, $(CF_3CO)_2O$

Scheme 1

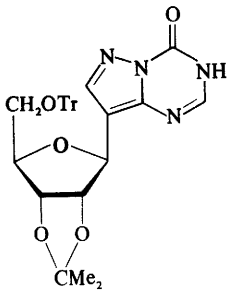


(15)

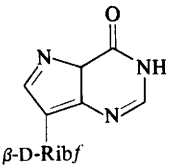
Reagents: i, $HCONH_2$, $h\nu$; ii, NaOMe–MeOH; iii, TFA–MeOH

Scheme 2

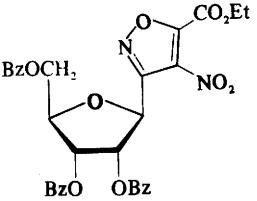
involved the photochemical addition of formamide to the αβ-unsaturated sugar acid, shown in Scheme 2. Similar reaction of the isomeric βγ-unsaturated acid yielded the α-anomer of (15).[46] A ribofuranosyl-methylcyanide derivative has been used to prepare the pyrazolotriazine nucleoside analogue (16),[47] and a related synthesis gave 9-deazainosine (17).[48] Another report describes the conversion of 3,4,6-tri-*O*-benzoyl-2,5-anhydro-D-allose to the pyrazofurin analogue (18).[49] D-Arabinofuranosyl *sym*-triazolopyridines (19) and *sym*-triazolopyrazines (20) have been prepared from the isomeric 2,5-anhydro-hexonthioimidate (21).[50] 2,3;4,5-Di-*O*-isopropylidene-D-*arabino*-hexulosonic acid has been used to prepare the benzimidazole *C*-glycosides (22) and related purine and 1-deazapurine derivatives from the appropriate aryl-1,2-diamines by cyclization of the initially formed *o*-aminoarylamides as illustrated in Scheme 3.[51]



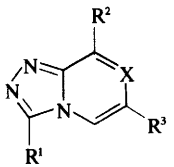
(16)



(17)

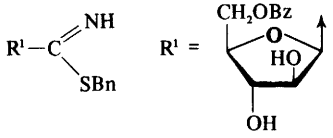


(18)



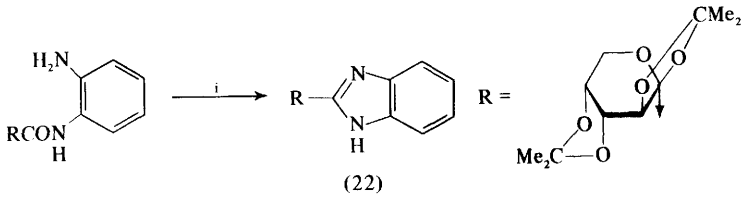
(19) X = CH,
(20 X = N

R^2, R^3 = H, H; H, NO_2; H, Cl



(21)

[46] A. Rosenthal and J. Chow, *J. Carbohydr., Nucleosides, Nucleotides*, 1980, **7**, 77.
[47] C. K. Chu, K. A. Watanabe, and J. J. Fox, *J. Heterocycl. Chem.*, 1980, **17**, 1435.
[48] M.-I. Lim, R. S. Klein, and J. J. Fox, *Tetrahedron Lett.*, 1980, **21**, 1013.
[49] J. A. Deceuninck, D. K. Buffel, and G. J. Hoornaert, *Tetrahedron Lett.*, 1980, **21**, 3613.
[50] G. Doukhan, Huynh Dinh Tam, E. Bisagni, J. C. Chermann, and J. Igolen, *Eur. J. Med. Chem. – Chim. Ther.*, 1979, **14**, 375 (*Chem. Abstr.*, 1980, **92**, 129 221).
[51] Y. Chapleur and B. Castro, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2683.



(22)

Reagent: i, Na_2CO_3

Scheme 3

Buchanan's group has reported further applications of *C*-alkynyl glycosides to the synthesis of *C*-nucleosides. A new synthesis of formycin involved the condensation of hydrazine with the alkynyl sugar (23) to yield the pyrazole derivative (24), which could be conventionally transformed to formycin (25),[52] and another paper describes the conversion of 2,3,5,6-di-*O*-isopropylidene-D-allofuranose, or better, 2,3,5-tri-*O*-benzyl-D-ribofuranosyl chloride to 3-α-D-ribofuranosylpyrazole and related compounds; the former procedure involves the interesting ring-closure shown in Scheme 4 that occurs spontaneously on standing in the dark, involving concomitant loss of the terminal isopropylidene group.[53] Another group has similarly cyclized the alkynyl ketone (26) with hydrazine to obtain the 5-phenyl analogue of (24).[54] Other reports describe the cyclization of polyhydroxyalkyl heterocycles prepared from sugars to yield *C*-nucleoside analogues, *e.g.*, (27) and (28).[55,56] The conversion of a phenylosazone to a 1,2,3-triazole *C*-nucleoside analogue is mentioned in Chapter 9.

Sato and Noyori and their co-workers have continued their studies on the synthesis of *C*-nucleosides from the adducts obtained from the addition of 1,1,3,3-tetrabromopropanone to furan derivatives. Following the use of 2-methylfuran reported last year (see Vol. 13, p. 186), analogous syntheses from 2-acetoxy-methylfuran,[57] 3-methylfuran,[58] and 2-phenylfuran[59] have led to racemic *C*-nucleosides which are 5-glycosylated uracils derived from branched-

[52] J. G. Buchanan, A. R. Edgar, R. J. Hutchison, A. Stobie, and R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2567; *ibid., J. Chem. Soc., Chem. Commun.*, 1980, 237.

[53] J. G. Buchanan, M. E. Chacon-Fuertes, A. Stobie, and R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2561.

[54] M. W. Logue and S. Sarangan, *Proc. N.D. Acad. Sci.*, 1980, **34**, 6 (*Chem. Abstr.*, 1980, **93**, 95 562).

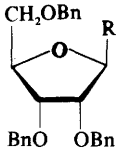
[55] F. G. Gonzalez, M. G. Guillen, J. A. G. Perez, and E. R. Galan, *Carbohydr. Res.*, 1980, **80**, 37.

[56] M. Gomez Guillen, J. Galois Perez, E. Roman Galan, and J. Espinosa Garcia, *An. Quim*, 1979, **75**, 745 (*Chem. Abstr.*, 1980, **92**, 129 241).

[57] T. Sato and R. Noyori, *Tetrahedron Lett.*, 1980, **21**, 2535.

[58] T. Sato, H. Kobayashi, and R. Noyori, *Tetrahedron Lett.*, 1980, **21**, 1971.

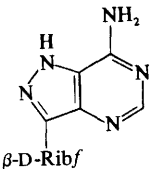
[59] T. Sato, M, Watanabe, and R. Noyori, *Heterocycles*, 1980, **14**, 761 (*Chem. Abstr.*, 1980, **93**, 95 563).



(23) R = C≡CCHO

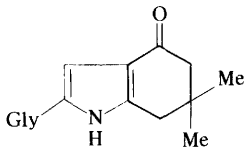
(24) R =

(26) R = COC≡CPh

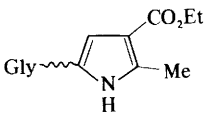


β-D-Ribf

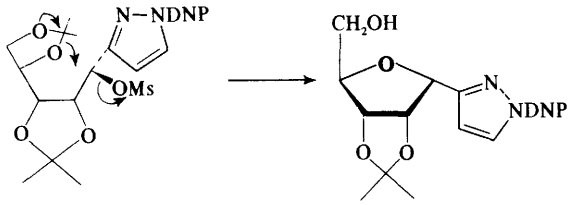
(25)



(27) Gly = α-D-Araf, αβ-D-Eryf, or β-D-Lyxp



(28) Gly = αβ-D-Lyxp



Scheme 4

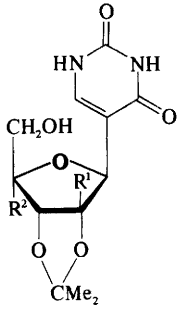
chain sugars, *e.g.*, (29) and (30). Alternative procedures from the bicyclic lactone intermediates led to homoshowdomycin (31) and homopyrazomycin (32).[60]

The synthesis of pyrazomycin (pyrazofurin) (33) from the corresponding 4-amino-5-cyano-3-ribofuranosyl-pyrazole has been reported.[61] The biosynthesis of pyrazomycin and formycin has been investigated using a mixture of [5-^{2}H]-ribose and [1-^{14}C]ribose as substrates with *S. candidus*; intact and specific incorporation of ribose into pyrazomycin was demonstrated from n.m.r. analysis of the labelled product, and a similar route for formycin was strongly suggested.[62]

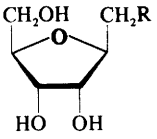
[60] T. Sato and R. Noyori, *Heterocycles*, 1979, **13** (Spec. Issue), 141 (*Chem. Abstr.*, 1980, **93**, 95 541).

[61] J. G. Buchanan, A. Stobie, and R. H. Wightman, *J. Chem. Soc., Chem. Commun.*, 1980, 916.

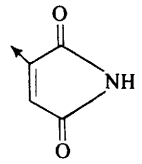
[62] J. G. Buchanan, M. R. Hamblin, G. R. Sood, and R. H. Wightman, *J. Chem. Soc., Chem. Commun.*, 1980, 917.



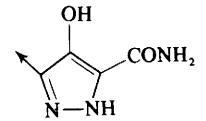
(29) R^1 = Me, R^2 = H
(30) R^1 = H, R^2 = CH_2OH or Ph

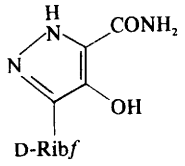


(31) R =



(32) R =





(33)

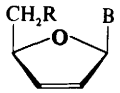
5′-Deoxy- and 5′-deoxy-5′-halo-derivatives of pseudo-uridine(5-β-D-ribofuranosyluracil) have been prepared by conventional methods, with the 5′-fluoro-derivative being prepared from 2′,3′-*O*-isopropylidene-pseudo-uracil by reaction with *N*,*N*-diethyl-*N*-(2-chloro-1,1,2-trifluoroethyl)amine as a less conventional fluorinating reagent.[63] Other papers report on the five possible *N*-monomethyl formycins[64] and the tautomeric equilibrium between the 7- and 8-protonated forms of formycin (25).[65] Further references to antibiotic *C*-nucleosides are made in Chapter 18.

5 Amino-sugar Nucleosides

The synthesis and biological response properties of new amino-sugar nucleosides have been reviewed.[66]

Several papers describe the synthesis of azido-sugar precursors to amino-sugar nucleosides. The unsaturated nucleosides (34) were converted to the corresponding amino-compounds (35) by sequential treatment with triphenylphosphine–tetrabromomethane and lithium azide followed by reduction, the product amines then being coupled to amino-acids to give amino-acyl derivatives, which showed slight antitumour activity.[67] A facile new synthesis of 2′-amino-2′-

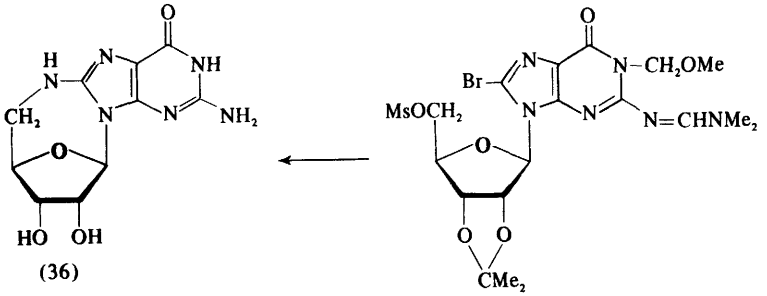
[63] R. A. Earl and L. B. Townsend, *J. Carbohydr., Nucleosides, Nucleotides*, 1980, **7**, 35.
[64] A. F. Lewis and L. B. Townsend, *J. Am. Chem. Soc.*, 1980, **102**, 2817.
[65] G. Dodin, O. Bensaude, and J.-E. Dubois, *J. Am. Chem. Soc.*, 1980, **102**, 3897.
[66] M. J. Robins, *Colloq. – Inst. Natl. Sante Rech. Med.*, 1978 (Publ. 1979), **81** (Nucleosides, Nucleotides, Appl. Biol.), 13 (*Chem. Abstr.*, 1980, **92**, 111 229).
[67] T. Adachi, Y. Arai, I. Inoue, and M. Saneyoshi, *Carbohydr. Res.*, 1980, **78**, 67.



(34) R = OH
(35) R = NH_2
} B = Cytosin-1-yl or Adenin-9-yl

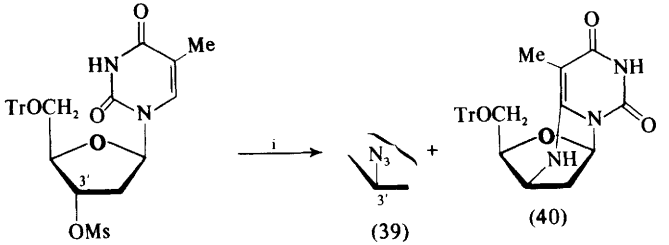
deoxyadenosine from commercially available Ara-A utilizes an azide displacement on a 2′-triflate derivative of this precursor.[68] The first natural occurrence of 2′-amino-2′-deoxy-adenosine has been reported in a strain of *Actinomadura*,[69] and an enzymatic synthesis of 2′-amino-2′-deoxy-inosine has been described from 2′-amino-2′-deoxy-uridine using a transamino-ribosylating enzyme in *Erwinia herbicola* in the presence of hypoxanthine.[70] Good yields of 2′-azido-2′-deoxy-nucleosides can be obtained from nucleosides *via* 2′,3′-orthoester intermediates by reaction with sodium azide in dimethylformamide in presence of chlorotrimethylsilane.[71] The use of the xylofuranose 3′-triflate derivative instead of the corresponding 3-tosylate doubles the yield of the 3′-azido-3′-deoxy-ribofuranose obtained in a simplified sequence leading to 3′-azido-3′-deoxy-adenosine.[72] Standard reactions on 3,5-disulphonate esters of 1,2-*O*-isopropylidene-α-D-xylofuranose have yielded 3′,5′-diamino-3′,5′-dideoxy derivatives of adenine, cytosine, and uridine.[73]

8,5′-Iminoguanosine (36) has been synthesized by reaction of the protected guanosine derivative (37) with hydrazine followed by 5′-*N*-deamination and deprotection.[74] Treatment of the thymidine derivative (38) with sodium azide



(36) (37)

[68] G. Butke, K. Quiggle, and S. Chladek, *J. Carbohydr., Nucleosides, Nucleotides*, 1980, **7**, 63.
[69] K. Matsuyama, Y. Takahashi, M. Yamashita, A. Hirano, and S. Omura, *J. Antibiot.*, 1979, **32**, 1367.
[70] T. Utagawa, H. Morisawa, T. Nakamatsu, A. Yamazaki, and S. Yamanaka, *FEBS Lett.*, 1980, **119**, 101.
[71] M. W. Logue and B. Hee Han, *J. Org. Chem.*, 1980, **45**, 5000.
[72] A. M. Ozols, A. V. Azhayev, N. B. Dyatkina, and A. A. Krayevsky, *Synthesis*, 1980, 557.
[73] A. M. Ozols, A. V. Azhayev, A. A. Krayevsky, A. S. Ushakov, N. V. Gnuchev, and B. P. Gottikh, *Synthesis*, 1980, 559.
[74] T. Sasaki, K. Minamoto, and H. Itoh, *Tetrahedron*, 1980, **36**, 3509.



(38) (39) (40)

Reagent: i, NaN_3–DMF

Scheme 5

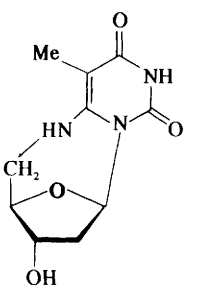
gave a mixture of the expected 3′-azido compound (39) together with the 6,3′-imino-nucleoside (40) (Scheme 5), the latter being considered to arise *via* a cyclic triazine intermediate; similarly 5′-azido-5′-deoxy-thymidine gave 6,5′-imino-thymidine (41) on treatment with lithium azide.[75]

5′-Diazonucleosides, *e.g.*, (42), prepared conventionally from corresponding 5′-acetamido-5′-deoxy-nucleosides, can be used as alkylating agents in esterification reactions.[76] Several *N*′-aminoacyl derivatives of 2′-amino-2′-deoxy- and 3′-amino-3′-deoxy-adenosine have been prepared conventionally from standard amino-acids.[77]

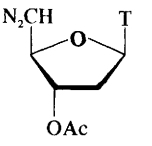
An amino-sugar derivative of adenosine is referred to below with related thio-sugar analogues.

6 Halo- and Deoxy-nucleosides

2′-[^{82}Br]-2′-Bromo-2-deoxy-uridine has been prepared either from 2,2′-anhydro-uridine using radiolabelled ammonium bromide[78] or by irradiation of unlabelled



(41)

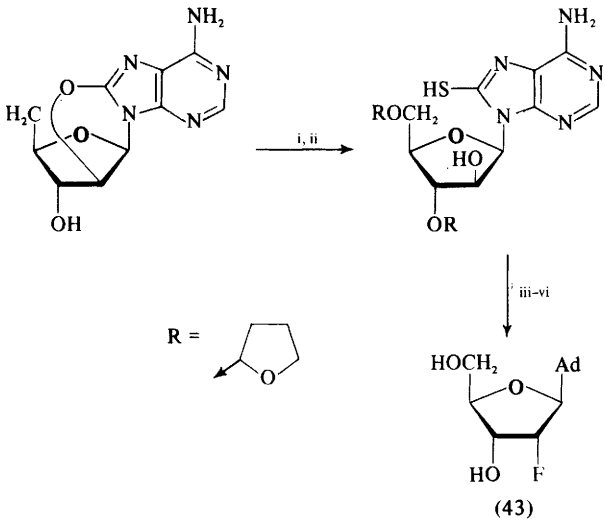


T = Thymin-1-yl

(42)

[75] A. Matsuda, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*, 1980, **45**, 3274.
[76] T. M. Chapman, J. M. Simpson, D. C. Kapp, and P. Butch, *J. Carbohydr., Nucleosides, Nucleotides*, 1980, **7**, 241.
[77] S. Chladek and G. Butke, *J. Carbohydr., Nucleosides, Nucleotides*, 1980, **7**, 297.
[78] Y. W. Lee, E. E. Knaus, and L. I. Wiebe, *J. Labelled Comp. Radiopharm.*, 1980, **17**, 269 (*Chem. Abstr.*, 1980, **93**, 150 544).

