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Carbohydrate Chemistry

VOLUME 28

Monosaccharides, Disaccharides, and Specific Oligosaccharides

A Review of the Literature Published in 1994

THE ROYAL SOCIETY OF CHEMISTRY

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A Review of the Literature Published during 1994

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Preface

Our subject bounds ahead, and the need to condense our abstracts still further persists to the extent that this is the last volume for which reporters will have no defined space constraints. As from Volume 29 we will all be contracted to provide camera-ready material of specific maximum length which, to say the least, will be an interesting challenge. Reporters with the tasks of preparing the chapters covering growth areas such as the synthesis of non-carbohydrates from carbohydrates, cyclitols, sugar acids and oligosaccharide syntheses are going to be particularly affected, while less pressure will be felt by those reporting on diminishing topics such as deoxy-sugars, halogeno-sugars and thio-derivatives. To this list must be added, with some surprise, antibiotics which seemingly illustrates a major emphasis change within the pharmaceutical industry.

Dr Neil Williams' invaluable contributions to this series have been acknowledged before (Vol. 25), but he has continued to help to a limited extent - especially with tasks to which others could not readily attend. For 11 years he did the art work by hand in most acceptable manner, but inevitably he was superseded by the computer which, with its attendant needs, has proved less reliable, and this Volume has suffered significant delay in consequence. All Neil's contributions, including those to this his last Volume, are again acknowledged with most sincere thanks.

Dr John Gardiner has joined the reporting team and has already provided most valuable input.

Mr Alan Cubitt, Royal Society of Chemistry, has given much cooperation and assistance which are acknowledged very gratefully.

R J Ferrier

August 1996

Contents

Abbreviations

The following abbreviations have been used:

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

SIMS	secondary-ion mass spectrometry
TASF	tris(dimethylamino)sulfonium difluorotrimethyl silicate
TBDMS	t-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
Tfa	trifluoroacetyl
TFA	trifluoracetic acid
THF	tetrahydrofuran
Thp	tetrahydropyranyl
TMS	trimethylsilyl
TPP	triphenylphosphine
TPS	tri-isopropylbenzenesulfonyl
Tr	triphenylmethyl
Ts	toluene *p*-sulfonyl
U	uracil-l-yl

1
Introduction and General Aspects

A description of the pioneering work of Emil Fischer in the period around 1890, especially relating to his elucidation of the molecular configuration of glucose and aspects of his philosophical view of chemistry, has appeared.[1] Lemieux and Spohr have looked in detail at how Fischer was led to the "lock and key" concept for enzyme specificity.[2] An animated 386-based PC program with VGA graphics has been produced to assist visualization of the relationship between Fischer and Haworth projections of monosaccharides.[3]

An ACS symposium was held in 1993 on the anomeric effect and associated stereoelectronic effects,[4] and as part of it J. T. Edward reviewed the influence of the anomeric effect in carbohydrates covering the origin of its postulation.[5] Several calculations relevant to carbohydrates have been reported. *Ab initio* M.O. methods have been applied to the axial and equatorial conformations of 2-methoxytetrahydropyrans,[6] and also 2-chloro- and 2-fluoro-tetrahydropyrans, the energy values obtained being found to be dependent on solvent.[7] Force fields have been calculated for monosaccharides and (1→4)-linked polysaccharides,[8] and a review has been written on path energy minimization (PEM), a novel method for generating a reaction path linking two known conformations of molecules. A test example considered the change in pucker angle of α-D-*threo*-pentulofuranose. The method can identify transition state structures and energy barriers.[9] A major review covering structural and conformational analysis of oligosaccharides of glycoproteins deals with n.m.r., mass spectrometric and molecular modelling methods.[10]

Considerable attention has been given in reviews to aspects of synthesis. The question of reactions which are promoted by water has been dealt with covering i) Diels Alder and hetero-Diels Alder reactions by which monosaccharides may be synthesized; ii) sigmatropic rearrangements of aglycons which lead to asymmetric induction; iii) indium promotion of allylation of aldehydes or ketones and iv) reductive debrominations using soluble tin hydrides and AIBN.[11] A further review has dealt with the hetero-Diels Alder reaction in asymmetric systems, and covered the use of carbohydrate chiral auxiliaries and the construction of pyranose rings from sugar butadien-1-yl ethers.[12] The trichloroacetimidate method for making glycosides which has become well established as of major importance has been reviewed by the developer, R. R. Schmidt,[13] and the use of aldonolactones in synthesis has covered *O*-substitution and deoxygenation, reactions with various nucleophiles including chain elongating reagents, reductions

and β-eliminations.[14] Tetrapropylammonium perruthenate has become recognized as a soluble, non-volatile, stable oxidising agent for converting alcohols to ketones; used with sodium hyperchlorite it cleaves α-diols, and its chemistry has been reviewed.[15]

New aspects of the synthesis of glycopeptides which contain glycosyl asparagine, serine and threonine has covered *O*- and *N*-glycosylations, and dealt with enzymic and solid phase procedures.[16] A review of the use of enzymic methods in protecting group technology includes cover of examples relating to carbohydrates and nucleosides,[17] and a further relates to chemo-enzymic methods for preparing derivatives of D-ribose containing one or more ^{13}C labels.[18]

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2
Free Sugars

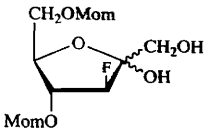
1 Theoretical Aspects

The relevant literature on lactose dissolution in water has been reviewed in a paper which describes a mathematical model for this process.[1] Short time scale molecular dynamics simulations of sucrose in water and DMSO indicated that the conformations in both solvents are similar to that accepted in the crystalline state.[2] Solid-liquid equilibria for aqueous sucrose have been studied by use of an UNIQUAC model.[3] A comparison of GROMOS force field and Ha force field in molecular dynamics simulations of glucose crystals indicated superior performance by the latter method.[3a] Predicted crystal structures of β-D-glucose, β-D-galactose, β-D-allose, α-D-glucose, α-D-galactose, and α-D-talose matched or nearly matched the X-ray-derived data in four cases.[3b]

2 Synthesis

The synthesis of aldose derivatives by iterative, diastereofacially selective addition of 2-lithio-1,3-dithiane to *O*-protected chiral α-hydroxyaldehydes, starting from 1,2-*O*-cyclohexylidene-D-glyceraldehyde, has been reported.[4] In a new modification of the aldolase-catalysed synthesis of ketose phosphates (see Vol. 27, Chapter 7, Ref. 71) the required dihydroxyacetone phosphate (DHAP) has been generated *in situ* from glycerol 1-phosphate by use of glycerol phosphate oxidase coupled with catalase.[5] A large number of ketosugars, for example the new fluorinated D-fructose derivative **1**, have been prepared by addition of the one-carbon nucleophile (benzyloxymethyl)lithium to suitably substituted and protected aldono-1,4-lactones.[6] Acetyl-protected free pento-, hexo- and hepto-furanoses, such as compounds **2**, have been obtained by reduction of the corresponding 1,4-aldonolactones with disiamylborane.[7] An interesting new approach to chiral precursors of C-3 branched alditol and aldose derivatives involving bis-epoxidation of silylated ketenes is covered in Chapter 18, and the oxidative degradation of galactose, lactose, cellobiose and maltose to the next lower aldoses by hydrogen peroxide in the presence of borate ions is referred to in Section 5 of this Chapter (Ref 83).

2.1 Trioses to Hexoses. – Mixtures of *erythro*- and *threo*-3-pentulose have been obtained in the base-catalysed aldol condensation between unprotected DL-*glycero*-tetrulose and formaldehyde, the



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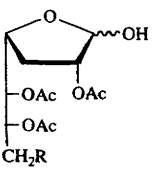
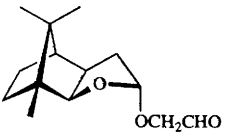


R = H or OAc

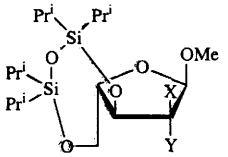
2



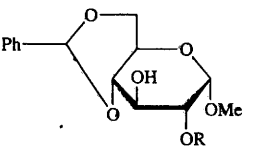
3

product ratio depending on catalyst and solvent.[8] In further studies on the aldolization of glycolaldehyde derivative **3**, use of lithium hydroxide as catalyst furnished DL-galactose as the major trimerization product in 7.5% yield, in contrast to previous experiments with NaOH or KOH which had produced allose as the main hexose (see Vol. 25, Chapter 2, Ref. 12).[9]

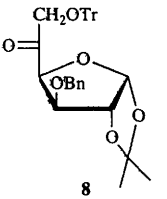
In the transketolase-catalysed condensation (see Vol. 27, Chapter 2, Refs. 6,16) of hydroxypyruvate with a mixture of all four 4-deoxytetrose isomers, only the 2*R*- isomers reacted and only products with *S*-stereochemistry at the new chiral centre (C-3), *i.e.*, 6-deoxy-D-fructose and 6-deoxy-L-sorbose, were formed.[10] A preparation of D- and L-fructose by enzymic aldol condensation is referred to below (Ref. 23), and the enzymic conversion of D- and L-*erythro*-pentulose, D-tagatose and D-psicose to the corresponding 3,4-*threo*-compounds is covered in Part 4 of this Chapter (Ref. 65).



4 X = H, Y = OH
5 X = OH, Y = H



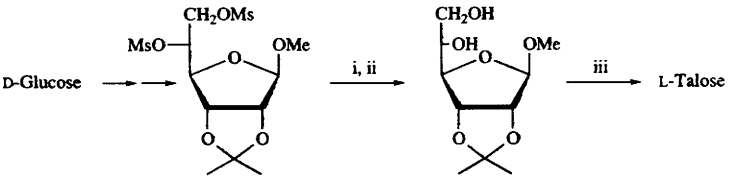
6 R = H
7 R = COC_3H_7



8

Oxidation/reduction at C-2 was used to convert the 4,6-*O*-Tips-protected methyl α-L-arabinoside **4** to the corresponding L-ribose derivative **5**.[11] Preferential secondary oxidation of 3,4-di-*O*-benzyl-D-mannitol with bis(tributyltin) oxide and bromine gave 3,4-di-*O*-benzyl-D-fructose in 87% yield.[12] Efficient new syntheses of methyl α-D-allopyranoside and methyl 3-deoxy-α-D-ribo-hexopyranoside relied on the selective enzymic acylation at the 2-position of methyl α-D-glucopyranoside derivative **6** to give **7**, which was subjected to oxidation/reduction and to deoxygenation, respectively.[13]

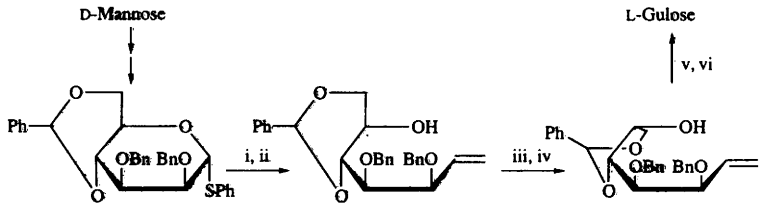
A new synthesis of L-talose from D-glucose, which is outlined in Scheme 1, involved inversion of configuration by oxidation/reduction at C-3 and sulfonate displacement at C-5. The



Reagents: i, NaOAc, DMF, ii, MeONa, MeOH; iii, H^+, H_2O

Scheme 1

L-talose was used for making new furanosyl- and pyranosyl-adenine nucleosides.[14] A preparation of L-gulose from D-mannose, incorporating as the key-step inversion at C-5 in an acyclic intermediate, is shown in Scheme 2.[15] The β-fragmentation/cyclization of carbohydrate anomeric alkoxy radicals, a novel method of descending the aldose series (see Vol. 27, Chapter 2, Refs. 12,13) has been applied to the preparation of pentoses from hexoses. Iodine and diphenylselenium hydroxyacetate, a stable and readily available crystalline compound, were used as reagents instead of iodosobenzene.[16]



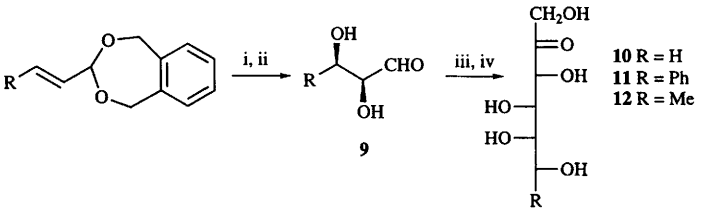
Reagents: i, NBS, CH_3CN, H_2O; ii, $CH_2{=}PPh_3$; iii, Swern oxidation; iv, L-Selectride; v, O_3–Me_2S; vi, $Pd(OH)_2$, H_2

Scheme 2

A practical method for the gram-scale preparation of D-[5-^{2}H]glucopyranose in 7 steps and 15% overall yield from diacetone glucose has been developed. The label was introduced by stereoselective reduction of the known ketone **8** with sodium borodeuteride.[17] Various methods were employed to synthesise D-[1-^{2}H]-, D-[4-^{2}H]-, D-[5-^{2}H$_2$]-, D-[(5R)-^{2}H]- and D-[(5S)-^{2}H]-ribose and thence specifically labelled 4-*N*-benzoylcytidines and, by deoxygenation, 2′-deoxy analogues.[18] D-[6-^{11}C]Glucose has been obtained from protected α-D-*xylo*-pentodialdo-1,4-furanose by use of a $^{11}CH_3I$-derived Wittig reagent.[19]

Selective cleavage of either diastereomer of phenyl or 4-nitrophenyl β-D-glucopyranosyl sulfoxide to give the free sugar has been achieved with β-glucosidases of various origins.[20]

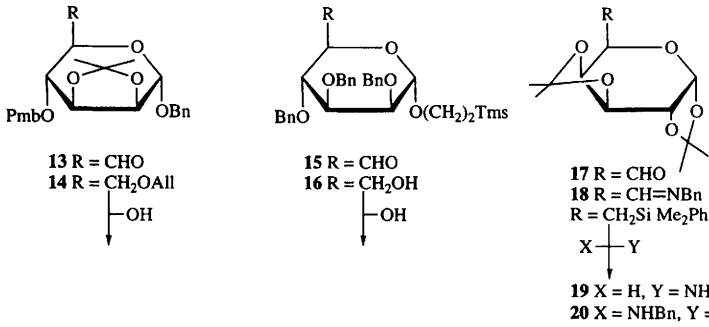
2.2 Chain-extended Compounds. – Higher sugars have been produced by osmylation of known heptenoses and oct-dienoses.[21,22] The rhamnulose 1-phosphate aldolase-catalysed condensation of



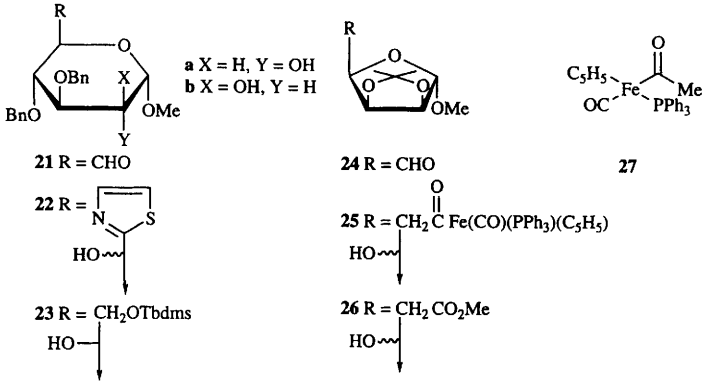
Reagents: i, AD-mix-β, Bu'OH, H_2O; ii, pH 1; iii , DHAP, rhamnulose1-phosphate aldolase; iv, phosphate

Scheme 3

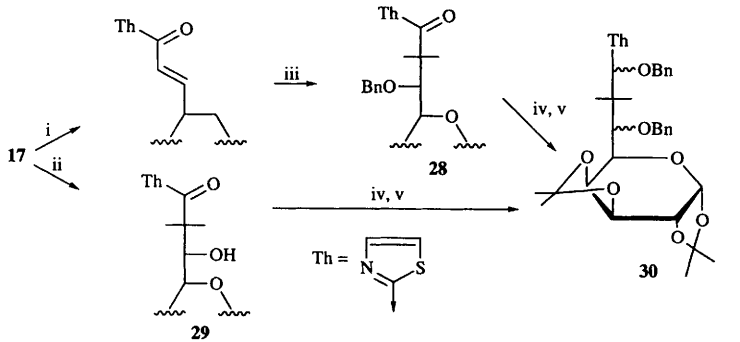
DHAP (see Vol. 25, Chapter 7, Ref. 44) with aldehydes **9**, obtained by asymmetric dihydroxylation, gave after phosphatase treatment L-fructose (**10**), 6-*C*-phenyl-D-*galacto*-2-hexulose (**11**) or 7-deoxy-D-*galacto*-2-heptulose (**12**), *i.e.*, products with *3R/4S/5S/*(*6R*)-stereochemistry, as shown in Scheme 3. The enantiomers of the three uloses were obtained by use of the hydroxylation auxiliary with the opposite chirality and fructose diphosphate aldolase as condensation catalyst.[23]



2.2.1 *Chain-extension at the "Non-reducing End".* – Dialdoses were again the substrates in a number of chain-elongations, by one to four carbons. The versatile LD-Hepp derivative **14** was the main product (63%) from the Grignard addition of allyloxymethylmagnesium bromide to hexodialdo-1,5-pyranoside **13**.[24] A similar synthesis using (dimethylphenylsilyl)methylmagnesium chloride followed by peracetic acid, that gave product **16** from starting compound **15** in comparable yield, has



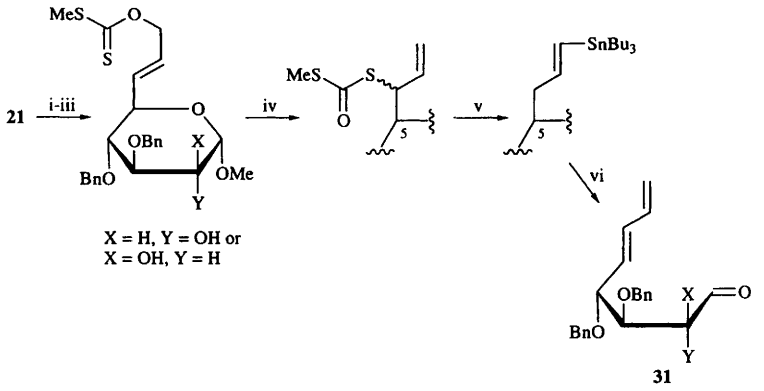
also been reported.[25] The conversion of LD-Hepp derivative **16** to its DD-isomer is referred to in Chapter 7. In the presence of metal ions, (dimethylphenylsilyl)methylmagnesium chloride reacted stereoselectively with the benzylimino compound **18**, obtained by exposure of **17** to benzylamine. Cerium(III) chloride and copper(I) iodide promoted the preferred formation of the *syn*- and *anti*-adducts **19** and **20**, respectively. The latter is a precursor of lincosamine..[26] The 2-trimethylsilyl thiazole homologation of the dibenzyl ethers **21** was non-selective (in contrast to that of **17**, see Vol. 27, Chapter 2, Ref. 20) as was oxidation/reduction of the addition products **22**. However, oxidation/L-selectride reduction of the deprotected, reduced, and 7-*O*-silylated products gave mainly the required D-*glycero*-D-*gluco*-(or *manno*)-heptopyranosides **23**; access to the methyl pyranoside of D-*glycero*-D-*altro*-*heptose*, a constituent of the O-antigen chains in certain lipopolysaccharides, was provided by epimerization at C-2 and C-3 of **23a** *via* the derived 2,3-D-*glycero*-D-*allo*-epoxide.[27]



Reagents: i, $ThCOCH{=}PPh_3$; ii, ThCOMe, Bu^{t}OK; iii, BnONa; iv, DIBAL or $Me_4NBH(OAc)_3$; v, BnBr, NaH

Scheme 4

Two-carbon chain-extension by condensation of α-D-*lyxo*-pentodialdo-1,4-furanose derivative **24** with the anion formed from the acetyliron complex **27** gave a 2:1 mixture of products **25**. Decomplexation with NBS in methanol furnished the separable methyl uronates **26**.[28] Two methods for three-carbon elongation, both using thiazole based reagents, are illustrated in Scheme 4. As the Wittig route was complementary, in stereochemical terms, to the enolate route and selective reduction of ketones **28** and **29** was readily achieved by choice of appropriate reaction conditions, all four stereoisomers **30** were available.[29]



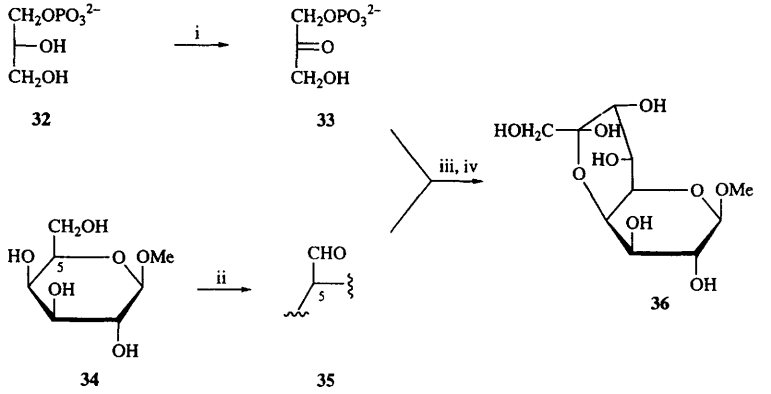
Reagents: i, $Ph_3P{=}CHCO_2Me$; ii, DIBAL; iii, NaH, CS_2–MeI; iv, 110 °C; v, Bu_3SnH; vi, $ZnCl_2$, ether, CH_2Cl_2

Scheme 5

Sugar allyltin derivatives, convenient precursors of dienoaldehydes such as compounds **31**, have been obtained by S_R2 reaction of trialkyltin radicals with allylic thiocarbonates which were, in turn, produced by Wittig condensation followed by a 3:3 thermal rearrangement, as shown in Scheme 5.[30]

In a further development of the aldolase-catalysed synthesis of sugars (see Ref. 4 above), both DHAP (**33**) and the aldehyde component **35** were generated *in situ* from glycerol 1-phosphate (**32**) and methyl β-D-galactopyranoside (**34**), respectively, by microbial oxidation. Use of rhamnulose 1-phosphate aldolase caused formation of a single nonose-8-ulose **36** (which underwent intramolecular hemiacetal cyclization) with the expected L-*threo*-stereochemistry across the new carbon-carbon bond (Scheme 6).[31] A new synthesis of *N*-acetylneuraminic acid derivatives and analogues involved as the key-step reaction of dialdose derivative **37** with the Wittig reagent **39** to give non-5-enose derivative **38** in 76% yield.[32]

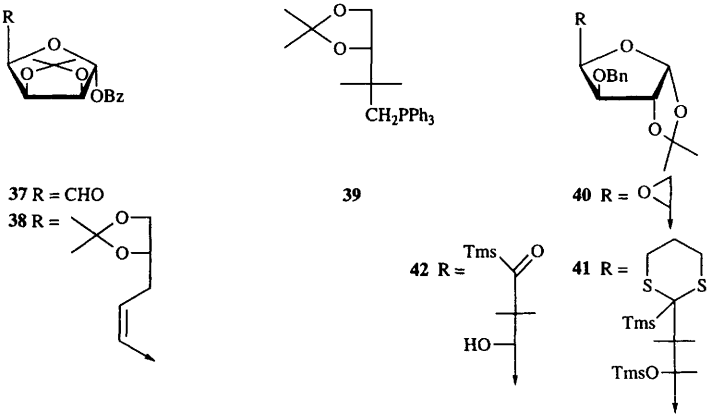
One carbon elongation has also been achieved by displacement of primary triflate groups with potassium cyanide,[33] and by opening of 5,6-epoxide **40** with 2-lithio-2-trimethylsilyl-1,3-dithiane to

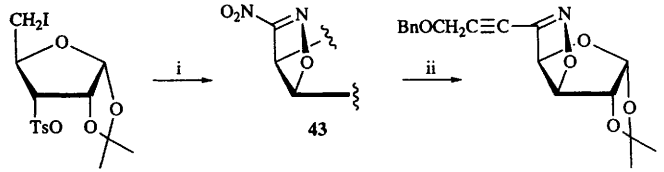


Reagents: i, Glycerol phosphate oxidase; ii, galactose oxidase; iii, L-rhamnulose phosphate aldolase; iv, phosphatase

Scheme 6

form **41** which on exposure to mercury(II) perchlorate gave acylsilane **42**.[34] Displacement of primary iodide by propyl nitrite accompanied by displacement/cyclization of secondary tosylate opened a route to optically pure 4-oxygenated 4,5-dihydroisoxazoles **43**. These compounds are potentially useful intermediates for further chain-extensions (Scheme 7).[35]

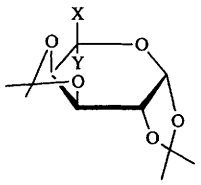




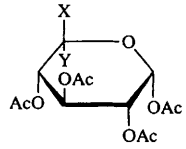
Reagents: i, $NaNO_2$, PrONO, DMSO; ii, $BnOCH_2C{\equiv}CLi$

Scheme 7

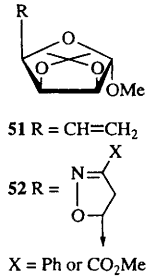
C-6-Allylated pyranoses and *C*-5-allylated furanoses were prepared from the corresponding iodides by Keck radical coupling with allyltributyltin (e.g. **44**→**45**).[36] The selective formation of product **47** in the chain-extension of the acetal-protected uronic acid derivative **46** by radical addition of methyl acrylate using Barton's method was ascribed to addition from the less hindered side to a conformationally stable radical intermediate; the peracetate **48** furnished a 1:1 mixture of **49** and **50**.[37]



44 X = CH_2I, Y = H
45 X = $(CH_2)_2CH{=}CH_2$ Y = H
46 X = CO_2Me, Y = H
47 X = H, Y = $CH{=}CHCO_2Me$



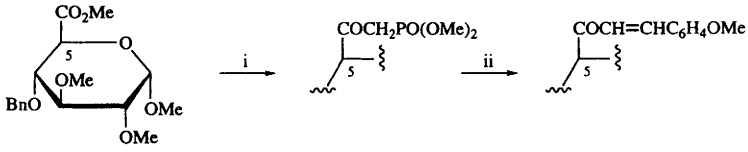
48 X = CO_2Me, Y = H
49 X = H, Y = $CH{=}CHCO_2Me$
50 X = $CH{=}CHCO_2Me$, Y = H



51 R = $CH{=}CH_2$
52 R =

X = Ph or CO_2Me

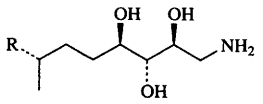
Cycloaddition of nitrile oxides to the D-*lyxo*-alkene **51** gave mainly the C-4/C-5-*erythro*-adducts **52** (see Vol. 25, Chapter 10, Refs. 91,92).[38] The nitrile oxide-isoxazoline route involving sugar-derived nitrile oxides as well as sugar-derived alkenes (see Vol. 27, Chapter 2, Ref. 39) has been applied to the synthesis of a 6-deoxy-dodecoses[39] and a 7-deoxy-tridecoses.[40] Sugar β-ketophosphonates have been employed in the synthesis of higher sugars. An example is given in



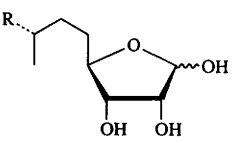
Reagents: i, $LiCH_2PO(OMe)_2$; ii, $MeOC_6H_4CHO$, Cs_2CO_3

Scheme 8

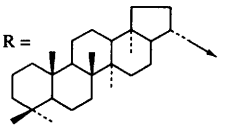
Scheme 8.[41] Use of a C_{12}-dialdose and a C_9-sugar ketophosphonate in a similar condensation gave an unsaturated C_{21}-sugar.[42]



53



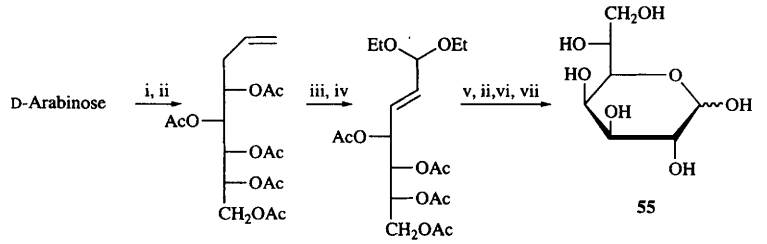
54



"C-Ribosylhopane" (**54**), a postulated bio-precursor of the bacteriohopanepolyols, was synthesized from the triolamine **53** by O-silylation and oxidation of the amine with dimethyldioxirane, followed by deprotection.[43]

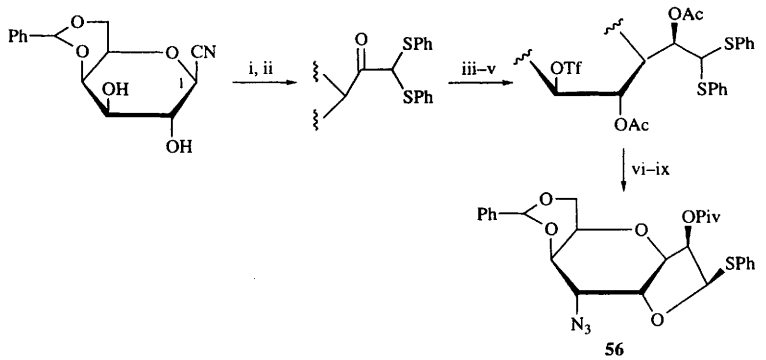
2.2.2 *Chain-extension at the Reducing End.* – Partially protected D-gluco-, D-allo-,[44] and L-rhamno-pyranose[45] have been converted in moderate yields to heptonic acid δ-lactones by Kiliani ascent. Several 2,6-anhydroheptoses have been prepared by ozonolysis of the corresponding sodium 2,6-anhydro-1-deoxyheptitol-1-nitronates.[46]

The tin- and indium-mediated allylation of unprotected carbohydrates in aqueous media has been reviewed.[47] The recent application of this methodology to the conversion of D-arabinose to D-*glycero*-D-*galacto*-heptose (**55**) in eight steps and 30% overall yield is shown in Scheme 9.[48] A



Reagents: i, In powder, AllBr, <<<; ii, Ac_2O, py; iii, OsO_4, KIO_4–Bu_4NBr; iv, $HC(OH)_3$, H^+; v, OsO_4, NMO; vi, MeO^-, MeOH; vii, H^+

Scheme 9



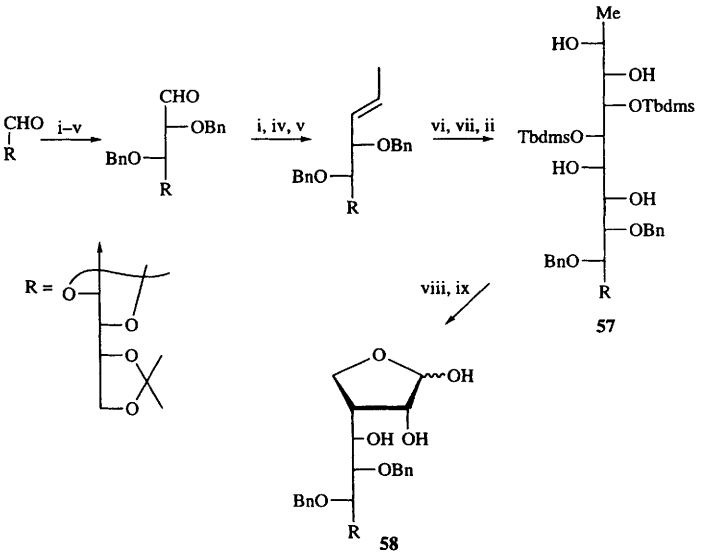
56

Reagents; i, $(PhS)_2CHLi$; ii, H_3PO_4, H_2O; iii, Tf_2O, py; iv, DIBAL; v, Ac_2O, Et_3N; vi, Bu_4NN_3; vii, NH_3, MeOH; viii, NIS, TfOH; ix, PivCl, py

Scheme 10

route to the bicyclic octose derivative **56**, required for the synthesis of the octosyl nucleoside moiety of the antibiotic ezomycin A_1, is outlined in Scheme 10.[49]

A powerful strategy for chain-extension by 7 carbon atoms using consecutively two Horner-



Reagents: i, Horner–Emmons; ii, OsO_4, NMO; iii, BnBr; iv, DIBAL; v, Swern oxidation; vi, Bu_3S OTbdms, BF_3•OEt; vii, TbdmsOTf; viii, HIO_4; ix, Bu_4NF, HOAc

Scheme 11

Emmons condensations and addition of a silyloxyallylic stannane, and involving highly stereoselective osmylation of three double bonds is illustrated in Scheme 11. The selectively protected D-*manno*-D-*manno*-D-*arabino* derivative **57** was obtained with excellent diastereoselectivity; regioselective diol cleavage furnished lactol **58**.[50,51]

The synthesis of sphingosine from 2,4-*O*-benzylidene-D-threose was hampered by failure to achieve *arabino*-selectivity in the addition of tetradecosylmagnesium bromide as well as in the oxidation/reduction of the resulting mixed alcohols by all methods tried except the samarium iodide-assisted Tishchenko reaction.[52]

3 Physical Measurements

Differential scanning calorimetry experiments revealed the presence of at least four types of lactose besides the known α- and β-modifications, some of which are dehydrated forms.[53] Attempts have been made to identify the rate-determining step in the dehydration of fructose to 5-(hydroxymethyl)furfural by measuring kinetic isotope effects.[54] A spin-probe EPR study at elevated temperatures of some sugars in connection with the desiccation tolerance of biological materials indicated that trehalose and sucrose-raffinose mixtures are distinguished by stability of their phase state and their low effective activation energy for rotational molecular motions.[55]

4 Isomerization

The tautomeric equilibria of aldopentoses, aldohexoses and hexuloses in DMSO have been examined by ^{13}C-n.m.r. spectroscopy;[56] the mutarotation kinetics of aqueous D-glucose have been investigated by i.r. methods,[57,58] and Raman spectroscopic data on the tautomeric transformations of glucose in aqueous solution over a wide pH range confirmed that the ring-chain tautomerism depends on pH.[59] The ring shapes of the two furanose and two pyranose forms of psicose in aqueous solution, shown by n.m.r. spectroscopy to be present in almost equal proportions, have been analyzed by MM3.[60]

Tandem m.s. and theoretical calculations have been used to study the gas-phase aldose-ketose isomerization. Results obtained with (1→3)-linked disaccharides supported a mechanism involving hydride transfer rather than a 1,3-hydrogen shift.[61] Related theoretical studies (*ab initio* and semiempirical MO methods) of aldose-ketose isomerization in aqueous solution suggested that the favoured pathways in the absence and presence of metal ions are proton transfer *via* an enediol and hydride transfer, respectively.[62] A strong influence of the acetonitrile mole fraction on the

kinetics of the heptamolybdate ion-catalysed epimerization of D-mannose to D-glucose in aqueous acetonitrile has been demonstrated.[63]

An investigation of the properties of the newly discovered D-ketose-3-epimerase (see Vol. 27, Chapter 2, Ref. 53) now named D-tagatose-3-epimerase, showed that it is most active on 3,4-*cis* configurated substrates, establishing a 30:70 *cis/trans* equilibrium. Thus the rare sugars D-sorbose and D-psicose have become available from D-tagatose and D-fructose, respectively.[64]

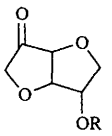
5 Oxidation

The direct electrooxidation of aqueous D-gluconic acid to D-arabinose on graphite has been performed in a very simple apparatus which may be suitable for practical application.[65] The electrocatalytic oxidation of sucrose on smooth, lead-modified platinum electrodes has been examined with a view to finding experimental conditions for the selective electrosynthesis of value-added compounds.[66] A paper in Bulgarian on the electrooxidation of diacetone-L-sorbose at low current densities in a nickel oxide electrolizer has been published.[67] The influence of the size of palladium particles and their location on the support on their activity in the oxidation of glucose has been examined.[68] An investigation of the effect of temperature and pH on the platinum-catalysed oxidation of sucrose showed that changes in temperature affect mainly the reaction rate, where changes in pH alter the selectivity.[69]

Kinetic studies have been reported on the silver mirror reaction,[70] on the oxidation of D-glucose to D-gluconic acid by aqueous Cu(II) at pH 4-5 and 110 °C,[71] on the oxidation of aldoses by dihydroxydiperiodato-nickelate (IV) ions in alkaline media,[72] on the oxidation of arabinose and xylose,[73] and of galactose and mannose[74] by iodine in alkaline solution, on the oscillating reaction of D-mannose with bromate ions in the presence of one equivalent of oxidizing agent (Belousov-Zhabotinskii reaction),[75] on oscillating systems containing carbohydrates (glucose, fructose, sorbose, sucrose), bromate, Ce(IV), sulfuric acid and a surfactant,[76] and on the oxidation of D-mannose with PCC.[77] In a study of the mechanism of the Ir(III)-catalysed NBS oxidation of sugars (arabinose, glucose, mannose, fructose, lactose), iridium(III) chloride in acid solution was used with mercury(II) acetate as $Br^{\cdot}$ scavenger.[78] An investigation of the oxidation of monosaccharides (D-glucose, D-galactose, D-mannose, D-fructose, D-ribose, D-xylose, L-arabinose, and L-sorbose and including acetoin as a simple model) by bromamide T in hydrochloric acid, revealed low reactivity of ketoses relative to aldoses and a low value for the ratio of second order rate constants $k_{2,\ acetoin}/k_{2,glucose}$, indicating that ring forms of the aldosugars are involved.[79]

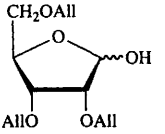
Incubation of D-xylose with an aqueous solution of bovine lens protein at 37 °C and pH 7.0 gave both xylitol and D-xylonic acid. It is believed that both, reduction and oxidation, are protein catalysed and unique to lens protein.[80]

The oxidation of the 5-*O*-benzoates or 5-*O*-acetates of 1,4:3,6-dianhydro-D-glucitol and -D-mannitol with PCC or PDC gave the corresponding 2-keto derivatives **59** in up to 85% yield, while no useful selectivity was achieved by treatment of the unprotected anhydro compounds with a variety of other oxidizing agents.[81] In a comparative study on the oxidation of protected free sugars, such as **60**, to the corresponding lactones by use of Swern procedures, PDC, and tetra-*n*-propylammonium tetraoxoruthenate(VII)/NMO, yields of 60, 86, and 94%, respectively, were achieved.[82] Galactose, lactose, cellobiose and maltose were degraded selectively and in high yield to the next lower aldoses by hydrogen peroxide in the presence of borate ions, which catalysed the reactions and protected the products from further degradation.[83] Methyl 4,6-*O*-benzylidene-α-D-glucoside was the model substrate in a search for optimal conditions for the C-2–C-3 glycol cleavage in starch; best results were obtained with RuO_4, formed *in situ* from catalytic amounts of Ru(III) and sodium hypochlorite.[84]