2′-bromo-2′-deoxy-uridine.[79] Likewise treatment of 2′,2′-anhydro-uridine with hydrogen fluoride in dioxan gave 2′-deoxy-2′-fluoro-uridine, a procedure which could be adapted to give the fluorine-18 labelled material for tumour-imaging.[80] Another report describes the synthesis of 2′-deoxy-2′-fluoro-adenosine (43) from 8,2′-anhydro-adenosine by the procedure outlined in Scheme 6; the yield was improved using the tetrahydrofuranyl protecting groups which were more readily removed by acidic hydrolysis than tetrahydropyranyl groups.[81]



(43)

Reagents: i, Dihydrofuran–H^+; ii, H_2S–py; iii, Raney Ni; iv, NaH–CF_3SO_2Cl; v, Bu_4NF; vi, $HOAc–H_2O$

Scheme 6

Using preformed 3-halo-3-deoxy-D-xylofuranose acetates, the series of 3′-halo-3′-deoxy-cytosine derivatives (44) have been prepared, together with the corresponding xylo-nucleoside derivatives (44, X = OMs or OTs), which were used in anti-leukaemic studies in comparison with Ara C.[82]

5′-Deoxy-5′-iodo-2′,3′-*O*-isopropylidene-thymidine, prepared conventionally from thymidine, has been used to prepare the 5′-modified nucleosides illustrated in Scheme 7.[83]

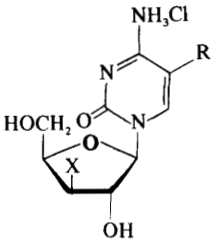
[79] Y. W. Lee, E. E. Knaus, and L. I. Wiebe, *J. Labelled Comp. Radiopharm.*, 1979, **16** (1, 2nd Int. Symp. Radiopharm. Chem.), 167 (*Chem. Abstr.*, 1980, **92**, 76 841).

[80] D. N. Abrams, E. E. Knaus, J. R. Mercer, and L. I. Wiebe, *J. Labelled Comp. Radiopharm.*, 1979, **16** (1, 2nd Int. Symp. Radiopharm. Chem.) 12 (*Chem. Abstr.*, 1980, **92**, 164 209).

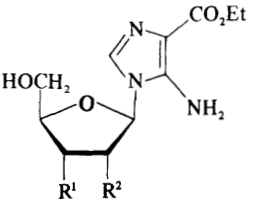
[81] M. Ikehara, A. Hasegawa, and J. Imura, *J. Carbohydr., Nucleosides, Nucleotides*, 1980, **7**, 131.

[82] K. A. Watanabe, U. Reichman, C. K. Chu, and J. J. Fox, *J. Med. Chem.*, 1980, **23**, 1088.

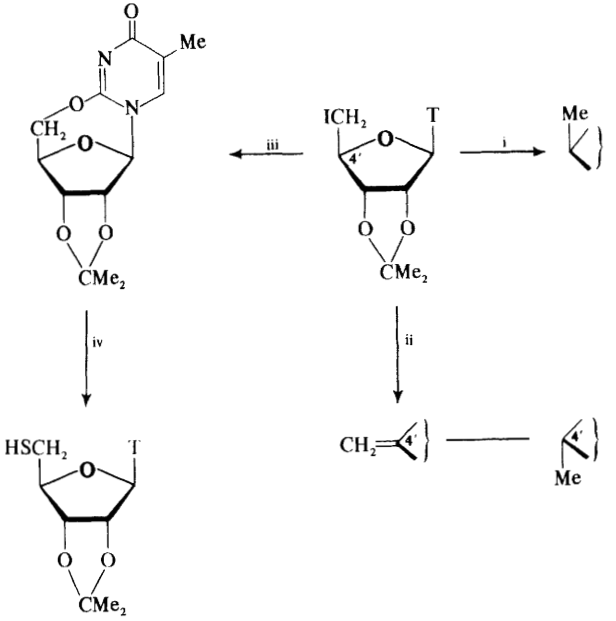
[83] V. Škaric and J. Matulić-Adamic, *Helv. Chim. Acta*, 1980, **63**, 2179.



(44) X = Cl, Br, or I
R = H or F



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

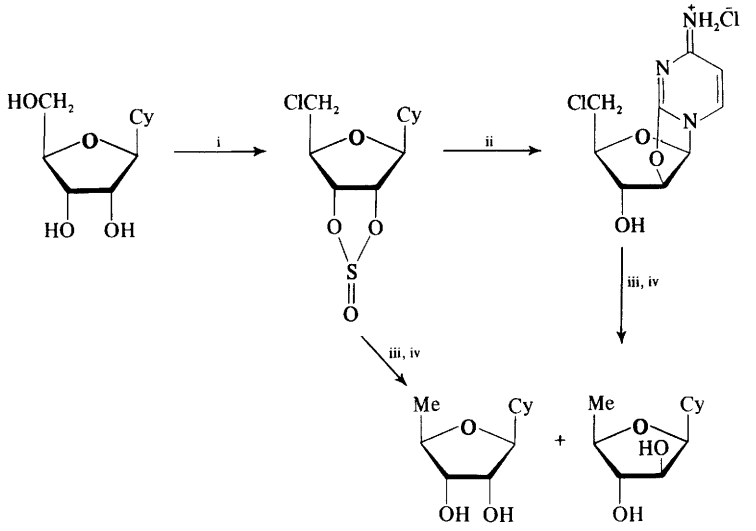


Reagents: i, H_2–Pd; ii, KOH–EtOH; iii, AgOAc; iv, H_2S

Scheme 7

The 2- and 3-deoxy-D-*erythro*-pentosyl derivatives of 4-amino-5-ethoxycarbonylimidazole (45) have been prepared from the corresponding ribofuranosyl derivative *via* 2′- and 3′-chloro-nucleosides prepared by treatment with *O*-acetylsalicyloyl chloride.[84] Scheme 8 shows the reaction of cytosine with thionyl chloride giving 5′-chloro-5′-deoxy-ribo- and -arabino-analogues, which were then

[84] V. V. Alenin, V. D. Domkin, E. N. Kalinichenko, and I. A. Mikhalopulo, *Zh. Obshch. Khim.*, 1979, **49**, 2775 (*Chem. Abstr.*, 1980, **92**, 181 528).

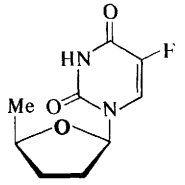


Reagents: i, $SOCl_2$; ii, Δ, DMF; iii, Resin–CO_3^{2-} form; iv, Bu_3SnH

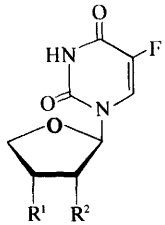
Scheme 8

reduced to 5′-deoxy-nucleosides; adenosine similarly gave 5′-deoxy-adenosine.[85] 2′-Deoxy-5-fluorouridine has been converted to 2′,5′-dideoxy- and 2′,3′,5′-trideoxy-analogues by reaction with methyltriphenoxyphosphonium iodide to give a 5′-deoxy-5′-iodo-intermediate that could be reduced to the 2′-5′-dideoxy-analogue, or further converted to the 2′,3′,5′-trideoxy-derivative (46) (a methyl analogue of FTORAFUR) by conventional reactions involving the 2′,3′-unsaturated nucleoside.[86] The 2- and 3-hydroxy-derivatives (47) of FTORAFUR have also been prepared from 1-(β-D-erythrofuranosyl)-5-fluorouracil by standard methods.[87] Other reports describe the preparation of 5′-*C*-methyl nucleosides from 6-deoxy-D-allose[88] and of 5′-deoxy-5-fluorouridine and its α-anomer from 5-deoxy-D-ribose using methyl ribofuranoside derivatives with the silylated base in presence of trimethylsilyl triflate, the α-anomer (48) predominating when the 2,3-*O*-isopropylidene sugar derivative was used; for this synthesis, the 5-deoxy modification of ribose was achieved by irradiation of the corresponding 5-*O*-acetate (Scheme 9).[89]

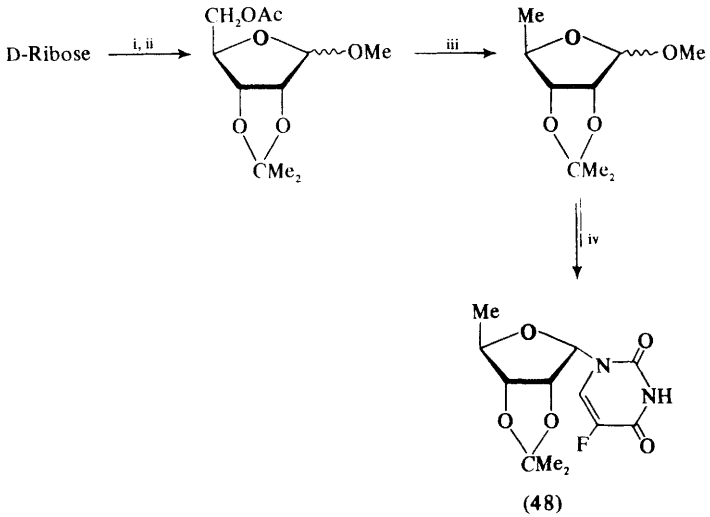
[85] H. Hřebabecký, J. Brokeš, and J. Beranek, *Collect. Czech. Chem. Commun.*, 1980, **45**, 599.
[86] A. F. Cook, M. J. Holman, and M. J. Kramer, *J. Med. Chem.*, 1980, **23**, 852.
[87] R. B. Meyer, jun. and C. H. Levenson, *Biochem. Pharmacol.*, 1980, **29**, 665 (*Chem. Abstr.*, 1980, **93**, 46 276).
[88] M. Ya. Karpeiskii and S. N. Mikhailov, *Bioorg. Khim.*, 1979, **5**, 895 (*Chem. Abstr.*, 1980, **2**, 6853).
[89] J. Kiss and R. D'Souza, *J. Carbohydr., Nucleosides, Nucleotides*, 1980, **7**, 141.



(46)



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



(48)

Reagents: i, $Me_2C(OMe)_2$–Me_2CO–MeOH–$CuSO_4$–H_2SO_4; ii, Ac_2O–py; iii, $h\nu$; iv, $CF_3SO_3SiMe_3$–2,4-bistrimethylsilyloxy-5-fluoropyrimidine

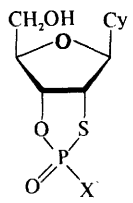
Scheme 9

7 Thio-sugar Nucleosides

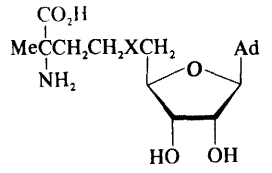
Uracil and cytosine derivatives of 4-thio-DL-erythrofuranose[90] and adenine and guanine nucleoside analogues of 4-thio-D-ribofuranose, 4-thio-D-xylofuranose, and 5-thio-D-xylopyranose[91] have been reported. Treatment of 2,2′-anhydrocytosine with phosphorus pentasulphide gave the cyclic thiophosphate derivatives (49), which was used to prepare other 2′-thio-cytidine derivatives.[92] The

[90] J. E. McCormick and R. S. McElhinney, *J. Chem. Res.* (*S*), 1980, 126.
[91] A. K. M. Anisuzzaman and M. Amin, *J. Bangladesh Acad. Sci.*, 1978, **2**, 59 (*Chem. Abstr.*, 1980, **93**, 47077).
[92] A. D. Patel, W. H. Schrier, and J. Nagyvary, *J. Org. Chem.*, 1980, **45**, 4830.

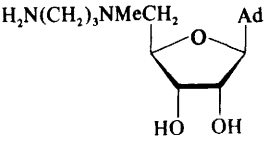
analogues (50) of *S*-adenosyl-methionine have been prepared, the parent sulphide being made by a standard thiolate–sulphonate displacement procedure, and a similar displacement using 2-cyanoethyl methylamine followed by reduction gave the related amino-sugar adenosine (51); both the sulphonium salt (50, X = $^{+}$SMe) and (51) were competitive inhibitors of *S*-adenosyl-L-methionine decarboxylase.[93] S^2, 2′-Cyclo-2-thiouridine has been used to synthesize 1-(2-deoxy-2-methylthio-β-D-arabinofuranosyl)-uracil and -cytosine.[94]



(49) X = O or S



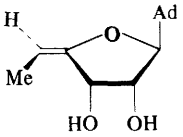
(50) X = S, $\overset{+}{S}$–$\bar{O}$, or $\overset{+}{S}$Me



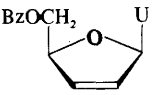
(51)

8 Unsaturated Nucleosides

Treatment of 9-(2,3-di-*O*-benzoyl-5,6-dideoxy-5-iodo-β-D-allofuranosyl)-6-*N*-benzoyl adenine with DBU followed by deprotection gave the *E*-isomer of the 4,5-unsaturated nucleoside (52), whereas the L-talo 5-epimer gave the *Z*-isomer.[95] The 2,3-unsaturated nucleoside (53) can be prepared from uridine derivatives by conversion to 2,3-dichloro-2,3-dideoxy-analogues using tetrachloromethane–triphenylphosphine–triethyl phosphate reagent followed by dechlorination using tributyltin hydride.[96] Glycosylation of N^4-benzoyl-cytosine with acetylated glycals leads to the expected rearranged, unsaturated nucleosides; 3,4-di-*O*-acetyl-*erythro*- and -*threo*-pent-1-enopyranoses gave the 4-*O*-acetyl-*glycero*-pent-2-enosyl-cytidines in which the acetyl group and base are *trans*-related.[97]



(52)

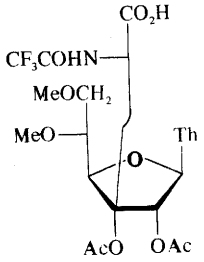


(53)

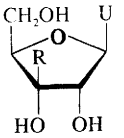
[93] M. Pankaskie and M. M. Abdel-Monem, *J. Med. Chem.*, 1980, **23**, 121.
[94] S. Shibuya and T. Ueda, *J. Carbohydr., Nucleosides, Nucleotides*, 1980, **7**, 49.
[95] L. M. Lerner, *J. Org. Chem.*, 1979, **44**, 4359.
[96] S. David and G. De Sennyey, *Carbohydr. Res.*, 1980, **82**, 45.
[97] A. A. Akhrem, I. A. Mikhailopulo, and N. B. Khripach, *Khim. Geterotsikl. Soedin.*, 1979, 1427 (*Chem. Abstr.*, 1980, **92**, 111 262).

9 Branched-chain Sugar Nucleosides

The branched-chain sugar nucleosides (54)[98] and (55)[99] have been prepared by conventional methods from the corresponding sugars, whose synthesis is referred to in Chapter 13. The branched-chain uridine derivatives show *in vitro* activity against cultured L 1210 cells.[99]



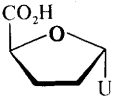
(54)



(55) R = Et or Bu

10 Uronic Acid Nucleosides

Various nucleoside 5′-carboxylic acids have been prepared from glycosyl chlorides of methyl D-riburonate and methyl D-lyxuronate.[100,101] Other groups have reported the synthesis of uridine α-nucleoside analogues from 2-alkoxycarbonyl-5-chloro-tetrahydrofuran and 5-substituted uracils, *e.g.*, (56),[102] and D-glucuronyl derivatives of 5-fluoro-uracil.[103]

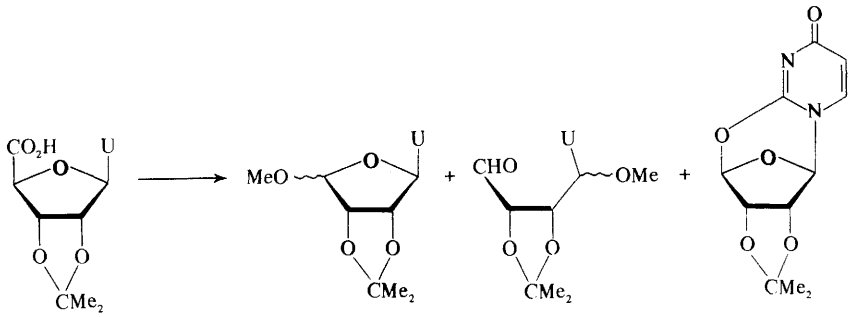


(56)

The electrolysis of 1-(2,3-*O*-isopropylidene-β-D-ribosyluronic acid) uracil in methanol yielded the products shown in Scheme 10. A 4′-carbonium ion was suggested to be the reactive intermediate involved.[104]

A series of amides of adenosine 5′-carboxylic acid have been prepared and were shown to possess potent cardiovascular activity.[105]

[98] A. Rosenthal and B. L. Cliff, *Carbohydr. Res.*, 1980, **79**, 63.
[99] A. Rosenthal and S. N. Mikhailov, *Carbohydr. Res.*, 1980, **79**, 235.
[100] K.-H. Jung and R. R. Schmidt, *Chem. Ber.*, 1980, **113**, 1775.
[101] R. R. Schmidt, G. R. Lösch, and P. Fischer, *Chem. Ber.*, 1980, **113**, 2891.
[102] R. A. Zhuk, A. Berzina, V. Silina, E. Liepins, and S. Hillers, *Khim. Geterotsikl. Soedin.*, 1979, 1128 (*Chem. Abstr.*, 1980, **92**, 6857).
[103] M. Carissimi, P. de Meglio, P. Gentili, and F. Ravenna, *Boll. Chim. Farm.*, 1979, **118**, 721 (*Chem. Abstr.*, 1980, **93**, 61 340).
[104] K. Kondo and I. Inoue, *J. Org. Chem.*, 1979, **44**, 4713.
[105] R. N. Prasad, D. S. Bariana, A. Fung, M. Savic, K. Tietje, H. H. Stein, H. Brondyk, and R. S. Egan, *J. Med. Chem.*, 1980, **23**, 313.



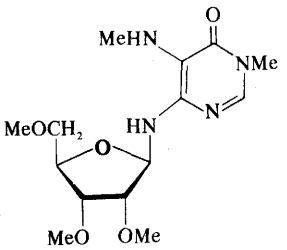
Scheme 10

11 Ether and Acetal Derivatives

Trimethylanilinium methoxide has been studied as a reagent for the methylation of nucleosides; *O*- and *N*-methylation occurred, with adenine giving a pentamethyl derivative, and guanosine hexamethyl derivatives of both tautomers, whereas inosine and xanthosine reacted further to give products with degraded heterocyclic rings [*e.g.*, (57) from inosine] and products of glycosidic bond cleavage.[106]

Transition-metal acetylacetonates promote the 2′- and 3′-*O*-methylation of ribonucleosides using trimethylsulphonium hydroxide as the methylating reagent; complexed ferric ion was particularly effective. Since *N*-methylation is also suppressed, co-ordination of the metal ion with the nitrogen of the bases may occur.[107]

The 2′- and 3′-*O*-methyl ethers of guanosine have been prepared by partial methylation of 5′-*O*-t-butyldiphenylmethyl guanosine with diazomethane in presence of tin(II) chloride.[108] 5′-*O*-Deuteriomethyl-2′-deoxyuridine has also been synthesized.[109]

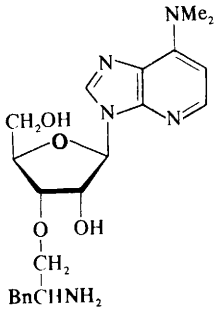


(57)

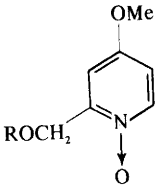
[106] G. R. Pettit, R. M. Blazer, J. J. Einck, and K. Yamauchi, *J. Org. Chem.*, 1980, **45**, 4073.
[107] K. Yamauchi, T. Nakagima, and M. Kinoshita, *J. Org. Chem.*, 1980, **45**, 3865.
[108] G. Ekborg and P. J. Garegg, *J. Carbohydr., Nucleosides, Nucleotides*, 1980, **7**, 57.
[109] C. Y. Shiue, A. P. Wolf, and D. N. Slatkin, *J. Labelled Comp. Radiopharm.*, 1980, **17**, 177 (*Chem. Abstr.*, 1980, **93**, 132 730).

Tetrahydrofuranyl ethers of thymidine and 2′-deoxycytidine have been prepared by acid-catalysed reaction of the nucleosides with 2,3-dihydrofuran; mixtures of the 3′- and 5′-mono- and 3′,5′-di-ethers were obtained. 3′-*O*-Tetrahydrofuranyl-thymidine was also obtained by etherification of 5′-*O*-palmitoyl thymidine followed by deacylation, and rat liver microsomes were found to convert the 3′,5′-diether selectively to the 5′-ether.[110] The puramycin analogues (58) has been prepared from a 5′-blocked adenosine derivative.[111]

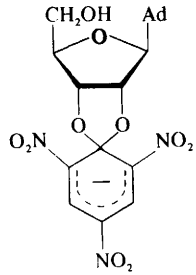
The use of 4-substituted-2-picolyl-1-oxide ethers as protecting groups for sugar hydroxyls in nucleosides has been explored. The groups can be removed by treatment with acetic anhydride at 45 °C, followed by deacetylation with methanolic ammonia, the 4-methoxy-derivative (59) being more readily cleaved than the unsubstituted analogue.[112] Adenosine with trinitrobenzenesulphonate gave a 2′,3′-*O*-Meisenheimer complex (60), which with acid gave exclusively the 3′-picryl ether.[113]



(58)



(59)



(60)

The 2′-*O*-t-butyldimethylsilyl protecting group in ribonucleosides is stable under a variety of conditions used to prepare ribonucleotides, including the chloro-phosphite coupling procedure, which was then used to prepare several 3′-phosphate esters of uridine.[114]

The synthesis of 5′-*O*-(β-D-glucopyranosyluronic acid)-6-azauridine has been reported.[115]

The synthesis of trityl ethers of nucleosides and their selective detritylation is referred to in Chapter 4.

[110] N. D. Chkanikov, G. A. Belitskii, A. Yu. Kolyada, M. G. Kiseleva, I. A. Khitrovo, and M. N. Preobrazhenskaya, *Bioorg. Khim.*, 1980, **6**, 1316 (*Chem. Abstr.*, 1980, **93**, 221 010).

[111] T. Kato and J. Zemlicka, *J. Org. Chem.*, 1980, **45**, 4006.

[112] Y. Mizuno, T. Endo, A. Takahashi, and A. Inaki, *Chem. Pharm. Bull.*, 1980, **28**, 3041.

[113] G. Ah-Kow, F. Terrier, M.-J. Pouet, and M.-P. Simonnin, *J. Org. Chem.*, 1980, **45**, 4399.

[114] K. K. Ogilvie and R. T. Pon, *Nucleic Acids Res.*, 1980, **8**, 2105.

[115] N. D. Chkanikov and M. N. Preobrazhenskaya, *Bioorg. Khim.*, 1980, **6**, 67 (*Chem. Abstr.*, 1980, **92**, 198 662).

12 Ester Derivatives

As usual, standard syntheses of nucleotides are not included in this survey. Using adenosine 5′-[(*R*)-^{16}O,^{17}O,^{18}O]phosphate, it has been shown that the conversion of adenosine 5′-phosphate to cyclic AMP and the enzymatic hydrolysis of the latter to the former both occur with retention of configuration at phosphorus.[116] Cyclic AMP can be used to prepare 2′-*O*-substituted adenosine derivatives; 2′-*O*-succinyl adenosine was synthesized by acylation followed by enzymatic dephosphorylation; on equilibration the 3′-*O*-succinyl isomer was slightly favoured (54%).[117]

The selective debenzoylation of nucleosides is mentioned in Chapter 6.

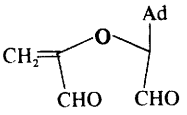
13 Reactions

The kinetics of the acid-catalysed hydrolysis of xanthosine has been studied by following the detritiation of [8-^{3}H]xanthosine; the results were consistent with earlier data.[118] Another study has established that, whereas cationic detergents have no effect on the rate of acidic hydrolysis, anionic detergents enhanced the rate, the extent being dependent upon the pK_a of the nucleoside.[119]

Dialdehydes, isolated as hydrates, have been prepared from a series of 6-deoxy-hexofuranosyl-adenine nucleosides by periodate oxidation, which were then used to study binding specificities with adenosine aminohydrolase.[120] Heating the dialdehyde obtained from adenosine in boiling water greatly increased its inhibiting power, and the authors suggest that dehydration occurs on heating to give the unsaturated dialdehyde (61), since a similar product was obtained by periodate oxidation of 4′-5′-unsaturated adenosine, and led to the same enediol on borohydride reduction.[121]

14 Miscellaneous Nucleosides

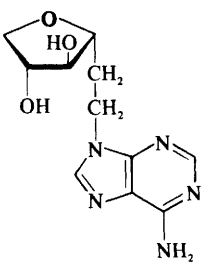
Bis-homonucleoside analogues, *e.g.*, (62), have been prepared by base-catalysed reaction of purine derivatives with 3,6-anhydro-hexitol 1-toluene-*p*-sulpho-



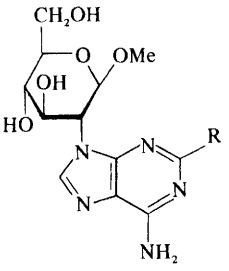
(61)

[116] R. L. Jarvest and G. Lowe, *J. Chem. Soc., Chem. Commun.*, 1980, 1145.
[117] C. Sauer and U. Schwabe, *Z. Naturforsch., Teil C*, 1980, **35**, 163 (*Chem. Abstr.*, 1980, **93**, 95 537).
[118] J. R. Jones and S. E. Taylor, *Int. J. Chem. Kinet.*, 1980, **12**, 141 (*Chem. Abstr.*, 1980, **93**, 47 078).
[119] M. Seno, K. Sawada, K. Araki, and H. Kise, *Nippon Kagaku Kaishi*, 1980, 469 (*Chem. Abstr.*, 1980, **93**, 47 079).
[120] A. J. Grant and L. M. Lerner, *J. Med. Chem.*, 1980, **23**, 39.
[121] A. J. Grant and L. M. Lerner, *J. Med. Chem.*, 1980, **23**, 795.

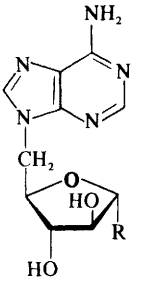
nates.[122] 2-Amino-2-deoxy-D-glucose has been used to prepare the iso-nucleosides (63) having the base attached at C-2,[123] and a sulphonate displacement procedure was adopted for the synthesis of reversed homonucleosides of adenine and uracil, *e.g.*, (64), from the dimethyl acetal of 2,3-di-*O*-acetyl-2,5-anhydro-6-*O*-tosyl-D-mannose.[124] The various positional isomers of the dimeric nucleosides (65) have been synthesized by condensation of appropriate 2′,3′-ortho-ester nucleosides of 6-chloro-purine and 6-*N*-(ω-alkylamino)adenine; these compounds, especially when $n = 4$, inhibit ribosomal peptidyl-transferase by simulating the 3′-terminal of the aminoacyl (acceptor) tRNA.[125] A new type of double-headed nucleoside (66) has been prepared from (5*S*)-1,2,3,4-tetra-*O*-acetyl-5-bromo-β-D-xylopyranose.[126]



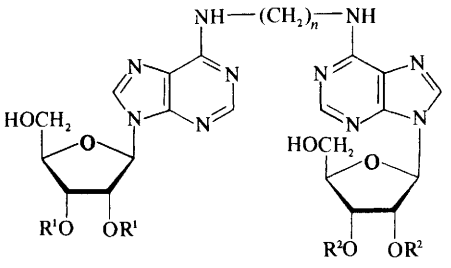
(62)



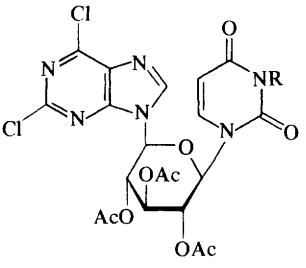
(63) R = Ph or SMe



(64) R = $CH(OMe)_2$ or CH_2OH



(65) R^1 = H, $COCH_2NH_2$
R^2 = H, Ac
n = 2 or 4



(66) R = H or Me

[122] G. Giovanninetti, V. Cavrini, L. Garuti, P. Roveri, M. Amorosa, R. Gaggi, and J. Defaye, *Eur. J. Med. Chem. – Chim. Ther.*, 1980, **15**, 23 (*Chem. Abstr.*, 1980, **93**, 72 189).

[123] L. E. Crane, Y. Maki, and G. P. Beardsley, *J. Carbohydr., Nucleosides, Nucleotides*, 1980, **7**, 281.

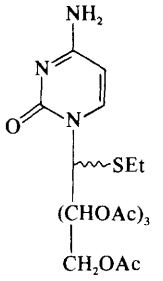
[124] P. Angibeaud, J. Defaye, and H. Franconie, *Carbohydr. Res.*, 1980, **78**, 195.

[125] M. Murata, P. Bhuta, J. Owens, and J. Zemlička, *J. Med. Chem.*, 1980, **23**, 781.

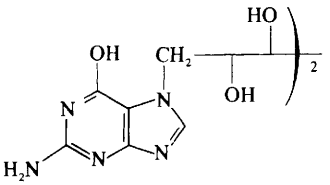
[126] R. J. Ferrier and P. C. Tyler, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2767.

Horton's Group have reported the syntheses of acyclic sugar nucleoside analogues derived from pentoses with cytidine and uracil, *e.g.*, (67),[127] 2-deoxy-D-*arabino*-hexose and 2-deoxy-D-ribopentose with 6-chloro-purine and 5-fluoro-uracil,[128] pentoses with 5-fluoro-uracil,[129] and D-glucose with 6-chloro-purine,[130] in each case condensing sugar dithioacetal or bromo-thioacetal derivatives with TMS or mercury derivatives of the heterocyclic bases. 1,2;5,6-Dianhydro-galactitol reacts with guanosine in acetic acid to yield the guanosinyl galactitol products expected from terminal-epoxide substitution by guanosine, including the bis-nucleoside analogue (68), which could also be isolated after treating DNA with the anhydrogalactitol and subsequent hydrolysis.[131]

Carbocyclic analogues of purine lyxo- and ribo-nucleosides have been prepared from intermediates obtained by osmium tetraoxide hydroxylation of an aminocyclopentene derivative.[132]



(67)



(68)

15 Structure and Analysis of Nucleosides

A statistical survey of crystal structures of nucleic acid constituents has led to the proposal that a full description of nucleoside molecular geometry can be given in terms of four parameters: the phase angle of pseudorotation, P, the puckering amplitude, ν_m, the conformation of the side-chain, δ, and the glycosidic torsional angle, χ; these allow the variability of bond and torsion angles to be described.[133]

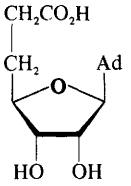
Theoretical calculations of ^{1}H n.m.r. J values have been made to assist conformational analysis of isomeric pentofuranosyl nucleosides; the results for cisoid hydrogens were used to calculate the conformation of α-xylo-, β-lyxo-,

[127] D. Horton and S. S. Kokrady, *Carbohydr. Res.*, 1980, **80**, 364.
[128] D. Horton and R. A. Markovs, *Carbohydr. Res.*, 1980, **80**, 356.
[129] D. Horton and R. A. Markovs, *Carbohydr. Res.*, 1980, **80**, 263.
[130] K. C. Blieszner, D. Horton, and R. A. Markovs, *Carbohydr. Res.*, 1980, **80**, 241.
[131] E. Institóris and J. Tamás, *Biochem. J.*, 1980, **185**, 659.
[132] R. Vince and S. Daluge, *J. Org. Chem.*, 1980, **45**, 531.
[133] H. P. M. De Leeuw, C. A. G. Haasnoot, and C. Altona, *Isr. J. Chem.*, 1980, **20**, 108 (*Chem. Abstr.*, 1980, **93**, 132 739).

and α-2′-deoxyribo-nucleosides in solution.[134] New values for $^3J_{H,H}$ along the C-4′–C-5′ bond in nucleosides and nucleotides have been proposed allowing conformational analysis of this bond using a generalized Karplus equation.[135] ^{1}H N.m.r. has been used to study the conformation of tricyclic base analogues of adenosine and guanosine in deuterioammonia solution; assuming the N ⇌ S furanoside equilibrium proposed by Altona and Sundaralingam, the S conformer was found to be favoured.[136] The *syn* ⇌ *anti* equilibrium about the glycosidic bond of purine nucleosides and 5′-nucleotides has been investigated in different solvent systems using ^{1}H and ^{13}C n.m.r. Quantitative values were improved by allowing for the effect of sugar C-5′-exocyclic group conformation on the chemical shifts of sugar ring protons, which was ascertained from a study of 8,5′-cyclic nucleosides.[137] Analysis of ^{1}H and ^{13}C n.m.r. spectra of uridine, 2′-deoxy-uridine, and other 2′-substituted uridines suggest a linear relationship between the electronegativity of the 2′-substituent and the ^{13}C chemical shift of C-2; the contribution of the N-form of the sugar ring (3′-endo-2′-exo) increases with the electronegativity of the 2′-substituent, and the authors suggest that this electronegativity effect could dominate the conformational influences in nucleosides, and be the principal force determining the differences between DNA and RNA.[138] Another ^{1}H n.m.r. study compares the solution conformations of uridine and pseudouridine and their phosphates; whereas pseudouridine and its 3′-phosphate favour a *syn*-conformation, uridine and its 3′- and 5′-phosphates are mostly *anti*.[139] The measurement of proton relaxation times for H-5 of pyrimidine bases and for H-1′ after H-8 exchange with deuterium in purines has allowed *syn* ⇌ *anti* equilibria to be estimated; the results suggest that the *anti*-conformation is generally preferrred in nucleosides and nucleotides, with purine nucleosides showing no preference, and 3′-AMP favouring a *syn*-conformation.[140] The conformations of 3′- and 5′-phosphates and 3′,5′-diphosphates of thymidine have been assessed from ^{13}C–^{31}P coupling-constant measurements.[141] ^{1}H and ^{13}C n.m.r. data confirm a correlation between the C-1 chemical shift and the H-1′, H-2′ coupling constant in cytidine and uridine.[142]

The conformation of 5′-deoxy-5′-adenosine acetic acid (69) regarded as a model for 5′-AMP, has been established by *X*-ray crystal-structure analysis.[143]

[134] A. Jaworski and I. Ekiel, *Int. J. Quantum Chem.*, 1979, **16**, 615 (*Chem. Abstr.*, 1980, **92**, 94664).
[135] C. A. G. Haasnoot, F. A. A. M. De Leeuw, H. P. M. De Leeuw, and C. Altona, *Recl. Trav. Chim. Pays-Bas*, 1979, **98**, 576 (*Chem. Abstr.*, 1980, **92**, 147114).
[136] G. Klimke, H. D. Luedemann, and L. B. Townsend, *Z. Naturforsch., Teil C*, 1979, **34**, 653 (*Chem. Abstr.*, 1980, **92**, 111260).
[137] R. Stolarski, L. Dudycz, and D. Shugar, *Eur. J. Biochem.*, 1980, **108**, 111.
[138] W. Guschlbauer and K. Jankowski, *Nucleic Acids Res.*, 1980, **8**, 1421.
[139] J. M. Neumann, J. M. Bernassau, M. Guéron, and S. Tran-Dinh, *Eur. J. Biochem.*, 1980, **108**, 457.
[140] I. D. Bobruskin, M. P. Kirpichnikov, M. Yu. Pokrovskaya, and V. L. Florent'ev, *Bioorg. Khim.*, 1980, **6**, 1163 (*Chem. Abstr.*, 1980, **93**, 221007).
[141] W. P. Niemczura and F. E. Hruska, *Can. J. Chem.*, 1980, **58**, 472.
[142] E. Kupce, *Khim. Prir. Soedin.*, 1980, 578 (*Chem. Abstr.*, 1980, **93**, 186722).
[143] T. Ishida, M. Inoue, A. Ota, and T. Kurihara, *J. Chem. Soc., Chem. Commun.*, 1980, 1074.