R = Ac or Bz

59



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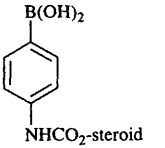

61

1,4-Dihydroxybutanone and glyceraldehyde have been identified as degradation products of L-threose under Maillard conditions. The latter product was shown to be formed by loss of C-1 from the starting sugar.[85] The stepwise mercaptolysis degradation method applicable to branched oligosaccharides (see Vol. 25, Chapter 2, Scheme 12) has been used to defucosylate 3-*O*-fucosyl-α-D-lactose.[86] Azo dyes carrying phenylboronic acid residues change colour on addition of saccharides, an effect caused by disaggregation of the dye molecules.[87] A new, highly sensitive method for detecting saccharides in aqueous solutions by fluorescence spectroscopy is based on a similar disaggregation of boronic acid-appended porphyrins on complexation with sugars.[88] Monolayers of compound **61** on a water surface have been tested as a complexing medium for monosaccharides; chiral recognition of the sugars was observed.[89]

An investigation of the lyoluminescence of lactose showed that radiation-induced free radicals are involved; oxygen is essential for initiation and light is produced by energy transfer from diffusing free radicals to sensitizer molecules.[90]

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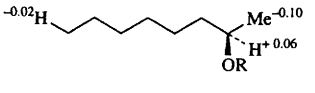
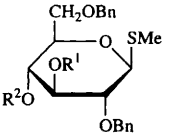
3
Glycosides

1 O-Glycosides

1.1 Synthesis of Monosaccharide Glycosides.–Conversions of secondary alcohols **1** into their tetra-*O*-benzoyl-β-D-glucopyranosides have the effects shown (on the δ-values) of the relevant protons, while the effects on these protons in the diastereoisomers produced from the enantiomers of **1** (R=H) are similar in magnitude but opposite in sign. The method, therefore, can be used for determining absolute configurations of such alcohol centres.[1]



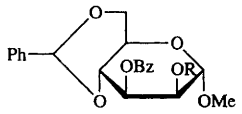
1 (R = H)



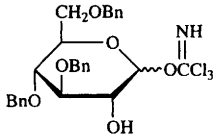
2 $R^1 = Me_2SiOC_8H_{17}$, $R^2 = Bn$
3 $R^1 = Bn$, $R^2 = Me_2SiOC_8H_{17}$

The intramolecular approach to the synthesis of glycosides is developing appreciably. It has been found possible to cause alkyloxy groups to migrate from relatively distant positions to the anomeric centre. Thus, for example, the silyl ether **2**, on treatment with *N*-iodo-succinimide, resulted in 22% of 2,4,6-tri-*O*-benzyl octyl glycosides with the α/β ratio 1:4 implying that there was some intramolecular delivery. This was substantiated when compound **3** was similarly treated and the α-glycoside was produced in 45% without any β-linked product. When the migration was attempted using a silyl ether group at O-6 of a thiophenyl α-glucoside, 1,6-anhydro glucose was the major product. However, analogous treatment of a 5-*O*-silylated 1-thio-α-D-ribofuranosyl glycoside resulted in the β-octyl ribofuranoside in 63% yield.[2]

Two groups have tried ingeniously to invert configuration at the anomeric centre of α-mannopyranosyl compounds with partial success. Thus compound **4**, converted into the corresponding debrominated free radical by treatment with tributyltin hydride, resulted in hydrogen abstraction from C-1 and inversion to give 48% of the β-anomer of the 2-*O* dimethylphenylsilyl derivative. Also produced was the α-*gluco*-compound formed following H-abstraction at C-2 (24%) and the α-*manno*-compound produced by reductive debromination (28%).[3] Entirely parallel work was effected using the acetal derivative **5** in which case the methyl β-mannopyranoside was obtained in 30% yield together with the α-mannoside and the corresponding 2-uloside. An analogous reaction effected in the nucleoside series with the acetal



4 R = $Me_2SiC_6H_4Br(o)$
5 R = $MeO(Me)CCH_2Br$



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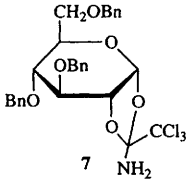
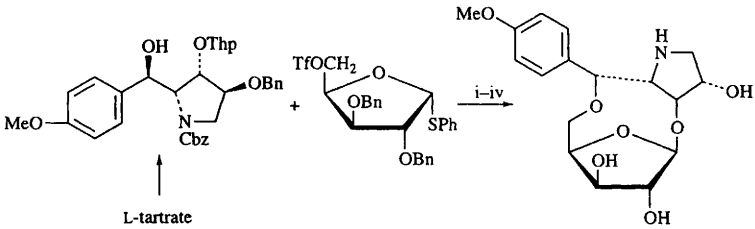


7

function at O-3′ resulted in H-4′ abstraction, deuteration and partial inversion of configuration at C-4′.[4]

Intramolecular glycosylation of a different sort resulted in the synthesis of compound AB3217-A (**8**), a novel anti-mite substance, as illustrated in Scheme 1.[5]

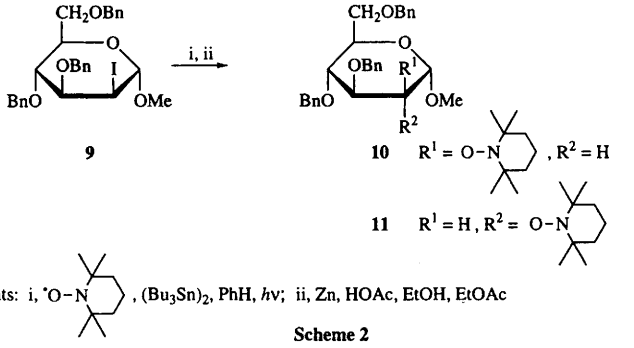


Reagents: i, BuLi; ii, H_3O^+; iii, NBS; iv, H_2, Pd/C

Scheme 1

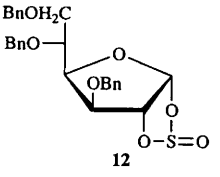
Schmidt and Kinzy have published a comprehensive review of the trichloroacetimidate method for making glycosides as the major part of a discussion of general aspects of the glycosylation process.[6] Schmidt and colleagues have shown for the first time that it is possible to make glycosyl trichloroacetimidates in the presence of hydroxyl groups elsewhere in the molecule. Thus 3,4,6-tri-*O*-benzyl-D-glucose, treated with trichloroacetonitrile in dichloromethane in the presence of potassium carbonate, led to the mixed anomers **6**, the α-isomer of which ring closed on treatment with DBU to give the orthoamide compound **7**.[7] A modified procedure for making α-D-glucopyranosides, especially allyl and substituted allyl compounds, is based on the use of the trichloroacetimidate derivable from 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-D-glucose which is treated *in situ* with alcohols in the presence of Lewis acid catalysts.[8] The trichloroacetimidate method has been applied to the synthesis of the 5-aminopentyl glycoside of β-*N*-acetylglucosamine, and such glycosides can also be produced from glycosyl acetates and *S*-ethyl thioglycosides.[9]

Deoxyiodo compounds have often been reduced to corresponding deoxy derivatives, but now it is established that the iodine may be replaced oxidatively to give means of introducing oxygen functions and hence hydroxyl groups. Thus, for example, as indicated in Scheme 2, the



Scheme 2

deoxyiodo-D-*manno* derivative **9** may be converted into the α-mannoside **10** and the α-glucoside **11** in the ratio 2:1. The hydroxylamine function may then be converted to the free alcohol by treatment with zinc in 10% acetic acid in ethanol.[10] Parallel results were obtained using the 2-deoxy-2-iodo methyl α-glycoside adduct produced from di-*O*-acetyl-L-rhamnal which afforded the L-*manno*- and L-*gluco*-2,3,4-triacetates in 82% yield, the ratio again being 2:1, under free radical conditions involving the use of tributyltin hydride, AIBN and air.[11] The use of 1,2-cyclic sulfites for the synthesis of glycosides has been developed, compound **12** derived from the corresponding diol, on treatment with lithium aryl oxides, giving access to aryl 3,5,6-tri-*O*-benzyl-β-D-glucofuranosides. A similar approach can be adopted in the pyranoside series to lead to aryl β-D-gluco- and xylo-pyranosides.[12] For this work di-imidazyl sulfoxide was used to prepare the cyclic esters, and the same reagent can be applied following hydroxylation of *O*-substituted glycals with osmium tetroxide to give, for example, compound **13**. Treated with alcohols in the presence of the unusual catalysts ytterbium or holmium triflates, this likewise gave glucosides in good yield with high β-selectivity.[13] 2,3,4,6-Tri-*O*-benzyl-D-glucose and trimethylamine/sulfur trioxide complex in acetonitrile affords a mixture of the anomeric sulfates which, treated with alcohols, using trimethylsilyl triflate catalyst, led to a new approach to glycosides, but the yields were not high nor were the α/β ratios encouraging.[14]



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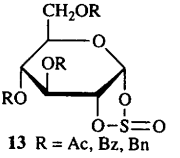
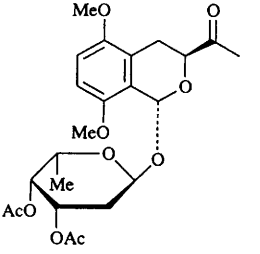


13 R = Ac, Bz, Bn

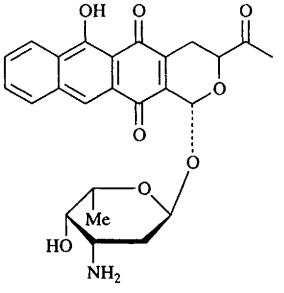


14

Full details have appeared on the use of *O*-protected glycosyl phosphites for Lewis acid-catalysed glycosidation (cf. *Synlett*, 1993, 115). Again anomeric mixtures were produced, but reasonable yields resulted - especially when *O*-benzyl protection was employed with glucosyl, galactosyl and mannosyl donors and with *O*-acetylated sialic acid donor.[15]

Sugars protected at all hydroxyl position other than the anomeric can be used in a variety of other ways for the synthesis of glycosides. Tetra-*O*-methyl-glucose and -mannose have been examined in alkane and aprotic solvents using methyl iodide in the presence of sodium hydride. Good selectivities were claimed depending upon the conditions used.[16]

O-Benzylated analogues activated with trimethylsilyl chloride and zinc triflate gave α/β mixtures in the cases of glucose, galactose and L-fucose, but mainly the α-anomer in the mannose series. The method was applied with methyl 9-hydroxynonanoate, with a terpene alcohol and with a sugar derivative bearing a free primary hydroxyl group.[17] A somewhat different approach is to convert 2,3,4,6-tetra-*O*-benzylhexose derivatives to the corresponding glycosyl chlorides by treatment with tris-dimethylaminophosphine and carbon tetrachloride, the reactions proceeding by way of the glycosyl-substituted phosphonium chlorides. The products then, on reaction with silver triflate or trimethylsilyl triflate in the presence of hydroxy compounds, gave glycosides. Examples of disaccharides produced in this way were described.[18] A novel approach involves 2,3,4,6-tetra-*O*-acetyl-D-glucose activated at O-1 by use of sodium hydride in dimethoxyethane. In this way the decyl glucosides were made in 70% yield and with high β-selectivity. With lactose heptaacetate the method was applied to afford coupling with a suitably protected long chain alcohol triflate and hence a glycosylated ceramide.[19] An unusual method of coupling compounds with free anomeric hydroxyl groups can be applied with aglycons having hetero-substituted benzylic positions. Thus, for example, a racemic isocroman oxidatively coupled with 3,4-di-*O*-acetyl-2,6-dideoxy-L-*lyxo*-hexose in the presence of DDQ gave compound **14** and its diastereoisomer with the same anomeric configuration but different configurations on the isocroman ring, each in 44% yield. The method is very applicable to the production of anthracycline analogues of which **15** is an example.[20]



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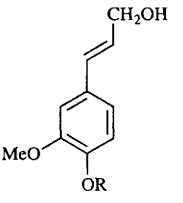


16

Thioglycosides are now widely accepted as being suitable precursors for glycoside synthesis, and many examples are given in the disaccharide section and in Chapter 4. Bis(trifluoroacetoxy)iodobenzene has been introduced as yet another activator for use with phenyl thioglycosides for the synthesis of *O*-glycosides. It apparently promotes S_N2 displacements with thioglycosides carrying *O*-methyl protecting groups; inversions of configuration occur to give high yields of products with anomeric selectivities of the order of 15:1.[21]

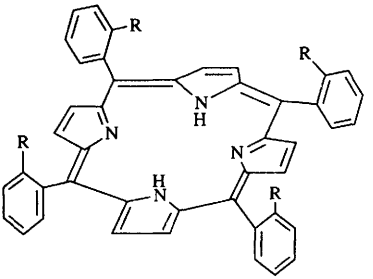
Several new examples of the use of enzymes in the production of glycosides have been reported. Almond β-glucosidase has been used by three groups of workers in the reverse sense to synthesise β-glucosides. Careful attention has to be paid to reaction conditions, particularly solvents, in work of this sort. Octyl β-D-glucopyranoside,[22] β-mercaptoethyl β-D-glucopyranoside,[23] and several other ω-hydroxy- and thio-alkyl glucosides have been produced by the procedure.[24] A sucrose phosphorylase isolated from *Leuconostoc Mesenteroides* acts as a glucose transferase with sucrose as glucose source. It has been used to produce the mono-α-D-glucopyranosides at each of the hydroxyl functions of kojic acid,[25] and also analogous derivatives of phenols, hydroxybenzoic acids, benzyl alcohols etc.[26] The use of a commercially available β-galactosidase in the synthesis of alkyl β-D-galactopyranosides has been optimized,[27] and applied to the synthesis of 2-fluoroethyl β-D-galactopyranoside and the disaccharide analogue having a further β-D-galactopyranosyl unit linked to O-6.[28] A β-xylosidase from *Aspergillus* causes transglycosylation from xylose oligosaccharides to hydroquinone as an acceptor,[29] and one from a *Trichoderma* is effective with primary, secondary and tertiary alcohols as acceptors.[30] Cell suspensions of *Rauwolfia serpentina* provided with hydroquinone produce the mono-β-D-glucopyranoside and the 1,6-linked dimer analogue.[30a]

An extensive range of aryl glycosides have been synthesized. Penta-*O*-acetyl-β-D-glucopyranose on treatment with tributyltin aryloxides in the presence of tin(IV) chloride, gives the β-glycosides as main products as expected. In the galactose and mannose series analogous chemistry led, as expected, to β- and α-products respectively.[31] In related work similar anomeric selectivities were exhibited on treating *O*-benzoylated glycosyl halides with potassium *p*-nitrophenate in chloroform in the presence of 18-Crown-6. The acetylated 2-azido-2-deoxy-altrosyl chloride gave only the β-anomer.[32] The β-D-glucopyranoside of salicylic acid has been prepared[33] as has 6-bromo-2-naphthyl α-L-arabinofuranoside.[34]

Coniferyl alcohol glycosides **16** have been made by use of the sodium salts of the alcohol and the appropriate acetohalogen sugars, and following deacetylation their abilities to induce the virulence genes of the crown gall *Agrobacterium Tumefaciens* have been determined.[35] Penta-*O*-acetyl β-D-glucopyranose with Lewis acid catalysis was used in the preparation of 4-alkoxyphenyl β-D-glucopyranosides with the alkyl groups having carbon numbers ranging from 1 to 11. Other

compounds with methyl groups on the aromatic rings were prepared, and the abilities of all the products to inhibit the release of histamine from rat peritoneal mast cells induced by *Concanavalon A* was determined. 4-Decyloxy-2,3,6-trimethylphenyl β-D-glucopyranoside was the most active compound.[36] In related work the same group have found that 4-hexyloxy-2,3,6-methylphenyl α-D-mannopyranoside was best inhibitor of the antigen-antibody reaction induced release of histamine from mast cells. Of eleven such glycosides belonging to the α-mannose, α- and β-glucose and α- and β-galactose series this is the best potential anti-allergy compound.[37]

Extended interest has been shown in porphyrins carrying glycosyloxy substituents (cf. Vol 27, p 18) which can be made by condensation of glycosyloxy benzaldehydes with pyrrole. Compounds with the carbohydrate substituents in the *ortho* positions have phenyl rings which do not have freedom of rotation with respect to the prophyrin rings, and studies have now been undertaken on the interconversion of the various rotomer forms of the compound. The all-*cis*



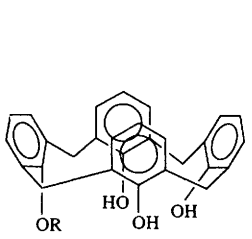
R = tetra-*O*-acetyl-β-D-glucopyranosyloxy

17

derivative **17** has been isolated for the first time following equilibrations in toluene- acetonitrile in the presence of silica gel.[38] The same group of workers have investigated analogous compounds having additional chlorine atoms on the phenyl rings and as manganese coordination compounds for use as asymmetric epoxidation catalysts. By their use *p*-chloro-styrene was converted into the corresponding epoxide, the *R* compound being produced in about 40% yield with about 20% ee.[39] Tetraphenylporphyrins carrying glycosidically-linked sugars on the phenyl groups were studied by photochemical hole-burning spectroscopy. A lactose-bonded compound in polyvinylalcohol shows excellent thermal stability against cyclic annealing.[40]

Related glycosylated macrocyclic compounds are the calix-4-arene derivatives **18**, with R= *O*-substituted D-mannofuranosyl, D-galactopyranosyl or D-glucopyranosyl units which were made using Mitsunobu conditions with sugars *O*-protected other than at the anomeric centre. Di- and tetra-glycosylated compounds were also reported.[41]

Refunctionalization of the double bonds of unsaturated alkyl glycosides continues to be of



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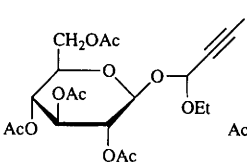
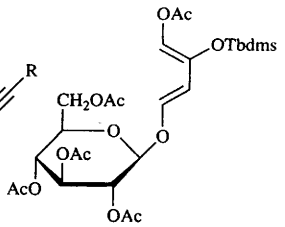
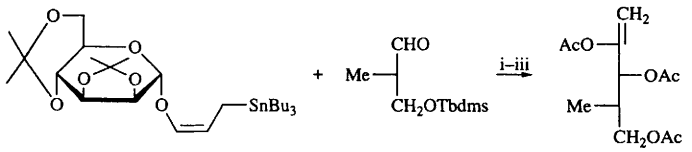


19 R = H
20 R = $(CH_2)_9CH_3$
21 R = Ph



22

synthetic value, a notable case being the tributylstannyl derivative **23** which is a chiral reagent applicable to the asymmetric α-hydroxyallylation of aldehydes (Scheme 3). The example illustrated is a "matched" case, whereas the mismatched case involves the enantiomer of the aldehyde and results mainly in the preparation of a D-*arabino* compound rather than the L-xylo



23

Reagents: i, $BF_3 \bullet OEt_2$, –78 °C; ii, HCl, iii, Ac_2O, Py

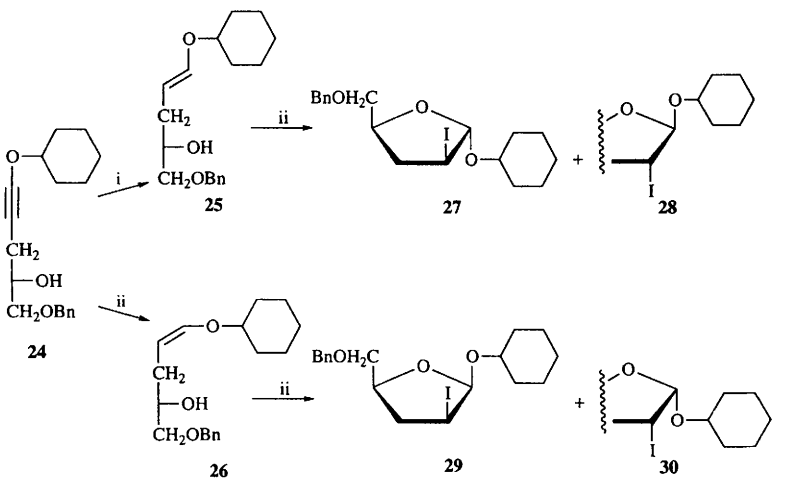
Scheme 3

illustrated.[42] Methylenation with diodomethane and diethylzinc of 2,3,6-tri-*O*-substituted allyl glycosides affords good yields of products with good stereoselectivities which depend upon the anomeric configurations as well as other factors which include the absence or presence of a substituent at *O*-2.[43] Various allyl *O*-substituted α-L-rhamnopyranosides have been ozonolized and the products reductively coupled with the ε-amino groups of the lysine residues of bovine serum albumin to give useful artificial antigens.[44]

Unusual unsaturated acetal glycoside **19** - **21** and the deacetylated analogues have been made following the condensation between tetra-*O*-acetyl-1-trimethylsilyl-β-D-glucopyranose with the corresponding diethyl acetals, in the presence of trimethylsilyl triflate.[45] The condensation of the diene glycoside **22** with various azadienophiles has given a set of glycosides having bicyclic aglycons containing cyclic diaza systems. Greater diastereofacial selectivity in the Diels-Alder reactions was observed than between compound **22** and cyclic alkene-based dienophiles.[46]

As always, unsaturated compounds have shown their value in the synthesis of glycosides. Thus, for example, the alkyne **24**, which was made by reaction between 1,2-anhydro-3-*O*-benzyl glycerol and an alkylaluminium compound, afforded the *E* and *Z* alkenes **25** and **26** on

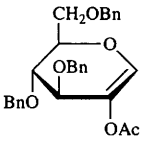
appropriate reduction. On iodine-induced ring closures these respectively afforded the *trans*-related 2-iodo glycosides **27** and **28** in 83% yield and in the ratio 91:9, and the *cis*-related isomers



Reagents: i, $LiAlH_4$; ii, KH, I_2; iii, H_2, Lindlar catalyst

Scheme 4

29 and **30** in 79% yield, ratio 84:16. (Scheme 4).[47] Reaction of the 2-acetoxyglycal derivative **31** with *N*-bromosuccinimide in ethanol affords the 2-ulosyl α-bromide which is a very reactive glycosylating reagent, and with alcohols in the presence of silver carbonate gives 2-ulosides very readily. Sodium borohydride reduces these compounds mainly to the β-mannoside derivatives **32**. The *manno*- to *gluco*- ratios were 2:1 at worst, and often better than 10:1. Many glycosides and thioglycosides and disaccharides were prepared in this way, the yields of the disaccharides being in the 60-90% range.[48]



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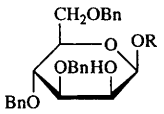

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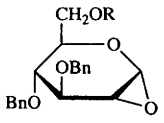
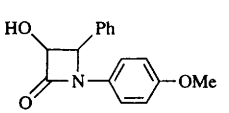


33 R = Bn
34 R = $SnBu_3$

A further route to β-mannopyranosides involves use of the 1,2-anhydride **33**, made by the Danishefsky method from tri-*O*-benzyl-D-glucal. Epoxide ring opening with alcohols in the presence of zinc chloride gives β-glucosides which, by oxidation and reduction, lead to the β-mannosides including β-mannosyl disaccharides.[49] Danishefsky has also adapted compound **33** for use as a precursor of α-glucosides. Treated with tributylstannylated alochols in the presence

of silver tetrafluoroborate the anhydride opens in *cis* fashion to give α-glucosides. A complex acyclic alcohol gave a 41% yield, whereas a diacetone-D-galactose, with a free primary hydroxy group, gave the corresponding α-glycosylated disaccharide in 57% yield. Compound **34** allows α-glycosylation by this method at *O*-6 and the double bond of the product may be epoxidized and the glycosylation procedure therefore iterated.[50] The racemic lactams **35** were resolved by treatment with tri-*O*-acetyl-D-glucal to give 2,3-dideoxy-α-glycosides as a diastereoisomeric pair which were separated. The unusual feature of the chemistry is that the allylic rearrangement reaction was induced by use of iodine in THF which normally produces 2-deoxy-2-iodoglycosides as adducts.[51]



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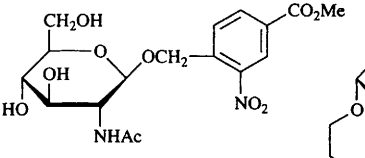

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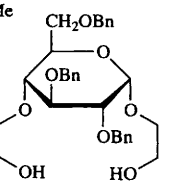


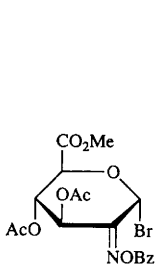
37

Several reports have concerned the preparation of substituted alkyl glycosides. The reaction of 2-alkoxy-2-fluoroglycosyl fluorides with benzyl alcohol which gives a mixture of benzyl glycosidic compounds and *C*-glycosidic isochromanes is referred to in Chapter 15. Glycoside **36** is a photo-sensitive compound which has been made chemically and enzymically and amide-linked to a polyacrylamide by way of the carboxylic acid group. Enzymic glycosylation then afforded *N*-acetyllactosamine which was released from the polymer photochemically. This approach clearly has its attractions, but a 2% yield only was achieved.[52] Related specific compounds to have been synthesized are 2-(indol-3-yl)ethyl α-L-arabinopyranoside[53] and 2-phenylethyl α-D-glucopyranoside.[54] In the area of 2-hydroxyethyl glycosides compound **37** has been made from the 1,4-di-*O*-allyl analogue by ozonolysis and reduction. Cyclization with α, ω ditosylates afforded crown ethers from this compound.[55] 2-Hydroxyethyl glucoside has been phosphorylated in the aglycon and linked through the phosphate group to *N*-acetyl-5-hydroxytryptamine to solublize the latter compound and prepare pro-drugs. Analogues with the D-*manno* configuration and the 2-deoxy analogue were also produced.[56] 2'-Trimethylsilylethyl glycosides have been used as starting materials for the preparation of glycosyl phosphates.[57] 2-Azidoethyl glycosides and 2-azidoethyl uronate esters are described in Chapter 16.

In the area of long-chain alkyl glycosides, 2,3,4,5,6-penta-*O*-acetyl-D-glucose treated with trimethylsilylated alcohols in the presence of trimethylsilyl triflate has been used to give the dialkylacetals following base catalysed deacetylation. Mild acid hydrolysis then gives the

furanosides, the anomers of which were separable in the case of the dodecyl glycosides, both products showing smectic A phases as liquid crystals.[58] 7-Formylheptyl glycosides derived from *N*-acetylglucosamine and a dirhamnose disaccharide, have been used to couple with bovine serum albumin.[59] Isolation of the *n*-alkyl β-D-glucopyranosides derived from alcohols ranging from hexanol to dodecanol has been effected by use of porous gels.[60]

Specific glycosides to have been reported include allyl β-D-fructopyranoside which can be made directly from the sugar and the alcohol with the aid of an acid catalyst. It crystallizes directly in approximately 50% yield.[61] Normally it is prepared from the 3-chloropropyl compound hydrogenation of which and of other ω-haloalkyl β-D-fructopyranosides provides a convenient route to alkyl β-D-fructopyranosides.[62] Methyl α-D-fructofuranoside may be obtained in approximately 32% yield from the free sugar by methanolysis in the presence of "silica-alumina cracking catalyst", a process which affords the required compound in 49% yield, the β-anomer in 14% and the pyranosides in 34% yield. Following the removal of the β-furanoside by enzymolysis the required compound is isolated by use of anion exchange chromatography.[63] Mukaiyama's latest contribution to the development of methods for making specific glycosides involves the use of 2,3,5-tri-*O*-benzyl-D-ribofuranosyl iodoacetate which, with trimethylsilylated alcohols in the presence of silver and lithium perchlorates affords α-ribofuranosides. In the case of the 3-phenylpropyl compound the yield was 90% and the α/β ratio 96:4.[64]



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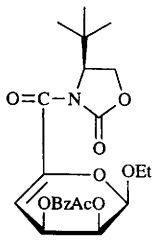

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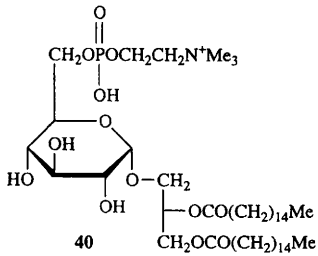
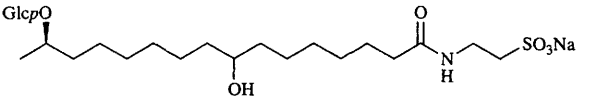


40

The glycosyl bromide **38**, derivable by radical bromination at C-1 of the corresponding *O*-benzoyloxime, gives access to β-glycosides of 2-acetylamino-2-deoxy-D-mannuronic acid, a disaccharide involving linkage to O-6 of a glucoside was reported.[65] Enantiomerically pure β-mannosides have been made with high enantioselectivity by an asymmetric hetero-Diels-Alder reaction which led to compound **39**. Refunctionalization, including a hydroboration step, gave ethyl β-D-mannopyranoside. This enantiomer was favoured when dimethylaluminium chloride was used as catalyst, but catalysis involving the use of trimethylsilyl triflate gave access to the enantiomer of **39** with good efficiency and high enantioselectivity and from this ethyl β-L-

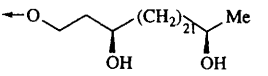
mannopyranoside was obtained.[66]

1.2 Synthesis of Glycosylated Natural Products and their Analogues.–Standard chemistry led to 2-*O*-β-D-glucopyranosyl glycerol,[67] and more extended work gave a large series of 1-β-D-galactopyranosyl mono- and di-acyl glycerols.[68] Enzymic transfer of α-D-glucopyranosyl units from 6′-chloro-6′-deoxysucrose to 2,3-*O*-isopropylideneerythritol and related tetrose derivatives have been examined and an extensive range of chiral substituted 1,3-dioxolane compounds were described.[69] The new glucosyl glycerolipid isolated from a culture HTLV-1-infected human helper T cells, compound **40**, has been synthesized by standard procedures starting from 1,2-anhydro-L-glycerol.[70] Compound **40a**, the oviposition-deterring pheromone of the European



40a

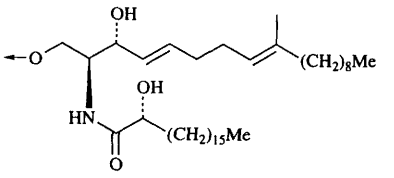
cherry fruit fly has been prepared.[71] In similar work, the α-glucoside with aglycon **41** was made by thioglycoside technology, it being the heterocyst glycolipid of a marine cyanobacterium.[72]



41

Glycosidation of long chain alcohols of glycolipids with *O*-acetylated 2-acetamido-2-deoxy-α-D-glucopyranosyl chloride using various activators has been reported.[73]

Tetra-*O*-benzyl-D-galactosyl fluoride was the glucosylating reagent used to prepare novel agelasphins which are unusual galactosyl ceramides in having the sugar α-linked.[74] A β-glucoside-containing cerebroside is based on the aglycon **42**,[75] and was isolated from a *Penicillium*. A new approach to the ribosylribitol derivative **43**, a key intermediate in the synthesis of *Haemophilus Influenzae* type B oligosaccharides, depends upon a trichloroacetimidate coupling reaction.[76]



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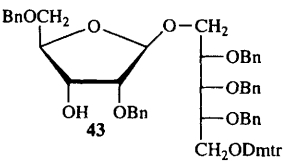
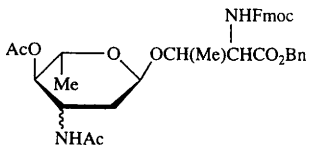


43

O-Glycosylated α-amino acids continue to receive considerable attention and several methods may be applied to their synthesis. For example, compounds **44**, based on threonine, are

produced in satisfactory yield by acid-catalysed addition to corresponding glycals, and in parallel fashion peptides having free hydroxyl groups bonded to threonine may be linked in this manner.[77] Other work concerned with the glycosylation of threonine and serine has involved the use of the following glycosylating agents, 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-β-D-galactopyranosyl chloride,[78] 3,4,6-tri-*O*-acetyl-2-allyloxycarbonylamino-2-deoxy-α-D-glucopyranosyl trichloroacetimidate[79] and the pentaacetate of glucosamine and hence the corresponding 1,2-oxazoline intermediate.[80] Also, enzymic methods have been adopted, transfer of β-D-glucopyranose and β-D-galactopyranose to the appropriate amino acid hydroxy groups being effected from the corresponding *o*-nitrophenyl glycosides.[81] Other hydroxy-containing α-amino acids to have been glycosylated are hydroxyproline which was converted to the 2-acetamido-2-deoxy-β-D-glucopyranoside by trichloroacetimidate technology[82] and a suitably protected tyrosin derivative which was converted into the β-D-galactopyranoside by use of the *O*-benzoylated glycosyl bromide prior to solid-phase glycopeptide synthesis. Analogous work was carried out with disaccharide and trisaccharide derivatives of tyrosin.[83] Other glycosylated peptides to have been produced include derivatives of the antidiuretic hormone arginine-vasopressin,[84] a dimeric Tn antigen-lipopeptide conjugate,[85] and penta-*O*-(*N*-acetyl-α-D-galactosaminyl)-MUC1 eicosapeptide, which is a glycosylated counterpart of the highly immunogenic tandem repeat sequence of carcinoma-associated mucin. This work involved solid-phase synthesis.[86]



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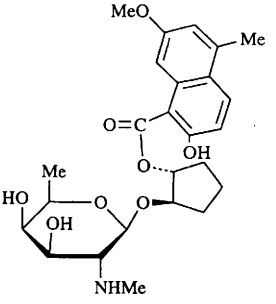
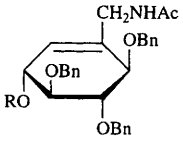


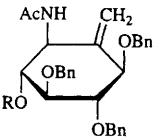
45

Interest continues in glycosylated derivatives of cyclitols and related compounds (see also Chapter 18). Thioglycoside technology was used to synthesize compound **45** which is an analogue of the chromophore of neocarzinostatin.[87] Various *myo*-[88, 89] and *chiro*-[88]inositol monophosphates carrying 2-amino-2-deoxy-α-D-glucose have been made as insulin-mimetics, and compounds **46** and **47** have been prepared by glycosylation procedures as potential enzyme inhibitors.[90]

In the field of glycosylated steroids the following have been synthesized: the 6-deoxy-β-D-



46 R = tetra-*O*-acetyl-β-D-glucopyranosyl



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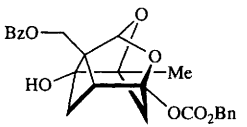
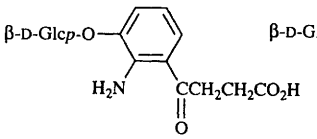


48

glucopyranosides and -α-L-mannopyranosides of androstane,[91] four β-D-glucopyranosides of 20-hydroxyecdysone,[92] and 6-*O*-glucuronides, glucosides and *N*-acetylglucosaminides of hyodeoxycholic acid.[93] In the search for new sweetening agents various glycosides including disaccharide glycosides of glycyrrhetic acid have been produced by synthetic methods,[94, 95] and a 3-*O*-mono-β-D-glucuronide, a potent sweetening agent, has been produced by selective biological hydrolysis of a disaccharide glycoside of this triterpene.[96] Enzymic methods were also used to produce the 28-*O*-β-galactopyranoside of oleanolic acid, phenyl β-D-galactopyranoside in organic solvents being used as the sugar source.[97] Glucosylation using the trichloroacetimidate method of the complex alcohol **48** led to a synthesis of the monoterpene glycoside (-)-paeoniflorin.[98]

Several reports have appeared on the synthesis of glycosides of flavanoid compounds. Methods used involved use of glycosyl fluorides[99] and bromides[100]and also enzymic[101] and electrochemical [101a] techniques. Other natural compounds to have been glycosylated are: 4″-*epi*-methylamino-4″-deoxyavermectin B, (thioglycoside method)[102] and gibberellin A5 which was glucosylated at the 13 position as well as at the carboxylic acid centre,[103] various ergot alkaloids which were mannosylated enzymically,[104] phosphate analogue of podophylotoxin.[105] and benz[A]anthracycline analaogues of 4-demethoxydaunorubicin. [106]



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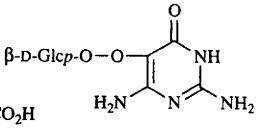

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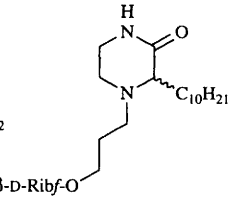


51

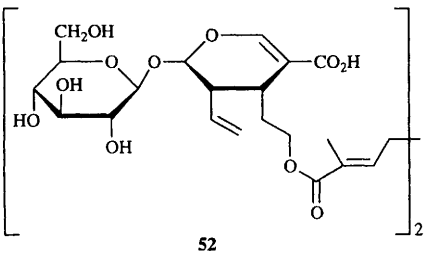
As always, interest has been taken in the preparation of glycosylated compounds containing aromatic aglycons. For example the *O*-β-D-glucopyranoside of 2-amino-3-hydroxyacetophenone has been prepared, it being a fluorescent compound which occurs in aging human lens.[107] The closely related glycoside **49** has been isolated from a protein-free extract of this tissue.[108] Compound **50**, vicene, a constituent of vetch seeds, has been constructed by condensation of a

glycoside derived from 2-hydroxycyanoacetic acid and guanidine. Use of urea instead of guanidine gave rise to the related heterocycle compound convicine.[109] The use of a galactosidase enabled the β-glycosylation of thiamine at the primary alcohol centre,[110] and in the area of modified nucleosides, 5-β-D-glucopyranosyloxymethyl-2'-deoxyuridine, which is a modified nucleoside of a *Trypanosoma* DNA has been made,[111] as has compound **51** which has some antiretroviral activity.[112]

1.3 *O*-Glycosides Isolated from Natural Products.—As usual, only compounds showing special features, either structural or biological, are dealt with in this section.