(69)

The influence of metal ions on the Raman and ^{13}C n.m.r. spectra of several nucleosides in DMSO has been investigated, and literature data on ion-nucleoside interactions in this solvent are also summarized.[144]

Ultrasonic methods have been used to study the *syn* ⇌ *anti* equilibrium of 2-deoxyadenosine in presence of ethidium bromide and indole-3-acetic acid, which, respectively, serve as models for an intercalating drug and a tryptophan unit at a protein binding site.[145]

The chromatographic parameters affecting the reversed-phase h.p.l.c. separation of major and modified nucleosides have been investigated, and the results applied to tRNA hydrolysates.[146]

[144] L. G. Marzilli, B. de Castro, J. P. Caradonna, R. C. Stewart, and C. P. Van Vuuren, *J. Am. Chem. Soc.*, 1980, **102**, 916.

[145] F. Jordan, S. Nishikawa, and P. Hemmes, *J. Am. Chem. Soc.*, 1980, **102**, 3913.

[146] C. W. Gehrke, K. C. Kuo, and R. W. Zumwalt, *J. Chromatogr.*, 1980, **188**, 129.

20

N.m.r. Spectroscopy and Conformational Features

1 Theoretical and General Considerations

Ab initio MO calculations on methoxymethyl formate and methoxymethyl acetate as models for the anomeric effect and stereochemistry of 1-*O*-acetylglycopyranoses have been undertaken. The results indicate that α-$^4C_1$ (D) conformation is more stable than that of β-$^4C_1$ (D), but that the energy difference is even more dependent on the disposition about the glycosidic bond. Small differences in C—O bond lengths observed for α- and β-anomers were reproduced by the calculations.[1] Equations for correlating the geometries of furanose rings with the pseudorotation phase angles and the amplitude of puckering have been developed.[2] The conformational energies for a series of α-D-glucopyranose compounds have been predicted using a 'TRIBBLE' molecular mechanics programme. The range of O-4 to O-1 distances between 360 and 500 pm in $^4C_1$ conformation were surveyed, and the energy minimum found to occur at 426 pm. Systematic valence- and torsion-angle changes were computed and compared to known examples in *X*-ray structures.[3] Excellent overall agreement was obtained between observed conformations of 1,6-anhydro-hexopyranoses and those calculated using Allinger's MM1-MMP1 programme.[4] A study of the accuracy with which geometries of pyranose and methyl pyranoside molecules are predicted by molecular mechanics calculations has been carried out. Calculations, using the MM1 programme, on $CH_2(OH)_2$, H_3COCH_2OH, and $CH_2(OCH_3)_2$ as models gave results that compare well with previous *ab initio* molecular orbital calculations. A satisfactory prediction of the energetic and conformational aspects of the anomeric effect was obtained, further supported by calculations on 2-methoxytetrahydropyran. A modified MM1 programme was used to calculate the geometrics of pyranose and methyl pyranosides whose crystal structures were known: good agreement was obtained when the C—C—O—H torsion angles were constrained to those observed in crystal analysis.[5] Theoretical studies of the conformational flexibility of the pyranose ring, using 2-methoxytetrahydropyran as a model, have shown that good agreement with observed data can be obtained. The differences in geometry resulting from axial compared to equatorial methyl glycosides were calculated and good agreement with observation and theoretical anomeric and exo-anomeric effects

[1] G. A. Jeffrey and J. H. Yates, *Carbohydr. Res.*, 1980, **79**, 155.
[2] E. Westhof and M. Sundaralingam, *J. Am. Chem. Soc.*, 1980, **102**, 1493.
[3] D. A. Pensak and A. D. French, *Carbohydr. Res.*, 1980, **87**, 1.
[4] G. A. Jeffrey and Y. J. Park, *Taehan Hwahakhoe Chi*, 1979, **23**, 206 (*Chem. Abstr.*, 1980, **92**, 129 207).
[5] G. A. Jeffrey and R. Taylor, *J. Comput. Chem.*, 1980, **1**, 99 (*Chem. Abstr.*, 1980, **93**, 72 126).

was found. The calculated and experimental values for energy differences for the $^4C_1$ and $^1C_4$ chairs agreed well, as did the average dipole moments. The conclusion was reached that the anomeric and exo-anomeric effects result quantitatively from the balance of intramolecular electrostatic factors and solvent electrostatic interactions.[6,7]

The puckering parameters of Altona and Sundaralingam have been compared to those of Cremer and Pople and the latter shown to be better predictors of furanose ring conformations.[8] Semi-empirical potential functions have been used to calculate the conformations of α- and β-D-glucose. Solvent accessibility was also calculated. The $^4C_1$ (D), although somewhat flexible, was the most favoured conformation. The boat and twist-boat conformers were calculated to be at least 21 kJ mol^{-1} higher in energy than $^4C_1$ (D), and are thus unlikely in polysaccharides. An energy barrier of 46 kJ mol^{-1} was calculated for interconversion of $^1C_4$ (D) and $^4C_1$ (D) chairs.[9] A FORTRAN-IV computer programme, based on an additive model of interatomic interactions in which the potential energy of the molecule is considered a function of its geometric parameters, has been used to calculate the conformation and vibrational spectrum of β-D-glucopyranose.[10] The same methods have been used for anomers of D-glucose, D-allose, D-galactose, D-gulose, D-mannose, and D-altrose.[11]

Energy calculations of the conformation of di-β-D-glucopyranose 1,6′:1′,6-dianhydride hexa-acetate have been compared to that shown by *X*-ray and n.m.r. data.[12] Molecular mechanics calculations on 2,3- and 3,5-*O*-isopropylidene-α- and -β-D-ribo- and -L-lyxo-furanose, 2,3- and 3,5-*O*-methylene derivatives of 1,4-anhydro-D-ribitol and L-lyxitol, and related *O*-isopropylidene derivatives have been reported. Geometries and energies were generally in good agreement with experimental data.[13] Considerable conformational flexibility was suggested by empirical force field calculations of conformations of β-gentiobiose.[14] Intermolecular molecular mechanics energy calculations have been carried out for doxorubicin interacting with two dinucleotide dimer sequences. The preferred mode of intercalation was predicted to be in the minor groove, with anthraquinone rings nearly perpendicular to the base pairs, and alternate C-3′-*endo*-C-2′-*endo*-sugar ring puckering, a preferred conformation nearly identical to that found in the crystal structure of *N*-bromoacetyldaunomycin.[15]

[6] T. Kožár and I. Tvaroška, *Theor. Chim. Acta*, 1979, **53**, 9 (*Chem. Abstr.*, 1980, **92**, 59 124).
[7] I. Tvaroška and T. Kožár, *J. Am. Chem. Soc.*, 1980, **102**, 6929.
[8] G. A. Jeffrey and R. Taylor, *Carbohydr. Res.*, 1980, **81**, 182.
[9] N. V. Joshi and V. S. R. Rao, *Biopolymers*, 1979, **18**, 2993 (*Chem. Abstr.*, 1980, **92**, 111 241).
[10] V. M. Andrianov, R. G. Zhbankov, and V. G. Dashevskii, *Zh. Strukt. Khim.*, 1980, **21**, 35 (*Chem. Abstr.*, 1980, **93**, 132 700).
[11] V. M. Andrianov, R. G. Zhbankov, and V. G. Dashevskii, *Zh. Strukt. Khim.*, 1980, **21**, 42 (*Chem. Abstr.*, 1980, **93**, 132 701).
[12] D. Gagnaire, S. Pérez, and V. Tran, *Carbohydr. Res.*, 1980, **82**, 185.
[13] U. Burkert, A. Gohl, and R. R. Schmidt, *Carbohydr. Res.*, 1980, **85**, 1.
[14] S. Melberg and K. Rasmussen, *Carbohydr. Res.*, 1980, **78**, 215.
[15] Y. Nakata and A. J. Hopfinger, *Biochim. Biophys. Res. Commun.*, 1980, **95**, 583.

High-resolution n.m.r. spectroscopy of carbohydrates and glycoproteins has been reviewed.[16] A new coupling-constant–torsion-angle relationship for three-bond ^1H–^1H spin–spin coupling has been derived. It is of the form of a Karplus equation with an additional term correcting for orientation and electronegativity of substituents.[17] Hydroxy-proton resonance shifts for a range of aqueous sugar solutions at low temperature over a narrow pH range have been measured. Some assignments were made.[18] High-resolution ^1H n.m.r. spectra of aqueous D-xylose solutions at pH 4.9 and 0 °C, or just below, revealed resolved signals due to the anomeric hydroxy-protons.[19] A comparative study of ^1H n.m.r. spectra of aqueous glucose solutions at various concentrations at 20 °C gave results for the energy of intermolecular hydrogen bonds.[20]

Spin–lattice values (T_1) for α-(2→3)- and α-(2→6)-isomers of *N*-acetylneuraminyl-lactose have been shown to be similar, suggesting that the internal motions are also similar.[21]

Trifluoroacetic anhydride has been recommended as a solvent for ^1H n.m.r. of carbohydrates since trifluoroacetylation of the hydroxy-groups, which occurs on dissolution, results in downfield shifts of the α-protons, giving well resolved spectra. The method was applied to 270 MHz studies of 2-acetamido-2-deoxyhexoses.[22]

Empirical shift parameters have been used to calculate the chemical shifts induced at any other carbon atom in the ^{13}C n.m.r. spectrum of D-xylose derivatives; agreement was poor unless the compounds are very similar.[23] A rapid micro-method ($\leqslant \mu g$) for determining ^{14}C-labelling patterns in carbohydrates based on ^{13}C n.m.r. has been developed. The results were useful for calculating the specific activity using field-desorption m.s. and the method avoids the use of chemical degradation.[24]

2 Acyclic Systems

By means of 250 MHz ^1H n.m.r. spectra, the solution conformations of stereoisomers of peracetylated aldohexose dimethyl acetals and diethyl acetals have been determined. With the exceptions of the D-*galacto*- and D-*manno*-isomers, which were extended planar, all isomers were in the sickle conformation. The results were interpreted on the basis of avoidance of parallel 1,3-substituent interactions.[25]

[16] J. F. G. Vliegenthart, *Adv. Exp. Med. Biol.*, 1980, **125** (Struct. Funct. Gangliosides), 77–91 (*Chem. Abstr.*, 1980, **93**, 3161).
[17] C. A. G. Haasnoot, F. A. A. M. De Leeuw, and C. Altona, *Bull. Soc. Chim. Belg.*, 1980, **89**, 125 (*Chem. Abstr.*, 1980, **93**, 16 323).
[18] M. C. R. Symons, J. A. Benbow, and J. M. Harvey, *Carbohydr. Res.*, 1980, **83**, 9.
[19] E. Lai and F. Framks, *Cryo-Lett.*, 1979, **1**, 20 (*Chem. Abstr.*, 1980, **92**, 129 208).
[20] M. D. Adamenkova, V. I. Ermakov, and V. V. Makhlyarchuk, *Vestn. Mosk. Univ., Ser. 2: Khim.*, 1980, **21**, 199 (*Chem. Abstr.*, 1980, **93**, 72 128).
[21] L. W. Jaques, S. Glant, and W. Weltner, *Carbohydr. Res.*, 1980, **80**, 207.
[22] M. Ranganathan and P. Balaram, *Org. Magn. Reson.*, 1980, **13**, 220.
[23] J.-P. Utille and P. J. A. Vottero, *Carbohydr. Res.*, 1980, **85**, 289.
[24] L. J. Altman, R. E. O'Brien, S. K. Gupta, and H.-R. Schulten, *Carbohydr. Res.*, 1980, **87**, 189.
[25] M. Blanc-Muesser, J. Defaye, and D. Horton, *Carbohydr. Res.*, 1980, **87**, 71.

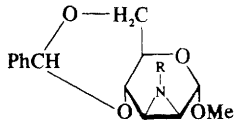
3 Pyranoid Systems

The non-selective spin–lattice relaxation times of the protons of the eight tri-*O*-acetyl-1,6-β-D-anhydrohexopyranoses have been measured. It was observed that, for comparative studies, the solvents, concentrations, and temperatures had to be constant. Interproton relaxation contributions were in accord with the $^1C_4$ conformation distorted by the anhydro-bridges.[26] Simple additivity rules for pyranose rings for predicting *anti* and *gauche* vicinal proton–proton coupling constants have been produced. The rules suggest that, in pyranose systems carrying an axial substituent at C-2, the difference in $J_{1,2}$ of the α- and β-anomers is determined exclusively by the electronegativity of the axial substituent.[27] A discussion on the conformations adopted by methyl 4,6-*O*-(*S*)- and -(*R*)-benzylidene-α-D-idopyranoside has been published. Contrary to earlier work, the ^{1}H 270 MHz n.m.r. shows that in chloroform both are in the $^4C_1$ (D) conformation, although the (*S*)-stereoisomer adopts the $^0S_2$ form if water is present, showing that hydrogen bonding controls the conformation adopted. Using $J_{1,2}$ values of 1.4 Hz for $^4C_1$ and 7.5 Hz for $^1C_4$ conformers, the proportion of $^4C_1$ present in methyl α-D-idopyranoside was shown to be 54%, in its 2-*O*-methyl ether 73%, in its 3-*O*-methyl ether 93%, and in the 2,3-di-*O*-methyl ether 82%. Methyl 3,6-anhydro-β-D-glucopyranoside is exclusively $^1C_4$, methyl β-L-sorbopyranoside is 75% $^5C_2$ and 25% $^2C_5$, methyl α-D-fructopyranoside is 67% $^5C_2$ and 33% $^2C_5$, and 1-*O*-methyl-muco-inositol is a mixture of the two chair forms with three axial and three equatorial hydroxy-groups.[28] The ^{1}H n.m.r. of the two epimines (1) and (2) have been re-examined and corrections made to earlier assignments of Hough *et al.*[29] A study of the conformation of levoglucosenone (3) by n.m.r. with analysis by the ITRCAL computer programme is reported.[30]

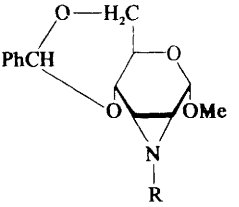
The anomeric configurations of the known carboxylates (4) and (5) have been determined by ^{13}C and ^{1}H n.m.r.[31]

The pyranoid conformations of the amino-deoxyoctoses (6) and (7) have been calculated using modified Karplus equations.[32] Enediol anion formation in inososes has been studied by u.v. and n.m.r. spectroscopy. The results suggested that the interpretation of n.m.r. data by Dufaye (*Appl. Polym. Symp.*, 1976, **28**, 955) was erroneous and that only small concentrations of enediolate ions are formed.[33]

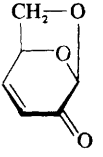
[26] K. Bock, L. D. Hall, and C. Pedersen, *Can. J. Chem.*, 1980, **58**, 1916.
[27] C. Altona and C. A. G. Haasnoot, *Org. Magn. Reson.*, 1980, **13**, 417.
[28] S. J. Angyal and Y. Kondo, *Carbohydr. Res.*, 1980, **81**, 35.
[29] G. Tóth, I. Pinter, J. Kovács, and A. Messmer, *Acta Chem. Acad. Sci. Hung.*, 1980, **105**, 231.
[30] G. Domburgs, I. Berzina, E. Kupce, and I. Z. Kirshbaum, *Khim. Drev.*, 1980, **99** (*Chem. Abstr.*, 1980, **93**, 132 705).
[31] F. M. Unger, D. Stix, and G. Schulz, *Carbohydr. Res.*, 1980, **80**, 191.
[32] K. G. R. Pachler, E. B. Rathbone, G. R. Woolard, and M. Woudenberg, *Carbohydr. Res.*, 1980, **79**, 29.
[33] G. DeWit, C. DeHaan, A. P. G. Kieboom, and H. van Bekkum, *Carbohydr. Res.*, 1980, **86**, 33.



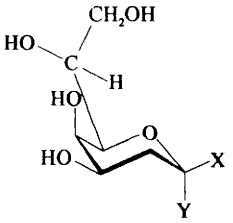
(1) R = Ac or $\overset{+}{P}Ph_3\bar{O}Ts$



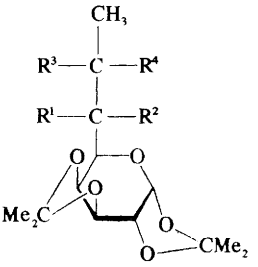
(2) R = Ac or $\overset{+}{P}Ph_3\bar{O}Ts$



(3)



(4) X = OMe, Y = CO_2NH_4
(5) X = CO_2NH_4, Y = OMe



(6) R^1 = R^2 = R^4 = H, R^3 = NHAc
(7) R^1 = OH, R^2 = R^3 = H, R^4 = NHAc

The conformations adopted by the Ca^{2+} complex of *N*-glycolylneuraminic acid are referred to in Chapter 16.

The ^{13}C n.m.r. of various anomeric pairs of alkyl L-arabinopyranosides, where alkyl was methyl, prop-1-yl, prop-2-yl, *trans*-4-t-butylcyclohexyl, t-butyl, and *d*- and *l*-menthyl, have been determined to study the glycosylation shift. Similar values to those of D-glucose derivatives were noted.[34] The ^{13}C n.m.r. of all mono-, di-, and tri-methyl ethers of methyl α-L-rhamnopyranosides have been interpreted.[35] All positional isomers of mono-*O*-myristoyl-α- and -β-D-glucopyranoses have been investigated by ^{13}C n.m.r. in [$^2H_5$]pyridine. Acylation shift parameters were found to be additive and independent of solvents and were used to determine the structures of tuliposide-A and spirarin.[36] Lanthanum, europium, praseodimium, and neodimium ions in ^2H_2O were examined as to their effects on ^{13}C n.m.r. spectra of sodium D-gluco- and -galacto-pyranuronates. This shifts and ^{13}C spin-lattice relaxation times were used to estimate the binding sites for the ions.[37]

4 Furanoid Systems

Non-selective proton spin-lattice relaxation times for several furanoid systems have been measured. Since epimers give significantly different values the method is of value for structural analysis.[38] Methyl tetrofuranosides have been studied

[34] K. Mizutani, R. Kasai, and O. Tanaka, *Carbohydr. Res.*, 1980, **87**, 19.
[35] J. Alföldi, P. Kočiš, and R. Toman, *Chem. Zvesti*, 1980, **34**, 514.
[36] K. Yoshimoto, Y. Itatani, and Y. Tsuda, *Chem. Pharm. Bull.*, 1980, **28**, 2065.
[37] K. Izumi, *Agric. Biol. Chem.*, 1980, **44**, 1623.
[38] K. Bock, L. D. Hall, and C. Pedersen, *Can. J. Chem.*, 1980, **58**, 1923.

by ^{13}C n.m.r. If the substituents at C-2 and C-3 are *cis* then C-1 resonates below 103 p.p.m., whereas if they are *trans* then C-1 appears above 106 p.p.m. It was not possible to determine the anomeric configuration from $J_{C\text{-}1,H}$ values.[39] Several derivatives of 2,3-*O*-isopropylidene-D-ribofuranoses have been studied by ^{1}H and ^{13}C n.m.r.[40]

5 Oligosaccharides

The use of ^{13}C n.m.r. spectroscopy in the quantitative analysis of food oligosaccharides has been reviewed.[41]

A complete series of α- and β-D-xylopyranosyl derivatives of methyl β-D-xylopyranoside and several other xylo-oligosaccharides have been studied by ^{13}C n.m.r. The derived data was used to assign the signals in red algae xylans.[42] Xylo- and cello-oligosaccharides have been similarly studied to assign signals in corresponding polymers.[43] The effect of trityl substitution at *O*-6 and *O*-6′ in β-cellobiosides in [$^{2}H_5$]pyridine on the ^{13}C n.m.r. spectral shifts and conformation has been investigated.[44] The carrabiose from the hydrolysate of the carrageenan-like polysaccharide from *Chondrus canaliculatus* has been examined by ^{1}H n.m.r. spectroscopy.[45]

Unusual upfield shifts in the signals due to C-1 and C-1′ have been observed in the ^{13}C n.m.r. spectra of 1,1′-linked D-glucopyranosyl D-glucopyranosides, and attributed to the conformation adopted by the glycosidic linkage.[46] Peracetylated trehalose and sucrose have been investigated by ^{1}H n.m.r. spectroscopy in the presence of Eu(fod)$_3$ shift reagent. All methine and methylene signals were assigned.[47] Complete assignment of the twelve ^{13}C resonances in sucrose has been achieved by ^{1}H and ^{13}C n.m.r. spectroscopy using selective decoupling.[48] Partially methylated sucrose derivatives studied by ^{1}H n.m.r. spectroscopy allowed only an unequivocal assignment of four of the eight possible methyl ether groups.[49]

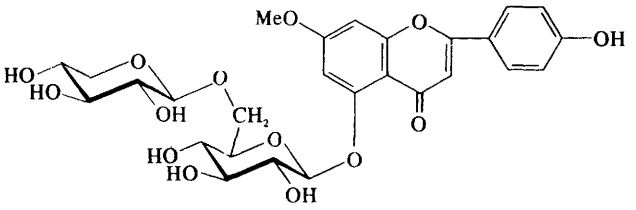
Conformations of β-D-Gal-(1→3)-β-D-GlcNAc and β-D-Gal-(1→4)-β-D-GlcNAc were investigated by ^{1}H and ^{13}C n.m.r. techniques, including NOE and coupling constant determinations.[50]

[39] J. Urban, M. Marek, J. Jarý, and P. Sedmera, *Collect. Czech. Chem. Commun.*, 1980, **45**, 2779.
[40] E. J. Freyne, R. A. Dommisse, J. A. Lepoivre, and F. C. Alderweireldt, *J. Carbohydr., Nucleosides, Nucleotides*, 1980, **7**, 263.
[41] B. Coxon, *Dev. Food Carbohydr.*, 1980, **2**, 351 (*Chem. Abstr.*, 1980, **92**, 196 416).
[42] P. Kovač, J. Hirsch, A. S. Shashkov, A. I. Usov, and S. V. Yarotsky, *Carbohydr. Res.*, 1980, **85**, 177.
[43] J. C. Gast, R. H. Atalla, and R. D. McKelvey, *Carbohydr. Res.*, 1980, **84**, 137.
[44] T. Utamura and K. Koizumi, *Yakugaku Zasshi*, 1980, **100**, 307 (*Chem. Abstr.*, 1980, **93**, 132 742).
[45] B. Matsuhiro and A. B. Zanlungo, *Carbohydr. Res.*, 1980, **81**, 335.
[46] S. Koto, S. Inada, and S. Zen, *Chem. Lett.*, 1980, 403.
[47] K. Izumi, *Agric. Biol. Chem.*, 1979, **43**, 2615.
[48] A. J. Jones, P. Hanisch, and A. K. McPhail, *Aust. J. Chem.*, 1979, **32**, 2763.
[49] M. Manley-Harris and G. N. Richards, *Carbohydr. Res.*, 1980, **82**, 356.
[50] R. U. Lemieux, K. Bock, L. T. J. Delbaere, S. Koto, and V. S. Rao, *Can. J. Chem.*, 1980, **58**, 631.

The ^{13}C n.m.r. spectra of five aldobiuronic acid derivatives,[51] and 5-*O*-β-D-primeverosyl genkwanine (8) and its acetate have been determined.[52]

Using two-dimensional n.m.r. techniques, the ^{13}C–^{1}H coupling constants in raffinose and the repeating unit of the cell-wall polysaccharide of *Klebsiella*-type K32 bacteria have been determined.[53]

The sugar chain in the glycopeptide active in inducing glomerulonephritis has been shown by ^{13}C n.m.r. spectroscopy to be α-D-Glc-(1→6)-β-D-Glc-(1→6)-NHCO-peptide.[54]



(8)

6 ^{13}C N.m.r. Spectroscopy

By means of specifically deuteriated derivatives, the ^{13}C n.m.r. of all pentitols and hexitols in water and their acetates in chloroform have been assigned. Qualitative correlations between chemical shift, configuration, and preponderant conformation were made, leading to practical empirical rules.[55]

A useful method for determination of the ring sizes of *O*-isopropylidene acetals based on the differences in shifts of the two methyl groups in the ^{13}C n.m.r. spectrum has been developed.[56]

^{13}C N.m.r. spectroscopy has been used to assign the configuration at quaternary centres in branched-chain sugars.[57]

Labelled carbohydrates have been used to study deuterium-induced ^{13}C shifts. New assignments were made for ^{13}C shifts in isomaltose and glucosamine.[58] A discussion of the ^{13}C n.m.r. spectra of several partially and fully acetylated L-rhamnose derivatives has appeared, including much tabulated data.[59]

The anomeric compositions of ketohexose phosphates and their conformations in solution have been investigated by ^{13}C n.m.r. spectra. The α:β ratio for D-fructose 6-phosphate was found to be 19:81; for D-fructose 1-phosphate,

[51] J. Alföldi, C. Peciar, P. Kočiš, and J. Hirsch, *Chem. Zvesti*, 1980, **34**, 679.
[52] A. Garcia-Granados and J. M. Saenz De Buruaga, *Org. Magn. Reson.*, 1980, **13**, 462.
[53] L. D. Hall and G. A. Morris, *Carbohydr. Res.*, 1980, **82**, 175.
[54] S. Shibata and H. Nakanishi, *Carbohydr. Res.*, 1980, **81**, 345.
[55] S. J. Angyal and R. LeFur, *Carbohydr. Res.*, 1980, **84**, 201.
[56] J. G. Buchanan, M. E. Chacón-Fuertes, A. R. Edgar, S. J. Moorhouse, D. I. Rawson, and R. H. Wightman, *Tetrahedron Lett.*, 1980, **21**, 1793.
[57] K.-I. Sato, M. Matsuzawa, K. Ajisaka, and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 189.
[58] P. E. Pfeffer, F. W. Parrish, and J. Unruh, *Carbohydr. Res.*, 1980, **84**, 13.
[59] V. Pozsgay and A. Neszmélyi, *Carbohydr. Res.*, 1980, **80**, 196.

24:76; for D-fructose 1,6-diphosphate, 23:77; for D-psicose 6-phosphate, 76:24; for D-tagatose 6-phosphate, 17:83; and for L-sorbose 6-phosphate, 82:18. Concentrations of the $^4T_3$ of the α-anomers and $^3T_4$ for the β-anomers were also computed and shown to vary directly with their phosphofructokinase activity.[60]

The ^{13}C n.m.r. spectra of aldoses complexed to molybdate show that D-ribose, D-talose, and D-allose behave as tridentate donors *via* hydroxy-groups at C-2, C-3, and C-4, whereas D-lyxose and D-mannose are donors *via* C-1, C-2, and C-3 hydroxy-groups.[61]

7 Other Nuclei

Deuterium-induced downfield shifts in ^{31}P n.m.r. spectra of labelled D-glucose 6-phosphate have been determined.[58]

That the aldehydo-group of streptomycin does not cyclize with either the methylamino- or the guanidino-groups to form a four-ring structure has been shown by ^{15}N n.m.r. spectroscopy. Instead it is suggested that the group is probably hydrated and stabilized by the C-3 hydroxy-group of L-streptose.[62]

[60] T. A. W. Koerner, R. J. Voll, L. W. Cary, and E. S. Younathan, *Biochemistry*, 1980, **19**, 2795.

[61] J. Alföldi, V. Bílik, and L. Petruš, *Collect. Czech. Chem. Commun.*, 1980, **45**, 123.

[62] W. E. Hull and H. R. Kricheldorf, *Liebigs Ann. Chem.*, 1980, 158.

21

Other Physical Methods

1 I.r. Spectroscopy

Various aspects of the structures of unsubstituted free sugars have been examined by the infrared method: details of the hydroxy-groups and their configurations[1-3] and hydrogen bonding[4] have been reported and the orientation of the hydroxymethyl group has been considered for α-aldohexoses.[5] The Raman technique has been used to investigate α- and β-D-glucopyranose (normal co-ordinate analysis used)[6] and also D-glucose,[7] D-fructose,[8] and sucrose[7] in aqueous solution. A special study was carried out on the dependence of the frequencies of bands for these sugars on concentration.[9] A separate study of D-glucose, D-maltose, and D-cellobiose in water and deuterium oxide, and of some specifically deuteriated glucose derivatives led to several absorption band assignments.[10]

2 U.v. Spectroscopy

An investigation has been reported of the enediol anions and products of β-elimination of cyclic α-hydroxyketones; the observations were correlated with n.m.r. results.[11]

3 Mass Spectrometry

As before, too many reports of the use of the technique have been described for individual mention; the following papers were concerned primarily with the

[1] V. M. Andrianov, *Zh. Prikl. Spektrosk.*, 1979, **31**, 737 (*Chem. Abstr.*, 1980, **92**, 111 236).
[2] M. A. Salimov, *Nauchn. Tr.-Mosk. Lesotekh. Inst.*, 1978, **108**, 101 (*Chem. Abstr.*, 1980, **93**, 168 509).
[3] R. G. Zhbankov, V. V. Sivchik, and T. E. Kolosova, *Zh. Prikl. Spektrosk.*, 1980, **33**, 827 (*Chem. Abstr.*, 1980, **93**, 168 506).
[4] V. N. Gritsan and R. G. Zhbankov, *Dokl. Akad. Nauk SSSR*, 1980, **24**, 691 (*Chem. Abstr.*, 1980, **93**, 168 508).
[5] V. V. Sivchik and R. G. Zhbankov, *Zh. Prikl. Spektrosk.*, 1980, **32**, 1056 (*Chem. Abstr.*, 1980, **93**, 220 986).
[6] P. Legrand, J. P. Huvenne, G. Vergoten, and G. Fleury, *Proc. Int. Conf. Raman Spectrosc., 6th*, 1978, **2**, 444 (*Chem. Abstr.*, 1980, **93**, 8400).
[7] M. Mathlouthi and D. V. Luu, *Carbohydr. Res.*, 1980, **81**, 203.
[8] M. Mathlouthi and D. V. Luu, *Carbohydr. Res.*, 1980, **78**, 225.
[9] M. Mathlouthi, C. Luu, A. M. Meffroy-Biget, and D. V. Luu, *Carbohydr. Res.*, 1980, **81**, 213.
[10] J. L. Koenig, *NATO Adv. Study Inst. Ser., Ser. C*, 1978 (Publ. 1979), **43** (Infrared Raman Spectrosc. Biol. Mol.), 125 (*Chem. Abstr.*, 1980, **92**, 76 807).
[11] G. De Wit, C. De Haan, A. P. G. Kieboom, and H. van Bekkum, *Carbohydr. Res.*, 1980, **86**, 33.

method and are categorized according to the nature of the substituents on the carbohydrate oxygen atoms.

The field-desorption spectra of several aldoses and ketoses ionized by attachment of potassium ions led to the identification of the characteristic fragments formed by loss of small molecules,[12] and related secondary ion analysis was carried out on various purine and pyrimidine nucleosides.[13] Also in the nucleoside field a set of mathematical procedures has been applied to the spectra derived from 125 compounds and has led to pattern recognition and interpretation.[14] Underivatized nucleosides have been studied by a method based on pulsed laser and fission fragment-induced desorption,[15] and also by a chemical ionization technique dependent on a direct exposure probe.[16]

Acetylated derivatives have been used in the characterization of dialdose dianhydrides,[17] partially methylated heptitols,[18] and aldobiuronic acid methyl ester methyl glycosides.[19] The origin of the fragments with even mass numbers derived from alditol acetates is based on elimination of keten, acetic acid, and acetic anhydride.[20]

Chemical ionization methods have been used with methyl ethers of methyl glycosides and have indicated that anomers with equatorial methoxy-groups decompose faster than those with axial groups.[21] The same method applied to permethylated disaccharides allows better distinction between isomers than does the electron-impact method.[22] A permethylated amino-sugar trisaccharide derivative has been studied[23] as have permethylated dialdose anhydrides.[24]

Trimethylsilyl ethers have been used (E.I. and C.I. spectra) to characterize carbohydrates present in serum,[25] and other silyl ethers (*e.g.*, t-butyldimethylsilyl ethers) were used to investigate various nucleosides. Fragmentations were dependent on steric crowding.[26]

A chemical ionization study has been carried out on the dimethyl acetals and diethyl dithioacetals of the aldo-pentoses and -hexoses with ammonia and

[12] J. Deutsch, *Org. Mass Spectrom.*, 1980, **15**, 240.
[13] A. Eike, W. Sichtermann, and A. Benninghoven, *Org. Mass Spectrom.*, 1980, **15**, 289.
[14] R. G. A. R. Maclagan and M. J. Mitchell, *Aust. J. Chem.*, 1980, **33**, 1401.
[15] B. Schueler and F. R. Krueger, *Org. Mass Spectrom.*, 1980, **15**, 295.
[16] R. J. Cotter and C. Fenselau, *Biomed. Mass Spectrom.*, 1979, **6**, 287 (*Chem. Abstr.*, 1980, **92**, 181 488).
[17] T. Fujiwara and K. Arai, *Carbohydr. Res.*, 1980, **86**, 17.
[18] J. Radziejewska-Lebrecht, V. Feige, M. Jensen, K. Kotelko, H. Friebolin, and H. Mayer, *Eur. J. Biochem.*, 1980, **107**, 31.
[19] T. Fujiwara and K. Arai, *Carbohydr. Res.*, 1980, **87**, 11.
[20] P.-E. Jansson and B. Lindberg, *Carbohydr. Res.*, 1980, **86**, 287.
[21] V. I. Kadentsev, A. G. Kaimarazov, and O. S. Chizhov, *Ivz. Akad. Nauk SSSR Ser. Khim.*, 1980, 330 (*Chem. Abstr.*, 1980, **93**, 26 723).
[22] E. G. De Jong, W. Heerma, and C. A. X. G. F. Sicherer, *Biomed. Mass Spectrom.*, 1979, **6**, 242 (*Chem. Abstr.*, 1980, **92**, 147 073).
[23] E. F. Hounsell, M. Fukvoa, M. E. Powell, T. Feizi, and S. Hakomori, *Biochem. Biophys. Res. Commun.*, 1980, **92**, 1143.
[24] T. Fujiwara and K. Arai, *Carbohydr. Res.*, 1980, **87**, 201.
[25] A. C. Schoots and P. A. Leclercq, *Biomed. Mass Spectrom.*, 1979, **6**, 502 (*Chem. Abstr.*, 1980, **93**, 3257).
[26] M. A. Quilliam, K. K. Ogilvie, K. L. Sadana, and J. B. Westmore, *Org. Mass Spectrom.*, 1980, **15**, 207.