Cyanogenic glycosides isolated from cassava include β-D-glucopyranosides of the cyanohydrin of acetone and butanone with the glucosyl units carrying further β-D-glucopyranosyl substituents at O-6.[113] (Z)-Hex-3-enyl β-D-glucopyranoside is the compound responsible for the "greenish" odour in vegetables and teas.[114] Hypertensive glycosides isolated from *Moringa oleifera* are phenyl 4-*O*-acetyl-α-L-rhamnopyranosides bearing substituents such as CH_2NHCO_2Et and $CH_2NHC(S)OMe$ in the *para*-positions.[115]

Apigenin 7-*O*-β-D-glucopyranoside, a known flavanoid glucoside, has shown anti-HIV properties,[116] and naringin, which is the bitter principal of grapefruit, and a closely related compound but with α-L-Rha*p*-(1→2)-β-D-Glc*p* as disaccharide unit, complexes with β-cyclodextrin by way of the phenolic ring, but carbohydrate-carbohydrate interactions were also deemed to be involved.[117] A new secoiridoid glycoside which has a very bitter taste is a dimer



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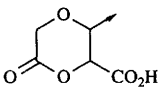
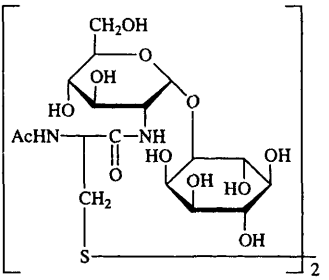


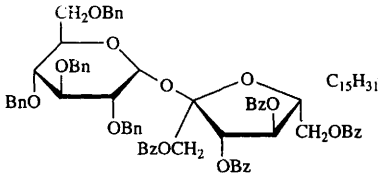
53

of the structural unit **52**,[118] and a glucuronic acid glycoside of oleanolic acid has the unusual cyclic substituent **53** on *O*-3 of the uronic acid unit.[119] Compound **54** is a very unusual glucosaminyl inositol compound which exists in a dimeric form linked by a cystinyl bridge.[120]



54

1.4 Synthesis of Disaccharides and their Derivatives.—Several non-reducing disaccharides of the homo- and hetero-type have been produced starting from *O*-benzylated derivatives of glucose, rhamnose and xylose having, on the one hand, free hydroxyl groups at the anomeric centre, and on the other, chlorine substituents. The mixed products were separated chromatographically and debenzylated.[121] Reaction of 2,3,4,6-tetra-*O*-benzyl-D-glucose with its α-trichloroacetimidate in the presence of an acid catalyst gave the α/β-linked non-reducing disaccharide and α,α-trehalose in 52% and 39% respectively. Similar condensations were effected starting from mannose and galactose derivatives.[122] Trimethylsilyl triflate also catalyses the dimerization of 1-hydroxy compounds without reliance on trichloroacetimidates. Products derived from D-glucose, D-galactose and D-xylose were described.[123] The same catalyst also caused the condensation of tetrabenzyl-D-glucose with 1,3,4,6-tetra-*O*-benzoyl-D-fructosyl diethyl phosphite and the derivative of the α,α-linked sucrose isomer **55** resulted.[124] Coupling of 3,4,6-tri-*O*-acetyl-2-deoxy-2-



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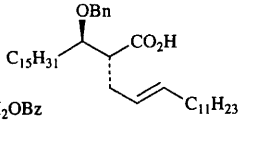

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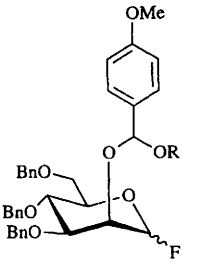


56a

phthalimido-D-glucose with 3,4,6-tri-*O*-benzoyl-2-deoxy-2-*N*-benzoyloxyimino-α-D-glucosyl bromide in the presence of silver triflate gave the product with β- and α-linkages of these sugars in 72% yield.[124a]

The enzymic transfer of fructose from sucrose to L-sorbose as acceptor gave 2-*O*-β-D-

fructofuranosyl-α-L-sorbopyranoside. When D-galactose and L-arabinose were used as acceptors, in addition to non-reducing products, fructofuranosyl disaccharides linked β-1,3 and β-1,4 were formed respectively.[125] Condensation of glucose and its 2-deoxy-derivatives in the presence of a trehalase resulted in α,α′-trehalose and the 2,2′-dideoxy-α,α′-analogue. The mixed reducing disaccharide was also described in the course of the work.[126] DCC coupling of suitably benzylated trehalose and the acid **56** gave access to the 6,6′-ester, a microbacterial 'cord factor'.[127] Examination of several disaccharides including non-reducing compounds by f.a.b.-m.s. led to the conclusion that the configurations of the inter-sugar linkages could be determined.[128]

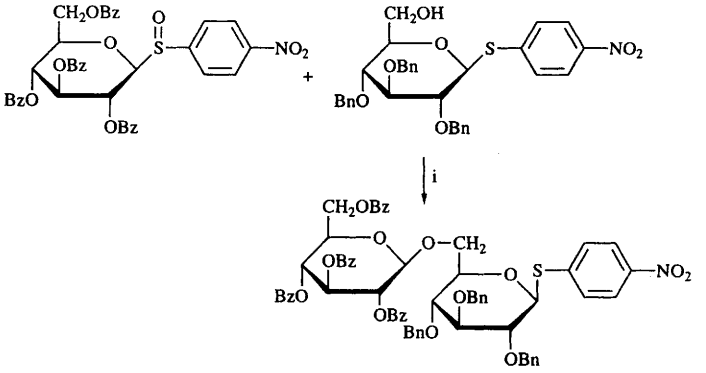
Much attention continues to be paid to inter-unit linking methods for the production of reducing disaccharides. A study of the effect of lithium perchlorate in organic solvents on the coupling of many glucosylating agents and alcohols has been reported. With primary sugar alcohols, disaccharides were formed in about 50% yields, and with glycosyl bromides, chlorides, fluorides or trichloroacetimidates there was only modest anomeric selectivity. However with glycosyl diphenylphosphates α- and β-compounds gave β-linked products with good and complete selectivity respectively.[129]

Vasella and coworkers have reported extensive studies on the condensation that occurs between the glycosylidene carbene derived from the *spiro*-diazirine of 2,3,4,6-tetra-*O*-benzyl-D-glucose and the following glucosyl acceptors: several methyl 4,6-*O*-benzylidine hexopyranosides,[130,131] methyl 6-*O*-trityl α-D-altropyranoside,[132] the anomeric benzyl-D-ribopyranosides[133] and allyl 6-*O*-benzyl-2-deoxy-2-phthalimido-α-D-allopyranoside.[134] In each case several products were identified and considerable attention was paid to the influences affecting anomeric configurations and regeoselectivities.

Glycosyl acetates as glycosylating agents can be condensed with tetrahydropyranyl ethers when trimethylsilyl triflate is used as catalyst and disaccharides can be made by this approach.[135]

Thioglycosides are now well established as glycosylating agents which have been shown to be activatable by use of I(III) reagents, for example PhIO,[136] or *N*-phenylselenylphthalimide in the presence of trimethylsilyl triflate. Some yields in excess of 90% were reported for disaccharide syntheses using this approach.[137] A considerable advantage of phenyl thioglycosides is that different members of the series may be selectively activated for glycosylation purposes as is illustrated in Scheme 5. Thus the sulfoxide is activated as a glycosylating species (even although it is *O*-benzoylated) ahead of the thioglycoside which is benzylated. Normally esterified glycosylating agents are deactivated.[138]

Intermediates of the type **56a** which are produced by treatment of the corresponding *p*-



Reagents: i, TmsOTf, $P(OEt)_3$

Scheme 5

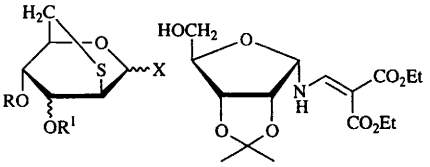
methoxybenzyl ether of the glycosyl fluoride with DDQ and the alcohol ROH, collapse on activation at the anomeric centre with silver triflate to deliver the alkoxy group from the β-direction. In this way β-mannosyl disaccharides have been made in approximately 70% yield.[139] The closely similar method starting from 2-*O*-isopropenyl 1-thiomannopyranosides (Vol. 25, p. 38) has been extended and found to be applicable to the exclusive synthesis of β-linked mannopyranosyl disaccharides. Yields were in the range 50-70%.[139a] A further paper on isopropenyl glycosides illustrates how they may be selectively activated as glycosyl donors by use of trimethylsilyl triflate in the presence of 4-pentenyl glycosidic compounds. This therefore enables the production of disaccharide 4-pentenyl glycosides which themselves are glycosyl donors and have been used to generate a trisaccharide.[140] In somewhat related work a *O*-benzylated 1-buten-3-yl-glucopyranoside has been isomerized with a rhodium coordination compound to the corresponding 2-en-2-yl-isomer. This, being a vinyl glycoside, is activatable with trimethylsilyl triflate in the presence of its precursor and thus a system can be developed whereby active glycosylating agents can be coupled with inactive hydroxy compounds and the products again activated.[141]

A further paper on glycosyl phosphites as glycosylating agents (cf ref. 124) describes the coupling of such compounds with sugar alcohols, the glycosylating phosphites being *O*-acetylated and members of the glucose, galactose, 2-deoxy-2-phthalimido-D-glucose and neuraminic acid series were examined. Yields generally near 60% were obtained with good 1,2-*trans* selectivity.[142] A related paper reports successful coupling of *O*-benzylated-L-rhamnose bis(2,2,2-trichloroethyl)phosphite with a 2-azido-4,6-*O*-benzylidene-2-deoxy-D-glucoside (75%, α-anomer), trimethylsilyl triflate being the catalyst. The donor was comparable with the corresponding trichloroacetimidate and had the advantage of being more stable. *O*-Acylated and 2-azido-2-deoxy

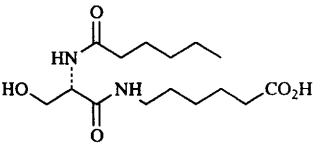
glycosyl phosphites gave lower yields of disaccharides.[143]

Conversion of 2,3,4,6-tetra-*O*-benzyl-D-mannose to the corresponding dimethyl phosphinothioates gave a useful α-mannosylating agent. Condensation is effected with silver perchlorate and the yield of disaccharide given with diacetone-D-galactose was 80%.[144]

Glycosyl tetrazols have been examined as glycosyl donors which can be activated with zinc chloride or trimethyloxonium tetrafluoroborate. The derivative obtained from 3,4-di-*O*-benzylolivose when condensed with diacetoneglucose gave 48% yield of the disaccharide with high α/β anomeric selectivity.[145] Examination of a set of compounds based on structures **57** has indicated a new route to glycosides of 2,6-dideoxy-sugars. Glycosyl acetates, fluorides and *S*-phenyl glycosides were examined, and by use of the last of these an α-1,4-linked dimer was produced from which an olivose-based disaccharide is obtainable.[146]



57 **58**



59

Disaccharides now will be dealt with according to the nature of the residues at the non-reducing termini. A note on the solid phase synthesis of oligosaccharides by the Danishefsky approach, that is zinc chloride-activated glycosylation using 1,2-anhydro-3,4,6-tri-*O*-benzyl-D-glucose and a glycal acceptor, states that this is not *a priori* a stereospecific process as has been suggested.[147] The synthesis of the lipoteichoic acid of *Enterococcus hirae*, which is based on a glyceryl glycoside of the α-1,2-linked glucobiose kojibiose with complex phosphate ester functions at the two sugar primary positions, has been reported.[148] Kojibiose has also been detected in the reaction products formed by sucrose phosphorylase reaction on α-D-glucose 1-phosphate and sucrose. Nigerose, the α-1,3-linked isomer, was also present in the mixture,[149] and laminaribiose, the β-1,3-linked glucobiose, has been found as a 6-malonyl ester in a natural product.[150] Laminaribiosides have also been produced synthetically from 2,4,6-tri-*O*-substituted glucosides and converted into their epoxyallyl and epoxybut-3-enyl glycosides.[151] A series of alkyl (C-7 to C-18) β-cellobiosides have been examined as thermotropic liquid crystals.[152] The boron trifluoride-catalysed reaction of tetra-*O*-acetyl-α-D-glycopyranosyl fluoride with methyl 2,3-*O*-benzoyl-4,6-tetra-isopropyldisilyloxy α-D-glucopyranoside causes desilylation and efficient glycosylation at the primary centre (Vol 25, Chap 3, Ref 121). An expansive study of this reaction has shown that a variety of compounds may be used to give excellent yields of β-1,6-linked products.[153]

An unusual synthesis of methyl α-isomaltoside involved electrolysis of methyl α-D-

glucopyranoside in DMF containing lithium bromide followed by the addition of acetobromoglucose. The α-1,6-linked disaccharide glycoside was obtained in 38% yield as the tetraacetate together with some products of deacetylation. It was suggested that the α-configuration follows the generation of a β-linked intermediate involving the solvent.[154] Conformational analyses by molecular mechanics of various glucobioses and some glucosyl fructoses have been reviewed.[155] A glucosyl transferase has been used to glycosylate the 4-position of *N*-acetylglucosamine bonded to an alkaloid, and similar work involving a galactose transferase was also reported.[156] Attention has been paid to methyl 4-*O*-α-D-glucopyranosyl-α-L-idopyranosiduronic acid. Several sulfates of the compound and of the glucosaminyl analogue were prepared as models of repeating units in central sequence of heparan sulfate.[157] Also in connection with heparin chemistry it has been reported that glycosylations of derivatives of L-idose give unexpected α/β-ratios. Glucopyranosylation, for example, of L-iduronic acid derivatives gives anomalous results whereas expected ratios are obtained with 1,6-anhydro-L-idopyranose.[158]

2-*O*-β-D-Glucopyranosyl-D-xylose is the disaccharide unit of a new quercitin glycoside. Its structure was established by synthesis.[159] The ribofuranosyl enamine **58** was condensed with several glycosylating agents to produce disaccharide analogues including the β-D-glucopyranosyl, β-D-galactopyranosyl and β-D-galactofuranosyl analogues.[160] Enzymic glucosylation of *N*-(benzyloxycarbonyl)-1-deoxynojirimycin gave various mixtures of 2-, 3- and 4-substituted products depending upon the source of the enzyme used. With yeast β-glucosidase the main product was the β-linked 2-substituted derivative.[161]

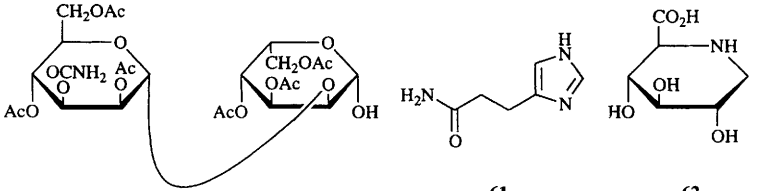
In the area of disaccharides terminating in galactose, enzymic methods of synthesis have become particularly significant, and β-galactosidase has been used to transfer galactose to the 6-position of β-glucosides and thioglucosides and analogous positions on corresponding galactosides.[162] Related transfer from *p*-nitrophenyl β-D-galactopyranoside to *N*-acetylglucosamine furnished *N*-acetyllactosamine together with some of the 1,6-linked isomer which is often the main product of some enzymic transfers.[163] Transfer to the 4-position of D-glucose linked by a photosensitive bridge to a resin gave a product which on photoirradiation gave lactose in good yield, so this represents an enzymic method which proceeds regioselectively in the solid phase.[164] Entirely parallel work has led to a synthesis of *N*-acetyllactosamine, the cleaving from the polymer, in this case being by hydrogenolysis.[165] A chemical-enzymic method has led to the synthesis of a glycopeptide by bonding *N*-acetylglucosamine to the peptide thence to a resin. By galactosyl transfer an *N*-acetyllactosamine peptide was obtained which was finally released from the resin.[166] Galactosyltransferase from bovine milk caused glycosylation at O-4 or O-1 of D-xylose, the reaction being considered in considerable detail.[167] A related study of

transfer to β-D-xylopyransides led to mixtures of β-1,3- and β-1,4-linked disaccharides. Conversions were about 20% and the isomer ratios differed largely according to the natures of the aglycons.[168] β-D-Arabinofuranosyl cytosine acted as an acceptor, galactosylation occuring at the primary hydroxyl group of the sugar.[169]

Chemical galactosylations have been reported as follows. A study of the influence of substituents on the aromatic ring of 1,2-*O*-cyanobenzylidine derivatives of galactose on the regiochemistry of the reaction with 3- and 6-trityl ethers of galactopyranosides indicated that the regioselectivity depended on these substituents.[170] For purposes associated with study of the recognizing abilities of a lectin, several disaccharides were synthesized as allyl glycosides. These involved linkage of the sugar to β-D-galactose by either 1,2- or 1,3-linkages, to α-D-mannose by 1,3-linkage and to α-D-*N*-acetylgalactosamine by α- and β-1,3-linkages. Several α-D-galactopyranosyl analogues were also produced.[171] Several lactose derivatives having 4,6-*O*-naphthylmethylidene acetal groups as well as complex alkyl aglycons were prepared as biofluorescence compounds for analysis of ceramide glycanase activity.[172] Alcohol **59** has been linked to β-lactose by solid phase methods to give a new glycolipid.[173] Methyl β-D-galactopyranosyl-D-xylopyranosides have been made by glycosylation of appropriate acetates which were made by enzymic selective acylation procedures,[174] and the conformations of methyl 4-*O*-(β-D-galactopyranosyl)-β-D-xylopyranoside and benzyl 3-*O*-(β-D-galactopyranosyl)-β-D-xylopyranoside have been determined by n.m.r. methods and by molecular mechanics calculation.[175] Various pyrimidine nucleosides have been found to be unreactive under Koenigs Knorr conditions, but can be galactosylated with the *O*-acetylated galactosyl α-trichloroacetimidate in the presence of BF_3.[176] Regioselective sulfation of lactose and other disaccharides by use of dibutylstannylene acetals is referred to in Chapter 7.

Elegant intramolecular approaches to the synthesis of β-mannosides have already been referred to (cf. refs. 3, 4, 139 and 139a). Several reports have appeared on the preparation of α-linked compounds. Thus the enzymic catalytic influence of recombinant *E. coli* cells allows the coupling of α-D-mannopyranosyl units to the 2-position of α-D-mannopyranosides. Several such disaccharide glycosides were made including glycopeptide compounds.[177] Large scale use of this technique and a wider range of examples have also been reported,[178] and the octyl glycoside of α-1,2-linked mannobiose has been made as its 6-phosphate ester.[179] Analogues of this phosphate containing glycosyl peptide units and α-1,6-linked isomers have been derived by chemical methods.[180] Separation of the *exo*- and *endo*-isomers (varying in the dioxolan rings) of methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside by fractional crystallization allowed their independent study in the presence of lithium aluminium hydride-aluminium trichloride, and they were found to open selectively with the *exo*-phenyl isomer yielding the 2-hydroxy-3-benzyloxy

compound while the *endo*-isomer gave a product with the benzyl on group *O*-2. In the course of this work derivatives of the α-1,2-linked mannobiose were described.[181] As part of the total synthesis of bleomycin A_2, the 2-*O*-α-D-mannopyranosyl-L-gulose disaccharide **60** was synthesized using a diphenyl glycosyl phosphate for interunit bonding, and the L-configurated sugar was produced by way of the 6-deoxy-5-ene also derived from methyl α-D-mannopyranoside.[182]

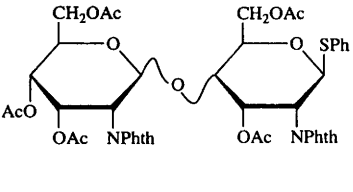


60 **61** **62**

Jacquinet and colleagues have investigated in some detail the use of *N*-trichloroacetyl derivatives of glucosamine, notably both anomeric trichloroacetimidates and the corresponding oxazoline in disaccharide synthesis. β-Products were obtained in about 80% yield and the choice of the glycosylating agent is dependent upon the nature of the hydroxyl group to be substituted.[183] Considerable interest has been shown in the synthesis of chitobiose compounds. The *N,N*-diacetyl disaccharide linked as the glycosylamine to the amide **61** inhibits the chitinase of brine shrimp.[184] The disaccharide itself has been produced by enzymic coupling, using the *p*-nitrophenyl glycoside as donor. In the reaction the β-1,6-linked isomer was also produced and relative rates of these coupling reactions were studied in detail.[185] Other work has reported disaccharide derivatives with phthalimido nitrogen protection.[186] Tetra-*O*-acetyl-2-allyloxycarbonylamino-deoxy-2-β-D-glucose has been satisfactorily linked to several other 2-amino glucose derivatives using trimethylsilyl triflate as catalyst,[187] and chitobiose having the amino group at the reducing unit *N*-acylated with a long chain fatty acid has been reported following a selective chemical substitution.[188]

The major lipopolysaccharide isolated from *Rhodobacter sphaeroides* is based on the β-1,6-linked glucosaminobiose. It has fatty acids linked to both amino groups and to *O*-3 and *O*-3′ as well as phosphate esters at *O*-1 and *O*-4′. Synthesis of two compounds which closely match the structure of the natural material failed to finalize that structure.[189] *N*-Acetyl-glucosamine has also been linked to *O*-4 of methyl β-D-glucuronide[190] and enzymically to *O*-3 of β-D-arabinofuranosyl cytosine[169] and *O*-4 of the glucuronic acid analogue **62**. The product in the latter case was sulfated at the primary position to give a potential heparanase inhibitor.[191] The glycosylating agent 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl trichloroacetimidate was found to be unreactive with a heavily substituted methyl glucoside containing a free hydroxyl at C-4.[192] Phenylselenoazidation of tri-*O*-methyl-D-glucal resulted in the 2-azido-2-deoxy phenylselenyl

glycoside with the α-*gluco*-configuration. Coupling of this with diacetone galactose gave the 2-azido-2-deoxy-trimethylglucosyl galactose disaccharide.[193] An improved synthesis of tetra-*O*-acetyl-2-deoxy-2-phthalimido-D-galactose has been reported, and solution and polymer supported approaches to the synthesis of 4-*O*-*N*-acetylgalactosaminyl galactosides have been developed.[194]



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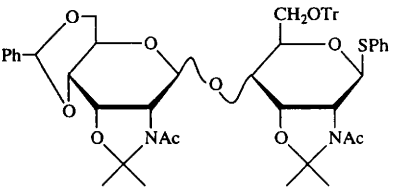
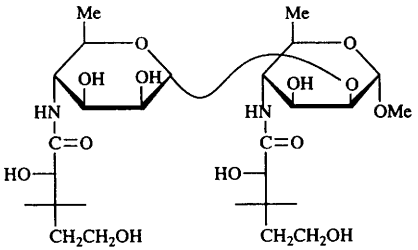


64

Chitobiose has been converted into glycosylating agent **63** in connection with synthetic studies on allosamidin which contains an allosaminobiose.[195] A further complete synthesis of this insecticidal compound has been reported,[196] and Kuzuhara and co-workers have described the preparation of the mono-de-*N*-methyl analogue. In the course of this work the glycosylating agent **64**, having the unusual acetal-like protecting groups, was reported.[197]



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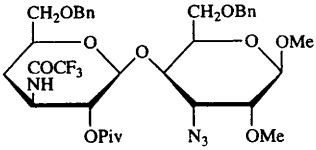
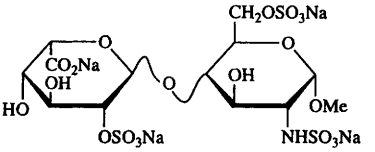


66

Synthesis of the methyl glycoside **65** of the disaccharide repeating unit of *Vibrio cholerae* polysaccharide has been completed using two approaches, the better of which involved completing the development of the two monosaccharide units prior to glycoside coupling.[198] Phenyl thioglycoside coupling was used to produce compound **66** in 96% yield in a model reaction for one to be applied to the synthesis of the enzomycin antibiotics which are highly functionalized hexosyloctosyl nucleosides.[199]

In the area of deoxyhexose-based disaccharides, the isomalto di- and tri-saccharide compounds devoid of oxygen at C-2 have been produced by standard methods.[200] 3-*O*-α-D-Fucopyranosyl-D-glucose has been synthesized with *O*-2 of the fucose unit carrying a methyl group,[201] and 6-*O*-α-L-rhamnopyranosyl-D-glucose has been prepared as a fully substituted glycosyl thiocyanate and used in the synthesis of a rhamnoglucan polysaccharide.[202]



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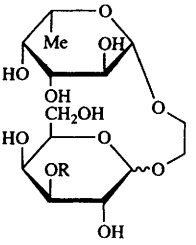


68 R = CH_2CO_2H

As always, considerable attention has been given to disaccharides based on sugar acids of different kinds. Thus compound **67**, a major repeating unit of heparin, as well as its 6-desulfated derivative, have been made.[203] By use of its acetylated glycosyl fluoride Kdo has been α-linked to other Kdo molecules through position 4 and position 8. Corresponding trisaccharides were then developed (see Chapter 4).[204]

Sialic acid derivatives, as always, have attracted appreciable attention. *N*-Acetyl-neuraminic acid has been dimerized by way of a 2,8-linkage using a glycosyl phosphite as glycosylating agent, and a derivative of the 1,7-lactone as acceptor.[205] In related work this dimer was phosphate linked to cytidine in the course of investigations of sialyl transferase.[206] A ganglioside M5 from sea urchin egg which has *N*-glycolyl neuraminic acid α-2,6-linked to glucose has been prepared,[207] and sialidase derived from a virus transfers sialic acid via an α-linkage to the 3-position of galactose.[163] The sialyl glycosyl xanthate has been used to glycosylate at the 6-position of *N*-acetylgalactosamine linked to threonine to give the sialyl T_n-epitope.[208] By standard methods using appropriately protected 7-deoxy-heptose compounds as acceptors, α-D-NeuAc-(2→6)(6Me,*R*)-β-D-Gal-OR′ and the corresponding diastereoisomer at C-6, have been described, together with corresponding compounds having sulfur instead of oxygen as the interunit connecting atom.[209, 210]

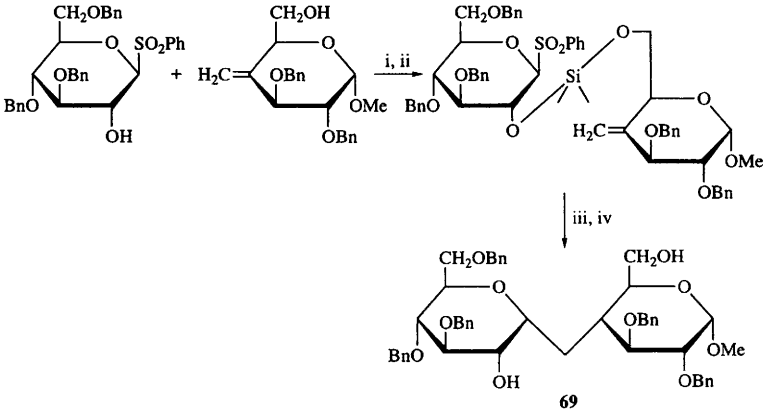
Pentosyl disaccharides have been reported as follows: 4-*O*-β-D-xylopyranosyl-D-xylose, prepared using a 2,3-diacetylxylose glycoside produced by stannylation procedures,[211] 6-*O*-β-D-xylopyranosyl-D-glucose occurs in oolong tea leaves as a component of terpenoid glycosides which are the precursors of aromas.[212, 213] Diacetone galactose condensed with 1,2-anhydro-3,4-di-*O*-benzyl-β-L-arabinopyranose in the presence of zinc chloride gives a high yield of the 6-linked arabinosylgalactose derivative with an α/β ratio 2:1.[214]

References to 2,3-unsaturated disaccharides are given in Chapter 13.

6-*O*-β-D-Apiofuranosyl-β-D-glucopyranosides with various terpenoid aglycons have been synthesized.[215]

1.5 Disaccharides with Anomalous Linking.—Several compounds have been described which have two sugar units linked by groupings other than simple glycosidic bonds. These are collected in this section which is used for first time in this volume. The bonds may be between the two anomeric centres and thus the products are analogues of non-reducing disaccharides, between one anomeric centre and a non-anomeric centre, and between two non-anomeric centres. These will be considered in turn.

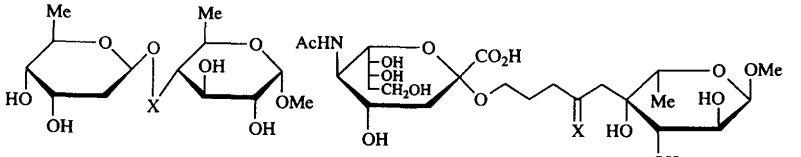
Two molecules of *N*-acetylglucosamine have been linked glycosidically by α,ω-alkadiyl residues containing 6, 8, 10 or 12 carbon atoms. Enzymic procedures were involved.[216] Related compounds having lengthy alkenediyl linkages have been produced by metathesis reactions of ω-unsaturated alkyl glucosides. For example *O*-substituted β-D-glucopyranosides of undec-2-en-11-ol on reaction with chloroaryloxy complexes of tungsten underwent such a dimerisation process to give two glucose units linked by way of a 20-carbon alkenyl chain, the double bond being in a central position.[217] Standard chemistry involving the use of trichloroacetimidate coupling with a 2-hydroxyethyl fucoside gave rise to galactosylfucosyl disaccharide analogue **68** which is a sialyl Le^x mimic.[218] Compound **69** is a disaccharide analogue having a methylene in place of the interunit oxygen atom and has been made as shown in Scheme 6 by means of a free radical



Reagents: i, BuLi; ii, Me_2SiCl_2; iii, SmI_2, PhH, HMPA; iv, HF

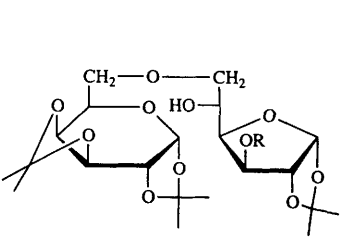
Scheme 6

intramolecular delivery procedure. The overall yield was 50%.[219] (See also refs. 283-291, 301) The branched-chain sugar disaccharide **70** (X=CH_2) and the hydroxylamine linked analogue with X=NH have been synthesized, and a combination of force field calculations and n.m.r. conformational studies have been used to investigate the impact of the hydroxylamine glycosidic

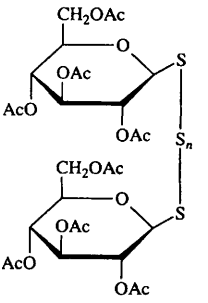


70 **71** X = O; H, OH

linkage on the shape of the calicheamycin oligosaccharide.[220] Compounds **71** (and analogues having longer bridges) were made by condensation of a neuraminic acid formylmethyl glycoside derivative with a phosphonate derived from a branched-chain sugar having three carbons in the branch. They were used in studies of sialyl Lewis^X, in particular to find the sialyl fucose optimal distance for binding.[221] The reaction of various monohydroxy monosaccharide derivatives with 5,6-anhydro-1,2-*O*-isopropylidine-D-glucose 3-ethers, under basic conditions, led to a set of disaccharide analogues linked through two carbon atoms neither being at the anomeric positions. In this way, for example, compound **72** was prepared, and such hydroxy compounds can again react with the anhydride to give pseudotrisaccharides.[222] Various reactions of the ether-linked disaccharides such as partial deprotection, *O*-alkylation etc were then described.[223]



72



73 *n* = *e.g.* 2,9

1.6 Hydrolysis and Other Features of Glycosides and Disaccharides.—Hydrolysis of isopropenyl α- and β-D-glucopyranoside at pH 3 occurs by alkyl-oxygen fission. Consistent with this, methanol can be added to the vinyl ether double bonds in the presence of an acid catalyst. The hydrolysis of the glycoside occurred with retention of configuration.[224] In a series of tetra-*O*-benzyl-β-D-glucopyranosides derived from ω-alkenyl alcohols only the pentenyl compound underwent hydrolysis following halonium ion formation. In the other cases bromohydrin adducts were produced.[225] Glycoside hydrolysis of *p*-nitrophenyl α- and β-D-glucopyranoside tetraphosphates involves intromolecular nucleophilic catalysis by the phosphate group at *O*-2 in the case of the β-anomer. The α-anomer shows no enhancement.[226, 227] The hydrolysis of the

p-nitrophenyl α-glycoside of *N*-acetylneuraminic acid has been further examined by use of ^{18}O-substituted at the glycosidic centre.[228]

Saccharides linked glycosidically to an α-hydroxy carbonyl compound cleave readily on treatment with hydrazine. Such glycosides are commonly encountered following periodate or lead tetraacetate cleavage of oligosaccharides.[229]

The transport of *p*-nitrophenyl β-glycosides of D-glucose, D-galactose and D-mannose through liquid organic membranes in the presence of organoboron compounds has been examined. Phenylboronic acid and diphenylborinic acid were amongst the boron derivatives used.[230] Dodecyl β-D-glucopyranoside 6-phosphate forms micelles above 0.225 mmol/l and the products have been used in capillary electrophoresis in a manner that allowed resolution of racemic amino acids, for example the dansyl derivatives of valine, phenylalanine.[231] Hexopyranose derivatives with a trifluoromethyl group at C-6 have been used as chiral dopans for ferroelectric liquid crystals.[232]

2 S- and Se-Glycosides

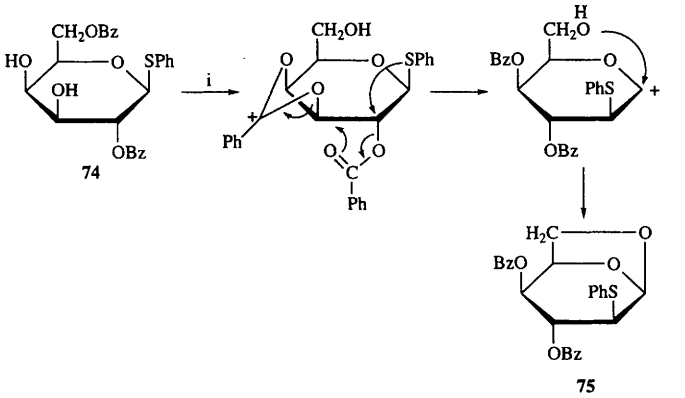
Thioglycosides are now fully established as useful glycosylating agents and have been utilized in many of the papers referred to in earlier sections of this chapter.