isobutane as reagent gases. Differences in configuration led to spectral differences that can be used to gain stereochemical information.[27] Isopropylidene derivatives of pentuloses and hexuloses have been used to detect and determine these compounds in mixtures,[28] and the fragmentations of exocyclic alkenes derived from 1,2 : 5,6-di-*O*-isopropylidene-α-D-*ribo*-hex-3-ulose have been considered in detail.[29] Compounds related to acetals, the diastereoisomers of thymidine 3′,5′-cyclic-phosphoroanilidothioate, have also been examined by mass spectrometry.[30]

4 *X*-Ray and Neutron Diffraction Crystallography

Jeffrey and Sundaralingam have provided a further bibliography of crystal structures of carbohydrates, nucleosides, and nucleotides,[31] and a paper of general interest relates to a survey of 161 published structures of pyranose derivatives. This led to the establishment of average orthogonal co-ordinates.[32]

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

Free Sugars and Simple Derivatives Thereof. – Partially deuteriated β-L-arabinopyranose and α-L-xylopyranose (n.d. refinement),[33] 1,2-*O*-cyclohexylidene- and 1,2-*O*-isopropylidene-α-D-glucofuranose 3,5,6-phosphites,[34] 5-*O*-acetyl-1,2 : 3,4-di-*O*-isopropylidene-α-D-galactoseptanose,[35] 3,4,6-tri-*O*-acetyl-1,2-*O*-(*R*)-ethylidene-α-D-allopyranose and 3,4,6-tri-*O*-acetyl-1,2-*O*-(*R*)-(1-t-butoxyethylidene)-α-D-galactopyranose,[36] and 1,4,6-tri-*O*-acetyl-3-*O*-[1′-(*R*)-carboxy]ethyl-β-D-glucose 2,2′-lactone.[37]

Glycosides and Simple Derivatives Thereof. – Methyl 2,3,4-tri-*O*-benzoyl-β-D-xylopyranoside,[38] methyl 2,3,4,5-tetra-*O*-acetyl-α-D-galactoseptanoside,[39] 2-pyridyl 1-thio-β-D-glucopyranoside,[40] the three methyl xanthates of methyl 4,6-

[27] M. Blanc-Muesser, J. Defaye, R. L. Foltz, and D. Horton, *Org. Mass Spectrom.*, 1980, **15**, 317.
[28] S. Morgenlie, *Carbohydr. Res.*, 1980, **80**, 215.
[29] A. Glangetas, F. O. Gülacar, J. M. J. Tronchet, and A. Buchs, *Helv. Chim. Acta*, 1980, **63**, 1740.
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[32] B. Sheldrick and D. Akrigg, *Acta Crystallogr., Sect. B.*, 1980, **36**, 1615.
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[34] L. A. Aslanov, S. S. Sotman, V. B. Rybakov, V. I. Adrianov, Z. Sh. Safina, M. P. Koroteev, and E. E. Nigant'ev, *Zh. Strukt. Khim.*, 1979, **20**, 1125 (*Chem. Abstr.*, 1980, **93**, 72 121).
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[37] J. H. Jordaan, J. J. Nieuwenhuis, and J. A. Pretorius, *S. Afr. J. Chem.*, 1979, **32**, 173 (*Chem. Abstr.*, 1980, **93**, 8396).
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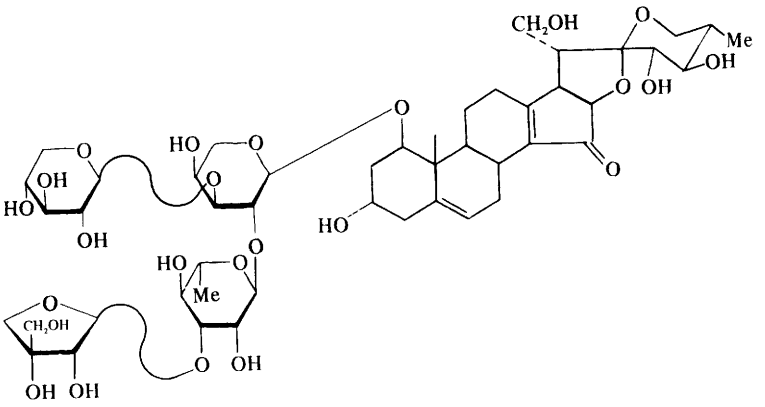
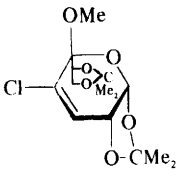
[39] W. Choong, J. F. McConnell, N. C. Stephenson, and J. D. Stevens, *Aust. J. Chem.*, 1980, **33**, 979.
[40] S. Nordenson and G. A. Jeffrey, *Acta Crystallogr., Sect. B.*, 1980, **36**, 1214.

O-benzylidene-2-deoxy-α-D-*arabino*- and -*ribo*-hexopyranoside and methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*arabino*-hexopyranoside,[41] methyl 2,4-di-*O*-acetyl-3-deoxy-3-*C*-methyl-3-nitro-β-DL-arabinopyranoside,[42] and the apiose-containing natural glycoside (1).[43]



(1)

Halogen- and Nitrogen-containing Compounds (Other than Nucleosides). — 2,3,4-Tri-*O*-benzoyl-2-chloro-α-D-xylopyranosyl chloride,[44] the 4-chloroheptose derivative (2),[45] 2-amino-2-deoxy-α-D-galactopyranosyl phosphate,[46] 1,3,4,6-tetra-*O*-acetyl-2-(*N*-acetylacetamido)-2-deoxy-β-D-galactopyranose,[47] 2-acetamido-1-*N*-(L-aspart-4-oyl)-2-deoxy-β-D-glucopyranosylamine,[48] and *N*-β-D-glucopyranosyl procaine.[49]



(2)

[41] P. Luger, B. Elvers, and H. Paulsen, *Chem. Ber.*, 1979, **112**, 3855.
[42] M. M. Abuaan, H. I. Ahmad, J. S. Brimacombe, and T. J. R. Weakley, *Carbohydr. Res.*, 1980, **84**, 336.
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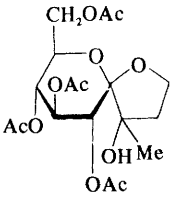
[47] Ž. Ružić-Toroš, B. Kojić-Prodić, and V. Rogić, *Acta Crystallogr. Sect. B*, 1980, **36**, 384.
[48] J. Ohanessian, D. Avenel, A. Neuman, and H. Gillier-Pandraud, *Carbohydr. Res.*, 1980, **80**, 1.
[49] O. Dideberg, J. Lamotte, and L. Dupont, *Acta Crystallogr., Sect. B*, 1980, **36**, 1500.

Unsaturated Compounds. – Methyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside and ethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside,[50] and 1,4,6-tri-*O*-acetyl-2-*N*-acetylacetamido-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranose.[51]

Anhydro-compounds. – 1,6-Anhydro-β-D-galactopyranose[52] and the *spiro*-non-4-ulose derivative (3).[53]

Acid Derivatives. – D-Arabinono-γ-lactone,[54] 2,3-di-*O*-acetyl-2-*C*-methylerythrono-1,4-lactone,[55] a 1:1 complex of L-serine and L-ascorbic acid,[56a] and methyl 4-*C*-acetyl-6-deoxy-2,3-*O*-methylene-D-galactonate.[56b]



(3)

Acyclic and Alicyclic Compounds. – 2,3:4,5-Di-*O*-isopropylidene-D-gulose diethyl dithioacetal[57] and 5-*O*-methyl-*myo*-inositol (sequoyitol).[58]

Disaccharides and Higher Saccharides. – Gentiobiose,[59] methyl 3-*O*-α-D-glucopyranosyl-α-D-glucopyranoside,[60] 6,6′-dibromo-6,6′-dideoxy-α,α-trehalose hexaacetate,[61] 1,2,4,6-tetra-*O*-acetyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-galactopyranose,[62] (*Z*)-*O*-β-D-xylopyranosyl-(1→6)-β-D-glucopyranosyloxy-

[50] J. W. Krajewski, Z. Urbańczyk-Lipkowska, P. Gluziński, J. Bleidelis. and A. Kemme, *Acta Crystallogr., Sect. B*, 1979, **35**, 2625.
[51] Ž. Ružić-Toroš, V. Rogić, and B. Kojić-Prodić, *Acta Crystallogr., Sect. B*, 1980, **36**, 607.
[52] C. Ceccarelli, J. R. Ruble, and G. A. Jeffrey, *Acta Crystallogr., Sect. B.*, 1980, **36**, 861.
[53] G. Rémy, L. Cottier, G. Descotes, R. Faure, H. Loiseleur, and G. Thomas-David, *Acta Crystallogr., Sect. B*, 1980, **36**, 873.
[54] T. Svinning and H. Sorum, *Acta Crystallogr., Sect. B*, 1979, **35**, 2967.
[55] A. Conde, E. Moreno, and R. Márquez, *Acta Crystallogr., Sect. B*, 1980, **36**, 1713.
[56] (*a*) V. Sudhakar, T. N. Bhat, and M. Vijayan, *Acta Crystallogr., Sect. B*, 1980, **36**, 125; (*b*) E. Kupfer, K. Neupert-Laves, M. Dobler, and W. Keller-Schierlein, *Helv. Chim. Acta*, 1980, **63**, 1141.
[57] J. F. McConnell, A. Schwartz, and J. D. Stevens, *Cryst. Struct. Commun.*, 1979, **8**, 855 (*Chem. Abstr.*, 1980, **92**, 86213).
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[59] D. C. Rohrer, A. Sarko, T. L. Bluhm, and Y. N. Lee, *Acta Crystallogr., Sect. B*, 1980, **36**, 650.
[60] A. Neuman, D. Avenel, F. Arène, H. Gillier-Pandraud, J.-R. Pougny, and P. Sinay, *Carbohydr. Res.*, 1980, **80**, 15.
[61] G. Williams, P. Lavallée, S. Hanessian, and F. Brisse, *Acta Crystallogr., Sect. B*, 1979, **35**, 2574.
[62] C. Foces-Foces, F. H. Cano, and S. García-Blanco, *Acta Crystallogr., Sect. B*, 1980, **36**, 377.

NNO-azoxymethane (the toxic glycoside macrozamin),[63] and α-D-mannopyranosyl-(1→3)-β-D-mannopyranosyl-(1→4)-2-acetamido-2-deoxy-D-glucose.[64]

Nucleosides, Nucleotides, Derivatives, and Related Compounds. – 5-Substituted uracils were examined for conformational dependence on the substituents,[65] uridine 5′-phosphate disodium salt,[66] 2′-deoxyuridine 5′-phosphate disodium salt,[67] 6-methyl-2′-deoxyuridine,[68] 5-*C*-acetyl-2′-deoxyuridine,[69] dihydrouridine 3′-phosphate potassium salt,[70] 5-hydroxymethyl-2′-deoxyuridine,[71] 4-thio-*pseudo*-uridine,[72] 2,5′-anhydro-2′,3′-*O*-isopropylidene-2-thiouracil,[73] 2,2′-anhydro-1-β-D-arabinofuranosyl-2-thiouracil.[74]

5-Iodocytidine,[75] *pseudo*-cytidine,[76] 8-thionoadenosine,[77] 3′-amino-3′-deoxyadenosine,[78] 3′-cyclobutylamino-3′-deoxyadenosine,[78] 3′-deoxyadenosine (cordycepin),[79] and 9-β-D-arabinofuranosyl-8-morpholinoadenine.[80]

Guanosine 5′-phosphate,[81] [Pd(diethylenetriamine) (guanosine)] $(ClO_4)_2$,[82] 6-methoxy-9-β-D-ribofuranosylpurine,[83] 7,2′-anhydro-β-D-arabinosylorotidine,[84]

[63] J. R. Cannon, C. L. Raston, R. F. Toia, and A. H. White, *Aust. J. Chem.*, 1980, **33**, 2229.
[64] V. Warin, F. Baert, R. Fouret, G. Strecker, G. Spik, B. Fournet, and J. Montreuil, *Glycoconjugate Res., Proc. Int. Symp., 4th*, 1977 (Publ. 1979), **1**, 317, ed. J. D. Gregory and R. W. Jeanloz, Academic Press, New York (*Chem. Abstr.*, 1980, **92**, 76 806).
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[66] T. P. Seshadri, M. A. Viswamitra, and G. Kartha, *Acta Crystallogr., Sect. B*, 1980, **36**, 925.
[67] M. A. Viswamitra, T. P. Seshadri, and M. L. Post, *Acta Crystallogr., Sect. B*, 1980, **36**, 2019.
[68] G. I. Birnbaum, F. E. Hruska, and W. P. Niemczura, *J. Am. Chem. Soc.*, 1980, **102**, 5586.
[69] P. J. Barr, P. Chananont, T. A. Hamor, A. S. Jones, M. K. O'Leary, and R. T. Walker, *Tetrahedron*, 1980, **36**, 1269.
[70] J. Amerson and M. Sundaralingam, *Acta Crystallogr., Sect. B*, 1980, **36**, 537..
[71] G. I. Birnbaum, R. Deslauriers, T.-S. Lin, G. T. Shiau, and W. H. Prusoff, *J. Am. Chem. Soc.*, 1980, **102**, 4236.
[72] C. L. Barnes, S. W. Hawkinson, and P. W. Wigler, *Acta Crystallogr., Sect. B*, 1980, **36**, 2299.
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[74] Y. Yamagata, J. Yoshimura, S. Fujii, T. Fujiwara, R. Tomita, and T. Ueda, *Acta Crystallogr., Sect. B*, 1980, **36**, 343.
[75] M. M. Radwan and H. R. Wilson, *Acta Crystallogr., Sect. B*, 1979, **35**, 3072.
[76] G. I. Birnbaum, K. A. Watanabe, and J. J. Fox, *Can. J. Chem.*, 1980, **58**, 1633.
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[78] W. S. Sheldrick and M. Morr, *Acta Crystallogr., Sect. B*, 1980, **36**, 2328.
[79] M. F. Radwan and H. R. Wilson, *Acta Crystallogr., Sect. B*, 1980, **36**, 2185.
[80] V. Swaminathan, M. Sundaralingham, J. B. Chattopadhyaya, and C. B. Reese, *Acta Crystallogr., Sec. B*, 1980, **36**, 828.
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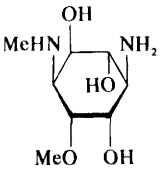
[83] W. J. Cook, G. L. Gartland, and C. E. Bugg, *Acta Crystallogr., Sect. B*, 1980, **36**, 2467.
[84] J. L. Smith, A. Chwang, and M. Sundaralingam, *Acta Crystallogr., Sect. B*, 1980, **36**, 833.

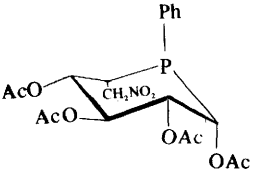
and 4-amino 1-[4-amino-2-oxo-1(2*H*)-pyrimidinyl]-1,4-dideoxy-β-D-glucopyranuronic acid (the nucleoside fragment of gougerotin).[85]

Antibiotics. – Fortamine (4)[86] and its dihydrochloride.[87]

Other Compounds. – The phosphorus-in-the-ring compound (5) has been shown to have the L-*ido*- rather than the D-*gluco*-configuration.[88]



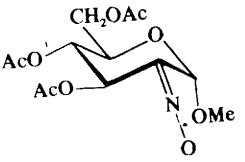
(4)



(5)

5 E.s.r. Spectroscopy

A study has been carried out on the radicals derived by lead tetra-acetate treatment of ulose oximes, *e.g.*, (6). The signals were intense and persistent and can be used to study stereochemical effects relating to the carbohydrate rings and also the oxime groups themselves.[89]



(6)

6 Polarimetry and Circular Dichroism Studies

Circular dichroism studies of the methyl ester methyl glycosides of hexuronic acids showed that D-galactopyranosyl compounds gave single positive bands, whereas D-glucuronosyl isomers gave two bands of opposite signs.[90] Acetylated

[85] P. Swaminathan, J. McAlister, and M. Sundaralingam, *Acta Crystallogr., Sect. B*, 1980, **36**, 878.

[86] N. Hirayama, K. Shirahata, Y. Ohashi, and Y. Sasada, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1514.

[87] N. Hirayama, K. Shirahata, Y. Ohashi, and Y. Sasada, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 3104.

[88] P. Luger, M. Yamashita, and S. Inokawa, *Carbohydr. Res.*, 1980, **84**, 25.

[89] A. Mackor, W. A. R. van Heeswijk, P. de Haan, and J. F. G. Vliegenthart, *Carbohydr. Res.*, 1980, **87**, 175.