A novel way of making thioglycosides is to treat O-protected glycosyl thiocyanates with Grignard reagents at low temperatures.[233] From a 1,2-*O*-(1-methoxyethylidine)-β-D-mannopyranose derivative, by treatment with methyl thiolacetate in the presence of boron trifluoride, the corresponding α-linked thiomannopyranoside was produced.[234] Synthesis of phenylthio compounds from 1,2-anhydrides is referred to in Chapter 8. Methyl thioglycosides of 2-, 3- and 4-deoxy-L-fucose have been produced from the corresponding glycosyl acetates by treatment with trimethylsilyl methylthioether under acid conditions.[235] In the pentofuranose series 2,3,5-tri-*O*-benzyl-D-xylose and D-arabinose, on treatment with thiols in the presence of concentrated hydrochloric acid, gave high yields of ethylthio-furanosides, the selectivities favouring the α- and the β-compounds respectively. No dithioacetals were observed with this chemistry unlike with the analogous reaction of 2,3,4-tri-*O*-benzyl-D-xylopyranose from which the ethyl diothioacetal, under some conditions, was produced in high yield. Treatment with concentrated hydrochloric acid in benzene resulted in the ring closure to give the ethyl thiopyranosides, but this approach was not successful in the case of the hexopyranosides.[236] Treatment of the glycosyl chloride with thiophenol in the presence of tetrabutylammonium sulfate, which represent very mild conditions, resulted in the α-phenyl thioglycoside of *N*-acetylneuraminic acid.[237] Nitrophenyl thioglycosides are very readily prepared using the

corresponding fluoronitrobenzenes and the *O*-acetylated 1-thiosugars.[238]

2-Glycosylthiobenzoquinones, which are irreversible glycosidase inhibitors, can be made by treatment of the *O*-acetylated glycosyl thiols with quinones in the presence of phenyl iodosodiacetate.[239] Heterocycles which have been linked to sugars by sulfur bridges include hydantoins,[240] various aryl pyrazoles,[241] and substituted pyrimidines.[242] Treatment of the pentaacetate of 1-thio-α-D-glucose with sodium methoxide followed by tetra-*O*-acetyl-2-*O*-triflyl-D-mannose resulted in the production of thiokojibiose. In similar fashion thionigerose and thioisomaltose were produced.[243] Similar type of linking between a 6-tosylate derived from *N*-acetylglucosamine gave rise to the 1→6-linked *S*-fucosyl thioglucosamine, and in related fashion *S*-fucosyl-thioglucose linked 1→4 was produced. 1→2- And 1→3-*S*-linked disaccharides were also described in this paper.[244] The 2-acetylthio-derivative of a substituted neuraminic acid, treated with various substituted monosaccharides having bromine at the primary positions, resulted in sulfur-linked disaccharides involving *N*-acetylneuraminic acid *S*-linked to *N*-acetylglucosamine, glucose and ribose via the primary centres.[245] Tetra-*O*-acetyl-1-thio-β-D-glucose, treated with various polysulfanes, has afforded a way of producing the polythio compounds **73**.[246]

When the phenyl thiogalactoside derivative **74** was treated with methyl pyruvate and boron trifluoride etherate without solvent, the mixed 3,4-acetals were obtained in 70% combined yield. When the reaction was repeated in the presence of dichloromethane, however, the only product obtained (30% yield) was the 1,6-anhydro-D-iodo compound **75**. As illustrated in Scheme 7 it



Reagents: i, CH_2Cl_2, $BF_3{\cdot}OEt_2$, $MeCOCO_2Me$

Scheme 7

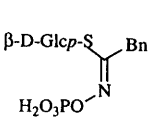
is speculated that the reaction was diverted by initial migration of the primary benzoate to O-4, and this induced an extensive intramolecular rearrangement.[247]

The first phosphate isostere, **76**, of a naturally occurring glucosinolate has been prepared in connection with studies of myrosinase activity.[248]

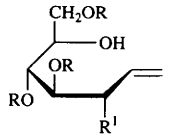
Addition of diphenyldiselenide and sodium azide in the presence of phenyl iodosodiacetate to tri-*O*-acetyl-D-glucal resulted in 2-azido-2-deoxy-α-phenylselenylglycosides. In the case of tri-*O*-acetyl-D-galactal the α- and the α-*galacto*-analogue was the only product formed (92%).[249] The same addition reaction has been applied to glycals derived from disaccharides.[250]

3 C-Glycosides

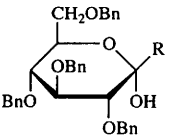
3.1 Pyranoid Compounds.—Mercury(II)-induced cyclization of compound **77**, followed by



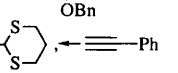
76



77 R = Bn, R^1 = H
78 R = Bn, R^1 = OBn
79 R = Tbdms, R^1 = H



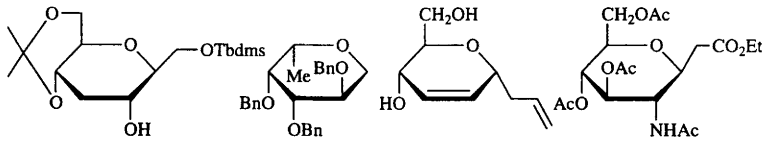
80 R =



81 R =

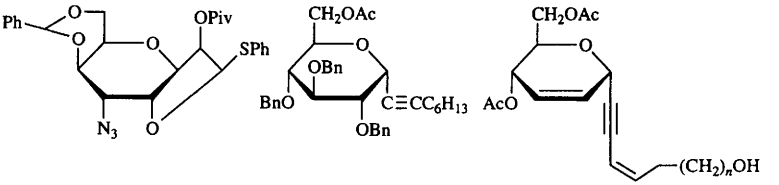
reduction of the carbon-mercury bond, led to the α- and β-*C*-methyl 2-deoxy-glycosides in the ratio 60:40, this result contrasting with a previous observation by Sinäy *et al.* (Volume 15, page 40) that compound **78** cyclized exclusively to give the α-compound. When compound **79** was cyclized it also led to the α-compound and these observations were considered in detail.[251] C-1-Lithiated pyranoid compounds treated with various electrophiles have led to new examples of C-glycosides. In particular α- and β-C-glycosides of *N*-acetylglucosamine have been described,[252] as have glucosyl compounds bearing unprotected hydroxyl groups at C-2. In this case the lithiated compounds were produced from 1,2-anhydro-derivatives by way of 2-hydroxy-glycosyltin intermediates.[253] Two papers have appeared on the synthesis of 1-C-formyl glucopyranosyl products starting from tetra-*O*-benzyl-D-glucono-1,5-lactone, compounds **80**[254] and **81**,[255] being intermediates in these reactions respectively. Compound **82** was made starting from a methyl 2,3-dideoxypyranoside and via a phenylsulfonyl derivative as a component of polycyclic polyether neurotoxins, for example brevotoxin.[256]

intermediates in these reactions respectively. Compound **82** was made starting from a methyl 2,3-dideoxypyranoside and via a phenylsulfonyl derivative as a component of polycyclic polyether neurotoxins, for example brevotoxin.[256]



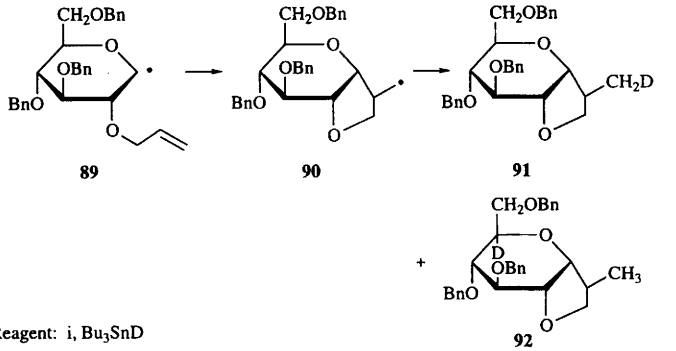
82 **83** **84** **85**

Trimethylsilyl triflate is a potent catalyst for the synthesis of C-glycosides. For example 1-*O*-acetyl-2,3,4-tri-*O*-benzyl-L-fucose can be added to isobutene under its influence, the product being compound **83**, formed in 71% yield. In the case of the D-mannose analogue the intermediate carbocation trapped the triflate anion.[257] Otherwise, and rather surprisingly, it catalyses the reaction of allyl trimethylsilane with unprotected glycals to give 2,3-unsaturated glycosides, D-glucal, for example, giving compound **84** in 91% yield with almost complete stereoselectivity.[258] Compound **85** was made from the corresponding glycosyl chloride using diethyl malonate with potassium hydride as base and 18-crown-6.[259]



86 **87** **88** $n = 0$–3

The bicyclic compound **86** has been made from β-D-galactopyranosyl cyanide tetraacetate by chain extension of the aglycon and cyclization. It was then used to introduce a pyrimidine



89 **90** **91** **92**

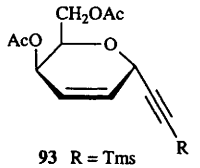
Reagent: i, Bu_3SnD

Scheme 8

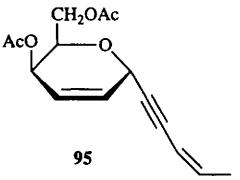
substituent in place of the phenylthio group.[260] Free radical **89**, produced from the corresponding phenyl selenylglycoside by treatment with tributyltin deuteride, afforded not just the expected product **91** but, in 78% yield, the isomer **92** carrying deuterium at C-5. This implies the intermediate radical **90** underwent not just direct deuteration to give **91** but also radical translocation prior to deuteration. (Scheme 8).[261]

Tributyltin alkynes react with glycosyl halides in the presence of silver tetrafluoroborate to give glycosyl alkynes, compound **87** being made by this method from the corresponding glycosyl chloride in 85% yield together with about 10% of the β-anomer.[262] Related work has described the acetylenic C-glycosides of various 2-amino-2-deoxy-sugar derivatives.[263]

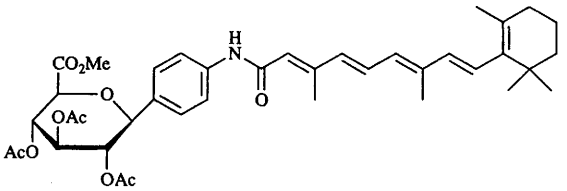
Several reports have appeared on aspects of the chemistry of acetylenic glycosides of unsaturated sugars. The series of compounds **88** were made from the simple *O*-acetylated glycosyl acetylene by palladium mediated substitution processes, and cyclizations were then effected on the acyclic portion of the molecules to give cobalt-containing 8-membered ring compounds. See also chapter 24.[264] See Chapter 13 for further examples of formation of cobalt complexes of carbohydrate acetylenes. Several glycosylacetylenes having double bonds in the sugar rings have been produced with halogens on the terminal acetylene carbon atom. Thus compound **93** was converted into **94** by use of *N*-bromosuccinimide and silver nitrate. Examples include diacetylenic compounds.[265] Dienyne **95**, converted to a cobalt hexacarbonyl complex and treated with triflic acid, undergoes epimerization and the β-anomer can be isolated. 3,4-Unsaturated analogues also undergo this isomerization.[266]



93 R = Tms
94 R = Br



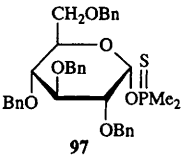
95



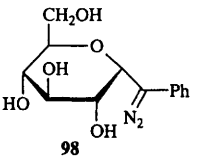
96

A review on the methods of synthesis of C-aryl glycosides has appeared.[267] The retinamidophenyl glucuronide **96** and related compounds, which have potential anticancer properties, were made from the corresponding *p*-aminophenyl derivative.[268] While the

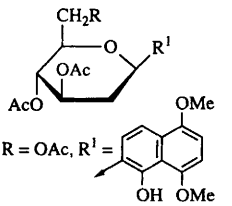
glycosylating agent **97** reacted with *m*-trimethylsilyloxyanisole in the presence of silver perchlorate to give the *O*-glycoside with replacement of trimethylsilyl group, reaction of the same compound in the presence of the same catalyst with 1,3,5-trimethoxybenzene afforded the C-glycoside with no substitution of alkoxy groups in 69% yield, only the β-product being obtained.[269] Reaction of acetobromoglucose with benzylmagnesium chloride followed by acetylation led to the benzyl *β-C*-glycoside and the isomeric *C-o*-tolyl compound in the ratio 1:3. Several acetohalogen sugars, however, led only to the benzyl *C*-glycosides.[270] α-D-Glucopyranosyl phenyldiazomethane, **98**, was synthesized from the α-aminobenzyl *C*-glycoside as a mechanism-based α-glucosidase inhibitor.[271]



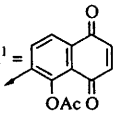
97



98

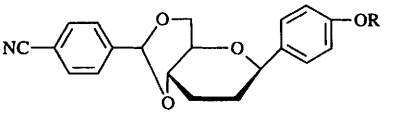


99 R = OAc, R^1 =

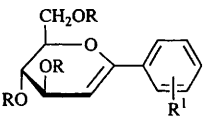


100 R = H, R^1 =

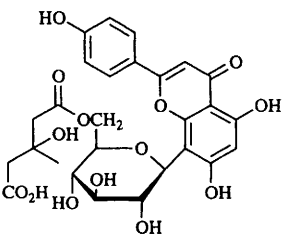
Reaction of *O*-unprotected methyl glycosides and free sugars with a range of α-naphthol compounds in the presence of trimethylsilyl triflate led to β-*C*-glycosides linked through the 2-position of the naphthol in good yields.[272] Condensation of the corresponding glycosyl acetates with 5,8-dimethoxy-α-naphthol in the presence of boron trifluoride gave β-*C*-glycosides **99** and **100**, the latter corresponds to the CD ring in the *C*-glycoside of the angucycline antibiotics.[273]



101 R = $(CH_2)_nCH_3$
n = 0, 5–13

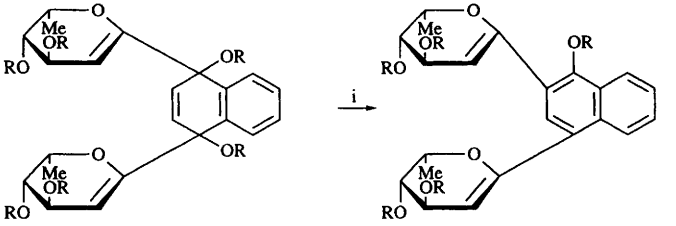


102 R = Tbdms



103

In the area of unsaturated *C*-glycosides, the series of compounds **101** was produced for studies of liquid crystal behaviour, tri-*O*-acetyl-D-glucal being the starting material.[274] Condensation of 1-stannylated glycals having silylated *O*-protection with aryl halides in the presence of palladium catalysts afforded compounds represented by **102**.[275] The bis-*C*-glycoside **104** was made from naphthoquinone using the C-1 lithiated glycal and underwent the dienone/phenol rearrangement on treatment with zinc chloride to give **105** which is a model compound for the antibiotic kidamycins which are antitumour agents. By using mixed glycals asymmetric compounds were obtained, and the direction of migration of the glycal group could

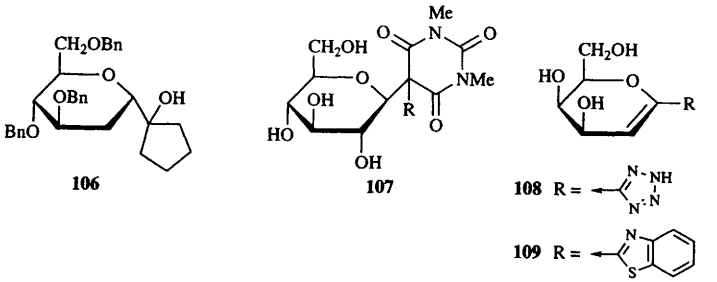


104 R = Tbdms **105**

Reagent: i, $ZnCl_2$

Scheme 9

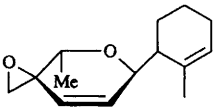
be controlled (Scheme 9).[276] A *C*-glycosylapigenin **103** has been isolated from millet and shown to have insect antifeedant actity.[277] A paper has appeared on the reaction of carbohydrate radicals and 1,4-benzoquinone and anthraquinone.[278] Reaction of 3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hexopyranosyl chloride with samarium diiodide in the presence of cyclopentanone gave 70% of the *C*-glycoside **106**. A samarium(III) intermediate was surmised as being present.



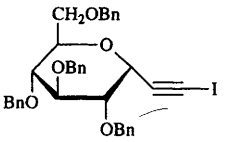
106 **107** **108** R = **109** R =

Phenylglycosyl sulphones also gave *C*-glycosides under these conditions, but elimination concurrently occurred.[279] Several compounds based on **107** (R=H) which allows alkylation and introduction of groupings with unsaturation within R have been prepared as potential monomers for the preparation of polyvinylsaccharides.[280] Elaboration of 1-cyanoglycals has allowed the

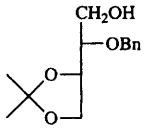
production of compounds of the type **108**, **109**.[281] Starting from the corresponding enones several α/β-unsaturated *C*-glycoside epoxides of the type **110** have been made.[282]



110



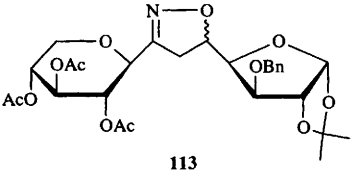
111



112

C-Linked disaccharides have been mentioned earlier in this chapter (cf ref. 219). References to several others are now given. A full report has appeared on the preparation of the *C*-linked analogue of sucrose (see *J. Chem. Soc. Chem. Commun.*, 1989, 642), the key step in the synthesis involving a Wittig reagent derived from a *C*-glycoside carrying a 3-carbon side chain with 2,3-isopropylidene glyceraldehyde.[283] A related approach used the iodoacetylene **111** and the L-threitol derivative **112** and led to the *C*-linked trehalose analogue, and in the course of the work the α/β- and β/β-anomers were also prepared. Solution conformations were as predicted on the basis of the diamond lattice analysis, and it was concluded that the α-*C*-bonds were conformationally more rigid than β-*C*-bonds.[284]

In the area of analogues of reducing disaccharides the methylene-linked 3-α-D-galactopyranosyl-D-mannose has been prepared by coupling of the *O*-protected galactosyl radical with an enone based on a "naked sugar" followed by refunctionalization of the latter.[285] Schmidt and Dietrich have prepared the *C*-analogue of lactose with methylene, hydroxymethylene and carbonyl group linkages, the key step being the coupling of a lithiated glycal derivative with a 4-*C*-formyl-4-deoxy glucose compound,[286] and Sinäy has produced closely related compounds based on lactose and cellobiose by intramolecular radical trapping between two sugar derivatives bonded by a silicon bridge between two oxygen atoms.[287, 288] Appropriate coupling of a glycosyl nitryl oxide and a 5,6-dideoxy-hex-5-enopyranose derivative led to compound **113** which provided



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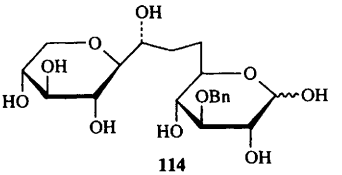
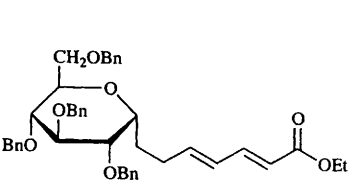


114

a means of obtaining the *C*-linked compound **114**.[289] Controlled hydroxylation of double bonds of compound **115** and reduction of the ester group to the aldehyde function, gave access to the

C-linked analogue of the α-1,6-linked D-glucopyranosyl-D-galactose and D-glucopyranosyl-D-



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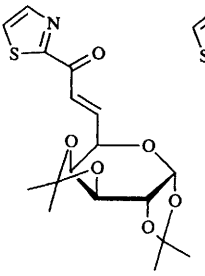
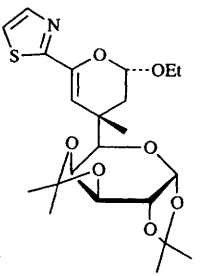


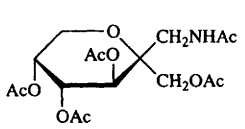
116



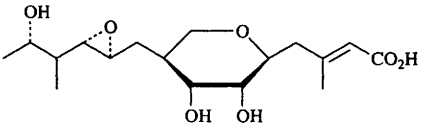
117

idose.[290] Compound **116**, coupled with ethyl vinyl ether, gave compound **117** and an isomer, from which were built disaccharide analogues having hexoses linked through *C*-3 to *C*-6 of D-galactose.[291] (See also ref. 301.)

Some compounds having two carbon substituents at the anomeric centre have been reported. Thus glycosyl cyanides prepared from sorbose and fructose have been described and have led, for



118

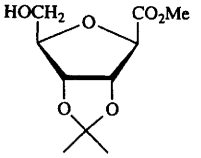


119

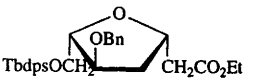
example, to the production of compound **118**.[292] Vasella's group have published further on their spiral addition of glycosyl carbenes to C_{60} and have produced acid-sensitive compounds from which fully deprotected products and partially deprotected compounds were prepared.[293] The readily available monic acid, **119**, which can be considered to belong to the branched-chain *C*-glycosidic class has been used to make many variants with aromatic units in place of the carboxylic acid group.[294]

3.2 Furanoid Compounds.—As has become usual, a range of methods have been applied to the synthesis of compounds of this series. Scandium perchlorate, an unusual Lewis acid catalyst, catalysed the reaction of 2,3,5-tri-*O*-benzoyl-β-D-ribopyranosyl acetate and α-(trimethylsilyloxy)styrene to give the benzoylmethyl *C*-furanosides in very high yield with 94:6 selectivity in favour of the α-anomer.[295] In parallel work the analogous benzylated ribofuranosyl

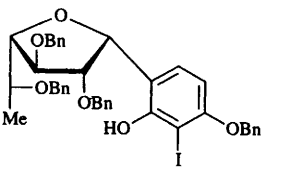
iodoacetates have been treated with allyltrimethylsilane and tin(II) chloride as catalyst to give the α-*C*-allyl glycoside again with very high α-selectivity.[296] Reference is made to *C*-allyl furanosides having unsaturation within the sugar rings in Chapter 13. Fleet and co-workers have prepared compound **120**, of obvious potential for the synthesis of *C*-nucleosides, by their based-catalysed ring-contraction of 3,4-*O*-isopropylidene-2-*O*-triflyl-D-altrono-1,5-lactone.[297] A



120

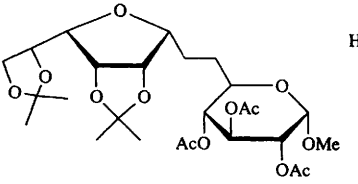


121



122

synthesis of compound **121** has been completed starting from *meso*-diethyl tartrate, whereas the *R,R* isomer led to the epimer of **121** at *C*-3.[298] Reaction 2-deoxy-3,5-di-*O*-tolyl-α-D-*erythro*-pentofuranosyl chloride with various phenylmagnesium bromide derivatives led to a series of β-linked compounds considered to be hydrophobic isosteres of the natural *C*-nucleosides.[299] 2,3,5-Tri-*O*-benzyl-D-fucofuranosyl acetate, coupled with 3-benzyloxy-2-iodophenol in the presence of dicyclopentadienyl hafnium dichloride gave high yields of mainly the α-compound **122** which was further tranformed in a number of steps into the *C*-glycosidic antibiotics "gilvocarcin M" and "gilvocarcin V". The reaction proceeds by initial *O*-glycosylation followed by *O*- to *C*-



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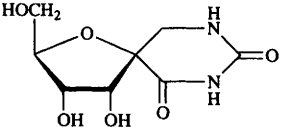

124

migration.[300] The *C*-linked disaccharide derivative **123** has been produced by radical addition of the pyranoid unit to the double bond of the furanoid precursor having an *exo*-difluoromethylene group at C-1[301] (cf. refs. 219, 283-291). Compound **124** which is an analogue of the natural herbicide hydantocidin, has been made from the corresponding psicosyl cyanide, but it lacked herbicidal activity.[302]

Other *C*-glycosides of interest as precursors of *C*-nucleosides are referred to in Chapter 20.

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4
Oligosaccharides

1 General

As previously, this Chapter deals with specific tri- and higher oligosaccharides; most references relate to their synthesis by specific chemical and, increasingly, enzymic or combined methods. Chemical features of the cyclodextrins are noted separately.

Considerable progress has been reported in the use of enzymes in synthesis. A review has been published on the synthesis of oligosaccharides by use of glycosyl transferases,[1] and a simplified procedure for obtaining irregularly linked oligosaccharides from starch involves the use of a novel maltogenic amylase and a further α-amylase, both obtained from a cloned bacillus.[2] 2-Deoxy-α-D-*arabino*-hexopyranosyl phosphate and 2-deoxy-maltooligosaccharides have been made from D-glucal, potassium dihydrogen phosphate, and a phosphorylase. With maltotetraose as a primer, oligomers of DP up to 22 were obtained. For the synthesis of the glycosyl phosphate starch can be used as the primer.[3] Further studies by Kobayashi's group (cf. *Carbohydr. Res.*, 1993, **249**, 127) have shown that β-D-lactosyl fluoride, in the presence of a cellulase, transfers lactose to a wide range of acceptors, with β-(1→4) links being always formed. With methyl β-D-glucopyranoside, -cellobioside and -cellotrioside, galactose-terminating tri-, tetra- and penta-saccharides were produced. In addition, methyl β-D-mannoside gave β-D-Gal*p*-(1→4)-β-D-Glc*p*-(1→4)-β-D-Man*p*-OMe.[4] Lysozyme hydrolysis of partially *N*-acetylated chitosans has led to *N*-acetylchito-oligosaccharides from the di- to the pentamers.[5] Several new bacterial α-D-xylosidases have been isolated and compared with a commercially available material. One showed novel α-1→3-xylosyl transfer activity.[6]

Catalysis by trityl perchlorate of the polymerisation of 4-*O*-acetyl-1,2-*O*-cyanoethylidene-3-*O*-trityl derivatives of D-fucose and of methyl D-galacturonate has led to oligomers containing five and six units, respectively.[7]

2 Trisaccharides

Compounds in sections 2.1 - 2.3 are categorized according to their non-reducing end sugars.

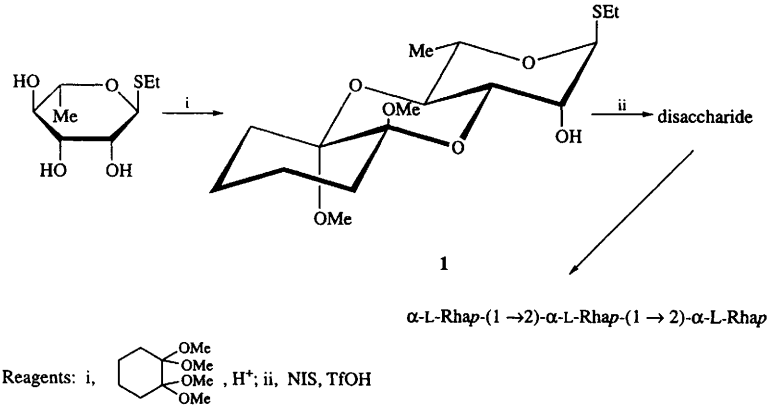
2.1 Linear Homotrisaccharides.—The non-reducing, trehalose-containing trisaccharide

bemisiose, α-D-Glc*p*-(1→4)-α-D-Glc*p*-(1→1)-α-D-Glc*p*, has been isolated from the honeydew of a Bemisia whitefly.[8]

Several aryl maltotriosides carrying 2-aminobenzyl or related substituents at O-2′ and O-3′ have been made as potential fluorescence-quenched substrates for α-amylases.[9]

A very elegant one pot synthesis has resulted in the production of a derivative of the β-1,6-linked glucotriose. Initially phenyl 2,3,4-tri-*O*-acetyl-1-thio-β-D-glucopyranoside was glycosylated, and the dimeric product was coupled (AgOTf activation) with methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside, the resulting trioside being obtained in 84% yield. Variations on this theme showed that acetylated glycosyl trichloroacetimidates and fluorides could be activated selectively in the presence of phenyl thioglycosides.[10] The α-(1→6)-β-(1→6)-linked glucotriose has been produced, also by use of phenyl 1-thioglycoside sulphoxide technology.[11] Attempts to get rid of the bitter aftertaste of the sweetening glycoside stevioside involved treatment with starch hydrolysate in the presence of dextranase and isoamylase, which produced further glycosylated compounds, amongst which was a steviol derivative containing α-D-Glc*p*-(1→6)-β-D-Glc*p*-(1→2)-β-D-Glc as well as other trisaccharides.[12]

A β-1,4-linked glucosamine trimer having *N*-phthaloyl protection and various substituents elsewhere suitable for selective deprotection has been described.[13] In the area of trimers of deoxysugars 4-*O*-benzyl-L-rhamnal has been used to give a trimer which ultimately led to a 1,3-linked trisaccharide derivative comprising 2,3,6-trideoxy-α-L-*threo*-hexose.[14] In related work ethyl 1-thio-α-L-rhamnopyranoside has been converted to derivative **1** and hence the α-1,2-linked trimer as indicated in Scheme 1.[15]



Scheme 1

Treatment of a hardwood with a bacterial β-xylanase afforded different xylo-oligosaccharides including the β-1,3, β-1,4-linked xylotriose. Two xylotetroses were also produced during this work.[16] The α-(2→8),α-(2→4)-linked Kdo trimer, which is the immuno-dominant fragment of the backbone of chlamydia LPS, has been made by synthetic methods in the modified form having the carboxylic acid groups reduced to the hydroxymethyl groups.[17]

2.2 Linear Heterotrisaccharides.—Methodology using the selectively activatable isopropenyl glycosides in the presence of 4-pentenyl analogues, has led to the synthesis of β-D-Glc*p*-(1→4)-β-D-Glc*p*-(1→6)-D-Gal.[18] β-D-Glc*p*-(1→4)-β-D-Glc*p*-(1→4)-β-D-cymaropyranose is a trisaccharide formed on acid hydrolysis of the plant product leptaculatin.[19] Enzymic glucosyl transfer to lactose has led to a trisaccharide,[20] and β-D-Glc*p*-(1→3)-α-D-Gal*p*-(1→4)-D-Gal has been made by chemical procedures together with analogues having D-galactose, glucosamine and 4-deoxy-glucose in the non-reducing terminal position.[21]

In the synthetic study of glycopeptides β-D-Glc*p*-(1→6)-α-D-Man*p*-(1→6)-α-D-Man*p*-1-*O*-L-serine and the corresponding compound have L-proline in place of serine have been made as potential phytoalexin elicitors,[22] and trisaccharides having β-D-Glc*p*-(1→6)-β-D-Man*p* at the reducing end have been prepared by inversion at C-2 of D-glucose analogues. The inversion was effected by oxidation reduction of 2-hydroxy compounds.[23] The trisaccharide 3-*O*-Me-β-D-Glc-(1→3)-α-L-Rha*p*-(1→2)-L-Tal with a pyruvic acid acetal at the 4,6 positions of the non-terminal unit,[24] and a close analogue with a methyl pyruvate acetal[25] were synthesized as parts of studies of the glycolipids of *Mycobacterium*. In related work β-D-Glc*p*-(1→3)-2-*O*-Me-α-L-Rha*p*-(1→3)-2-*O*-Me-α-L-Rha*p* was prepared.[26] Kestose [(α-D-Glc*p*-(1→2)-β-D-Fru*f*-(1→2)-β-D-Fru*f*)] was the major compound formed on transfructosylation of sucrose.[27]

A new derivative of ara-C isolated from a·microbacterial culture filtrate has been identified as a nucleoside containing the trimer β-D-Gal*p*-(1→4)-β-D-Gal*p*-(1→3)-D-Ara*f*.[28] β-D-Gal*p*-(1→4)-β-D-Glc*p*-(1→4)-6-deoxy-D-Glc, prepared with an incorporated crown ether built upon *O*-2 and *O*-3 of the reducing entity, has been made as a potential drug-targeting vector,[29] and an analogous trimer, but with the deoxy centre on the nonreducing moiety and with α,α-interunit bonds, has been prepared for use in the synthesis of acarbose.[30] β-D-Gal*p*-(1→6)-β-D-Glc*p*-(1→6)-β-D-Glc was made by coupling by chemical methods an enzyme-prepared galactosyl glucose derivative with a glucose compound having a free hydroxyl group at C-6.[31] Trimer α-D-Gal*p*-(1→3)-α-L-Rha*p*-(1→3)-L-Rha is a trisaccharide related to the *Klebsiella* type 9 antigen and has been made synthetically.[32] β-D-Gal*p*-(1→4)-β-D-Glc*p*NAc-(1→6)-D-Man has been reported as part of the HIV virus and synthesized with a sulfate ester group on the central unit.[33] The related compound β-D-Gal*p*-(1→4)-β-D-Glc*p*NAc-(1→3)-β-L-Fuc*p* has also been prepared.[34]

α,α-Trehalose carrying glucosamine β-linked at *O*-4 has been synthesized, and a derivative was subjected to detailed n.m.r. study.[35] *N*-Acetylchitobiose β-1-linked to *O*-2 of a D-galactose phosphate ester has been made as a structural analogue of moenomycin A.[36] β-D-Glc*p*NAc-(1→6)-α-D-Man*p*-(1→6)-D-Man and the corresponding trimer with glucose in place of mannose at the reducing terminus have been made as *p*-nitrophenyl glycosides, the nitro groups have been reduced and the compounds have been coupled to proteins for immunochemical purposes,[37] and the closely related β-D-Glc*p*NAc-(1→2)-α-D-Man*p*-(1→6)-β-D-Glc, which is the specific *N*-acetylglucosamine T-V acceptor, has served as a model for three analogues which have been prepared; it was concluded that none of the hydroxyl groups in the central residue were essential for binding.[38] The glycosylated lactose β-D-Glc*p*NAc-(1→4)-β-D-Gal-(1→4)-D-Glc has been produced by chemical methods,[39] and the analogue carrying the *N*-acetylglucosamine residue at position 6 of the galactose moiety has been obtained by β-galactosidase hydrolysis of a tetrasaccharide.[40] In the course of this work four trisaccharides were isolated from goat colostrum. They were: α-L-Fuc*p*-(1→2)-β-D-Gal*p*-(1→4)-D-Glc, α-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→4)-D-Glc, β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→4)-D-Glc and β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→4)-D-Glc.[40]

In the area of trisaccharides containing deoxysugars, the 2-deoxy-galactose compound 2-deoxy-α-D-Gal*p*-(1→4)-β-D-Gal*p*-(1→4)-D-Glc has been made in the course of studies of the neoglycolipids of deoxyglobotrioses,[41] and the rhamnose-containing compound α-L-Rha*p*-(1→2)-β-D-Gal*p*-(1→2)-Glc*p*A is a component of chromosaponin 1, the anti-oxidative effects of which have been investigated.[42] The novel antitumour antibiotics, the chrymutasins, contain the fucose trimer 3-*O*-Me-α-L-Fuc*p*-(1→2)-α-L-Fuc*p*-(1→2)-L-Fuc,[43] and α-L-Fuc*p*-(1→2)-β-D-Gal*p*-(1→3)-Gal*p*NAc, which has been synthesized, is part of the hexasaccharide of the antigen from MCF7, a breast cancer cell line.[44]

Three publications have appeared on the synthesis of α-D-Neu*p*-(2→6)-β-D-Gal*p*-(1→4)-D-GlcNAc by chemical/enzymic processes. The first of these also coupled the trimer to a ceramide to provide a glycosphingolipid.[45-47] The *O*-acetylated methyl ester with a phenylthio group at C-3 and in the *S*-ethyl glycosidic form, allowed clean α-sialylation of a lactose derivative and gave access to α-NeuNAc-(2→3)-β-D-Gal*p*-(1→4)-Glc.[48] Koenigs-Knorr procedures were used in the preparation of Glc*p*A(1→3)-α-D-Gal*p*-(1→3)-2-Ac-L-Rha.[49]

The xylobiose derivative α-D-Xyl*p*-(1→3)-α-D-Xyl*p*-(1→3)-D-Glc, a presumed breakdown product of blood coagulation factors VII and IX and protein Z, has been identified in human urine and characterized as a pyridylamino derivative,[50] and β-D-Xyl*p*-(1→6)-β-D-Glc*p*-(1→6)-β-D-Glc, isolated from a triterpene glycoside, is able to suppress the sweetness of 0.4 M sucrose solutions at 1mM concentration.[51] Trimer β-D-Xyl*p*-(1→2)-β-D-Man*p*-(1→4)-D-Glc, which occurs in

microbiological ceramide oligosaccharides, has been synthesized by an ingenious route involving the use of 3,4,6-tri-*O*-benzyl-D-*arabino*-hexos-2-ulosyl bromide.[52]

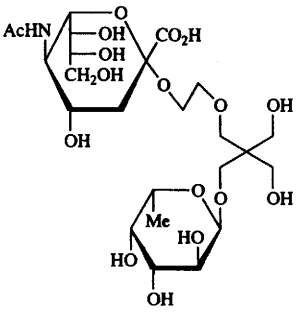
2.3 Branched Homotrisaccharides.—By use of glycosyl dimethylphosphinothioate derivatives the branched mannotriose α-D-Man*p*-(1→6)-[α-D-Man*p*-(1→3)]-D-Man has been prepared.[53]

2.4 Branched Heterotrisaccharides.—Compounds in this section are categorized according to their reducing end sugars.

Glycosylation of methyl α-D-glucopyranoside at positions 2 and 3 have given a set of trisaccharides for conformational analysis. The bonded groups were α-D-mannopyranosyl, β-D-galactopyranosyl, α-L-rhamnopyranosyl and β-L-fucopyranosyl.[54] The blood group trisaccharides α-L-Fuc*p*-(1→2)-[α-D-Gal*p* or Gal*p*NAc]-D-Gal have been prepared with spacer aglycons, some of the monosaccharide components required for the work having been made on 0.5-1 Kg scale,[55] and Lewis[a] trisaccharide α-L-Fuc*p*-(1→4)-[β-D-Gal*p*-(1→3)]-D-GlcNAc has been produced as the sulfate ester at *O*-3 of the galactose moiety.[56] The isomer of the unsulfated form of this trisaccharide having the fucose and galactose substituents in the exchanged positions has been produced as a glycopeptide cluster; that is, several trisaccharides were substituent on the one polypeptide backbone.[57] A long paper on the use of glycosyl phosphites as glycosylating agents has described the use of the method in the synthesis of the branched trisaccharide β-D-Gal*p*-(1→4)[α-NeuNAc-(2→3)]-D-GlcNAc.[58]

2.5 Analogues of Trisaccharides.—Calicheamycin has a trisaccharide component with two of the units joined by way of a hydroxamino linkage (cf. Volume 27 p. 65), and considerable advances have been made in its chemistry this year, the total convergent synthesis having been reported by Danishefsky's group.[59] Kahne and his team have applied the glycosyl sulfoxide method to put together the relevant trisaccharide.[60]

N.m.r. spectroscopy has been used by Nicolaou's group to examine the complex formed between a DNA duplex and a calicheamycin *S*-acetyl derivative and with calicheamycin's oligosaccharide unit, with the results suggesting that the oligosaccharide component is the primary binding element.[61] Kinetic analyses have been reported on related studies also by Nicolaou's group.[62] Compound **2** has been prepared by Hanessian and Prabhanjan as a model of the sialyl Lewis[x] antigen. It showed essentially no binding to selectin IgG.[63] Two new analogues of trisaccharides containing *N*-methylnojirimycin to have been produced are: α-Neu5Ac-(2→3)-β-D-



2

Gal*p*-(1→4)-*N*MeDNJ and α-Neu5Ac-(2→6)-β-D-Gal*p*-(1→4)-*N*MeDNJ.[64]

3 Tetrasaccharides

Compounds of this set are classified according to whether they have linear or branched structures and then by the nature of the sugars at the reducing termini.

3.1 Linear Homotetrasaccharides.—Sophorose has been glycosidically linked to the 4 position of trehalose, both anomeric products having been formed.[65] A tetramer having maltose β-linked to *O*-4 of trehalose has been prepared in a sulfated form as an analogue of trestatin A. It had heparin-like anti-proliferative activity but no anti-coagulant effect. Related tetra- and pentasaccharides were also described.[66] By treatment of pullulan and glucose in the presence of an α-amylase the tetramer α-D-Glc*p*-(1→6)-α-D-Glc*p*-(1→4)-α-D-Glc*p*-(1→4)-D-Glc was produced as well as the isomer having the 1-6 linkage at the reducing end.[67]

In the area of chitotetraose chemistry, the derivative having a 16-carbon acyl group bonded to the amino function at the non-reducing end and a sulfate ester group at *O*-6 of the reducing moiety was isolated and characterized as the root nodule inducing factor of a *rhizobium*.[68] Two formal syntheses of the compound both using trichloroacetimidate technology have been described.[69,70]

3.2 Linear Heterotetrasaccharides.—The glucotriose having L-*glycero*-D-*manno*-heptose bonded at the non-reducing end L-α-D-Hep*p*-(1→6)-α-D-Glc*p*-(1→2)-α-D-Glc*p*-(1→3)-α-D-Glc has been synthesized,[71] as has the related β-D-galactopyranosyl glucotriose β-D-Gal*p*-(1→3)-β-D-Glc*p*-(1→4)-β-D-Glc*p*-(1→4)-β-D-Glc. This compound was prepared with pyruvate acetals at *O*-4 and

O-6 of the two hexose units at the non-reducing end during work carried out in connection with studies of *Rhizobium* exopolysaccharides.[72] Preparation of the lactose 1→3-linked dimer β-D-Gal*p*-(1→4)-β-D-Glc*p*-(1→3)-β-D-Gal*p*-(1→4)-D-Glc has been reported,[73] as has that of the related lactose-containing tetraose β-D-Gal*p*NAc-(1→3)-α-D-Gal*p*-(1→4)-β-D-Gal*p*-(1→4)-D-Glc.[74] Synthesis of GD_3, α-D-Neu5Ac-(2→8)-α-Neu5Ac-(2→3)-β-D-Gal*p*-(1→4)-β-D-Glc*p*, as its 4-methyl-3-pentenyl glycoside has been reported, and it was coupled to a carrier protein in connection with studies of human serum albumin.[75]

Several tetrasaccharides terminating in the *N*-acetylglucosamine units have been described. β-D-Glc*p*A-(1→3)-β-D-Glc*p*NAc-(1→4)-β-D-Glc*p*A-(1→3)-D-GlcNAc, prepared as the *p*-methoxyphenyl glycoside, is a structural element of an extra-cellular hyaluronic acid.[76] β-D-Glc*p*-(1→6)-α-D-Glc*p*NAc-(1→3)-6-deoxy-α-L-Glc*p*NAc-(1→3)-β-D-Glc*p*NAc is a fragment of the cell wall polysaccharide of *Proteus vulgaris*,[77] and β-L-Rha*p*-(1→2)-α-L-Rha*p*-(1→2)-α-L-Rha*p*-(1→6)-D-Glc*p*NAc is the repeating unit of the *Serratia marcescens* O18 polysaccharide.[78] Both have been synthesized.

Other tetrasaccharides to have been described, following synthesis, are the tetramer of hyaluronic acid having glucuronic acid at the reducing end. This represents the alternative possibility to that reported in reference 76.[79] β-D-Gal*p*-(1→4)-α-D-Man*p*-(1→4)-β-D-Gal*p*-(1→4)-D-Man phosphorylated at *O*-6 of the non-terminal galactose unit, which is a portion of the phosphoglycan of a *Leishmania* lipophosphoglucan, and a related hexa- and octa-saccharide have been reported,[80] and β-D-Glc*p*A-(1→3)-β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→4)-β-D-Xyl was prepared glycosidically linked to L-serinylglycine with, on the one hand, a sulfate at position 4 of one of the galactose units, and on the other a phosphate at position 2 of the xylose unit. These structures are found in a carbohydrate-protein linkage region of several proteoglycans.[81]

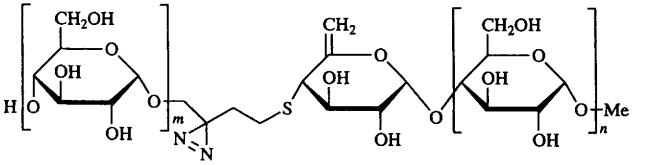
3.3 Branched Homotetrasaccharides.—α-D-Glc*p*-(1→4)-α-D-Glc*p*-(1→6)-[α-D-Glc*p*-(1→4)]-D-Glc and the isomer having the β-configuration at the 1→6 linkage have been described as their *S*-thiophenyl glycosides,[82] and β-D-Glc*p*-(1→3)-[β-D-Glc*p*-(1→6)]-β-D-Glc*p*-(1→3)-D-Glc*p* has been prepared as the 8-methoxycarbonyloctyl glycoside and linked to bovine serum albumin for immunological work.[83]

3.4 Branched Heterotetrasaccharides.—Glucose derivatives to have been reported are: α-D-Neu*p*NAc-(1→3)-[β-D-Gal*p*NAc-(1→4)]-β-D-Gal*p*-(1→4)-D-Glc, synthesized as a modified ganglioside, de-*N*-acetyl GM_2,[84] and α-L-Rha*p*-(1→2)-[β-D-Xyl*p*-(1→3)]-[α-D-Ara*p*-(1→6)]-D-Glc

which is a tetrasaccharide from a triterpene saponin isolated from the flowers of a *Heteropappus*.[85] α-Man-(1→6)-[β-GlcNAc-(1→2)-α-Man-(1→3)]-β-Man and a series of derivatives having various substituents on *O*-3 of the non-reducing mannose terminus have been prepared by recombinant enzyme technology. Other related tetrasaccharides were also described,[86] and chemical methods were used to prepare α-D-Man*p*-(1→3)-[3-*O*-Me-α-D-Man*p*-(1→6)]-β-D-Xyl*p*-(1→2)-D-Man and a close isomer.[87] In the area of 6-deoxyhexose tetrasaccharides, β-D-Qui*p*-(1→3)-[α-L-Rha*p*-(1→2)]-β-D-Qui*p*-(1→2)-D-Qui, which is the tetrasaccharide moiety of plant regulator Calonyctin A, has been produced by chemical methods,[88] as has α-D-Glc*p*A-(1→3)-α-D-Gal*p*-(1→3)-[β-D-Glc*p*-(1→4)]-L-Rha which is the repeating unit of the antigen of *Klebsiella* type 55.[89] The glucuronic acid-terminating β-D-Xyl*p*-(1→2)-α-L-Ara*p*-(1→3)-[β-D-Gal*p*-(1→2)]-D-GlcA has been isolated as a saponin component of tea leaves,[90] and the xylose-based tetrasaccharide α-L-Ara*p*-(1→4)-β-D-Xyl*p*-(1→3)-[α-L-Ara*p*-(1→2)]D-Xyl, containing several points of acetylation, is a component of a marine sponge.[91]

Very considerable interest continues in branched tetrasaccharides terminating in *N*-acetylglucosamine because of their importance in human biololgy. Sialyl Le^x, which is α-D-Neu*p*NAc-(2→3)-β-D-Gal*p*-(1→4)-[α-L-Fuc*p*-(1→3)]-D-GlcNAc, has been produced with several modifications to the galactose moiety; deoxy and deoxyfluoro compounds were described.[92] The analogue with glucose in place of *N*-acetylglucosamine has also been made,[93] an aminopropyl silica solid support has been used for the preparation of SLe^x bonded to a glycopeptide,[94] and physical organic studies have been carried out on the binding of the Lewis b human blood group related tetrasaccharide α-L-Fuc*p*-(1→2)-β-D-Gal-(1→3)-[α-L-Fuc-(1→4)]β-D-GlcNAc to a lectin.[95]

T. Ogawa and his group have recorded the synthesis of the *N*-terminal glycoheptapeptide of human glycophorin Am in which the tetrasaccharide is α-D-Neu*p*5Ac-(2→3)-β-D-Gal*p*-(1→3)-[α-Neu5Ac*p*-(2→6)]-α-D-Gal*p*NAc,[96] and also the making of α-D-Gal*p*NAc-(1→3)-[α-L-Fuc*p*-(1→2)]-β-D-Gal*p*-(1→3)-α-D-Gal*p*NAc, which is a blood group A determining substance. It was prepared as its *N*,*N*-dimethylserinyl glycoside.[97]



m	*n*
1	2
2	1
3	0

3

3.5 Tetrasaccharide Analogues.—Two units of a derivative of 6-*O*-β-D-glucopyranosyl-D-glucosamine have been linked by thiophosgene and through the amino groups to give a tetrasaccharide analogue with the central units linked by way of a thiourea linkage.[98] The set of tetrasaccharide analogues **3** were made in radioactive form to use as photo-affinity probes for the chemical modification of porcine pancreatic α-amylase. It was intended to place the photolabile group in different binding sites of the enzyme.[99]

4 Pentasaccharides

4.1 Linear Pentasaccharides.—The following pentamers with reducing D-glucose groups have been made by chemical methods: α-D-Gal*p*NAc-(1→3)-β-D-Gal*p*NAc-(1→3)-α-D-Gal*p*-(1→4)-β-D-Gal*p*-(1→4)-D-Glc*p*,[100] α-NeuAc*p*-(2→8)-α-NeuAc*p*-(2→8)-α-NeuAc*p*-(2→3)-β-D-Gal*p*-(1→4)-D-Glc,[101] α-KDO-(2→8)-α-KDO-(2→4)-α-KDO-(2→6)-β-D-Glc*p*NAc-(1→6)-Glc*p*NAc,[102] and α-KDN-(2→3)-β-D-Gal*p*-(1→3)-β-D-GlcNAc*p*-(1→3)-β-D-Gal*p*-(1→4)-D-Glc*p*.[103] For α-NeuAc*p*-(2→3)-β-D-Gal*p*-(1→4)-β-D-Glc*p*NAc-(1→3)-β-D-Gal*p*-(1→4)-D-Glc, which was prepared as a ceramide glycoside, a combination of chemical and enzymic methods was employed.[104]

β-D-Gal*p*-(1→4)-β-D-Glc*p*NAc-(1→3)-β-D-Gal*p*-(1→4)-β-D-Glc*p*NAc-(1→6)-D-Gal*p*-NAc, which contains two *N*-acetyllactosamine units, has been made by conventional methods as the serinyl glycoside,[105] and standard step-wise procedures have been used to make the pentasaccharide α-L-Rha*p*-(1→3)-α-L-Rha*p*-(1→2)-α-D-Gal*p*-(1→3)-α-D-Glc*p*NAc-(1→3)-L-Rha, which is related to the *O*-specific polysaccharide of *Shigella dysenteriae* Type I.[106] Amongst the oligosaccharides found in the hydrolysate of a glucoxylan by use of a β-xylanase, a pentamer comprising β-D-glucopyranose 1→4-linked to the terminal unit of β-1,4-linked xylotetraose has been isolated. Similar fragments were also produced and characterized.[107]

4.2 Branched Pentasaccharides.—Interest in the chemistry of the gangliosides and related compounds has led to the synthesis of several compounds of this set. Thus the total synthesis of ganglioside GD2 α-Neu5Ac-(2→8)-α-Neu5Ac-(2→3)-[β-D-Gal*p*NAc-(1→4)]-β-D-Glc*p*-(1→4)-β-D-Glc*p*-(1→1)Cer has been reported.[108,109] Higher saccharides closely related to GD2 have been produced by extending the branching chain. A hexamer, GD1b, a heptamer, GT1b, and an octamer, GQ1b, were described.[108] In related work the pentamer α-NeuAc-(2→6)-[β-D-Gal*p*-(1→3)]-β-D-Gal*p*NAc-(1→4)-β-D-Gal*p*-(1→4)-β-D-Glc*p* has been prepared as the ceramide derivative to give GM1α,[110] and α-L-Fuc-(1→3)-[β-D-Gal-(1→4)]-β-D-GlcNAc-(1→3)-β-D-Gal-

(1→4)-Glc, which is the Le^X pentasaccharide, has been described with a sulfate group on *O*-2 and *O*-3 of the non-reducing galactose moiety.[111] Sialyl Le^x compound α-NeuAc*p*-(2→3)-β-D-Gal*p*-(1→4)-[α-L-Fuc*p*-(1→3)]-β-D-Glc*p*NAc-(1→3)β-D-Gal has been made with a set of analogues having deoxy groups in the fucose unit,[112,113] and also with ketodeoxynonulosonic acid in place of the neuraminic acid group,[103] and the Le^y blood group determinant, which is the pentamer isomer having L-fucose replacing the neuraminic acid on the galactose unit, has been synthesized,[114] as has β-D-Gal*p*-(1→3)-[α-L-Fuc-(1→4)]-β-D-Glc*p*NH_2-(1→3)-β-D-Gal*p*-(1→4)-D-Glc, the Le^a pentasaccharide antigen. In this case glycosyl phosphite methodology was used for forming three of the glycosidic bonds.[115] β-D-Glc*p*NAc-(1→2)-α-D-Man-(1→3)-[β-D-Xyl*p*-(1→2)]-β-D-Man-(1→4)-D-Glc, a component of the glycolipid of spermatazoa of bivalves, has been synthesized,[116] as has the pentamer comprising D-*N*-acetylgalactosamine with *N*-acetyllactosamine condensed through *O*-3 and *O*-6 in the form of the ceramide glycoside.[117]

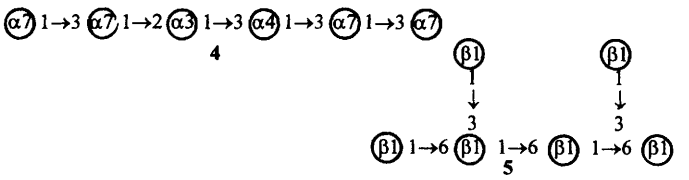
5 Hexasaccharides

As has become customary in these volumes, an abbreviated method is now used for representing higher saccharides. Sugars will be numbered as follows, and linkages will be indicated in the usual way:

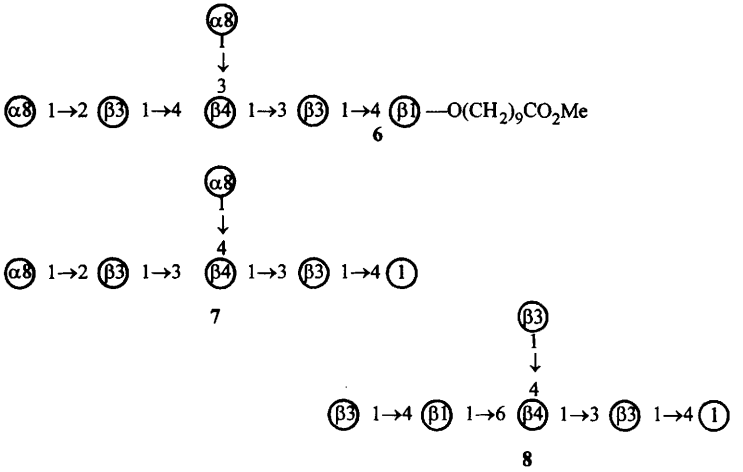
① D-Glc*p*	② D-Man*p*	③ D-Gal*p*
④ D-Glc*p*NAc	⑤ D-Gal*p*NAc	⑥ Neu*p*Ac
⑦ L-Rha*p*	⑧ L-Fuc*p*	⑨ D-Xyl*p*
⑩ D-Glc*p*NH_2	⑪ D-Glc*p*A	⑫ D-Qui (6-deoxy-D-glucose)
⑬ L-*Glycero*-D-*manno*-heptose		⑭ L-Ara*f*

5.1 Linear Hexasaccharides.—Maltohexaose and heptaose were acetylated with potassium acetate as catalyst to give high β- to α- ratios of peracetates, the β-isomers reacting with long chain alcohols in the presence of iron(III) chloride to give anomerically mixed glycosidic products.[118] Chemical methods were used to extend the chain of *p*-nitrophenyl α-maltopentaoside by the attachment of a β-D-glucopyranosyl unit to *O*-6 of the non-reducing terminus. Hexamers with β-D-ribofuranose bonded to *O*-4 or *O*-6 of this residue were also described, as was a di-ribofuranosyl derivative having two furanose units attached to the terminal group.[119] A sulfated hexamer comprising three units of β-D-Gal*p*-(1→4)-α-L-Ido*p*A-(1→3) is an analogue of deaminated dermatan sulfate and binds with high affinity to heparin cofactor II. The hexamer was synthesized starting from a 1,6-anhydro-L-idose derivative.[120] A closely related hexamer carrying

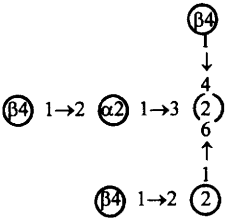
a sulfate group on each sugar unit and comprising three α-L-Ido*p*A-(1→3)-β-D-Gal*p*NAc-(1→4) units, which is a specific part of dermatan sulfate, has also been synthesized and it also activates heparin cofactor II.[121] Hexamer **4** has been prepared representing one of the epitopes of the *O*-specific polysaccharide of *Shigella dysenteriae* type 1.[122]



5.2 Branched Hexasaccharides.—The glucohexaose **5** has been put together by a one-pot strategy involving the linking of the non-reducing terminal trimer with a glucose derivative followed by a coupling of the tetramer to a biose. The product is elicitor-active.[123]



The hetero hexamer **6** has been prepared by Schmidt's group; it is the Le^y antigen,[124] and Danishefsky and Randolph have reported the synthesis of the isomeric compound **7** with the substituent linkages to the *N*-acetylglucosamine unit reversed. In this work key use was made of glycal-derived 1,2-epoxides.[125] The structural element **8** of the capsulate polysaccharide of *Streptococcus pneumoniae* type 14 has also been synthesized.[126]



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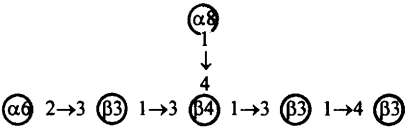

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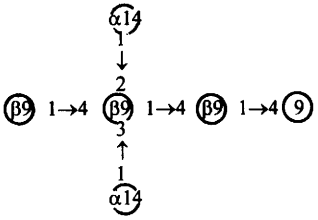
A branching *N*-acetylglucosaminyl transferase was used to bond the 1→4-linked glucosamine unit to the precursing pentasaccharide to give **9**,[127] and the D-galactose-terminating hexamer **10** linked to a ceramide, which is the sialyl Le^a antigen, has been described.[128] ^{13}C n.m.r. spectroscopy has allowed the characterization of hexamer **11** isolated from a wheat bran polysaccharide.[129] A further doubly-branched hexamer, **12**, has been made. It corresponds to a part of the *Salmonella Ra* core polysaccharide.[130]



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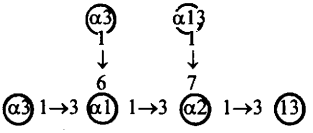

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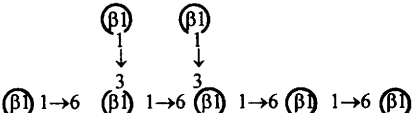
6 Heptasaccharides



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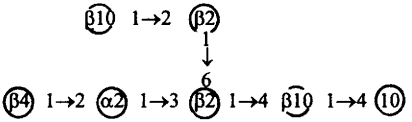
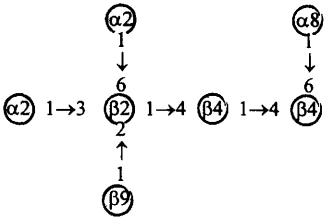


14

The glucoheptaose **13**, which has phytoalexin elicitor activity, has been prepared using a polymer- supported solution synthesis.[131] Compound **14** with *N*-phthaloylation was made as a fully substituted glycosyl azide in work associated with tumour-related *N*-bonded glycans,[132] and related work on glycoprotein led to the preparation of the xylose-containing heptasaccharide **15**.[133]



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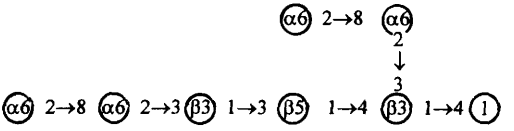
7 Octasaccharides

In the ganglioside field compound GQ16, **16**,[134] and an I-active ganglioside analogue **17**[135] have been described, both glycosidically linked to a ceramide.



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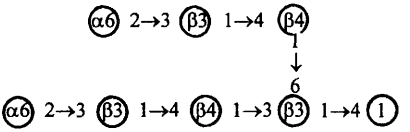
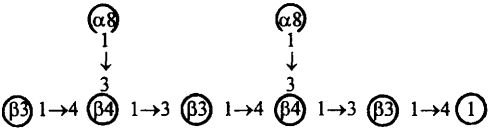


17

In the Lewis antigen series the dimer **18** of Le^x has been described[124] as well as the higher oligosaccharides containing 11 and 14 sugar units formed by introducing further central trimers of the molecule.[136] The linear high rhamnose-containing compound **19** has been made as a fragment of the *O*-specific polysaccharide of *Shigella dysenteriae* type 1.[137]



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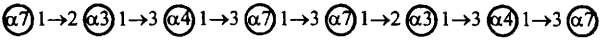
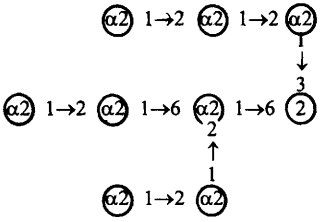


19

8 Higher Saccharides

The mannonoaose **20**, representing the high mannose oligosaccharide of the glycoprotein of the viral coat of HIV1, has been prepared by the use of *n*-pentenyl glycosides.[138] Reference 136 contains descriptions of the synthesis of branched oligosaccharides containing 11 and 14 units which are trimeric and tetrameric Le^x compounds.



20

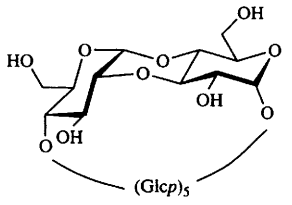
9 Cyclodextrins

A review has been published on cyclodextrins as building blocks for supramolecular structures and functional units. Included was a treatment of the the synthesis of cyclodextrins, their inclusion properties, catenanes derived from them and their use as catalysts.[139]

The α-1→6-linked glucotriose as its 4-pentenyl glycoside and *O*-benzylated except at the terminal 6-position, on treatment with iodonium dicolidine perchlorate, produced the unusual 1→6-linked cyclic trioside in 47% yield, and the cyclic hexaoside in 12%.[140] Related work with the α-1→4-linked glucopentaose methyl *S*-thioglycoside afforded the first glucose-based cyclodextrin containing five sugar units.[141] Analogous technology was used to make the cyclo-L-rhamnopentaose.[142] Permethylated derivatives of cycloinulohexaose and heptaose were made and their metal binding properties were examined; these are based on α-1→2-linked fructofuranose units.[143] Oxidation of β-cyclodextrin to the monoaldehyde was effected using DMSO and *N*-ethyldiisopropylamine. Under other oxidizing conditions the aldehyde underwent β-elimination, thus giving a mono-unsaturated acyclic heptamer which could be reduced to the corresponding compound terminating at one end in D-glucitol and the other in 4-deoxy-glucose.[144]

β-Cyclodextrin with one of the units in the form of 2,3-anhydro-D-mannose, on hydrolysis in water, gave the analogue with the anhydro unit converted to the α-D-altro structure. In alkaline conditions, however, the epoxide ring was opened by *O*-4 of a neighbouring glucose unit and the product had the 4,2′-anhydride structure **21**.[145]

In the area of cyclodextrin ethers the β-compound has been converted into a set of five tris-Tbdms ethers, all substituted at their various 6-positions, which were separated by hplc and characterized by ^{13}C n.m.r. spectroscopy.[146] Related work applied to γ-cyclodextrin gave the various 6,6′-disubstituted ethers.[147] 5-Bromo-1-pentene was used to produce the 2-*O*-mono-4-pentenyl ether of β-cyclodextrin which was then permethylated and the product was chemically bonded to silica gel to form an efficient hplc stationary phrase for the separation of enantiomers.[148] Peroctyl α-cyclodextrin has been studied as a chiral receptor for the ephedrinium ion.[149] Various octyl ethers of α-, β- and γ-cyclodextrin ranging in their substitution from the diethers to completely alkylated products were characterized by electrospray mass spectrometry and ^{13}C n.m.r. methods applied to methylated derivatives.[150] The 2,6-didodecyl derivative of β-cyclodextrin has been used as a potentiometric sensor.[151] In the field of aromatic ethers, naphthyl carboxylate substituents have been bonded at the 6-positions and the products were able to transfer excitation energy to complexed merocyanine held in the cavities of those molecules. These phototransfer processes were extremely efficient.[152] β-Substituted cyclodextrin derivatives with *p*-allyloxybenzoyl or various benzyl substituents at *O*-2 or *O*-3 were incorporated by hydrosilylation to give hydromethylpolysiloxane polymers used as chiral phases for chromatographic resolution of enantiomers.[153] Cyclodextrins with complex benzyl-like ethers are illustrated in **22**[154] and **23**.[155] The latter were prepared as artificial redox enzymes.



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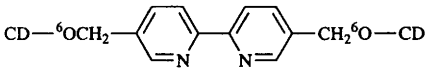

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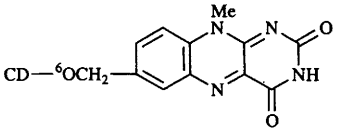


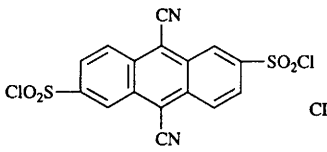
23

In the field of esters of cyclodextrins, α-, β- and γ-compounds carrying one *p*-(dimethylamino)benzoyl group were made as fluorometric molecular recognition indicators,[156] and β-cyclodextrin carrying 6-*O*-carboxymethyl and 2,3-di-*O*-methyl groups in all sugar units was prepared for attachment to peptides and lipids. Tryptophan methyl ester was also attached.[157]

Several sulfonates have been reported. Treatment of cycloinulohexaose with naphthalene sulfonyl chloride resulted in characterized mono-, di- and tri-6-sulfonates,[158] and similarly dansyl (5-*N*,*N*-dimethylaminonaphthyl 1-sulfonate) groups have been introduced at *O*-2, *O*-3 or *O*-6.

Fluorescence characteristics of the products were studied in relationship to complexing activity, and the 2- and the 6-derivatives can be used as fluorescence sensors.[159] Treatment of β-cyclodextrin with the disulfonyl chloride **24** gave capped derivatives linked through *O*-6 of the AD rings or AC rings in the ratio 76:24. Yields were low, but the products are potential hosts for photo-induced electron transfer reactions.[160] In related work cycloinulohexaose was capped by use of diphenyl-4,4′-disulfonyl chloride through *O*-6 of the A-C related units. This allowed displacement reactions and, for example, phenylthio-derivatives could be made in the AC relationship.[161]

Several nitrogen-containing derivatives of cyclodextrins have been reported. Thus treatment of the per-6-deoxyiodo-derivatives of α- and β-cyclodextrin can be converted to the corresponding nitriles and then by use of the borane/dimethyl sulfide complex, to the analogues comprising 7-amino-6,7-dideoxy-D-glucoheptoses.[162] The product is a ditopic receptor for nucleotides, and adenosine monophosphate has been found to bind with the ribose unit inside the cyclodextrin cavity.[162a] β-Cyclodextrin hydroxylamines (*J. Am. Chem. Soc.*, 1991, **114**, 1493), on oxidation, give the corresponding oximes as *Z,E* mixtures and from them the corresponding carbonyl compounds can be made following treatment with sodium bisulphite.[163] A copper(II) complex of a histamine-modified cyclodextrin (6-deoxy-6-N-histaminyl-β-cyclodextrin) has been used to modify a stationary phase for hplc chromatography of aromatic amino acids.[164] A rhenium-containing complex **25** was synthesized from 6-deoxy-6-iodo-β-cyclodextrin and it trapped *N,N*-



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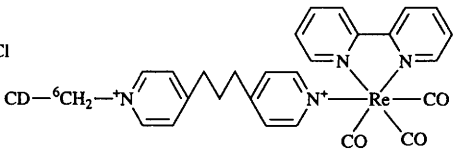

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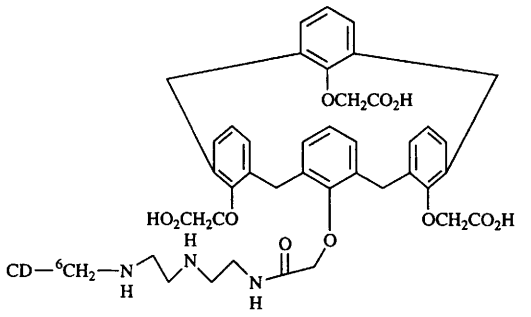
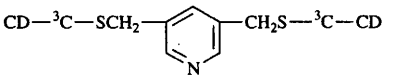


26

diethylaniline. The luminescience of the host was quenched by the guest after trapping.[165] A

product, **26**, comprising β-cyclodextrin linked to calix[4]arene has been reported.[166]

Several sulfur-containing derivatives have been reported. Hepta-6-bromo-6-deoxy-β-cyclodextrin, treated with the sodio derivative of 1-thio-β-D-galactopyranose, afforded the cyclodextrin with further galactose units linked through the sulfur atom.[167] Mitsunobu chemistry has been used to convert β-cyclodextrin into analogous thiocompounds with phenyl-, benzoyl-, heterocyclic and carbohydrate substituents joined to β-cyclodextrin through sulfur.[168] Two reports have appeared on the preparation of two β-cyclodextrin rings linked through dithio-bridges. In the first, β-cyclodextrin having one of the monomeric units in the 2,3-anhydro-mannose form, was treated with dithiomethyl piridine to produce **27**.[169] In the other compound, **28**, the lengths of



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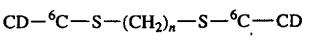

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the dithio bridges were examined and the binding with a set of naphthylamine derivatives was studied as a function of *n*.[170] Derivatives of β-cyclodextrin containing 6-deoxy-6-(2-thioethyl)-amino groups have been described.[171]

Cyclodextrin derivatives having other sugar units attached have been formed by enzymic procedures. Thus coffee bean α-galactosidase has been used to transfer galactose from melibiose to cyclodextrins.[172] Compounds of this type carrying β-glucose, α-maltose and β-maltose attached groups were mannosylated in these attachments by use of an α-mannosidase from jackbean and methyl α-D-mannopyranoside as donor. The α-mannosyl groups bonded α-1,6 to the extraannular sugar units.[173]

Several physical studies have been carried out on cyclodextrin derivatives. Thus the X-ray structure of per-(6-bromo-6-deoxy-2,3-di-*O*-methyl)β-cyclodextrin has been examined by single crystal X-ray diffraction analysis. The conformation deviates significantly from C_7 symmetry.[174] Likewise the X-ray structure of heptakis-2,3,6-tri-*O*-methyl-β-cyclodextrin shows that one of the seven rings is inverted.[175] Conformational analysis of an extensive set of per-*O*-substituted β-cyclodextrins reveals that several show conformational isomerism. The relevance of this to the use of cyclodextrins in molecular device design is examined.[176] Related work undertook n.m.r. and molecular modeling studies on α-cyclodextrin in which one of the units is in the 3,6-anhydro from. The work included the examination of two model disaccharide units.[177]

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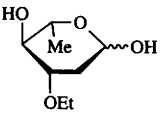
5
Ethers and Anhydro-sugars

1 Ethers

1.1 Methyl Ethers. — All the possible monomethyl ethers of methyl β-D-lactoside have been prepared by conventional methods[1] while *O*-stannylene acetals have been utilised in the synthesis of the 3-*O*-methyl ethers of methyl α-D-galacto-, α-L-rhamno-, α-D-manno- and α-L-fuco-pyranoside.[2] A number of phase transfer catalysts have been compared in the *O*-methylation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose.[3] Diazomethane treatment of some aryl *C*-glucosides unexpectedly resulted in the 6-hydroxy groups being partially methylated.[4] The substrate specificity of a cloned α-(1→2) fucosyl-transferase has been studied by synthetically modifying the acceptor, octyl β-D-galactopyranoside, by making the 3-, 4- and 6-*O*-monomethyl ethers.[5] Similarly some *O*-monomethyl ethers of octyl α-L fucopyranosyl-(1→2)-β-D-galactopyranoside have been prepared with the modifications in the galactose moiety,[6] and monomethyl ethers of a trimannose oligosaccharide have been prepared[7] while syntheses of methyl 3,6-di-*O*-(3-*O*-methyl-α-D-mannopyranosyl)-2-*O*-β-D-xylopyranosyl-β-D-mannopyranoside, methyl 6-*O*-α-D-mannopyranosyl-3-*O*-(3-*O*-methyl-α-D-mannopyranosyl)-2-*O*-β-D-xylopyranosyl-β-D-mannopyranoside and methyl 3-*O*-α-D-mannopyranosyl -6-*O*-(3-*O*-methyl-α-D-mannopyranosyl)-2-*O*-β-D-xylopyranosyl-β-D-mannopyranoside have been described.[8] The synthesis of 2′-*O*-methyluridine is mentioned in Chapter 20.

1.2 Other Alkyl and Aryl Ethers. — L-Dianose **1** has been isolated from *Dianthus chinensis*.[9] A new simple route to 6-*O*-alkyl hexopyranosides involves a hypochlorite-mediated displacement applied to 6-deoxy-6-iodo derivatives with the corresponding alkyl alcohol as solvent.[10] Treatment of diol **2** with 1,1,1,3,3,3-hexafluoro-2-phenylisopropyl alcohol under Mitsunobu conditions has afforded the ether **3**. The ether group is stable to conditions used for the removal of Bn, Tbdps, Thp, Mem, Bz and Tr protecting groups, but can be removed with lithium napthalenide.[11] Syntheses of methyl 4′,6′-di-*O*-*n*-hexyl-β-D-lactoside and methyl 4′,6′-di-*O*-*n*-octyl-β-D-lactoside have been achieved in order to study their surfactant properties.[12] Treatment of carbohydrate isopropylidene acetals with methyl magnesium iodide under forcing conditions (benzene, 60°C) has afforded, with high selectivity, *tert*-



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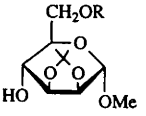


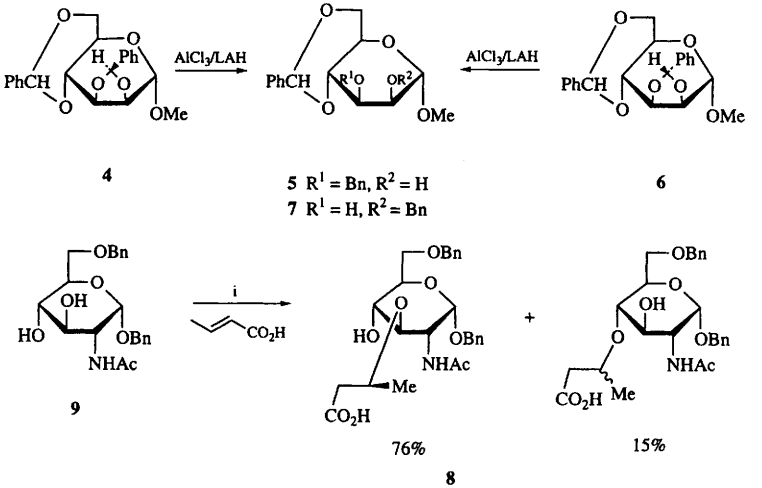
2 R = H
3 R = $C(Ph)(CF_3)_2$

butyl ether alcohols. Thus, methyl 2,3:4,6-di-*O*-isopropylidene-α-D-glucopyranoside gave 95% of methyl 3-*O*-*tert*-butyl-4,6-*O*-isopropylidene-α-D-glucopyranoside whereas 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose generated 6-*O*-*tert*-butyl-1,2-*O*-isopropylidene-α-D-glucofuranose in 65% yield, and 1,2:3,4-di-*O*-isopropylidene-6-*O*-methyl-α-D-galactopyranose afforded 52% of 3-*O*-*tert*-butyl-1,2-*O*-isopropylidene-6-*O*-methyl-α-D-galactopyranose.[13] Treatment of some carbohydrate alcohols with epoxides has afforded the corresponding carbohydrate *O*-2′-hydroxyethyl ether derivatives[14]. Some ether-linked (as opposed to glycsidically linked) disaccharides have been prepared by the nucleophilic opening of carbohydrate oxiranes and other anhydro-sugars (including oxetanes) by sugar alcohol derivatives;[15] and further examples are discussed in Chapter 3. The synthesis and antimicrobial properties of some methyl 3-*O*-alkyl-D-glucopyranosides are discussed in Chapter 19.

Carbohydrate allenyl ethers have been prepared *via* the corresponding propargyl ethers,[16] and sucrose *O*-octadienyl ethers have been synthesized by a novel telomerisation of butadiene with sucrose in the presence of $Pd(acac)_2$ and Ph_3P.[17] Radical bromination of allyl ethers using NBS in CCl_4 in the presence of isopropylidene acetals, acetates and benzoates has allowed the selective removal of the allyl ethers with a hydrolytic work-up.[18]

Dimethyldioxirane has been used to cleave benzyl or substituted benzyl ether groups from primary and secondary positions in sugar derivatives to the corresponding alcohols.[19] Use of phase transfer conditions has surprisingly allowed the synthesis of secondary *O*-benzyl ethers from primary-secondary diols. For example, 3-*O*-allyl-5-*O*-benzyl-1,2-*O*-isopropylidene-α -D-glucofuranose was obtained from 3-*O*-allyl-1,2-*O*-isopropylidene-α-D-glucofuranose (50% NaOH, Bu_4NBr, BnBr).[20] Benzylation of allyl β-D-glucopyranoside under solvent-free conditions (NaH, BnCl) has afforded the 2,4,6-tri-*O*-benzyl ether in moderate yield,[21] whereas similar conditions (powdered KOH, BnBr) applied to methyl α-D-glucopyranoside has afforded the corresponding tetrabenzyl ether in 65% yield even when only six equivalents of benzyl bromide were used.[22] An efficient preparation of allyl 2,3,6,2′,3′,6′-hexa-*O*-benzyl-β-D-lactoside has been reported,[23] while 4,6-di-*O*-benzyl-, 3,4,6-tri-*O*-benzyl-, and 3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose have been prepared for NMR

conformational studies.[24] The reductive opening of benzylidene acetal **4** has afforded **5** whereas the diastereomer **6** gave **7**.[25] The mono-benzylation of 1,4:3,6-dianhydro-D-glucitol at either O-2 or O-5 has been achieved by using known mono-acetylation procedures followed by benzylation (BnBr, Ag_2O) and then deacetylation.[26]



Reagents: i, Bu_4NHSO_4, aq. NaOH, CH_2Cl_2

Scheme 1

A particular mole ratio of bis(tributyltin)oxide was reportedly required to regioselectively effect the tributyltin ether mediated 2-*O*-alkylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside.[27] Dibutyltin oxide mediated alkylation of the same compound (BnBr, DMF) afforded predominantly the 2-*O*-benzyl ether in contrast to previous claims (c.f. Vol 27, Ch 5, ref. 15). Addition of caesium fluoride to the reaction gave a 2:1 ratio of 3- to 2-*O*-benzyl ethers.[28] The regioselective benzylation of some methyl hexopyranosides has been studied (i,Bu_2SnO, toluene; ii,BnBr, 85°C). Generally the same products were obtained as with $(Bu_3Sn)_2O$, but often in better yields.[29]

Phase transfer conditions have been utilized in the alkylation of monosaccharide derivatives with methyl bromoacetate and sodium chloroacetate,[30] and muramic acid analogue **8** has been prepared by alkylation of diol **9** under phase-transfer conditions (Scheme 1).[31]

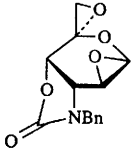
The alkali metal complexing abilities of crown ethers incorporating ether linked D-glucose derivatives has been studied,[32] and some other crown ethers incorporating 1,4-linked D-glucose units have been made from allyl 4-*O*-allyl-α-D-glucopyranoside derivatives which were ozonolysed and reduced prior to linking with polyethers.[33] Some 6-amino-6-deoxy-D-glucose-containing crown ethers are mentioned in Chapter 9.