[90] S. Bystricky and T. Sticzay, *Symp. Pap.-IUPAC Int. Symp. Chem. Nat. Prod., 11th*, 1978, **2**, 290 (*Chem. Abstr.*, 1980, **92**, 42 301).

methyl glycosides show $n \rightarrow \pi^*$ bands at 210–215 nm[91] and, likewise, D-arabino-hexulose phenylosazone and the 2,4-dinitrophenylosazone give single bands.[92]

A 'dodecant rule' has been developed for xanthate esters following a study of 30 carbohydrate esters. Cotton effects are given at 355 nm, and the preferred conformations have the ester ring hydrogen atoms and the ester thiono-groups *syn*-periplanar.[93] Chiral alcohols added to the achiral nematic liquid crystal *N*-*p*-methoxybenzylidene-*p*-n-butylaniline give rise to liquid-crystal-induced dichroism (LCICD) and the signs of the effects correlate with the configurations of the alcohols.[94]

The 'ring oxygen helicity rule' has been extended to phenyl- and phenylthio-glycosides.[95]

[91] A. A. Nabiullin, E. V. Evtushenko, and S. E. Odinokov, *Khim. Prir. Soedin.*, 1980, 54 (*Chem. Abstr.*, 1980, **93**, 26 725).

[92] J. Koput, A. Maciejewski, and J. Wojtczak, *Monatsh. Chem.*, 1980, **111**, 493 (*Chem. Abstr.*, 1980, **93**, 114 856).

[93] H. Paulsen, B. Elvers, H. Redlich, E. Schüttpelz, and G. Snatzke, *Chem. Ber.*, 1979, **112**, 3842.

[94] W. H. Pirkle and P. L. Rinaldi, *J. Org. Chem.*, 1980, **45**, 1379.

[95] K. Kohata, T. Konno, and H. Meguro, *Tetrahedron Lett.*, 1980, **21**, 3771.

22

Separatory and Analytical Methods

1 Chromatographic Methods

Gas–Liquid Chromatography. – The use of a chiral stationary phase (*N*-propionyl-L-valine-t-butylamide polysiloxane) for the separation of alditol acetates by capillary g.l.c. has been reported to give good separations for those derived from the common neutral sugars, including those from 3-*O*- and 4-*O*-methyl-glucose.[1] Low concentrations of carbohydrates present in natural lake water have been analysed by g.l.c., after sequential freeze drying, hydrolysis, reduction with borohydride, and acetylation.[2] A critical study of the alditol acetate method for the quantitative analysis of hexoses and hexosamines present in glycolipids has been made and conditions described for optimum results.[3] The retention times for acetylated and trifluoroacetylated *O*-ethylsorbitols have been reported, and have been correlated with structure on the assumption that additive contributions arise from each structural unit present.[4]

The g.l.c. separation of various methylated derivatives of mannose, galactose, and glucosamine as their trimethylsilylated derivatives has been described using 0.3–0.4% OV 225 on Chromosorb that had been surface modified by a high molecular weight polyethylene glycol.[5] Conditions have been found for the separation of the TMS ethers of arabinose, xylose, mannose, α- and β-glucose, fructose, sorbose, xylitol, mannitol, and sorbitol on Chromosorb W-NAW with 15% Carbowax 20M,[6] and a g.l.c. method for the quantitative determination of trehalose as its TMS ether has been reported.[7]

The quantitative determination of fructose as its *O*-methyloxime (TMS ether) involves g.l.c. on glass capillary columns. The method provides a good separation of glucose, galactose, and fructose, which each gave rise to two peaks arising from the *syn*- and *anti*-forms of the oximes,[8] and g.l.c.–m.s. of peracetylated oximes of ketoses has been proposed as a means of identification of ketoses.[9]

Several di-*O*-isopropylidene derivatives of fructose, sorbose, and sorbitol have been separated by g.l.c. using various polar stationary phases,[10] and g.l.c.–m.s. analysis of permethylated glucosaminylglucosaminitols permits unequivocal

[1] G. Holzer, J. Oro, S. J. Smith, and V. M. Doctor, *J. Chromatogr.*, 1980, **194**, 410.
[2] M. Ochiai, *J. Chromatogr.*, 1980, **194**, 224.
[3] L. A. Torello, A. J. Yates, and D. K. Thompson, *J. Chromatogr.*, 1980, **202**, 195.
[4] K. Kajiyama and K. Kajita, *Sen'i Gakkaishi*, 1979, **35**, T419 (*Chem. Abstr.*, 1980, **92**, 111 245).
[5] A. A. Akhrem, G. V. Avvakumov, I. V. Sidorova, and O. A. Strel'chenok, *Vestsi Akad. Navuk, BSSR, Ser. Khim. Navuk*, 1979, **111** (*Chem. Abstr.*, 1980, **92**, 6836).
[6] R. Novina, *Kem. Ind.*, 1979, **28**, 589 (*Chem. Abstr.*, 1980, **92**, 226 151).
[7] K. A. Killick, *Carbohydr. Res.*, 1980, **82**, 1.
[8] H. Zegota, *J. Chromatogr.*, 1980, **192**, 446.
[9] F. R. Seymour, E. C. M. Chen, and J. E. Stouffer, *Carbohydr. Res.*, 1980, **83**, 201.
[10] R. Novina, *Kem. Ind.*, 1980, **29**, 107 (*Chem. Abstr.*, 1980, **93**, 186 691).

establishment of not only the position of the linkage, but also differentiates anomers.[11]

Liquid Column Chromatography. – A report[12] of the application of silica gel modified by amino-derivatives for the h.p.l.c. of carbohydrates, concludes that it provides a rapid method of separation particularly suitable for routine analysis. No pretreatment of the sample is required and the rate of elution is dependent upon the water content of the solvent used (aqueous acetonitrile). Where possible u.v. detection was preferred over that based on differential refractometry since it afforded a lower detection limit. Similarly, silica gel modified with polyamines, particularly 1,4-diaminobutane, permits the separation of glucose oligomers (d.p. 2–20) by h.p.l.c. in less than 40 min.[13] The use of amine-modified silica gel in h.p.l.c. enabled the separation of anomers of sugars, provided the separation was conducted at 0 °C. Mono- and di-saccharides separated well at ambient temperatures.[14] However, anomers of sugars can also be separated by h.p.l.c. within 20–30 min by the use of a macroreticular anion-exchange resin in the sulphate form using aqueous ethanol as solvent.[15] Modification of silica gel by boronic acids provides a stationary phase for the h.p.l.c. of nucleosides and nucleotides, but in this case the resolution is limited by the slow attainment of equilibrium between ligand and solute.[16]

An alternative means of detecting non-reducing oligosaccharides in the effluent of h.p.l.c. columns has been proposed. The effluent is passed through a small reaction column packed with strongly acidic cation-exchange resin maintained at 100 °C, and the reducing sugars formed then detected by reaction with *p*-hydroxybenzoyl hydrazide. Because of the stability of trehalose towards acid, the method is rather inefficient for this disaccharide.[17]

Reverse-phase h.p.l.c. on Wates μ-Bondapak C-18 column has been used successfully for the fairly rapid separation of mono-, di-, and tri-saccharides using water as the mobile phase[18] and, for the separation of partially methylated sugars, 1% ammonium acetate was used as mobile phase, with ethanol being added to elute the more highly methylated sugars.[19]

The separation and quantitative determination of glucosamine and galactosamine at the nanogramme level has been reported by prior reaction with a suitable sulphonyl chloride, followed by h.p.l.c. The use of toluene-*p*-sulphonyl chloride was more rapid (10 min) but less sensitive (0.4–50 μg) than that using 5-dimethylaminonaphthalene 1-sulphonyl chloride (0.02–2 μg in 25 min).[20]

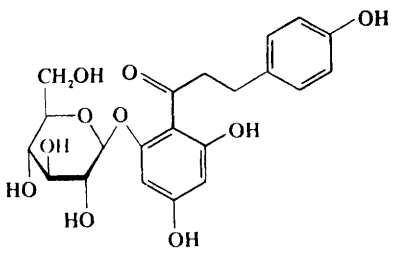
[11] M. Jensen, D. Borowiak, H. Paulsen, and E. T. Rietschel, *Biomed. Mass Spectrom.*, 1979, **6**, 559.
[12] H. Binder, *J. Chromatogr.*, 1980, **189**, 414.
[13] C. A. White, P. H. Corran, and J. F. Kennedy, *Carbohydr. Res.*, 1980, **87**, 165.
[14] V. Kahle and K. Tesařík, *J. Chromatogr.*, 1980, **191**, 121.
[15] R. Oshima, N. Takai, and J. Kumanotani, *J. Chromatogr.*, 1980, **192**, 452.
[16] M. Glad, S. Ohlson, L. Hansson, M. O. Mansson, and K. Mosbach, *J. Chromatogr.*, 1980, **200**, 254.
[17] P. Vrátný, J. Ouhrabková, and J. Čopíková, *J. Chromatogr.*, 1980, **191**, 313.
[18] A. Heyraud and M. Rinaudo, *J. Liq. Chromatogr.*, 1980, **3**, 721.
[19] N. W. H. Cheetham and P. Sirimanne, *J. Chromatogr.*, 1980, **196**, 171.
[20] A. Hjerpe, C. A. Antonopoulos, B. Classon, and B. Engfeldt, *J. Chromatogr.*, 1980, **202**, 453.

The h.p.l.c. analysis of unsaturated disaccharides obtained by enzymic hydrolysis of heparan sulphate and heparin was found to be more rapid and much more sensitive than the previously described method which employed paper chromatography.[21]

Conditions for the separation of methyl ethers of methyl α-L-rhamnopyranoside on silica gel columns have been reported[22] and the separation of mixtures of alditols on cation-exchange resin in the La^{3+} form has been described.[23]

The separation of sugars by gel filtration on Bio-gel P-2 is not only related to molecular size, so that care must be exercised in the interpretation of results. For example, the smaller fucose is eluted more rapidly than mannose, and fucosylmannoses were eluted before mannobioses, but mannose and xylose had the same retention time.[24] The β-glucoside Phlorizin (1) obtained from the roots of apple trees can be polymerized by cross-linking with formaldehyde to give a polymer in which the β-glucopyranoside units are unchanged. The polymer consequently serves as a very effective affinity gel for the separation of sugar-binding proteins.[25]

Thin-layer and Paper Chromatography. – Malto-oligosaccharides (d.p. 2–8) are separable by paper chromatography as their 4-nitrophenylhydrazones, and the method has been used as for the assay of oligomers in the urine of patients



(1)

suffering from pancreatitis.[26]

Sintered t.l.c. plates produced by heating a layer of silica gel–powdered glass deposited on a soda glass support at high temperature have been evaluated for separation of sugars. The plates may be used repeatedly after cleaning with chromic acid, and the results suggest that they are superior to the conventional t.l.c. plate. Several solvent systems were examined and n-butanol–acetone–water (4 : 5 : 1) was recommended for simple sugars with prior impregnation of the plate with disodium hydrogen phosphate.[27]

[21] G. J. L. Lee and H. Tieckelmann, *J. Chromatogr.*, 1980, **195**, 402.
[22] E. V. Evtuschenko, N. M. Vakhrusheva, and Yu S. Ovodov, *J. Chromatogr.*, 1980, **196**, 331.
[23] L. Petruš, V. Bílik, L. Kuniak, and L. Stankovič, *Chem. Zvesti*, 1980, **34**, 530.
[24] H. Yamada, Y. Ohshima, K. Tamura, and T. Miyazaki, *Carbohydr. Res.*, 1980, **83**, 377.
[25] J. T. Lin and R. Kinne, *Angew, Chem. Int. Ed. Engl.*, 1980, **19**, 540.
[26] V. Bílik, J. Zemek, K. Babor, R. Sandtnerová, and J. Kozák, *Chem. Zvesti*, 1980, **34**, 524.
[27] N. Iizima, M. Fujihara, and T. Nagumo, *J. Chromatogr.*, 1980, **193**, 464.

Two-dimensional t.l.c. on cellulose has been reported to result in the resolution of all the amino-compounds commonly found in lipopolysaccharides and in the peptidoglycans found in bacterial cell walls, together with fucosamine, quinovosamine, and muramic acid.[28] The microdetermination of reducing sugars, by spraying the t.l.c. plate with ethylenediamine sulphate and measuring the fluorescence when irradiated at 365 nm, is an adaptation of a previous method which used paper chromatography (Honda *et al.*, *Anal. Chim. Acta*, 1973, **64**, 310). The detection limit was about 0.05 μg.[29] The t.l.c. of sugars on cellulose layers impregnated with tungstate buffers (pH 6 or 8) has been examined and R_f values reported for aldoses and alditols.[30] A qualitative t.l.c. method for the separation of 1,5-anhydroglucitol in the presence of other sugars employs silica gel impregnated with borate buffer.[31]

2 Other Analytical Methods

A potentiometric method for the determination of D-glucose, D-mannose, and D-fructose in a mixture of hexoses and pentoses employs fermentation by *Streptococcus mutans*. The response is based on the selective fermentation of these three carbohydrates by the organism, followed by measurement of hydronium ion. The response time is 4 min and other hexoses and pentoses do not interfere.[32]

A modification of the uronic acid – imidazole reaction (Cariotti reaction) has been described that eliminates interference by DNA.[33]

[28] E. A. Ryan and A. M. Kropinski, *J. Chromatogr.*, 1980, **195**, 127.
[29] J. Iwakawa, H. Kobatake, I. Suzuki, and H. Kushida, *J. Chromatogr.*, 1980, **193**, 333
[30] J. Briggs, I. R. Chambers, P. Finch, I. R. Slaiding, and H. Weigel, *Carbohydr. Res.*, 1980, **78**, 365.
[31] K. Lajunen, S. Purokoski, and E. Pitkänen, *J. Chromatogr.*, 1980, **187**, 455.
[32] S. R. Grobler and C. W. Van Wyk, *Talanta*, 1980, **27**, 602 (*Chem. Abstr.*, 1980, **93**, 197225).
[33] B. E. F. De Arcuri, M. E. F. de Recondo, and E. F. Recondo, *Carbohydr. Res.*, 1980, **85**, 165.

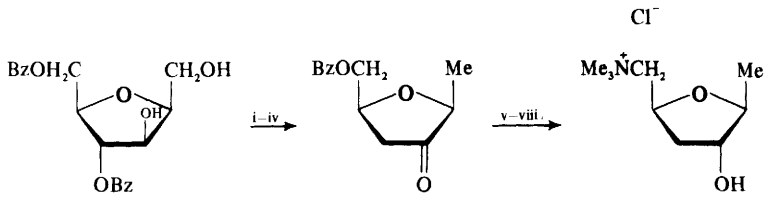
23

Synthesis of Enantiomerically Pure Non-carbohydrate Compounds from Carbohydrates

Considerable developments are taking place in this area as evidenced by the wide range of syntheses reported below. An important review of progress to date 'Carbohydrate derivatives in the asymmetric synthesis of natural products' has been provided by Fraser-Reid and Anderson.[1] A further review covers the preparation of asymmetric crown ethers from carbohydrates.[2] Highly abbreviated Schemes are used in this report because space does not permit the reproduction of the lengthy routes used in many of the syntheses.

1 Tetrahydrofuran Compounds

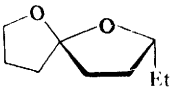
(+)-Muscarine (1) has been produced from the 2,5-anhydro-D-glucitol compound (2) by methods outlined in Scheme 1,[3] and the four stereoisomers of the spiro-compound (3) were synthesized by way of dithiane derivatives such as (4),



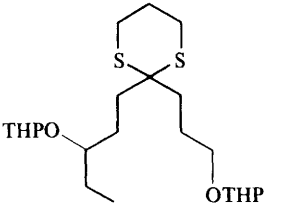
(2) (1)

Reagents: i, Ph_3P–CCl_4; ii, Bu_3SnH; iii, pyridinium chlorochromate; iv, $CrCl_2$; v, $NaBH_4$; vi, TsCl–py; vii, Me_3N; viii, Cl^-

Scheme 1



(3)

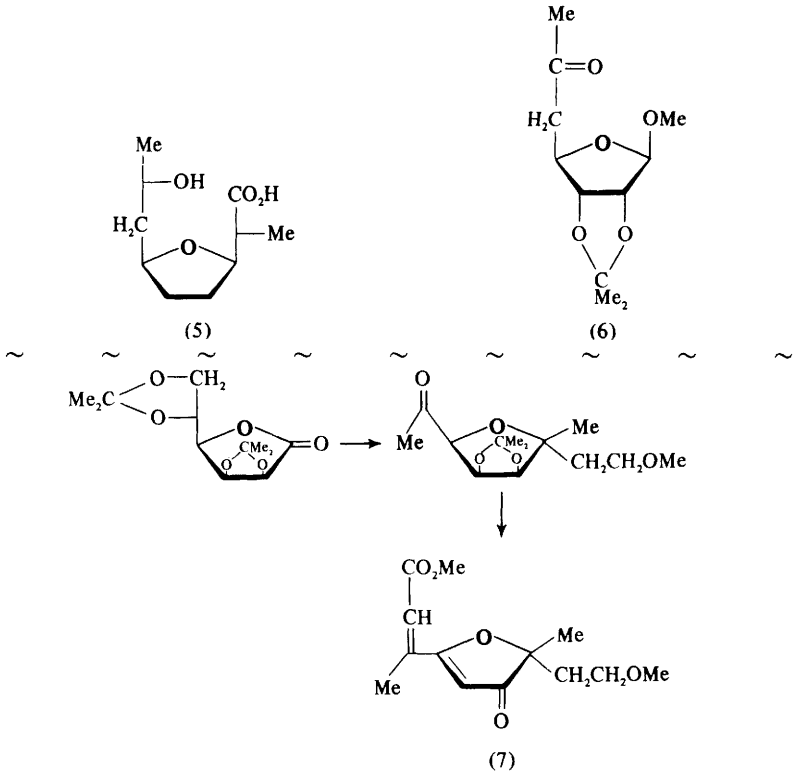


(4)

[1] B. Fraser-Reid and R. C. Anderson, *Fortschr. Chem. Org. Naturst.*, 1980, **39**, 1.
[2] J. F. Stoddart, *Chem. Soc. Rev.*, 1979, **8**, 85.
[3] A. M. Mubarat and D. M. Brown, *Tetrahedron Lett.*, 1980, **21**, 2453.