1.3 Silyl Ethers. — Surprisingly, treatment of methyl 6-chloro-6-deoxy-α-D-glucopyranoside with excess $^{t}BuMe_2SiCl$ (DMF, imidazole, 40°C, 50 h) gave the 2,3-di-*O*-silyl ether and none of the per-silylated product. Hydrogen bonding between the 4-OH and the 6-Cl was postulated to explain the low reactivity of the former group.[34] A one step acetolysis of triethylsilyl ethers to give acetate esters has utilized acetyl bromide in the presence of catalytic tin (II) bromide[35]. In a novel development, silylation of alcohols has been achieved using silyl ethers of pent-1-ene-5-ol and iodonium dicollidine perchlorate as the silylating reagents.[36]

2 Intramolecular Ethers (Anhydro-sugars)

2.1 Oxiranes. — Syntheses of 1,2-anhydro-3,4,5-tri-*O*-benzyl-β-D-fructopyranose[37] and 1,2-anhydro-3,4-di-*O*-benzyl-β-L-arabinopyranose[38] have been reported, while glycals and hex-4-enopyranosides have been stereoselectively epoxidised with a MCPBA-KF complex.[39] Epoxidation of some 5,6-unsaturated glycals with dimethyldioxirane has been investigated and the products, *bis*-epoxides **10** and **11**, proved surprisingly stable towards methanolysis.[40] 1,2-Anhydro-3,4-di-*O*-benzyl-α-D-xylopyranose has been prepared and used as a glycosylating agent.[41] A general method for making epoxides from terminal 1,2-diols involves the preparation of the 1,2-cyclic sulfites, opening with iodide ion, and treatment of the resulting iodo-alcohols with base.[42] The racemic epoxides **12** - **15** have been prepared and their ring opening reactions with a variety of nucleophiles under chelating and non-chelating conditions have been studied.[43,44]

2.2 Other Anhydrides. — The natural product Ascopyrone T is reduced by several bacteria to 1,5-anhydro-4-deoxy-D-*erythro*-hex-3-ulositol.[45] Improved syntheses of 1,3-anhydro-2,4-di-*O*-benzyl-



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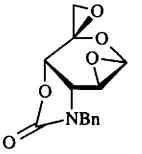

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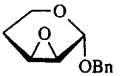

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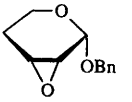

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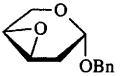

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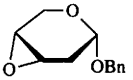

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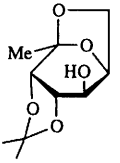

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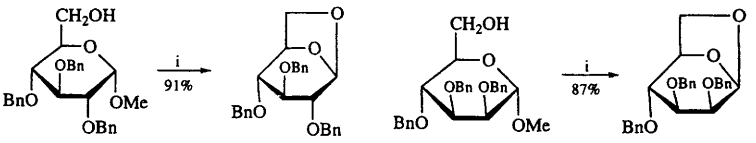
β-L rhamnopyranose and 1,3-anhydro-2,4,6-tri-*O*-benzyl-β-D-mannopyranose from allyl α-L-rhamnopyranoside and allyl α-D-mannopyranoside, respectively, have been reported,[46] while 1,4-anhydro-2,3-di-*O*-benzyl-6-*O*-pivaloyl-α-D-glucopyranose and 1,4-anhydro-3,6-di-*O*-benzyl-2-*O*-pivaloyl-α-D-glucopyranose have been synthesized as potential intermediates for the chemical synthesis of cellulose.[47] Treatment of the 5,6-cyclic sulfate of 1,2-*O*-isopropylidene-α-D-glucofuranose with phosphines (xylene, 70°C) afforded moderate yields of 3,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose.[48] The 2,7-anhydroketose derivative **16** has been synthesized as a bicyclic mimic of α-L-fucose.[49]

Some 1,6-anhydro-β-D-hexopyranoses were synthesized by base treatment (NaOMe, MeOH) of 2,3,4,6-tetra-*O*-acetyl-1-*O*-*p*-toluenesulfonyl-D-hexopyranoses. Varying proportions of methyl glycosides were formed as by-products[50]. Use of a Lewis acid has allowed the synthesis of 1,6-anhydro derivatives **18, 20, 22** from **17, 19, 21** respectively (Scheme 2).[51] The montmorillonite derived reagent "claysil" has been used to catalyse the Ferrier rearrangement so that 3,4-di-*O*-acetyl-D-glucal afforded the 1,6-anhydro-hex-2-enopyranose **23**. This reaction has been extended to disaccharide glycal derivatives.[52] *O*-Stannylation [$(Bu_3Sn)_2O$] of D-galactal followed by treatment with iodine has afforded predominantly 1,6-anhydro-2-deoxy-2-iodo-β-D-galactopyranose. This was transformed by base treatment into 1,6:2,3-dianhydro-β-D-talopyranose.[53] Treatment of phenyl 2,6-di-*O*-benzoyl-1-thio-β-D-galactopyranoside with Lewis acid ($BF_3.OEt_2$) has afforded the 1,6-anhydro derivative **24** by way of a series of benzoxonium ion rearrangements.[54] 1,6-Anhydro-β-D-glucopyranose is selectively acylated at *O*-4 by the lipase *Candida antartica* in 1,4-dioxane[55].



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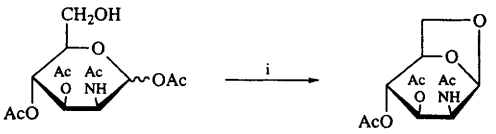
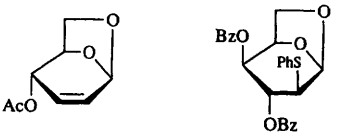


21 22

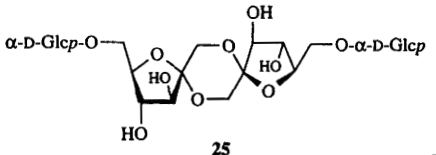
Reagents: i, $Fe(ClO_4)_3$, MeCN

Scheme 2



23 24

The anhydrodisaccharides α-D-fructofuranose-β-D-fructopyranose 1,2′:2,1′-dianhydride and α-D-fructofuranose-β-D-fructofuranose 1,2′:2,1′-dianhydride have been identified in the ethanol-soluble products from the thermolysis of sucrose.[56] These same products, along with di-β-D-fructofuranose-1,2′:2,1′-dianhydride, were found in caramelized sucrose.[57] Dissolution of sucrose in anhydrous HF afforded a complex mixture of difructose dianhydrides and their glucosylated derivatives as well as oligosaccharides up to dp 14. α-D-Fructofuranose-β-D-fructopyranose 1,2′:2,1′-dianhydride was the main component in the mixture, either free or glucosylated at various positions.[58] The reaction of some disaccharides with anhydrous HF has afforded some dimeric dianhydrides. Palatinose, leucrose and maltulose gave, respectively, the dianhydrides **25**, **26** and **27**.[59] α-D-Fructofuranose-β-D-fructofuranose-1,2′:2,1′-dianhydride has been converted into the *bis*-3,6-anhydro-derivative, which,



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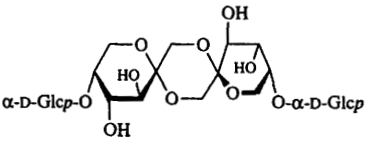

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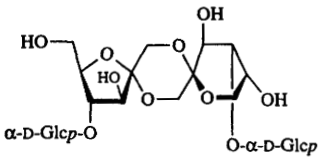

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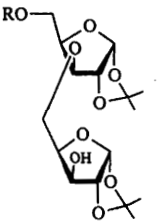
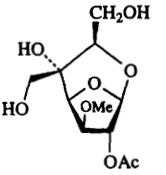


28 R = Bn, All, $C_{12}H_{25}$, $C_{16}H_{33}$



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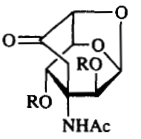
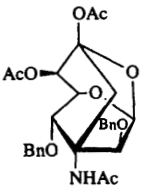


30 R = Ac
31 R = Bn



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after acid hydrolysis afforded 3,6-anhydro-D-fructose.[60] Treatment of 3,5-anhydro-1,2-*O*-isopropylidene-α-D-xylofuranose with alcohols under basic conditions gave the corresponding ring-opened 5-*O*-alkyl-1,2-*O*-isopropylidene-α-D-xylofuranose, but under some conditions the dimer **28** predominated.[61]

The 1,6-anhydro-heptofuranose **29**, which is structurally similar to the core of zaragozic acid, has been synthesized from D-glucose.[62] Some radical conjugate addition reactions applied to levoglucosenone are covered in Chapter 15. Attempted acetolysis of caged anhydro sugar **30** (Et_3SiOTf, Ac_2O, 65°C, 1h) afforded only starting material, whereas the "armed" benzyl ether **31** (Et_3SiOTf, Ac_2O, O°C, 1h) led to rearranged material **32**.[63]

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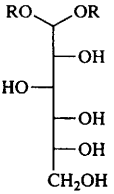
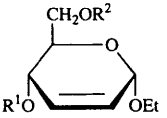
6
Acetals

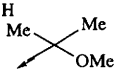
1 Acyclic Acetals

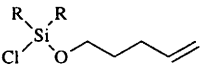
The liquid crystalline properties of dialkylacetals **1** have been described.[1] In the presence of DDQ as catalyst, hexopyranose derivatives having free hydroxyl groups at C-6 or at C-5 and C-6 reacted with 2,2-dimethoxypropane and acetone to give primary acyclic isopropylidene mixed acetals (*e.g.*, **2** → **3**).[2] Non-symmetrical silaketals **5** have been prepared by use of monochloro-dialkyl 4-pentenyl silyl ethers **4** as reagents, as shown in Scheme 1.[3]



R = $(CH_2)_nMe$
n = 5, 7, 9, or 11
1

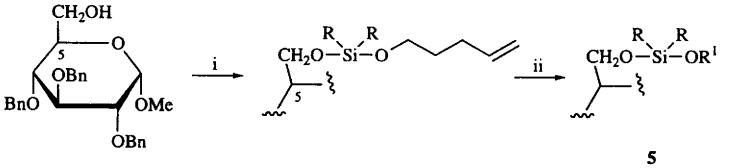


R^1 = H or Ac
2 R^2 = H
3 R^2 = 



R = Pr^i or Ph
4

The formation of a glycosidic bond between two sugar moieties temporarily tethered by a silaketal linkage is covered in Chapter 3.



5

R = Pr^i or Ph, R^1 = C_8H_{17},  , or 

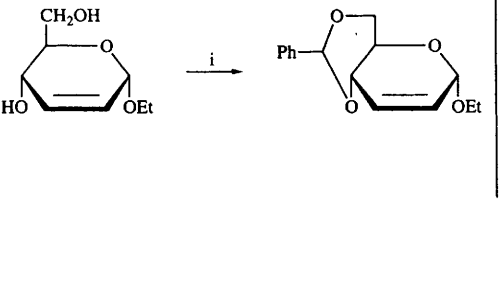
Reagents: i, **4**, Et_3N, DMAP, ii, R^1OH, iodonium dicollidine perchlorate

Scheme 1

2 Isopropylidene, Ethylidene, Cyclohexylidene, and Benzylidene Acetals

Di(pent-4-enyl) acetals are versatile acetalising reagents which can be employed with neutral promoters such as NBS or iodonium dicollidine perchlorate if necessary, although yields and reaction rates are greatly enhanced by addition of an acid catalyst such as camphorsulfonic acid or triethylsilyl triflate; an example is given in Scheme 2.[4] The first step in a convenient synthesis of C-3-modified methyl β–lactosides (see Chapters 8, 10, 12) was a new isopropylidenation method using acetone and catalytic trimethylsilyl chloride.[5]

The reaction of D-glucose diethyl dithioacetal with acidic acetone furnished the two diacetonides **6** and **7** in the ratio 3:1; their structures which were proposed thirty years ago without proof (P.A.J. Gorin, *Can. J. Chem.*, 1965, **43**, 2078) have now been firmly established with the help of extensive n.m.r. spectroscopic analysis.[6] Experimental details for the one-pot preparation of 1,2-*O*-isopropylidene-α-D-xylofuranose in 80% yield from D-xylose have been published.[7] 2′,3′:4,6:,4′,6′-Tri-*O*-cyclohexylidene-α,α′-trehalose was an important synthetic precursor of mycobacterial 2,3-di-*O*-acyl derivatives of α,α′-trehalose; in connection with this preparation the cyclohexylidenation, isopropylidenation, and ethylidenation of this disaccharide by use of dimethoxycyclohexane, 2-methoxypropene, and acetaldehyde, respectively, in acidic media have been studied in some detail.[8]



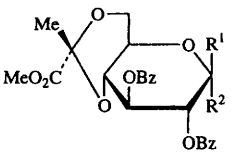
Reagents: i, PhCH(O)$_2$, NBS, camphorsulfonic acid

Scheme 2

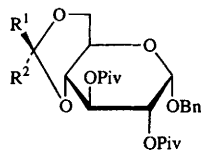
The n.m.r. spectroscopic investigation of the reactions of pentonolactones with acetone and benzaldehyde in acidic media is covered in Chapter 21, as are conformational studies on 2,3-*O*-isopropylidene-α-L-sorbopyranose derivatives. 1,2-*O*-Isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose dimers are referred to in Chapter 22, and some 7-carbon sugar lactones which were characterized as their isopropylidene-and cyclohexylidene-acetals are noted in Chapters 2 and 16.

3 Other Acetals

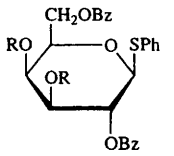
Full details on the efficient preparation of 4,6-*O*-[(*R/S*)-(1-ethoxycarbonyl)ethylidene] derivatives (pyruvyl acetals) of hexopyranosides with α- or β-D-*gluco*-, α- or β-D- *galacto*-, or α-D-*manno*-configuration, by reaction of the respective 2,3-di-*O*-benzyl-4,6-di-*O*-Tbdms ethers with ethyl pyruvate and catalytic trimethylsilyl triflate, have been published (preliminary report see Vol. 22, Chapter 6, Ref. 11); under the reaction conditions used, the β-D-*manno* analogue underwent competitive ring contraction.[9] Alkyl 2,3-di-*O*-benzoyl-4,6-*O*-[(*R*)-1-(methoxycarbonyl)ethylidene]-β-D-glucopyranosides **8** and the related thioglucosides **9** have been prepared conventionally (methyl pyruvate/$BF_3.OEt_2$) and converted to a variety of glycosyl donors for use in the synthesis of 5-aminopentyl β-D-glucopyranoside 4,6-pyruvate.[10] While use of acetonitrile as cosolvent in the conventional 4,6-pyruvylation of benzyl 2,3-*O*-pivaloyl-α-D-glucopyranoside promoted formation of the thermodynamic product **10**, the solvent-free reaction proceeded under kinetic conditions to give mainly diastereoisomer **11**; similar results were obtained in the *manno* series.[11] Under the same, solvent-free reaction conditions, diol **12** gave a 3:1 (*R/S*)-mixture of acetals **13**; when dichloromethane was added as cosolvent, however, rearrangement to a 1,6-anhydride took place. This is covered in Chapter 5.[12]



8 R^1 = H, R^2 = OMe, OAll or OBn
9 R^1 = SEt or SPh, R^2 = H



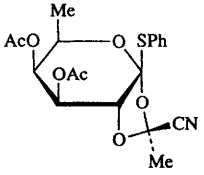
10 $R^1 = CO_2Me$, R^2 = Me
11 R^1 = Me, $R^2 = CO_2Me$



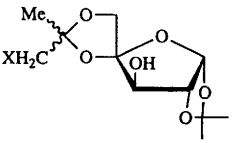
12 R = H
13 R, R = 

Acetal **14**, a precursor for the trityl cyanoethylidene polycondensation (see Chapter 4), has been produced by treatment of tri-*O*-acetyl-α-D-fucopyranosyl bromide with sodium cyanide and tetrabutylammonium bromide.[13] Acetals **15** with functionalized isopropylidene groups were obtained by ultrasound-assisted transacetalation of the corresponding acetonides with iodoacetone in the presence of *p*-toluenesulfonic acid and subsequent nucleophilic displacement of iodine in HMPA.[14] The diastereoselective reaction of D-erythronolactone with 4-(phenylsulfonyl)-2-butanone to give the (*R*)-acetal **16** in high yield was a key-step in a new route to (+)-*endo*-brevicomin (see Chapter 24).[15]

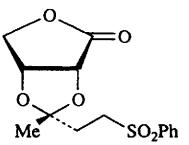
The DCC-promoted formation of trichloroethylidene acetal **18** took place with inversion of



14

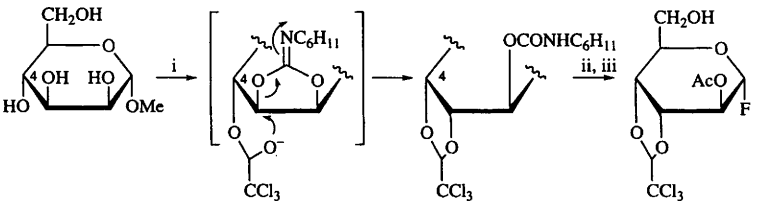


15 X = I, N_3, or SPh



16

configuration at C-3 *via* isourea intermediate **17** which was attacked by a neighbouring deprotonated hemiacetal oxygen atom as illustrated in Scheme 3; acetal **18** was converted to the glycosyl donors **19**. Several other examples, all involving *cis-trans*-arranged triols, are given; not surprisingly, methyl α-D-glucopyranoside did not undergo this reaction.[16,17] 3,4-*O*-Hexafluoroacetonides were prepared analogously by use of hexafluoroacetone instead of chloral.[18]

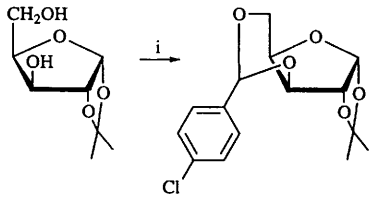


17 18 19

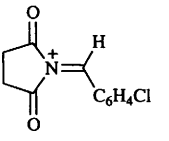
Reagents: i, Cl_3CCHO, DCC; ii NaOMe, MeOH; iii, HF, $MeNO_2$, Ac_2O

Scheme 3

The reaction of D-glucitol with 4-isobutylbenzaldehyde in acidic methanol, which furnishes mainly the 1,3:2,4-di-*O*-acetal, has been discussed.[19] A novel method for the synthesis of substituted benzylidene acetals involved treatment of a diol with the appropriate benzaldehyde in the presence of TPP and NBS which are thought to form a reactive species **20**; an example is shown in Scheme 4.[20] The 4,6-*O*-(4-cyanobenzylidene) acetals **21**, required for liquid crystal studies, have been prepared by exposure of the corresponding 4,6-diols to cyanobenzaldehyde dimethylacetal and toluenesulfonic acid in DMF.[21]

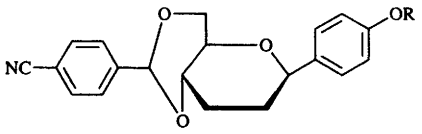


Reagents: i, TPP, NBS, 4-chlorobenzaldehyde

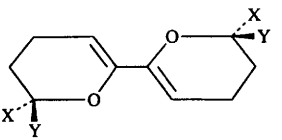


20

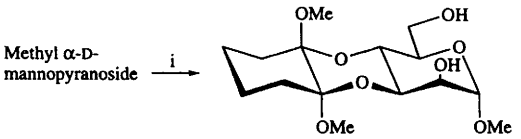
Scheme 4

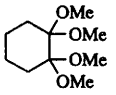


$R = (CH_2)_nMe$
$n = 0, 5–13$
21



22 X = Y = H
23a X = Ph, Y = H
23b X = H, Y = Ph



Reagents: i  , MeOH, $CH(OMe)_3$, camphorsulfonic acid

Scheme 5

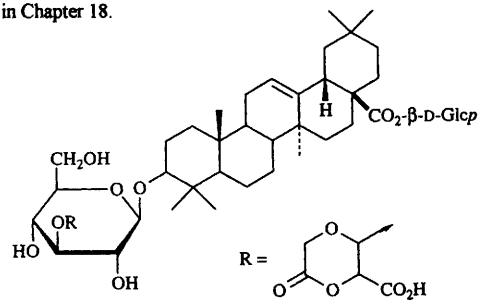
Cyclohexane-1,2-diacetal protection, a new protecting technique for vicinal diols, is illustrated in Scheme 5. It is selective for *trans*-disposed hydroxyl groups giving mainly the 2,3-acetal of methyl α-D-galactopyranoside, the 3,4-acetals of methyl α-D-manno- and α-L-rhamno- and α-D-lyxo-pyranoside, and 2,3/3,4-mixtures in the *gluco*-series.[22] The 3,4-*O*-(cyclohexane-1,2-diacetal) derivatives of methyl α-L-rhamnoside and ethyl 1-thio-α-L-rhamnoside were used successfully in a trisaccharide synthesis (see Chapter 4).[23]

Selectivities similar to those just described for cyclohexane-1,2-diacetals were observed in the dispiroketal ("dispoke") protection of vicinal diols (see Vol. 26, Chapter 6, Ref.15). Thus tetrahydro-6,6'-bi-2*H*-pyran (**22**) reacted with glucopyranosides non-selectively to give mixtures of 2,3- and 3,4-products.[24] Use of the chiral 6,6'-disubstituted reagents **23**, however led to highly regio- and enantio-selective diketal formation in the *manno*- and *galacto*-, as well as in the *gluco*-series; the (*S,S*)-isomer **23a** reacted, for example, exclusively with the 3,4-diol and the (*R,R*)-enantiomer **23b** exclusively with the 2,3-diol of methyl 6-*O*-Tbdms-α-D-glucopyranoside.[25,26] Chiral recognition of enantiomeric *trans*-1,2-diol relationships in the dispoke protection of 2,5-di-*O*-benzoyl-*myo*-inositol is covered in Chapter 18.

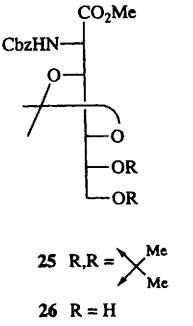
The unusual oleanic acid "seco-glycoside" **24** has been isolated from sugar beet; it was postulated that the acetal linked dicarboxylic acid lactone fragment is derived from a pentoside or from a glucuronide with concomitant decarboxylation.[27]

4 Reactions of Acetals

DOWEX 50W XS resin in 90% aqueous methanol has been recommended for the selective cleavage of terminal acetonides in open-chain carbohydrate diacetonides, in particular derivatives of α-amino aldonic acids (*e.g.*, **25**→**26**).[28] The use of compound **26** in the synthesis of 2,5-dideoxy-2,5-imino-D-mannitol is referred to in Chapter 18.



24



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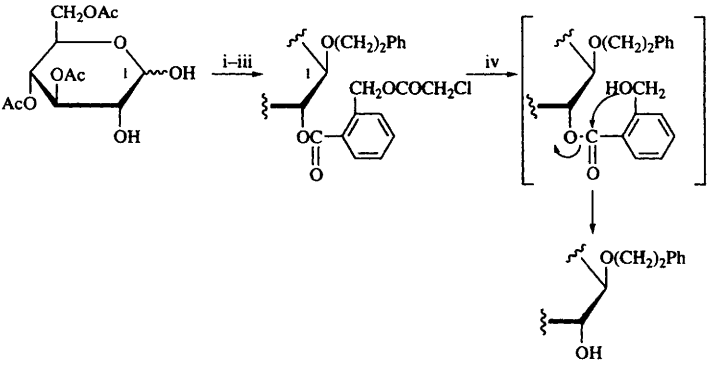
7
Esters

1 Carboxylic Esters

1.1 Synthesis. – In a theoretical study on the alkylation and esterification of monosaccharides, the reactions of 1,6-anhydro-β-D-galactopyranose under phase transfer conditions have been considered.[1] A MNDO-PM3 study on the selective activation of 1-*O*-methoxyacetyl sugars by Zn(II) or Y(III) ions endeavours to explain why 1-*O*-methoxyacetates are the best donors among glycosyl-esters in Lewis acid-promoted glycosylations.[2]

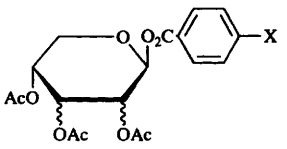


Reagents: i, 2-(Chloroacetoxymethyl)benzoyl chloride, Py; ii, HBr, HOAc; iii, $HO(CH_2)_2$ Ph, AgOTf; iv, $SC(NH_2)_2$

Scheme 1

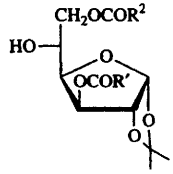
The 2-(chloroacetoxymethyl)benzoyl (CAMB) group, a novel protecting group which combines the high stability of the benzoates with the ease of removal of chloroacetates has been developed especially for protection at O-2 of glycosyl donors; an example is given in Scheme 1.[3] The diphenylacetylation of methyl α-D-glucopyranoside with the acyl chloride (1.5 equivalents) in pyridine proceeded with moderate selectivity to give the 6-mono-, 2-mono- and 2,6-di-esters in 40, 6, and 25% yield, respectively. Removal of this new protecting group under neutral conditions was achieved by use of NBS followed by thiourea.[4]

The synthesis of 1-*O*-aroyl-2,3,4-tri-*O*-acetyl-β-D-xylo-and -arabino-pyranoses **1** under phase transfer conditions has been reported.[5] 2-Deoxyglycosyl phosphorodithioates have been converted to



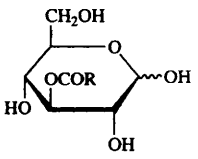
X = H, OH, OMe, NO_2

1



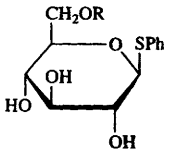
2 R^1 = H, R^2 = $(CH_2)_nMe$

3 R^1 = $(CH_2)_nMe$, R^2 = H



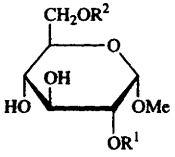
4 R = $(CH_2)_nMe$

n = 2, 6, 10, 14 or 16



5 R = H

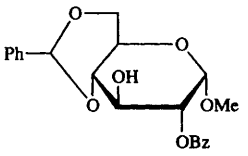
6 R = Bz



7 R^1 = H, R^2 = Tbdms

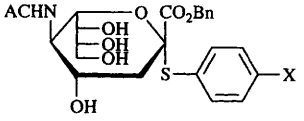
8 R^1 = Bz, R^2 = Tbdms

9 R^1 = H, R^2 = $CO(CH_2)_8Me$

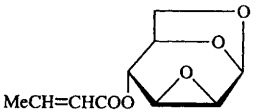


10

glycosyl esters by treatment with carboxylic acids in the presence of silver carbonate.[6] Monoester derivatives **2** - **4** of D-glucose, potential surfactants and antitumour agents, have been prepared conventionally by way of diacetone glucose.[7] The monobenzoates **6** and **8** were produced within minutes and in high yields by microwave heating of precursors **5** and **7**, respectively, in toluene in the presence of benzoyl chloride and dibutyltin oxide.[8] Methyl 6-*O*-acyl-D-glycosides, *e.g.* compound **9**, have been prepared selectively by use of *S*-(2-pyridyl)alkanethioates in pyridine at 80 °C.[9] During a reinvestigation of the dibutyltin methoxide-mediated esterification of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, the 2-benzoate **10** and the corresponding 2-tosylate were isolated in 72 and 69% yield, respectively,[10] which is inconsistent with earlier claims that these conditions favour reaction at the 3-position (see Vol. 27, Chapter 5, Ref. 15). By careful choice of reagent (trimethyl orthoacetate, dimethylacetamide dimethylacetal) and of reaction conditions, the 8-mono-, 9-mono-, 8,9-di-, 4,9-di-, or 4,8,9-tri-*O*-acetates of the *N*-acetylneuraminic acid derivatives **11** and **12** were obtained without protecting group techniques; the 7,8,9-triesters were available by controlled Zemplen deacetylation of the peracetates, and the 4-*O*-monoacetates were accessible by use of isopropylidene protection in the side-chain.[11] Various methods have been explored for the preparation of monomethacrylates of 1,6-anhydro-β-D-glycopyranose derivatives, *e.g.* 4-ester **13**, without the requirement for chromatographic purification.[12] Little selectivity and poor yields were encountered in the benzoylation of the nucleoside model 1-(β-D-xylopyranosyl)-3,5-dimethylpyrazole (**14**) with benzoyl chloride/pyridine at -10 °C.[13] Radical cyclization reactions involving α,β-unsaturated esters are covered in Chapter 14.



11 X = NO_2
12 X = NH_2



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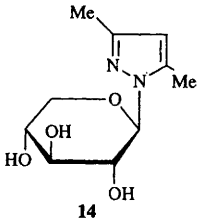
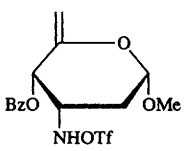


14

A paper on the cleavage of ester protecting groups by use of magnesium in methanol included two carbohydrate examples, namely the deacetylation of di-*O*-acetyl-L-fucal in 95% and the debenzoylation of the unsaturated amino-trideoxy sugar **15** in 91% yield.[14] Hydrazine hydrate in acetonitrile caused preferential de-*O*-acetylation of disaccharide peracetates at O-1. On increasing the proportions of the reagent, ester groups were, in addition, removed from O-2 and/or O-3.[15] Under carefully controlled acetolysis conditions the 1-*O*-acetyl-tri-*O*-benzyl-L-pentofuranosides **16** and **17** were obtained from the corresponding methyl glycosides in yields of 89 and 59%, respectively.[16] The one-step conversion of carbohydrate silyl ethers to the corresponding acetates by use of acetyl bromide/$SnBr_2$ is covered in Chapter 5.



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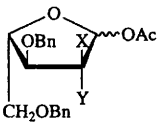
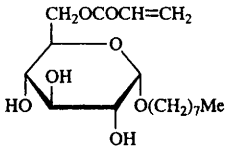


16 X= H, Y = OBn
17 X= OBn, Y = H



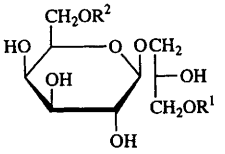
18

The enzymic synthesis of carbohydrate esters has been reviewed (27 pp., 37 refs.).[17]

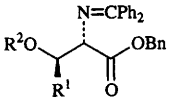
A three-stage process involving two primary deacetylations, before and after 4→6 acetyl migration, has been proposed for the preferential formation of methyl 2,3-di-*O*-acetyl α-D-glucopyranoside on exposure of the tetraacetate to *Candida* lipase.[18] A study of the enzymic acylation of a series of methyl D- and L-hexopyranosides by different lipases suspended in organic solvents indicated that an axial hydroxyl group at C-3 affects the primary selectivity unfavourably; 6-*O*-butanoates of D-

allopyranose derivatives, for example, were formed in low yields.[19] The selective 6-*O*-acylation of alkyl α-D-glucopyranosides by use of lipase and functionalized ethyl esters to give products such as acrylate **18** has been reported.[20] Several unprotected 2-deoxy hexoses were acylated or alkoxycarbonylated at the primary position exclusively by *Candida antarctica* lipase in pyridine or 1,4-dioxane.[21] Lipozyme-promoted acyl transfer of *N*-Boc-protected 4-aminobutanoate from 2,2,2-trichloroethanol to butyl α-D-glucopyranoside, followed by removal of the Boc group with trifluoroacetic acid, gave the 6-*O*-(4-aminobutanoate) in 60 % overall yield.[22]

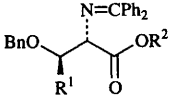
The enzymic transfer of acyl groups from polyunsaturated fatty acid methyl esters to methyl glucoside, octyl glucoside and methyl galactoside by various lipases in benzene/pyridine has been studied with a view to finding optimal reaction conditions.[23] The lipase-catalysed acetylation of alkyl β-D-xylopyranosides gave 2,4- and/or 3,4-diacetates, the ratios depending on the aglycon (methyl or octyl) and the solvent (acetonitrile or hexane) used.[24] The selective lipase-catalysed propanoylation at O-2 of methyl 4,6-*O*-benzylidene α-D-glucopyranoside is referred to in Chapter 2. A lipase from *Achromobacter* sp. catalysed the primary acylation of 3-*O*-β-D-galactopyranosyl-*sn*-glycerol in pyridine using fatty acid vinyl esters as donors, products **19** and **20** being formed in the ratio 95:5 approximately.[25] The esterifications of glucosides and galactosides of glycerol and trimethylolpropane with a variety of middle- and long-chain fatty acids, mediated by lipase from *Candida cylindracea* have been investigated.[26]



19 $R^1 = CO(CH_2)_nMe$, $R^2 = H$
20 $R^1 = H$, $R^2 = CO(CH_2)_nMe$
$n = 10–16$



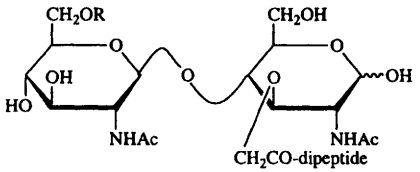
R^1 = H or Me
21 R^2 = H
22 R^2 = β-D-Gal*p*$(OAc)_4$



R^1 = H or Me
R^2 = β-D-Gal*p*$(OAc)_4$
23

Acetyl esterase removed selectively the anomeric ester group of α-D-glucopyranose pentaacetate, the two secondary ester groups of triacetyl-D-glucal, and the secondary *O*-acetate of acetylated deoxynucleosides, while phenylacetamido groups bonded to the base moieties of deoxynucleosides remained intact. Alternatively, the latter groups were hydrolysed selectively in the presence of primary and secondary *O*-acetates by penicillin G acylase.[27] A number of different enzymes have been examined for their selectivities in the deacetylation of sucrose octaacetate in organic solvents. The hepta-, hexa-, and penta-acetates formed were characterized by ^{1}H-n.m.r. spectroscopy after perdeuteroacetylation.[28]

Reaction of protected β-hydroxy-α-amino acids **21** with acetobromosugars in the presence of zinc chloride proceeded with prior benzyl group migration to give β-glycosyl α-aminoacyl esters, such as



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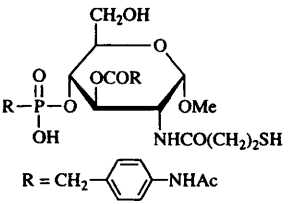


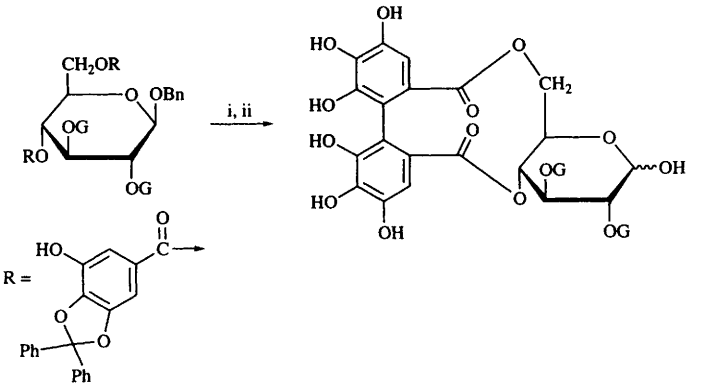
25

compounds **23**; the expected β-glycosides **22** did not rearrange to esters **23** under the reaction conditions used.[29] The cord factor trehalose 6,6′-dicorynomycolate and its three isomers with different stereochemistry in the ester moiety have been prepared by DCC-mediated coupling of 2,2′,3,3′,4,4′-hexa-*O*-benzyl-trehalose and benzyl-protected stereoisomeric corynomycolic acids.[30] The synthesis of 2,3-di-*O*-acyl-α,α-trehaloses, useful as micobacterial antigens, has been achieved by way of 2′,3′:4,6:4′,6′-tri-*O*-cyclohexylidene intermediates.[31]

Standard methods have been employed to prepare the 6′-*O*-stearoyl- and 6′-*O*-(2-tetradecylhexadecanoyl)-disaccharide dipeptides **24** as lipophilic analogues of the natural muramoyl dipeptide.[32] A large number of non-reducing subunit analogues of Lipid A carrying 2- or 3-acyloxytetradecanoyl- and 2- or 3-hydroxyacyl-groups of different chain-lengths at O-3 and N-2, respectively, have been systematically synthesized.[33,34] The related diester **25** has been obtained in 7 steps from methyl 2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside for raising monoclonal antibodies.[35] Maltohexaose, maltoheptaose and laminaripentaose were peracetylated with acetic anhydride/potassium acetate at 140 °C to achieve high β/α ratios; the conversion of the β-anomers to long-chain alkyl glycosides is referred to in Chapter 3 and their sulfation in Part 2 of this Chapter.[36] Good yields of hexakis-(2,6-di-*O*-acyl)-α-cyclodextrin and of octakis-(6-*O*-acyl)-α-cyclodextrin were obtained on treatment of the unsubstituted cyclodextrins with pivaloyl chloride or diphenylacetyl chloride in pyridine at -15 °C. β-Cyclodextrin furnished mixtures of the corresponding mono- and di-esters under similar reaction conditions.[37]

13-*O*-β-D-Glucopyranosyl giberellin A_5-β-D-glucopyranosyl ester has been made by reaction of the glucosylated giberellic acid with acetobromoglucose in the presence of triethylamine, followed by Zemplen deacetylation.[38] In the first total synthesis of a natural elagitannin, tellimagrandin (**26**) has been prepared from benzyl β-D-glucopyranoside; the final two reaction steps are shown in Scheme 2.[39] An *O*-protected form of compound **26** has been independently prepared by DCC-promoted coupling of (*S*)-4,4′,5,5′,6,6′-hexamethoxy-2,2′-diphenic acid to a glucose core.[40] Galloyl esters of 1,5-anhydro-2,3-

dideoxy-D-*erythro*-hexitol have been made and subjected to a variety of oxidants with a view to producing bi-aryl compounds as simple elagitannin analogues (see Vol. 27, Chapter 2, Ref. 65).[41]



Reagents: i, $Pb(OAc)_4$; ii, Pd/C

Scheme 2

1.2 Isolation from Natural Sources. – New caffeic glycoside esters have been isolated from *Gratiola officinalis*.[42] A family of diacyltrehaloses from *Mycobacterium fortuitum* have been identified as the derivatives esterified at O-2 and O-3 with straight chain (C_{14}-C_{18}) and/or methyl-branched chain (C_{17}-C_{21}) fatty acids.[43] 2,6- And 3,6-di-*O*-galloyl-α/β-D-glucose were found for the first time in the galls of the Egyptian plant *Tamaryx aphylla*.[44] An unusual α-configurated galloylglucose, 1,3,6-tri-*O*-galloyl-α-D-glucose, has been obtained from *Euphorbia humifusa*.[45]

The cyclic trimer elagitannin Hirtellin T_2 was one of several new ellagitannins extracted from the leaves of *Reaumuria hirtella*.[46] Hamamelitannin (2,5-di-*O*-galloylhamamelose), a major constituent of *Hamamelis virginiana*, is a new potent active oxygen scavenger.[47] Three new saponins from the corms of *Crocosmia masoniorum* have novel diglycosylated trioxygenated palmitic acid structures.[48] The structure a new triterpene saponin **27** from the flowers of *Heteropappus biennis* has been shown by multidimensional n.m.r. spectroscopy and molecular modelling to contain a branched tetrasaccharide moiety acylated at the reducing end with arjunolic acid (2α,3β,23-trihydroxyolea-12-en-28-oic acid).[49] The diterpene glycosides atractyloside and carboxyatractyloside, which contain 2-*O*-isovaleroyl-β-D-

glucopyranoside 3,4-disulfate residues, were identified as the toxic principles of *Iphiona aucheri*, a plant responsible for poisoning of camels in Arabia.[50] {6″-*O*-[Delphinidin 3-*O*-(β-gentiobiosyl)]} {6′-*O*-[apigenin 7-*O*-β-D-glucopyranosyl)]} malonate was isolated from the flowers of *Eichhornia crassipes*, as the pigment responsible for the blue-purple colour.[51]

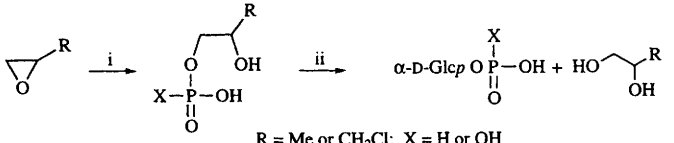
α-D-Ara*p*-(1→6)
β-D-Xyl*p*-(1→3)–β-D-Glc*p*-O-arjunoloyl
α-L-Rha*p*-(1→2)

27

2 Phosphates and Related Esters

The synthesis of sugar phosphates by enzyme-catalysed aldol condensations is covered in Chapter 2.