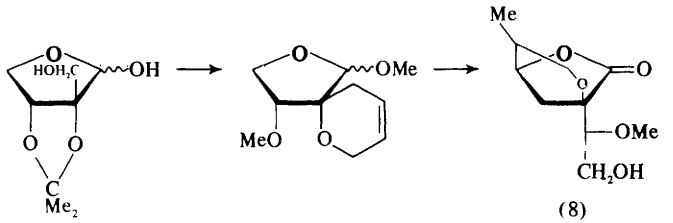
which were specifically prepared from deoxy-sugar precursors.[4] The four spiroethers together comprise the aggregation pheromone of a bark beetle.

Two syntheses of (+)- and (−)-(5)-nonactic acid have been reported. One uses a furanoid glycal as starting material,[5] and the other the furanoside (6) which led to the (−)-isomer of the product and which also could be inverted at C-4 to give a ketone from which the (+)-isomer was obtained.[6]



(5) (6) (7)

Scheme 2



(8)

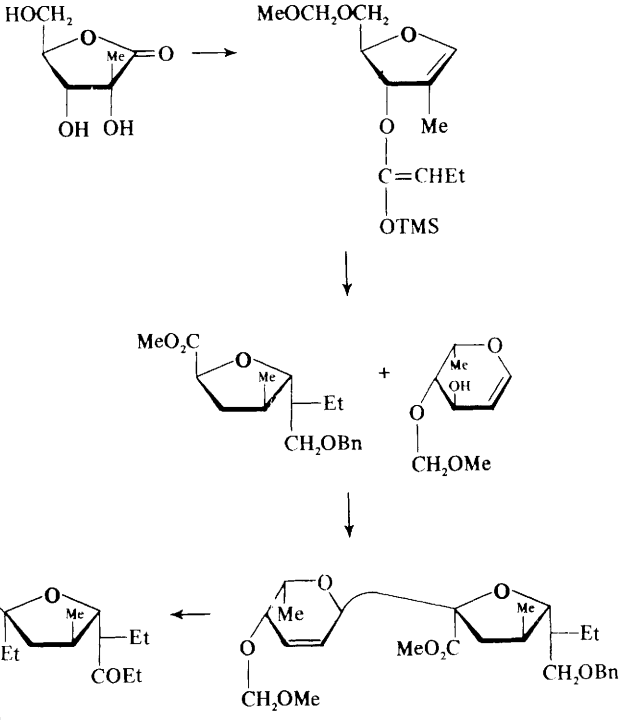
Scheme 3

[4] H. Redlich and W. Francke, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 630.
[5] R. E. Ireland and J.-P. Vevert, *J. Org. Chem.*, 1980, **45**, 4259.
[6] K. M. Sun and B. Fraser-Reid, *Can. J. Chem.*, 1980, **58**, 2732.

Tam and Fraser-Reid have also prepared the geometric isomers of compound (7) as analogues of the furenone moieties found in many germacranolide sesquiterpenes (see outline in Scheme 2),[7] and compound (8) is a further branched-chain furanoid product obtained from a carbohydrate (Scheme 3). It is a synthon for the macrolide natural product maytansine.[8]

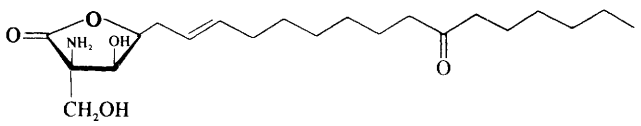
Ireland's group have also used carbohydrate derivatives to obtain a compound (9) of lasalocid A, a polyether antibiotic (Scheme 4).[9]

Compound (10) is the (−)-enantiomer of anhydromyriocin, the γ-lactone of m iocin (thermazymocidin), and has been synthesized from L-arabinose.[10]



(9)

Scheme 4



(10)

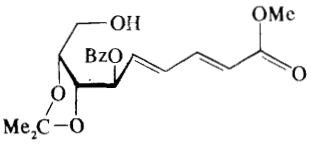
[7] T. F. Tam and B. Fraser-Reid, *J. Org. Chem.*, 1980, **45**, 1344.
[8] P.-T. Ho, *Can. J. Chem.*, 1980, **58**, 858.
[9] R. E. Ireland, S. Thaisrivongs, and C. S. Wilcox, *J. Am. Chem. Soc.*, 1980, **102**, 1155.
[10] G. Just and D. R. Payette, *Tetrahedron Lett.*, 1980, **21**, 3219.

2 Tetrahydrothiophene Compounds

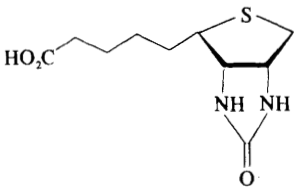
The diene ester (11), obtainable from 2-*O*-benzoyl-3,4-*O*-isopropylidene-D-arabinose by use of a Wittig reagent, on hydrogenation gave a tetrahydro-product that is a good precursor of (+)-biotin (12), and this approach represents an improvement in the synthesis of this compound.[11]

3 Pyrrolidine Compounds

Reductive cyclization of the tosylate (13) afforded the pyrrolidine (14), which is related to detoxinine (15).[12]



(11)



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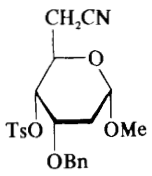

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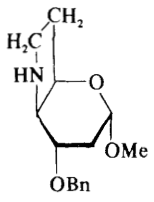
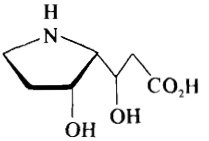


(14)



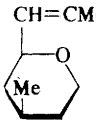
(15)

4 Tetrahydropyran Compounds

(—)-*cis*-Rose oxide (16) has been synthesized in 19 steps from D-glucose by way of 1,6-anhydro-3,4-dideoxy-3-*C*-methyl-D-*xylo*-hexose,[13] and the same group have also produced the branched-chain uloside derivative (17) from the same sugar.[14] Compound (17) was then used to prepare derivatives (18) and (19), which represent the chiral parts of antibiotic A23187 obtainable from *S. chartreusensis*.[15]

By use of the dithane (20) [*c.f.*, compound (4)], prepared from 4,6-dideoxy-D-*xylo*-hexose by thioacetalation and base-catalysed elimination, lithium

[11] F. G. M. Vogel, J. Paust, and A. Nürrenbach, *Liebigs Ann. Chem.*, 1980, 1972.
[12] K. Kakinuma, T. Ogita, N. Otake, and H. Yonehara, *Pept. Chem.*, 1979 (Publ. 1980), **17**, 53 (*Chem. Abstr.*, 1980, **93**, 221 026).
[13] T. Ogawa, N. Takasaka, and M. Matsui, *Int. Congr. Essent. Oils [Pap.], 7th*, 1977 (Publ. 1979), **7**, 289 (*Chem. Abstr.*, 1980, **92**, 146 929).
[14] Y. Nakahara, K. Beppu, and T. Ogawa, *Tennen Yuki Kogobutsu Toronkai, Koen Yoshishu, 22nd*, 1979, 493 (*Chem. Abstr.*, 1980, **93**, 95 506).
[15] Y. Narahara, K. Beppu, and T. Ogawa, *Koen Yoshishu-Tennen Yuki Kagobutsu Toronkai, 22nd*, 1979, 493 (*Chem. Abstr.*, 1980, **92**, 215 726).



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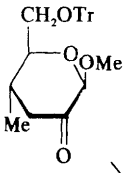

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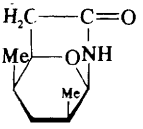

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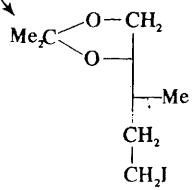

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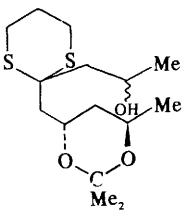

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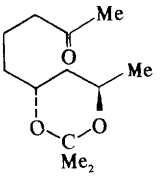

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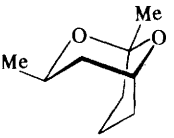


(22)

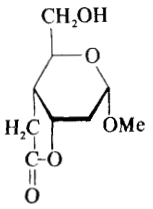
aluminium hydride reduction, and α-alkylation, the ketone (21) was obtained and hence the dioxabicyclo[3,3,1]nonane (22), which is an isomer of a host-specific substance found in Norway spruce infested with *Trypodendron lineatum*.[16] The work was then extended to give the isomer of the compound with the secondary methyl group *endo*, and also the enantiomers of both isomers.[17]

1,6 : 3,4-Dianhydro-2-*O*-toluene-*p*-sulphonyl-β-D-galactopyranose has been used to prepare the lactone (23) (*c.f.*, Vol. 11, p. 228) which, by standard methods of prostaglandin chemistry, has been converted into thromboxane B_2. The branch group at C-4 led to the α-chain and C-6 was extended into the ω-chain.[18]

5 Acyclic Compounds

4,5-*O*-Isopropylidene-L-arabinose diethyl dithioacetal offers a direct route to 2,3-*O*-isopropylidene-L-glycerol, which is the less accessible enantiomer.[19] 5,6-*O*-Isopropylidene-L-ascorbic acid has been used for the same purpose, and the

[16] H. Redlich, B. Schneider, and W. Francke, *Tetrahedron Lett.*, 1980, **21**, 3009.
[17] H. Redlich, B. Schneider, and W. Franke, *Tetrahedron Lett.*, 1980, **21**, 3013.
[18] A. G. Kelly and J. S. Roberts, *J. Chem. Soc., Chem. Commun.*, 1980, 228.
[19] K. Patrick and M. A. Wells, *J. Lipid Res.*, 1980, **21**, 257 (*Chem. Abstr.*, 1980, **93**, 72 149).



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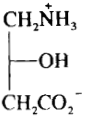

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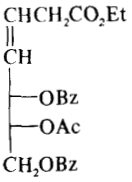

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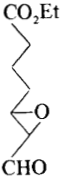

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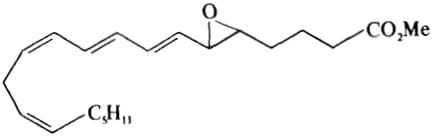

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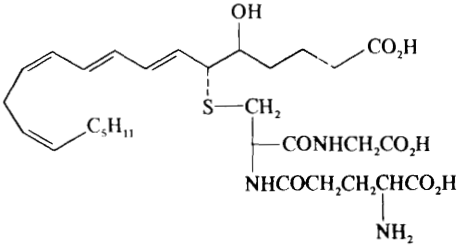


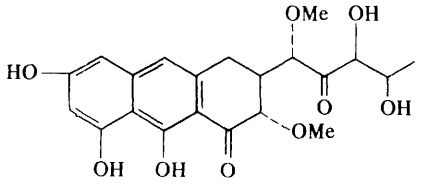
(28)

product was further converted to the amino-acid (24), which has hypotensive and antiepileptic properties.[20]

Reaction of 2,3,5-tri-*O*-benzoyl-D-ribose with a Wittig reagent gave access to the unsaturated aldonic acid derivative (25) from which the epoxide (26) was obtained. This was then used to prepare the tetraene (27) and hence (28), which is the 'slow reacting substance' of anaphylaxis.[21]

The side-chain of chromomycinone (29) has been prepared from D-arabinose in the form of compound (30) which, with butyl-lithium followed by benzaldehyde, gave the diastereoisomers (31) of a model antibiotic.[22]

[20] M. E. Jung and T. J. Shaw, *J. Am. Chem. Soc.*, 1980, **102**, 6304.
[21] E. J. Corey, D. A. Clark, G. Goto, A. Marfat, C. Mioskowski, B. Samuelsson, and S. Hammerström, *J. Am. Chem. Soc.*, 1980, **102**, 1437.
[22] J. Thiem and H. P. Wessel, *Tetrahedron Lett.*, 1980, **21**, 3571.



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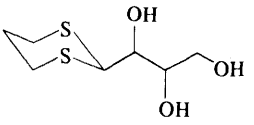

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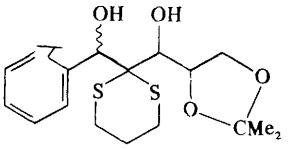

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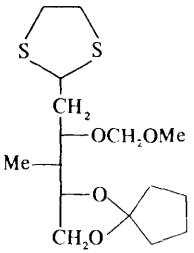

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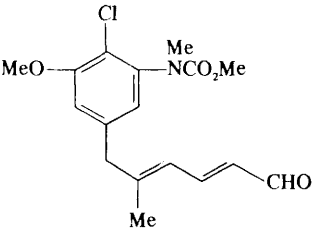

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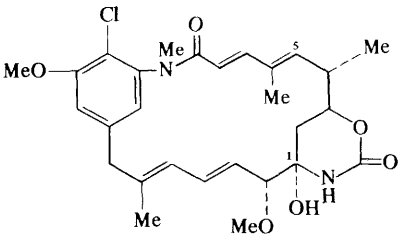


(34)

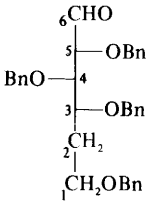
6 Macrocyclic Compounds and Components Thereof

Standard carbohydrate conversions were used to convert methyl 3,4-anhydro-2-deoxy-6-*O*-trityl-α-D-*ribo*-hyxopyranoside into the dithioacetal (32), which was then condensed with the dienal (33) in a synthesis of the natural enantiomer of *N*-methylmaysenine (34) (the sugar carbon atoms are indicated).[23]

[23] E. J. Corey, L. O. Weigel, A. R. Chamberlin, and B. Lipshutz, *J. Am. Chem. Soc.*, 1980, **102**, 1439.

Compounds (35) and (36) were prepared using 5-deoxy-1,2-*O*-isopropylidene-D-*xylo*-hexose and methyl 4,6-dideoxy-α-D-*xylo*-hexopyranoside, respectively, and, together with the Wittig reagent (37), were built into the macrocyclic lactone antibiotic (38). The source of each carbon atom in the product is indicated.[24]

In related work the ketone (39), derived from 5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-hexofuranose, was used, together with the enal (40), in a synthesis of the macrocycles of carbomycin B (41) and josamycin.[25]



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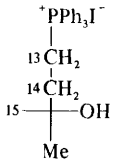

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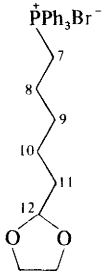

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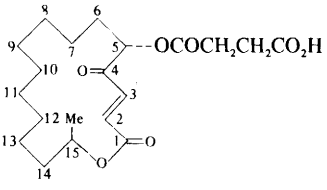

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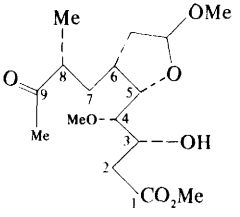

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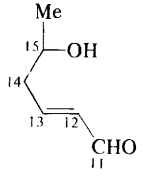

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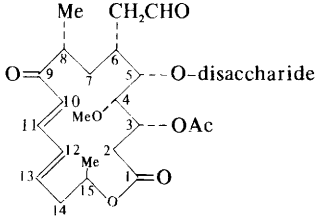
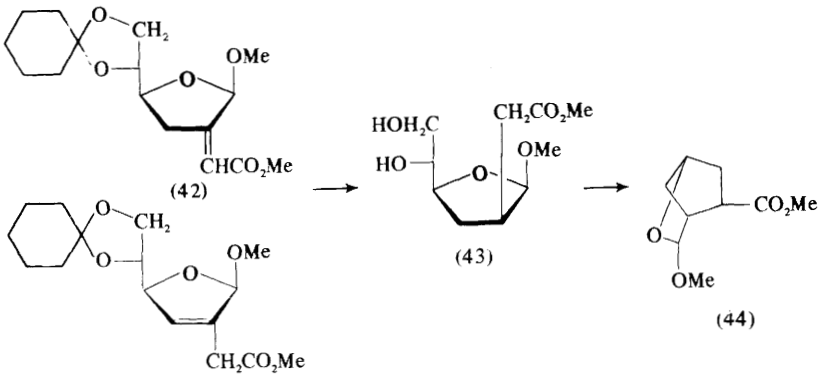
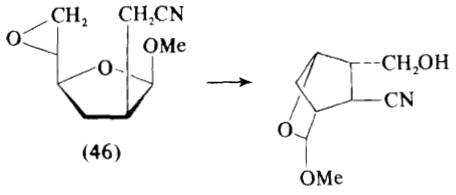


(41)

[24] K. Tatsuta, A. Nakagawa, S. Maniwa, and M. Kinoshita, *Tetrahedron Lett.*, 1980, **21**, 1479.

[25] K. Tatsuta, Y. Amemiya, S. Maniwa, and M. Kinoshita, *Tetrahedron Lett.*, 1980, **21**, 2837.





7 Cyclopentane Compounds

The branched-chain alkenes (42), prepared by standard methods, on reduction and partial hydrolysis afforded the diol (43), which was cleaved with periodate and cyclized to give the bicyclic derivative (44). This is a possible synthetic precursor of brefeldin A. The cyano-derivative (45), which is stereochemically related to the prostaglandins, was then synthesized by use of the epoxide (46).[26]

[26] H. Ohrui and H. Kuzuhara, *Agric. Biol. Chem.*, 1980, **44**, 907.

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