α-D-Galactofuranose 1-phosphate has been obtained from D-galactose by standard procedures.[52] α-D-Glucopyranose 1-phosphate and 1-phosphonate have been produced with excellent regio- and stereoselectivity in the reaction shown in Scheme 3, which allegedly involves intermediate **28**.[53]



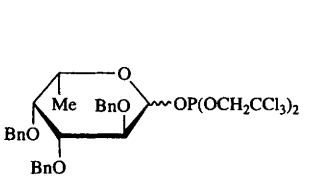
28

Reagents: i, XH_2PO_3; ii, D-glucose

Scheme 3

Glycopyranose 1-bis(trichloroethyl)phosphites, such as L-fucose derivative **29**, which were evaluated as glycosyl donors (see Chapter 3), were obtained in *ca.* 90% yield by treatment of protected free sugars with bis(trichloroethyl) phosphorochloridite.[54] The phosphorylase-catalysed reaction of glucal with potassium dihydrogen phosphate required maltotetraose or starch as primer and furnished 2-deoxy-α-D-*arabino*-hexopyranosyl phosphate in 50% yield after 6 days.[55]

The LD-Hepp derivative **30** was converted to its DD-isomer **32**, *via* mesylate **31**, and was further processed to give the α-1-phosphate **33**, the α-1-diethyl dithiophosphate ester **34** and α-1-methylphosphonate **35**.[56] The anomeric Kdo 2-phosphates, both new compounds, have been synthesized by direct phosphorylation of the acetochloro methylester with silver dibenzyl phosphate; the kinetic (β)



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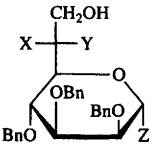
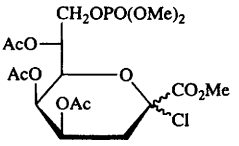


30 X = H, Y = OH, Z = $O(CH_2)_2Tms$
31 X = H, Y = OMs, Z = $O(CH_2)_2Tms$
32 X = OH, Y = H, Z = $O(CH_2)_2Tms$
33 X = OH, Y = H, Z = $OPO(OH)_2$
34 X = OH, Y = H, Z = $SPS(OEt)_2$
35 X = OH, Y = H, Z = OPO(OH)Me

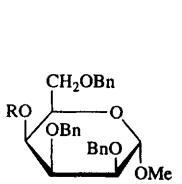


36

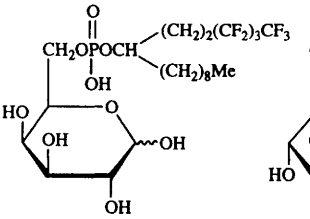
and thermodynamic (α) products were isolated with good selectivity after short and long reaction times, respectively; the 8-phosphate was obtained enzymically from D-arabinose 5-phosphate and phosphoenol pyruvate and converted *via* chloride **36** to the Kdo α- and β-2,8-diphosphates.[57]

All four monophosphates of methyl α-D-mannopyranoside have been synthesized from the appropriate monohydroxy compounds (*e.g.* **37**→**38**) by reaction with $P(Im)_3$, followed by treatment with benzyl alcohol, oxidation and hydrogenolysis.; the n.m.r. spectroscopic examination of these compounds is covered in Chapter 21.[58] The acceleration of glycopyranoside hydrolysis by phosphate groups at O-2 is referred to in Chapter 3.

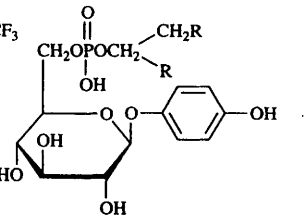
Dodecyl β-D-glucopyranoside 6-phosphate, available in 4 steps from acetobromoglucose, forms micelles and has been used as a novel surfactant in capillary electrophoresis,[59] and "double-tailed" (perfluoroalkyl)alkyl phosphosugars, such as compound **39**, are useful as components for drug-targeting systems.[60] Phosphatase-catalysed transfer of a dipalmitoylphosphatidyl residue from 1,2-dipalmitoyl-3-*syn*-phosphatidylcholine was employed in the synthesis of arbutin derivative **40**.[61] β-D-Mannopyranosyl) methylphosphonate diphosphate (**41**), an analogue of *myo*-inositol 1,4,5-triphosphate, has been prepared in a multi-step process from D-mannose.[62]



37 R = H
38 R = PO_3H_2

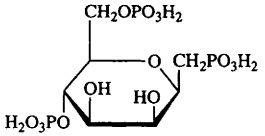


39

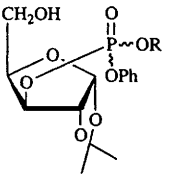


R = $O_2C(CH_2)_{14}Me$

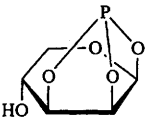
40



41



42 R = Me
43 R = H



45

The methylated phosphate **42** cyclized to the 3,5-cyclic phosphate 10^5 times faster than its unmethylated analogue **43**; both diastereomers at phosphorus of **42** were made and used in a model study on enzyme-catalysed phosphate transfer.[63] Selective phosphorylation of D-ribose, D-lyxose, D-xylose and D-glucose with reagents **44** gave tricyclic phosphites, such as lyxopyranose derivative **45**,[64] and similar reactions have been undertaken with 2,4-di-*O*-methyl-D-glucose.[65] Several reactions (*e.g.* acetylation) of compound **45** have been investigated.[66]

PX_3 X = imidazol-1-yl, or benzimidazol-1-yl, or 3,5-dimethylpyrazol-1-yl

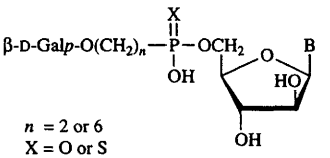
44

The four monophosphates of α,α′-trehalose have been obtained as a separable mixture in 10.7% combined yield by reaction of trehalose with sodium phosphate at pH 5.5.[67] Gram-scale preparation of the 6-mono- and 6,6′-di-phosphate of α,α′-trehalose has been achieved by taking advantage of the selective deprotection of the pertrimethylsilylated sugar at the primary positions.[68] Known methodology has been employed to synthesize the 6′-phosphate of octyl 2-*O*-(α-D-mannopyranosyl)-α-D-mannopyranoside and the corresponding methyl diphosphate,[69] UDP 4-deoxy-4-fluoro-α-D-glucose and -galactose,[70] GDP-4-deoxy-β-L-fucose,[71] and some galactosyl phosphate- and thiophosphate-diesters of AraA and AraC, *e.g.* compounds **46**.[72] An efficient process for the continuous enzymatic production of dTDP glucose by use of a membrane reactor and sucrose as glucose source has been described.[73]

The phosphoric acid diesters comprising glucose or galactose linked through O-6 to 7-β-hydroxycholesterol have been made as pro-drug forms of the cytotoxic cholesterol derivative.[74] *S*-Glycosyl phosphorodithioates are referred to in Chapter 11 and nucleoside phosphates in Chapter 20.

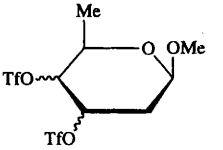
3 Sulfonates

The dibutyltin oxide-mediated tosylation of carbohydrate terminal 1,2-diols furnished the primary ester with good selectivity. Hexamethylenestannylene intermediates, however, reacted preferentially at the secondary oxygen atoms and afforded monotosylates **47** and **48** (Scheme 4), for example, in the ratio 24:1 in 99% combined yield.[75] Excellent yields of the 6-*O*-tosylate were formed in the dibutyltin oxide-promoted sulfonylation of methyl α-D-mannofuranoside.[76,77] Treatment of the four isomeric ditriflates **49** with tetrabutylammonium benzoate and tetrabutylammonium nitrite, respectively, gave the double displacement products accompanied by greater or lesser amounts of the usual by-products (see Vol. 27, Chapter 7, Ref.87).[78]



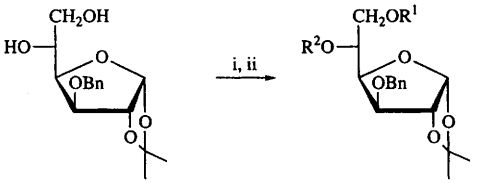
n = 2 or 6
X = O or S
B = Ade or Cyt

46



49

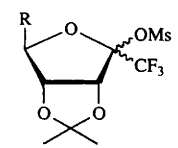
The conversion of a LD-Hepp derivative to its DD-isomer *via* a mesylate is referred to in Part 1 of this Chapter (Ref. 56), and the synthesis of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allononitrile from D-glucose *via* a trimesylate is covered in Chapter 10. Displacement of mesylate at the anomeric centre of 1-deoxy-1,1,1-trifluoro-2-ulose derivatives **50** by nucleophilic reagents such as tetrabutylammonium acetate, lithium azide, or hydrogen difluoride in the presence of triethylamine proceeded in 40-90 % yield; the CF_3 group stabilizes the sulfonate and destabilizes the cation at the anomeric centre.[79]



47 R^1 = H, R^2 = Ts
48 R^1 = Ts, R^2 = H

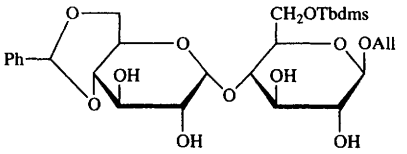
Reagents: i, Hexamethylenetin oxide, toluene, Δ; ii, TsCl, $CHCl_3$

Scheme 4



R = H or CH_2OH

50

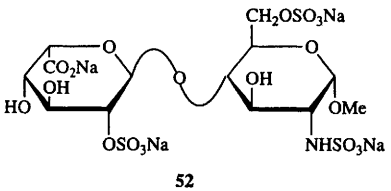


51

4 Other Esters

The regioselective sulfation of several mono- and di-saccharide derivatives *via* dibutylstannylene acetals has been investigated: methyl 4,6-*O*-benzylidene-α-D-gluco- and -galacto-pyranoside were sulfated at O-2 in 84 and 79% yield, respectively,[80] and *p*-methoxybenzyl 6-*O*-*t*-butyldimethylsilyl-β-D-galactopyranoside at O-3 in 92% yield;[81] phenyl 1-thio-β-lactoside gave the 3′-sulfate in 76% yield, accompanied by 10% of the 3′,6′-disulfate, and similar results were obtained with phenyl 2-acetamido-2-deoxy-1-thio-β-lactoside,[82,83] whereas the maltose derivative **51** reacted preferentially at O-2′.[83]

Disaccharide **52**, a major repeating unit of heparin, and its 6-*O*-unsulfated analogue have been synthesized by use of standard protecting group techniques from an appropriately protected disaccharide precursor.[84] Maltohexaose, maltoheptaose and laminaripentaose, on treatment with piperidine-*N*-sulfonic acid in DMSO at 80 °C or with SO_3-pyridine, gave products containing 2.2-3.1 sulfate groups per molecule which showed strong anti HIV activity.[36] Insights into the stereochemical features of sulfated carbohydrates have been provided by X-ray crystallography and modelling experiments of, for example, the 2-, 3-, 4-, and 6-monosulfates of methyl α-D-galactopyranoside.[85] F.a.b. m.s studies on multisulfated oligosaccharides are covered in Chapter 22.



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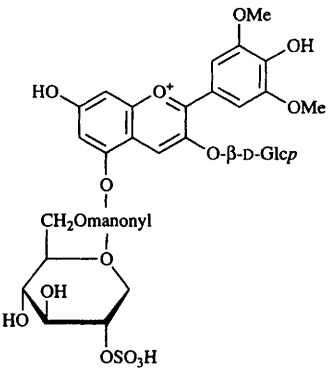
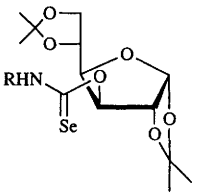


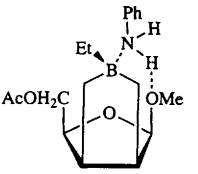
53

Two unusual sulfated natural products, eclalbasaponin, a oleanane triterpene glycoside containing β-D-glucopyranosyl 2-sulfate residues,[86] and malvidin 3,5-diglucoside derivative **53**, an anthocyanin,[87] have been isolated from *Eclipta alba* and *Babiana stricta*, respectively. Sulfate-containing diterpene glycosides are referred to in Ref. 50 of this Chapter.



R = Ph, C_6H_{11}, etc

54



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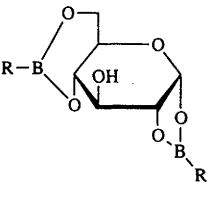


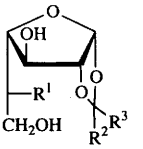
R = 7β-cholesteryl-O_2CNH—

56

Crystallographic studies on the coronary vasodilators 1,4:3,6-dianhydro-D-glucitol 2-mono- and -2,5-dinitrate have been published.[88]

A mild method for removing allyloxycarbonyl protecting groups utilizes catalytic Pd(0) formed *in situ* from $Pd(OAc)_2$ and sodium triphenylphosphine-*m*-sulphonate in aqueous media containing diethylamine.[89] A one-pot synthesis of isoselenocyanates from corresponding formamides allowed the synthesis of various *O*-alkylselenocarbamates including the sugar examples **54**.[90] The formation of carbamates in the DCC-mediated preparation of trichloroethylidene acetals is referred to in Chapter 6, and the synthesis of structural analogues of the carbamoyl group containing antibiotic moenomycin A is covered in Chapter 19.

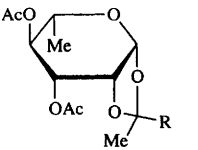
Borylated β-D-lyxofuranoside derivatives bind primary amines to form crystalline *endo*-



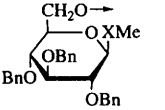
57 R^1 = OH, R^2 = H, R^3 = CCl_3

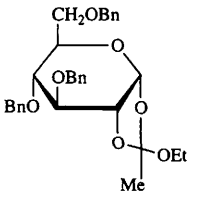
58 R^1, R^2 = O, R^3 = $CHCl_2$

59 R^1 = OH, R^2, R^3 = 



60 R = MeC_6H_4S—

61 R = 



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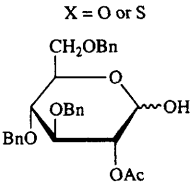

63

coordination complexes with an N–B bond, stabilized by hydrogen bonding, for example complex **55**.[91] A full paper on the involvement of phenylboronates in the transport of *p*-nitrophenyl β-D-gluco-, galacto-, manno-, and xylo-pyranosides through liquid organic membranes has been published (see Vol. 27, Chapter 7, Ref. 113).[92] The 2:1 complexes formed between sugars and a cholesterol-derived boronic acid, *e.g.*, the α-D-glucopyranose complex **56**, have gel-forming properties which depend on the chirality of the sugar.[93]

Treatment of trichloroethylidene acetals with potassium *t*-butoxide gave tricyclic orthoesters (*e.g.*, **57**→**58**), presumably by way of dichloroketene acetals (*e.g.* **59**).[94] Under catalysis by IDCP or NIS without added acid, 1,2-thio-orthoester **60** reacted with the primary hydroxyl groups of glycosides and thioglycosides to give 1,2-orthoester linked disaccharides such as compounds **61**.[95] Optimized conditions for the four-step synthesis of the free sugar **63** on a 100 g scale from β-D-glucose pentaacetate by way of orthoester **62** have been established.[96]

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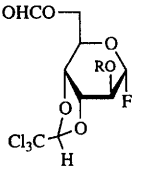
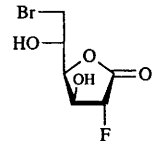
8
Halogeno-sugars

1 Fluoro-sugars

The glycosyl fluorides **1** and **2** have been prepared as glycosylating agents,[1] and kinetic isotope effects on the hydrolyses of α- and β-D-glucopyranosyl fluorides have been studied in order to investigate the reaction transition states.[2] Treatment of 5-*O*-benzoyl-3-deoxy-D-*erythro*-pentofuranose with DAST has afforded 5-*O*-benzoyl-2,3-dideoxy-2-fluoro-D-*threo*-pentofuranosyl fluoride,[3] and methyl 5-*O*-benzoyl-3-deoxy-3-fluoro-α,β-D-xylofuranoside with this reagent gave methyl 5-*O*-benzoyl-2,3-dideoxy-2,3-difluoro-α,β-D-lyxofuranoside.[4] 3-*O*-Benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose when treated with DAST gave predominantly the corresponding 5-deoxy-5-fluoro-L-*ido*-derivative, whereas 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose, under the same conditions, gave a mixture of the 5-deoxy-5-fluoro epimers. Attempted fluorination of sulfonate derivatives of these alcohols gave mostly unsaturated products[5].



1 R = $CONHC_6H_{11}$
2 R = Ac



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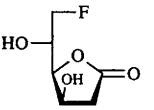
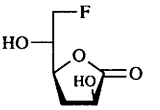
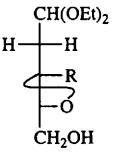


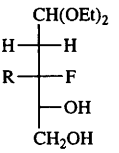
4



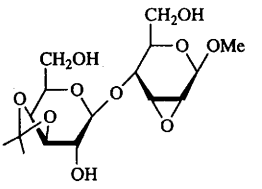
5



6 R = H, Me



7 R = H, Me



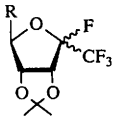
8

The reaction of DAST on appropriately *O*-protected derivatives of methyl β-lactoside has afforded the corresponding 6-, 3′-, 4′-*epi*- 4′- and 6′- deoxyfluoro compounds.[6] UDP-4-Deoxy-4-fluoro-D-glucose and -galactose have been prepared.[7] In a study of synthetic approaches to methyl 6-deoxy-6-fluoro-3,4-*O*-isopropylidene -α-D-galactopyranoside, DAST treatment of methyl 3,4-*O*-isopropylidene-α-D-galactopyranoside gave a mixture of products. Various sources of fluoride ion and solvents were studied in displacement reactions applied to corresponding 6-sulfonate derivatives, and tris(dimethylamino) sulfur (trimethylsilyl) difluoride in dichloromethane afforded the 6-fluoride derivative in 45% overall yield from methyl α-D-galactopyranoside.[8]

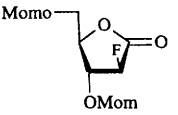
During a study of the substrate specificity of a fucosyltransferase, octyl 3-, 4-, and 6-deoxyfluoro-β-D-galactopyranosides were prepared,[9] while methyl 2-*O*-α-L-rhamnopyranosyl-α-D-galactopyranoside derivatives selectively fluorinated at the 3-, 4-, or 6- positions of the galactose moiety have been prepared as analogues of the antigenic determinant of the polysaccharide of *Shigella dysenteriae*.[10]

Treatment of some epoxyaldonolactones with hydrogen fluoride-amine complexes has afforded products of epoxide opening with fluoride ion, e.g. **3** - **5**.[11] Epoxy derivatives **6** have been opened by fluoride ion [$Ti(O^iPr)_4$ - TiF_4] at the more hindered position to give deoxyfluoro compounds **7**,[12] and epoxide **8** has been regioselectively opened at *C*-3 to give the corresponding 3-deoxy-3-fluoro derivative.[13]

The stereoselective preparation of 6-deoxy-6,6,6-trifluorohexopyranoses has been reviewed,[14] and the use of such derivatives in liquid crystals is mentioned in Chapter 3. Some substitution reactions at the anomeric centre of 1-deoxy-1,1,1-trifluoro-2-ulose derivatives included synthesis of glycosyl fluorides **9** from the corresponding 1-*O*-mesylates.[15]



9 R = H, CH_2OMom



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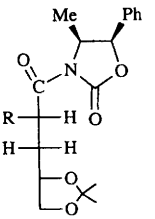


11 R = H
12 R = F

The synthesis of 2-deoxy-2-*C*-fluoromethyl- and -trifluoromethyl-pentofuranose derivatives is discussed in Chapter 14, and enzymatic syntheses of fluoroethyl glycosides is mentioned in Chapter 3, along with the synthesis of fluorinated *C*-glycosides. Addition of benzyloxymethyl lithium to aldonolactone **10** afforded, after deprotection, 3-deoxy-3-fluoro-D-fructose.[16] Electrophilic fluorination of the chiral aldonic acid amide **11** ($NaN(TMS)_2$, PhSONHF) afforded fluoro derivative **12**.[17] The conformational analysis in solution of 4-deoxy-4-fluoro-D-glucose and -galactose is covered in Chapter 21, and the influence of fluorine atoms on the e.i. and c.i. mass spectra of all the methyl mono deoxyfluoro-per-*O*-methyl-β-D-galactopyranosides has been evaluated.[18] Both D-glucose and 2-chloro-2-deoxy-D-glucose have been identified, by mass spectroscopic means, as impurities in 2-deoxy-2-[^{18}F] fluoro-D-glucose, prepared *via* a mannose-2-*O*-triflate intermediate.[19]

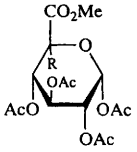
2 Chloro-, Bromo-, and Iodo-sugars

Treatment of methyl 3,6-dichloro-3,6-dideoxy-β-D-allopyranoside with lithium chloride in *N,N*-dimethylacetamide at 80°-100°C results in an equilibrium mixture of starting material and methyl 3,6-dichloro-3,6-dideoxy-β-D-glucopyranoside with the *gluco*-isomer predominating.[20]

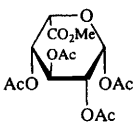
A facile synthesis of L-iduronic acid was achieved by photobromination of the α-glucopyranuronate **13** to give 5-bromo compound **14** and subsequent reduction (Bu_3SnH) to give a 3:1 ratio of the L-idopyranuronate **15** and starting material **13**.[21] Photobromination of glycopyranuronate oxime derivative **16**, on the other hand, afforded the *C*-1 bromide **17** which has been used as a donor for making 2-acetamido-2-deoxy-β-D-mannuronic acid glycosides.[22] Radical bromination of amide **18** gave the glycosyl bromide **19** which was converted to (+)- hydantocidin.[23]

The chemisry of the hexulosyl bromide **20** has been studied[24] and a facile synthesis of the azidogalactosyl bromide **21** by way of D-galactal triacetate has been outlined.[25] The conversion of 6-bromo-6-deoxyaldonolactones into 3,6-anhydro-aldonic acids is covered in Chapter 16 and the conversion of difructose dianhydride by way of deoxyhalo derivatives into 3,6-anhydro-keto-D-fructose is mentioned

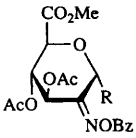
in Chaper 5. Evidence has been obtained from ^{1}H nmr spectroscopy and deuterium incorporation experiments to support the enolisation and consequent *C*-2 epimerisation of 2-deoxy-2-halo-D-glucose and -mannose on reaction with sodium hydride or potassium hydride or with caesium carbonate in methanol.[26]



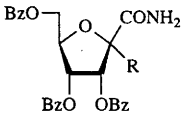
13 R = H
14 R = Br



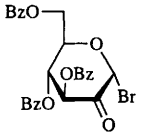
15



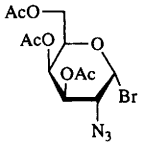
16 R = H
17 R = Br



18 R = H
19 R = Br



20



21

Radical oxygenation of 2-deoxy-2-iodo-sugar derivatives to give 2-hydroxy compounds has been achieved *via* two methods [$(Bu_3Sn)_2$, TEMPO; or Bu_3SnH, AIBN, air, toluene] affording predominantly 1,2-*trans* products.[27,28] 4-Deoxy-4-iodo-D-glucose has been prepared by iodide displacement of a galactose-4-triflate derivative,[29] and 6-deoxy-6-iodoaldonates have been made by treatment of acetylated aldonolactones with trimethylsilyl iodide.[30] Displacement with inversion at *C*-5 of 3-deoxy-1,2-*O*-isopropylidene-6-*O*-(silyl, ester or ether protecting group)-α-D-glucofuranose (Ph_3P, I_2, imidazole) has afforded 3,5-dideoxy-5-iodo-1,2-*O*-isopropylidene-β-L-*lyxo*-hexofuranose derivatives,[31] while treatment of 1,2-*O*-cyclohexylidene-5-*O*-mesyl-(or-tosyl)-α-D-xylofuranose with ion exchange resin (in the Br^- or I^- form) gave the 5-bromo-(or-iodo-) 5-deoxy-xylofuranose derivatives.[32]

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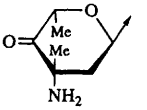
9
Amino-sugars

1 Natural Products

2-Acetamido-4-*O*-[(S)-1-carboxyethyl]-2-deoxy-D-glucose, a positional isomer of N-acetylmuramic acid, has been isolated from the *O*-specific polysaccharide of *Proteus penneri* 35.[1] 4-Amino-4,6-dideoxy-2-*O*-methyl-mannose has been isolated from the lipopolysaccharide of *Vibrio cholerae* O1.[2] The branched-chain amino-aldulose unit **1** is present in the new vancomycin class of glycopeptide antibiotic balkimycin; it exists as a hydrate in solution.[3]

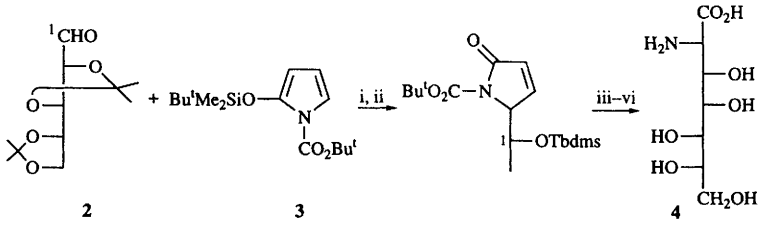


1

2 Syntheses

Syntheses covered in this section are grouped according to the method used for introducing the amino-functionality.

2.1 By Chain extension. — Addition of the glycine anion equivalent **3** to aldehydo-sugar derivatives such as L-*arabino*-**2**, led to various 2-amino-2-deoxy-aldonic acids, such as 2-amino-2-deoxy-D-*glycero*-L-*galacto*-heptonic acid **4** which was obtained in 35% overall yield (Scheme 1).[4,5]

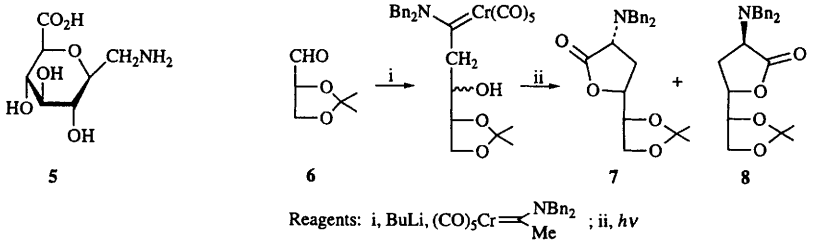


2 **3** **4**

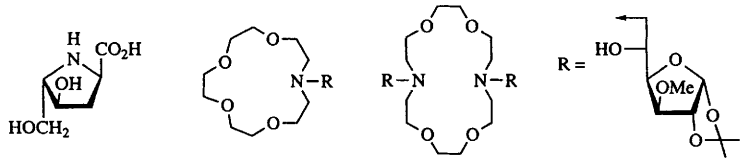
Reagents: i, $SnCl_4$; ii, TbdmsCl; iii, $KMnO_4$; iv, LiOH; v, $NaIO_4$, RuO_2; vi, H_3O^+

Scheme 1

The peptidomimetic sugar amino acid **5** was prepared in four steps from D-glucose, the process involving nitromethane addition at C-1 and oxidation at C-6 over a platinum catalyst. It is a good rigid mimic of many β-turns, and was incorporated into analogues of the peptides enkephalin and somatostatin, some of which showed good biological activity.[6] Aldol reaction of a chromium aminocarbene couple with 2,3-*O*-isopropylidene-D-glyceraldehyde **6** followed by photolysis gave a 1:1 mixture of the 2-amino-aldonolactones **7** and **8** (Scheme 2). The latter was converted to (+)-bulgecinine **9** in 5 steps.[7]



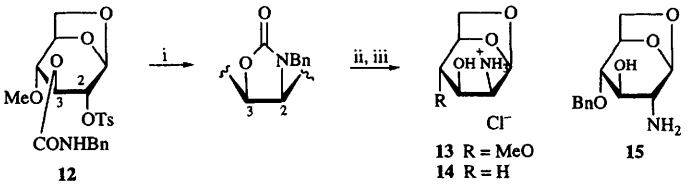
Scheme 2



9 **10** **11**

2.2 By Epoxide Ring Opening. — 6-Deoxy-6-trimethylammonio-D-glucose chloride was obtained both by reaction of a 5,6-anhydro-sugar derivative with trimethylamine, and by quaternization of 6-amino-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose.[8] Azacoronands and azapodands with pendant sugar groups such as **10** and **11** were obtained by reaction of the aza-crown compounds with 5,6-anhydro-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose.[9] The synthesis of (+)-galactostatin in 13 steps from L-quebrachitol, which involves the opening of a cyclitol epoxide with azide ion and a Baeyer-Villiger ring expansion of a keto-cyclitol derivative to a lactone as key steps, is covered in detail in Chapter 18.[10]

2.3 By Nucleophilic Displacement. — Intramolecular cyclization of urethane **12** followed by hydrolysis provided 1,6-anhydro-2-amino-2-deoxy-4-*O*-methyl-β-D-mannopyranose **13** (Scheme 3).

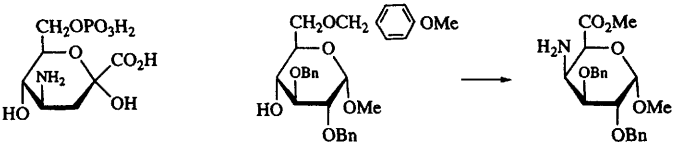


12 **13** R = MeO, **14** R = H **15**

Reagents: i, KOBu^t, DMSO; ii, NaOH, H_2O, EtOH; iii, H_2, Pd/C, HCl

Scheme 3

The interactions of **13**, its 4-deoxy-analogue **14** and the 2-amino-1,6-anhydro-D-glucose derivative **15** with copper(II) ions in aqueous solution were compared; none formed a dimeric complex as seen for 2-amino-1,6-anhydro-2-deoxy-β-D-glucopyranose.[11] A facile synthesis of a 1,6-anhydro-2-azido-2-deoxy-D-glucopyranose derivative is covered in Chapter 10. 4-Amino-3,4-dideoxy-D-*arabino*-heptulosonic acid 7-phosphate **16** was synthesized in 14 steps, 10% overall yield from 2-deoxy-D-ribose, the nitrogen functionality being introduced by azide ion displacement of a triflate. Compound **16** is a proposed intermediate in the biosynthesis of 3-amino-5-hydroxybenzoic acid, and was shown to act as a substrate for the relevant enzymes.[12] The 4-amino-4-deoxy-D-galacturonic acid derivative **18** was synthesized in good yield from glucoside **17** in a six step process incorporating azide ion displacement of a 4-mesylate (Scheme 4).[13] Japanese workers have reviewed their approach to the preparation of sialic acid and its analogues (cf. Vol.16, p.171 and 173). This involves aldol condensation of D-glucose with oxalacetic acid and leads to methyl pyranoside or furanoside isomers of 3-deoxy-D-*glycero*-D-*gulo*-nonulosonic acid methyl ester. Selective protection and introduction of nitrogen-functionality at C-5 with inversion was then applied. The approach is suggested as a practical means of obtaining such compounds in quantity.[14]

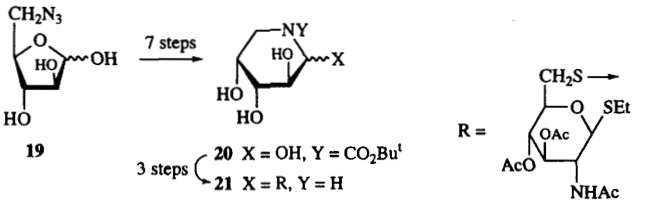


16 **17** **18**

Scheme 4

The novel potential glycosidase inhibitor **21** has been synthesized from 5-azido-5-deoxy-D-arabinose **19** (Scheme 5), itself prepared in six steps from D-arabinose by way of azide displacement of a 5-mesylate. Construction of the *N*-protected 5-amino-5-deoxy-D-arabinose **20** entailed the

preparation and Swern oxidation of a 2,3,4-tri-*O*-benzyl protected acyclic intermediate. Preparation of **21** involved acid catalysed *N*-deprotection of **20**, followed by base catalysed condensation of the product with a 6-thio-glucoside.[15]

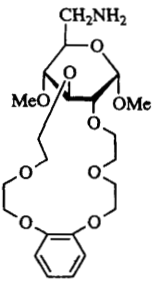


Scheme 5

In studies of the substrate specificity and inhibition of the glycosyltransferases which transfer α-D-GalNAc*p* and α-D-Gal*p* to *O*-3 of the β-D-Gal*p* residue of the disaccharide α-L-Fuc*p*-(1→2)-β-D-Gal*p*,[16] and the fucosyltransferase that transfers α-L-Fuc*p* to *O*-2 of β-D-Gal*p*,[17] Hindsgaul and co-workers have prepared numerous octyl β-glycoside acceptor analogues that are modified in the galactose residue through specific *O*-methylation, epimerization, and replacement of 2-, 3- or 4-OH by -NH_2 or -NHAc, amongst other variations. The 6-amino-derivative was obtained by Mitsunobu displacement of the hydroxy-group by phthalimide and the 3-amino-derivative by displacement of 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose 3-triflate with azide ion. The 3-amino-derivatives were modest inhibitors of these enzymes.

The benzo-crown ether **22** and its naphtho-analogue were synthesized from the corresponding 6-bromo-6-deoxy-derivatives by azide ion displacement. They are able to sequester dopamine presumably with the assistance of hydrogen bonding between the 6-amino-group and the phenolic hydroxyl functions on dopamine.[18]

The synthesis of a D-glucarolactam derivative is covered in chapter 16.



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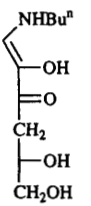
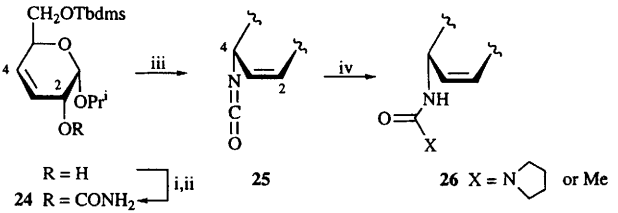


23

2.4 By Amadori Reaction. — 1-Amino-1-deoxy-D-fructose derivatives (Amadori compounds) have been prepared by reaction of D-glucose with a series of aliphatic amino acids (e.g. glycine, β-alanine, γ-aminobutyric acid, δ-aminovaleric acid, ε-aminocaproic acid and N^{α}-formyl-L-lysine), and characterized by ^{1}H- and ^{13}C-n.m.r. and FAB-mass spectrometry and pH-potentiometric titration. The β-pyranose form dominates in aqueous solution. The basicity of the amino-group in these compounds is decreased (by ~1.5 of the K_a value) relative to the parent amino acid.[19] The formation of 1-*N*-butylamino-1-deoxy-4-*O*-(α-D-glucopyranosyl)-D-fructose by Amadori reaction of maltose and butylamine, and its conversion to the amino-reductone **23** have been reported.[20]

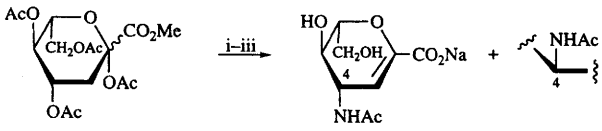
2.5 From Unsaturated Sugars. — Allylic rearrangement of allyl cyanates, formed *in situ* from carbamates such as **24** (derived originally from D-glucal triacetate), yielded isocyanates, e.g. **25**, that could then be converted to allylic amine derivatives, e.g. **26** (Scheme 6).[21] Trapping of an allylic



Reagents: i, $Cl_3CCONCO$; ii, K_2CO_3, MeOH, H_2O; iii, Ph_3P, CBr_4, Pr^i_2NEt; iv, HN or Me_3Al

Scheme 6

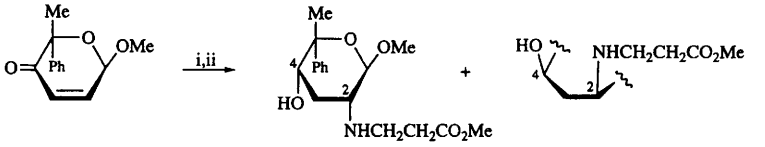
carbonium ion by a molecule of acetonitrile was inferred as the mechanism for the production of the isomeric unsaturated acetamido-sugar derivatives **28** and **29** on treatment of the 3-deoxyheptulosonate tetraacetate **27** with Lewis acid in this solvent (Scheme 7).[22] Michael-like addition of amino acids to 5-*C*-substituted 2,3-dideoxy-hex-2-en-4-ulopyranosides such as **30**,



Reagents: i, Me_3SiOTf, MeCN; ii, MeONa, MeOH; iii, NaOH, H_2O

Scheme 7

followed by *in situ* reduction gave conjugates such as **31** (68%) and **32** (9%) with good stereoselectivity (Scheme 8).[23] Adducts formed by conjugate addition of *N*-benzylhydrazine to α,β-unsaturated sugar lactones are covered in Chapter 10, section 5.

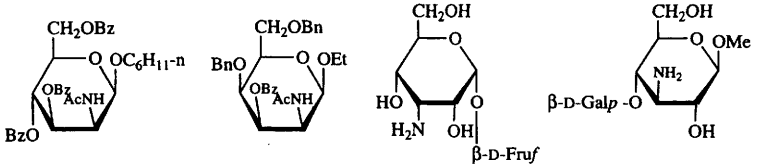


30 **31** **32**

Reagents: i, $H_2NCH_2CH_2CO_2Me$, MeOH, Et_3N ; ii, $NaBH_4$

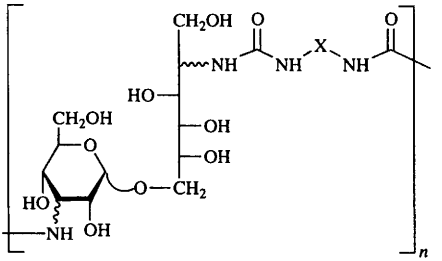
Scheme 8

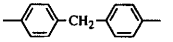
2.6 From Alduloses. — The stereoselectivity of the reduction (with $LiBH_4$, Me_3SiCl, followed by acetylation) of *O*-methyloxime and *O*-benzyloxime derivatives of α- and β-D-*arabino*- and *lyxo*-hex-2-ulopyranosides to give 2-acetamido-2-deoxy-hexopyranosides has been investigated. While the β-anomers gave D-manno- and D-talopyranosides, e.g. **33** and **34,** respectively, and the α-D-*arabino*-oxime gave the D-glucopyranoside, the α-D-*lyxo*-oximes gave varying selectivity between the D-galacto- and D-talo-pyranoside products depending upon the *O*-protecting groups employed.[24] 2,2′-Diacetamido-2,2′-dideoxy-α,β-trehalose derivatives were synthesized by coupling per-*O*-protected 2-oximino-α-D-*arabino*-hexosyl bromides as α-selective donors and 3,4,6-tri-*O*-protected 2-deoxy-2-phthalimido-D-glucose as β-selective donors, with subsequent reduction ($LiBH_4$, Me_3SiCl) of the oximino function. Analogues were also constructed using a galactose donor.[25] 3-Amino-3-deoxy-3-*epi*-sucrose **35** was synthesized in 35% yield by oximation and hydrogenation (H_2, Raney Ni, 120 bar, 50°C) of 3-ketosucrose, which is available by microbial oxidation of sucrose by *Agrobacterium tumefaciens*.[26] Methyl 3-amino-3-deoxy-β-lactoside **36** was synthesized by reduction ($LiAlH_4$) of the *O*-benzyloxime of an *O*-benzyl-protected 3-keto-derivative, which gave *gluco*- and *allo*-epimers in 43 and 25% yield, respectively. Its binding to ricin toxin was studied.[27]

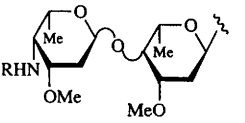


33 **34** **35** **36**

Sugar-containing polymers **37** have been obtained by polymerization of a diamino-substituted glycosyl-alditol monomer with diisocyanates. The monomer was obtained from isomaltulose by oxidation to 3′-keto-isomaltulose with *Agrobacterium tumefaciens* (Noll-Borchers *et al*, *Biotechnol. Lett.*, 1993, *15*, 139) followed by reductive amination (i, NH_2OH; ii, Pd/C, H_2), so avoiding the use of protecting groups.[28]



37 X = $(CH_2)_6$ or  *n* = 40–3400



38 R = H or Me

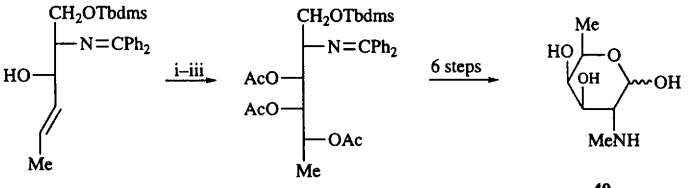
The 4″-*epi*-amino-4″-deoxyavermectin B_1 and its *N*-methyl-derivative, which have the disaccharide constituents **38**, were synthesized by reduction ($NaBH_4$) of the imine and *N*-methylimine formed from the corresponding 4″-ketone by zinc chloride catalyzed reaction with hexamethyl- and heptamethyl-disilazane, respectively.[29]

Full details of the synthesis of 5-amino-5-deoxy-D-gluconolactam and 1-deoxynojirimycin (Vol.27, p.206) have been published, and the method, which involved reduction of a 5-keto-aldonamide, has been applied to the synthesis of 5-amino-5-deoxy-D-galactonolactam, 4-amino-4-deoxy-D-arabinonolactam, and a mixture of 5-amino-5-deoxy-D-mannono- and L-gulono-lactams.[30]

Syntheses of α-azido-*C*-formyl branched-chain sugars are covered in Chapters 14 and 24.

2.7 From Aminoacids. — The total synthesis of amino-sugars from α-amino acids has been reviewed (118 refs, in English).[31] 2-Deoxy-2-*N*-methylamino-D-fucose **40** has been synthesized by *cis*-hydroxylation of the alkene **39** derived from methyl L-serinate (Scheme 9).[32] The glycoside **43** of the amino-sugar constituent of the enediyne antitumour agent kedarcidin has been synthesized from D-threonine *via* its derivative **41** (Scheme 10). The stereochemistry at C-3 in **43** was determined by a highly stereoselective reduction of the ketone **42**.[33] The deoxyaminofuranosides **44** have been synthesized from *N,O*-protected L-serinal and L-threoninal derivatives by chain extension

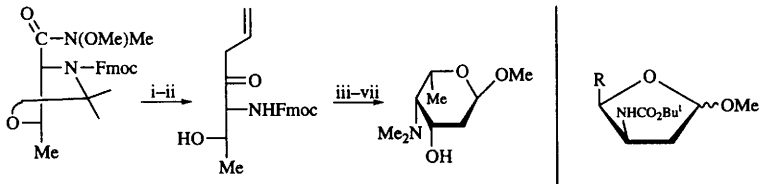
using methoxymethylene Wittig reagents.[34] Full details of the stereocontrolled synthesis of methyl α-D-lincosaminide from D-threonine (c.f. Vol.26, p.115, ref. 32) have been published.[35]



39 **40**

Reagents: i, $K_2OsO_2(OH)_2$; ii, K_2CO_3, $K_3Fe(CN)_6$; iii, Ac_2O, Py

Scheme 9

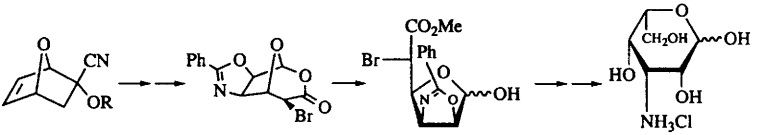


41 **42** **43** **44** R = H, Me

Reagents: i, MgBr; ii, CF_3CO_2H, MeOH; iii, $Me_4N\,BH(OAc)_3$;
iv, O_3, MeOH; v, MeOH, H^+; vi, NH_4HCO_3, Pd/C;
vii, HCHO, H_2, Pd/C

Scheme 10

2.8 From Chiral Non-carbohydrates. — The Diels-Alder adduct **45** of furan and 1-cyanovinyl (1*S*)-camphanate has been transformed into 3-amino-3-deoxy-L-talose **46** by a multistep sequence (Scheme 11). The initial steps involved (a) the formation of an *N-tert*-butoxycarbonyl-aziridine (through dipolar cycloaddition of *tert*-butyl azidoformate to **45**, followed by irradiation of the resulting triazolines), (b) changing the *N*-protection group (from CO_2Bu^t to Bz), and (c) rearrangement of the *N*-benzoyl-aziridine to an oxazoline.[36] Full details of the synthesis of aza-sugars, including mannojirimycin and (+)-kifunensine, from a chlorobenzene microbial oxidation production (c.f. Vol.27, p.120 and 182) have been published.[37] A route for the synthesis of 2-amino-2-deoxyaldonic acids from 2,3-*O*-isopropylidene-D-glyceraldehyde is covered in Section 2.1.

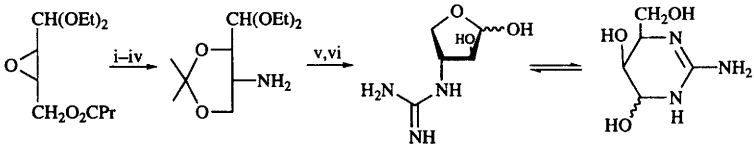


R = (1*S*)-camphanoyl

45 **46**

Scheme 11

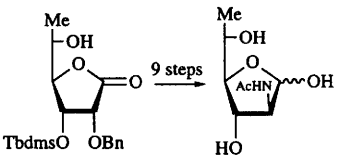
2.9 From Achiral Non-carbohydrates. — 3-Deoxy-3-guanidino-D-threose **48** equilibrates with **49**, a transition state inhibitor for galactosidase. It was synthesized as shown in Scheme 12 from epoxide **47**, which was obtained by porcine pancreatic lipase catalysed enantioselective esterification of the racemic epoxy-alcohol precursor.[38] 6-Deoxy-L-talonolactone **50** was synthesized by an asymmetric aldol condensation - dihydroxylation sequence (Vol.24, p.152) in improved diastereoselectivity and was converted into 2-acetamido-2,6-dideoxy-L-fucose (shown as its furanose isomer **51** in Scheme 13), 3-acetamido-3,6-dideoxy-L-idose and 5-acetamido-5,6-dideoxy-D-allose by S_N2 displacements of triflate with azide ion.[39] 4-Amino-4-deoxy-DL-erthrose **53** was obtained from the hetero-Diels-Alder adduct **52** by a sequence of reactions including *cis*-dihydroxylation (OsO_4, NMNO) of the alkene moiety (Scheme 14).[40] The synthesis of a racemic branched-chain lactam is covered in Chapter 16.



47 **48** **49**

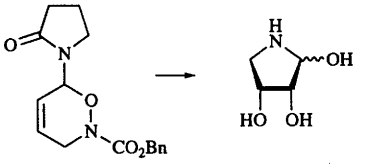
Reagents: i, NaN_3; ii, K_2CO_3, MeOH; iii, $Me_2C(OMe)_2$, H^+; iv, H_2, Pd/C; v, $(Bu^tO_2CHN)_2C{=}S$; vi; H^+

Scheme 12



50 **51**

Scheme 13



±-52 ±-53

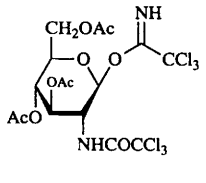
Scheme 14

Syntheses of dideoxyiminoalditols are covered in Chapter 18, and amino-nucleosides in Chapter 20.

3 Properties and Reactions

3.1 Biological and Other Properties. — From a study of the cleavage of DNA catalyzed by a number of amino-sugars and their derivatives it was concluded that activity correlated with the amount of acyclic form bearing both free aldehydo- and amino-groups present at equilibrium. The order of activity was 1-amino-1-deoxy-D-fructose ("D-isoglucosamine") > 2-amino-2-doexy-D-mannose > 2-amino-2-deoxy-D-galactose > 2-amino-2-deoxy-D-glucose, and activity increased with the introduction of an acidic group (i.e. phosphate) at C-6.[41] A vibrational spectroscopic study of 2-acetamido-2-deoxy-D-glucose is reported in Chapter 22.

3.2 *N*-Acyl Derivatives. — *O*-Protected 2-deoxy-2-trichloroacetamido-D-glucopyranosyl trichloroacetimidates, e.g. **54**, have been used in the synthesis of β-linked disaccharides with some success (see Chapter 3). The products could be converted into the corresponding 2-acetamido-derivatives by radical dechlorination (Bu_3SnH, AIBN). The 2-trichloromethyl-oxazoline derivative **55**, formed from 3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-D-glucosyl acetate (on reaction



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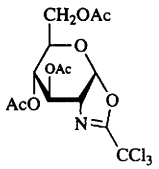

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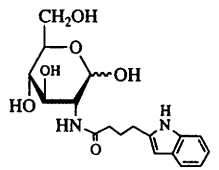

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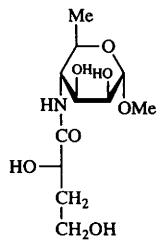


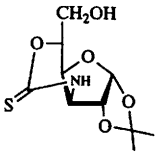
57

with Me_3SiBr, Bu_4NBr, $BF_3.OEt_2$, *sym*-collidine) was also an effective glycosylating agent.[42] The corresponding 2-methyloxazolines can be synthesized from anomeric mixtures of amino-sugar peracetates by the action of Lewis acid in the presence of a proton acceptor such as metallic calcium.[43] Sugar azido-groups in *O*-glycopeptide derivatives can be converted into acetamido-groups by reaction with thioacetic acid; sulphur and nitrogen are produced concurrently (cf. Vol.24, p.111, ref.21).[44] A variety of *N*-acyl 2-amino-2-deoxy-D-glucose derivatives were synthesized and evaluated as acceptor substrates for galactosyltransferase. The 4-(2-

indoly)butyramido-derivative **56** was a 14-fold better acceptor than the corresponding acetamido-derivative.[45] Chito-oligosaccharides (DP 2-4) *N*-fatty acid acylated specifically on the reducing sugar residue were obtained by direct substitution using equimolar proportions of acylating reagents. Three different coupling procedures being evaluated.[46] An improved synthesis of the 4,6-dideoxy-4-(3-deoxy-L-*glycero*-tetronamido)-D-mannoside **57** (cf. Vol.22, p.94, ref.24), a constituent sugar of the O-polysaccharide of *Vibria cholerae* O:1, involved reaction of the free amine with 2-acetoxy-4-hydroxy-butyrolactone.[47] *N*-Formyl and -acetyl-di-*O*-isopropylidene derivatives of 6-amino-6-deoxy-α-D-galactopyranose and -α-D-glucofuranose, and 1-amino-1-deoxy-β-D-fructopyranose were synthesized from the corresponding free amines by reaction with formic acetic anhydride or acetic anhydride, respectively. They were converted into the corresponding *N*-thioformyl and *N*-thioacetyl derivatives by reaction with phosphorus pentasulphide.[48]

Attempted dephthalimidoylation of some amino-sugar containing di- and tri-saccharide derivatives (with $H_2NNH_2.H_2O$ EtOH) led to the formation of intramolecular glycosylamine bond formation; see Chapter 10 for further details.[49] *N*-Thioacyl derivatives of sialic acids are covered in Chapter 16.

3.3 Isothiocyanates and Related Compounds. — Various *O*-protected amino-sugars have been converted into the corresponding isothiocyanato-sugars (by reaction with $CSCl_2$, $CaCO_3$).[50-52] Acid hydrolyses of the di-*O*-isopropylidene derivatives of, for example, 3-deoxy-3-isothiocyanato-α-D-glucfuranose and 1-deoxy-1-isothiocyanato-β-D-fructopyranose yielded bicyclic derivatives such as **58**[50] and **59**[51], respectively. Further hydroysis of **58** led to **60**. Thioureyl-linked oligosaccharides, e.g. **61**, were obtained by condensation of sugars bearing free amino groups with isothiocyanato-sugar derivatives.[52] An NMR study of thioureido-sugar derivatives is reported in Chapter 21.



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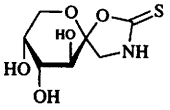

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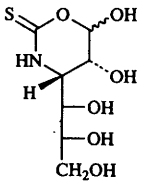

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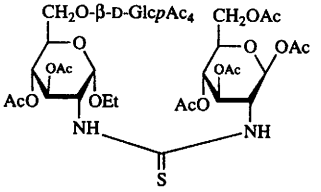
3.4 *N*-Alkyl Derivatives. — Quaternization of an amino-sugar derivative[8] has been covered in section 2.2. The azi-derivative **62**, required as a photoaffinity label, was synthesized from 2-amino-2-deoxy-D-glucose by reductive amination with the appropriate aldehyde,[53] as was the pyrimidine derivative **63**, the bactericidal activity of which was studied.[54] Addition of dialkyl phosphite to the Schiff base adduct of 4-methyl- or 4-methoxy-benzaldehyde with tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucose gave isomeric adducts, e.g. **64**. The proportion of the *R*-isomer formed increased with the size of the alkyl group.[55]



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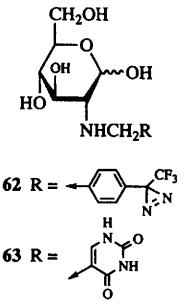
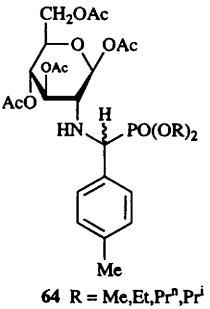




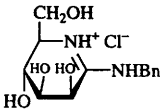
64 R = Me,Et,Pr^n,Pr^i

3.5 Imine Derivatives. — The absolute sense of twist between vicinal OH and NH_2 groups in an amino-sugar glycoside (e.g. methyl β-L-daunosaminide), or between 1,3-related NH_2 groups in a diamino-sugar glycoside (e.g. methyl kasugaminide), can be predicted from the sign of the exciton-split c.d. curves of derivatives prepared by *O*-5-(4-methoxyphenyl)-penta-2,4-dienoylation (in the amino-hydroxy case) and Schiff base formation with e.g. 4-dimethylaminobenzaldehyde and the NH_2 group(s).[56]

3.6 Muramoyl Dipeptide Analogues. — The chemical synthesis of both anomers of UDP-*N*-acetylmuramic acid has been reported. The α-anomer was identical to naturally occurring material.[57] A preliminary note on the synthesis of an amide-linked conjugate of muramic acid with an HIV-derived oligopeptide, and its ability to induce antibodies to the peptide moiety, has appeared.[58]

3.7 Amidine, Guanidine and Imidazole Derivatives. — 5-Amino-5-deoxy-D-mannonolactam and -D-fuconolactam have been converted, *via* thionolactam intermediates, into the amidine and amidrazone derivatives **65**[59] and **66**[60], respectively (cf. Vol.24, p.120 for similar methodology).

They were potent inhibitors of mannosidase and α-L-fucosidase, respectively. The synthesis and glycosidase inhibitory properties of cyclic guanidinium derivatives such as **67** and **68** have been reported. Isomeric 1,3-diamino-2,4-*O*-benzylidene-1,3-dideoxy-tetritols were separately condensed with an aromatic or a sugar isothiocyanate, and the resulting thiourea adducts (involving only the primary amino groups) were cyclized (PbO, EtOH) to guandinium derivatives and deprotected.[61,62] Condensation of 2-amino-2-deoxy-D-galactose with 2-methyl-2,4-dinitroimidazole led to 2-deoxy-2-*N*-(2-methyl-4-nitroimidazol-1-yl)-D-galactose.[63]



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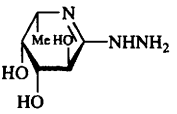

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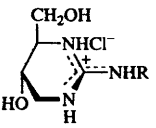
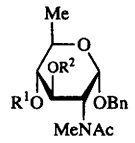


67 R = $C_6H_4NH_3Cl^-(p)$

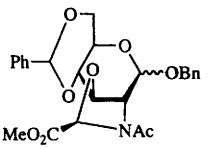
68 R = D-glucos-6-yl

3.8 Assorted Derivatives. — The 2-amino-2,6-dideoxy-D-glucose derivatives **69** and **70** were synthesized from 2-amino-2-deoxy-D-glucose as glycosyl acceptors for the construction of sequences in the polysaccharides of some *Bordetella pertussis* toxins.[64] 4-*O*-(Amino acid esters) of 2-amino-2,3-dideoxy-DL-*erythro*-pentopyranose were prepared as analogues of the natural antibiotic prumycin (see also section 4).[65] Syntheses of the 4′- and 6′-*O*-(hydroxyethyl) and -(2-hydroxypropyl) ether derivatives of 2-acetamido-2-deoxy-D-glucose have been reported.[66] 2-Acetamido-2,3-dideoxy-D-*arabino*-hexono-1,4- and 1,5-lactone derivatives have been obtained by highly stereoselective hydrogenation of previously reported α,β-unsaturated lactone derivatives obtained from 2-amino-2-deoxy-D-gluconic acid (cf. Vol.23, p.139).[67]



69 R^1 = H, R^2 = $CH_2C_6H_4OMe(p)$

70 R^1 = Bz, R^2 = H



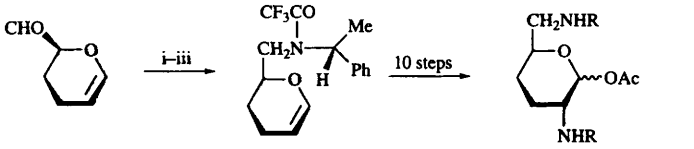
71

The electron impact mass spectra of 29 oxazolidines derived from sugars, such as **71**, have been recorded.[68] Potentiometry has been used to study the acid-base and metal ion complexing properties of 2-benzylamino-2-deoxy-D-*glycero*-D-*talo*-heptonic acid in aqueous solution. Complexation was similar to that seen with alanine and the D-*glycero*-D-*gulo*-analogue, with both

ML and ML_2 forms being present.[69] Syntheses of 2-acetamido-2-deoxy-*C*-glucosides and 2-amino-2-deoxy-D-glucals are reported in Chapters 3 and 13, respectively.

4 Diamino-sugars

4.1 Synthesis by Introduction of Two Amino-groups. — Acrolein dimer **72** has been converted into both enantiomers of purpurosamine C, as shown in Scheme 15 for the D-isomer **74**, in a form suitable for use as glycosyl donors for making sannamycin-type antibiotics. Reductive amination with (*R*)- or (*S*)-α-methylbenzylamine then *N*-trifluoroacetylation led to mixtures of diastereoisomers, from which the D- (i.e. **73**) or L-glycals, respectively could be obtained by crystallization. The 2-amino-function was introduced by addition of nitrosyl chloride to the glycal,

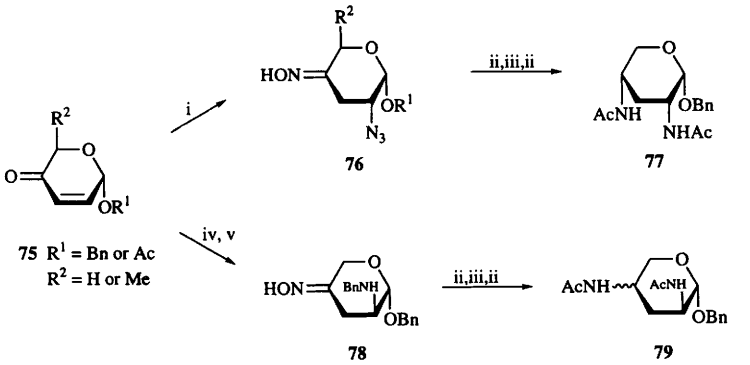


±-72 73 74 R = 2,4-dinitrophenyl

Reagents: i, (*R*)-Ph(Me)$CHNH_2$, $NaBH_4$; ii, $(CF_3CO)_2O$; iii, crystallisation

Scheme 15

reaction with methanol and reduction of the resulting 2-oximino-glycoside. Related 2-azido-derivatives were obtained by reaction of a 2-amino-intermediate with triflyl azide.[70] Sequential



75 R^1 = Bn or Ac
R^2 = H or Me

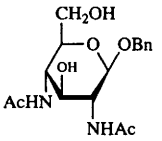
76 77 78 79

Reagents: i, HN_3 then NH_2OH; ii, Ac_2O; iii, $NaBH_4$, $NiCl_2$; iv, $BnNH_2$, –40 °C; v, NH_2OH, NaOAc

Scheme 16

addition of hydrazoic acid then hydroxylamine to the enones **75** gave predominantly or exclusively the 2-azido-stereoisomers **76**, while sequential addition of benzylamine then hydroxylamine led to the C-2 epimeric **78** (Scheme 16). These were reduced to the 2,4-diamino-sugars **77** and **79**, the latter as a separable mixture of D-*threo*- and L-*erythro*-isomers.[71] Ethyl 4,6-diamino-2,3,4,6-tetradeoxy-α-D-*threo*-hexopyranoside has been synthesized from D-glucose by a procedure essentially the same as previously published by Malik *et al* (Vol.17, p.101).[72]

4.2 Synthesis from Amino-sugars. — Benzyl 2,4-diacetamido-2,4-dideoxy-β-D-glucopyranoside **80** has been synthesized from benzyl 2-acetamido-2-deoxy-β-D-galactopyranoside by conventional techniques involving displacement of a 4-mesylate by azide ion. Compound **80** showed modest inhibition of bovine β-1,4-galactosyltransferase activity, whereas its 4-amino- and 4-azido-analogues were inactive.[73] Full details (cf. Vol.25, p.118) of the syntheses of the 2,4-diamino-2,3,4-trideoxy-DL-pentose derivatives **81** and **82**, 3-deoxy-analogues of the natural antibiotic prumycin, have been published.[65] Syntheses of 6-azido- and 6-amino-1,6-dideoxy-nojirimycin are covered in Chapter 18.



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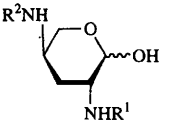
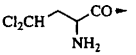
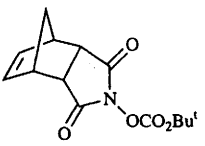


81 $R^1 = R^2$ = D-Ala, L-Ala, D-Ala-D-Ala or



82 R^1 = H, R^2 = as above

4.3 Reactions. — The reagent **83** has been used for the selective *tert*-butoxycarbonylation of unhindered amines. Thus the 6-*N*-protected derivative **84** of neamine was obtained in 65% yield.[74] The 4-deoxy-4-guanidino derivative **85**, a potent inhibitor of influenza viral sialidase and an influenza drug candidate, was synthesized from the corresponding *O*-protected 4-azide.[75]



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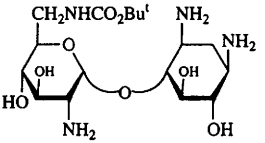

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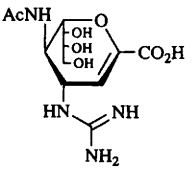

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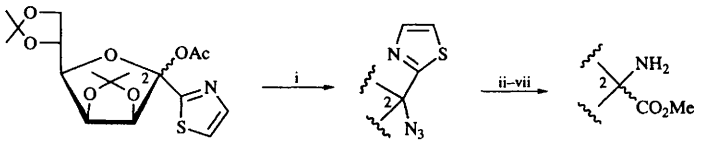
10
Miscellaneous Nitrogen Derivatives

1 Glycosylamines and Related Glycosyl-N-bonded Compounds

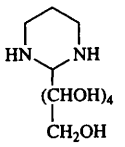
1.1 Glycosylamines. — α-D-Mannopyranosylamine was synthesized by reduction (H_2 - Adams cat.) of the corresponding glycosyl azide (see this Chap., Section 2).[1] *N,N*-Di-(β-D-galactopyranosyl)amine was obtained by transglycosylation of β-D-galactopyranosylamine, and β-D-mannopyranosylamine and 2-acetamido-2-deoxy-β-D-glucopyranosylamine were also reported.[2] A general route to glycosylamines of ulosonic acids, "anomeric α-amino acids", has been described, as exemplified in Scheme 1.[3]



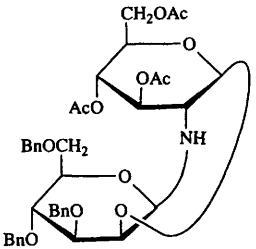
Reagents: i, Me_3SiN_3–Me_3SiOTf; ii, TfOMe; iii, $NaBH_4$; iv, $HgCl_2$,H_2O; v, Ag_2O; vi, CH_2N_2; vii, Pd/C, H_2

Scheme 1

The major species present in aqueous solutions of equimolar amounts of hexoses (Glc, Gal or Man) and propylamine or ethylenediamine were the *N*-alkylglycosylamines, whereas with 1,3-diaminopropane, the acyclic hexahydropyrimidines **1** were dominant.[4] Dephthalimidation (with $NH_2NH_2.H_2O$, EtOH) of di- and tri-saccharide derivatives containing 2-*O*-(2-deoxy-2-phthalimido-



1



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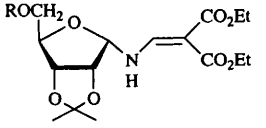
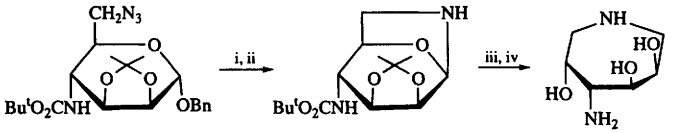


3 R = H
4 R = β-D-Glc*p*-Ac_4

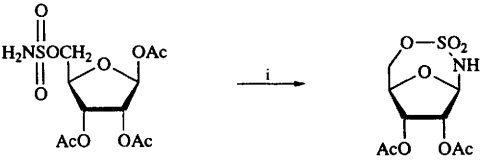


5 **6** **7**

Reagents: i, $NaIO_4$, RuO_2; ii, H_2, Pd; iii, $NaBH_3CN$, HOAc; iv, HCl, MeOH

Scheme 2

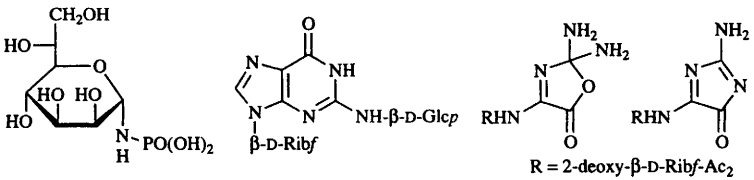
β-D-glucopyranosyl)-α-D-mannopyranosyl acetate moieties led to tricyclic intramolecular glycosylamines such as **2**.[5] The ribopyranosylenamine **3** has been used as a glycosyl acceptor in Koenigs-Knorr syntheses of disaccharides such as **4**.[6] Oxidative removal of the 1-*O*-benzyl ether in **5**, followed by hydrogenation, led to the surprisingly stable bicyclic hemiaminal **6** which was converted to 4-amino-1,4,6-trideoxy-1,6-imino-D-mannitol **7** on reductive ring opening (Scheme 2).[7] The sulphamate-bridged bicyclic compound **9** was formed by cyclization of the ribose-5-sulphamate derivative **8** (Scheme 3).[8] The D-*glycero*-α-D-*manno*-heptosyl amidophosphate **10**, a potential inhibitor of bacterial heptose synthetase, was obtained from the perbenzylated glycosyl azide by the use of the Staudinger reaction [i, $P(OBn)_3$; ii, Na, NH_3].[9]



8 **9**

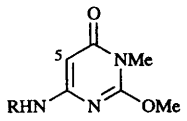
Reagents: i, Me_3SiOTf, MeCN

Scheme 3



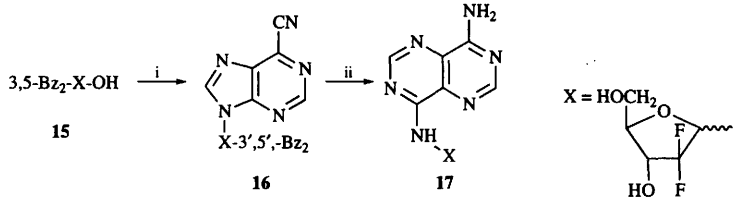
10 **11** **12** **13**

R = 2-deoxy-β-D-Rib*f*-Ac_2



14 R = β-D-Rib*p*, β-D-Rib*f*, β-D-Xyl*p* or β-D-Xyl*f*

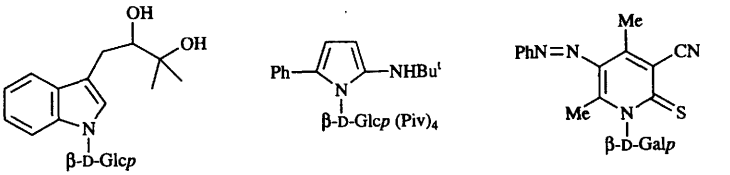
When glucose and guanosine are heated in aqueous buffer (pH 7, 100°C) the glucosylamine derivative **11** is the main product, suggesting that *N*-glucosylation of nucleotides may occur under physiological conditions and represent a feature of the chemistry of diabetes.[10] The oxazolone **12** and its precursor **13** were formed by reaction of 3′,5′-di-*O*-acetyl-2′-deoxyguanosine with hydroxyl radicals.[11] The glycosylaminopyrimidines **14** were synthesized by $SnCl_4$-catalyzed coupling of peracetylated pentoses with the corresponding aminopyrimidine, followed by de-*O*-acetylation, and were nitrosated at C-5.[12] The antileukaemic pyrimidino[5,4-*d*]pyrimidine derivative **17** was obtained by rearrangement of the nucleoside derivative **16**, that had been prepared by condensation of the free sugar **15** with 6-cyanopurine (Scheme 4).[13]



Reagents: i, 6-cyanopurine, DEAD, Ph_3P; ii, NH_3, H_2O, MeOH

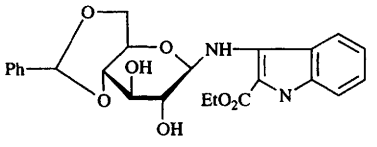
Scheme 4

Bruceolline F **18**, an *N*-glucosyl-indole, has been isolated from root wood of *Brucea mollis*.[14] Stable, separable atropisomers of the *N*-glucosyl-pyrrole derivative **19** were obtained by elaboration of 2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosylamine (i, PhC≡CC(OEt)=M$(CO)_5$ where M=Cr or W; ii, Bu^tNC); the isomers result from restricted rotation about the glycosidic bond.[15] *N*-Gluco- and galactosyl-pyridine-2(1*H*)-thione derivatives such as **20** have been synthesized by



condensation of the base with acetohalogenosugars.[16,17] Direct condensation of D-glucose with aminoindoles containing electron-withdrawing substituents (i.e. 5-amino-3-dimethylsulphamoylindole and 3-amino-2-ethoxycarbonylindole led to anomeric mixtures of derivatives *N*-D-glucopyranosylated on the primary amine group. Reaction of the latter indole with 4,6-*O*-benzylidene-D-glucose gave a good yield of the β-pyranosyl form **21**.[18] Condensation of 1,4-

dinitroimidazole or its 3-methyl-analogue with D-glucopyranosylamine gave the N^1-glucosyl-4-nitroimidazoles **22**.[19] Synthesis of 8-methyl-6-thio-7-(β-D-xylopyranosyl)theophylline by reaction of the corresponding 6-oxa-analogue with Lawesson's reagent, and the use of these compounds in n.m.r. spectroscopic and molecular mechanic studies of *syn-anti* equilibria, has been reported.[20] Other *N*-glycosylated heterocycles are treated as nucleosides in Chapter 20, while the synthesis of *N*-glycosyl-tetrazoles and their applications as glycosyl donors is covered in Chapter 3.



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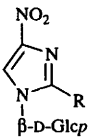
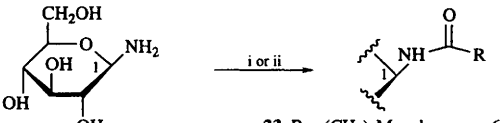


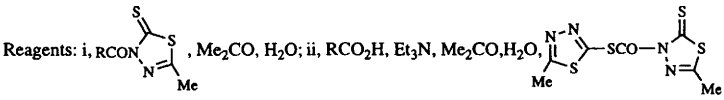
22 R = H or Me

1.2 Glycosylamides Including *N*-Glycopeptides. — Surfactants, e.g. **23**, and *N*-glycopeptide building blocks, e.g. **24**, have been synthesized in >70% yields by direct coupling of free β-glycopyranosylamines (of Glc, Gal, GlcNAc, Lac) with acylating agents as shown in Scheme 5 (cf. Vol.25, p.122, ref.17 for similar studies but in aprotic solvent).[21] Peptide T-cell epitopes with N^4-



23 R = $(CH_2)_n$Me where n = 6, 8, 10, 12

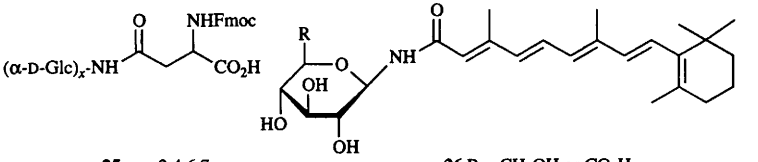
24 R = —CH_2C(CO2Bn)—H, NHCO2Bn



Scheme 5

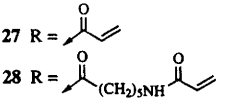
malto-oligosaccharide containing *N*-terminal asparagine residues were synthesized by i) amination of malto-oligosaccharides (DP=2, 4, 6 or 7) with aq. NH_4HCO_3; ii) coupling the resulting β-glycosylamines with a pentafluorophenyl ester activated L-aspartic acid derivative followed by *O*-deprotection (CF_3CO_2H) to give **25**; and iii) solid phase peptide synthesis. The incorporation of such malto-oligosaccharide residues did not alter the conformation of the peptide backbone, but

inhibited dimerization through disulphide bridge formation.[22] The other glycosylamines referred to below were obtained by synthesis and reduction of *O*-protected glycosyl azides. The *N*-glucosyl and -glucuronosyl retinoamides **26** were prepared by *N*-acylation of *O*-protected glycosylamines, and



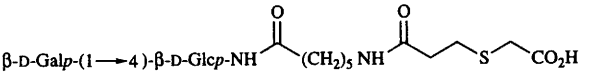
25 x = 2,4,6,7 **26** R = CH_2OH or CO_2H

$(Ac)_7$-β-D-Gal*p*-(1→4)-β-D-Glc*p*-NHR



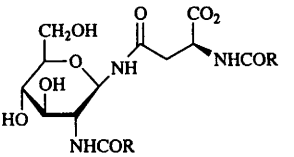
27 R =

28 R =



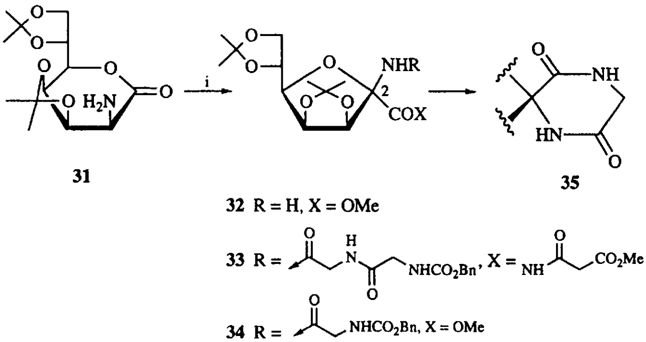
29

were evaluated as anti-cancer agents with improved stability towards β-glucuronidase relative to the corresponding *O*-glucuronide of retinoic acid.[23] Lactose cluster compounds (with 2-4 lactoses) required to test the valency of D-galactose binding lectins were synthesized either by radical catalyzed oligomerisation (^{t}BuSH, AIBN) of acrylamide-containing lactosamine derivatives **27** and **28**, or by coupling the acid **29**, obtained from **28** and methyl 2-mercaptoacetate, to both amino-groups of lysine methyl ester.[24] *N*-Glycosylated peptides linked through glutamine or asparagine have been obtained by coupling 2-acetamido-2-deoxy-β-D-glucopyranosylamine with acidic amino acids of peptides supported on a solid resin, followed by cleavage from the resin.[25] *N,N'*-Di-fatty acyl derivatives of N^4-(2-amino-2-deoxy-β-D-glucopyranosyl)-L-asparagine, e.g. **30**, have been synthesized as mimics of lipid A, but had only weak mitogenic activity.[26]



30 R = $(CH_2)_{12}Me$

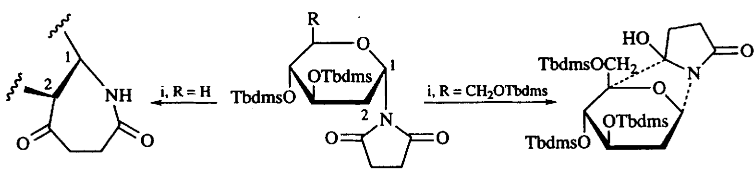
Tri- and tetra-peptide analogues incorporating an α-amino acid at the anomeric position, e.g. **33**, were synthesized by way of a novel oxidative ring contraction of 2-amino-2-deoxy-heptonic acid derivative **31** to give heptulosonic acid glycosylamine **32** and its anomer (Scheme 6).[27] The spirocyclic diketopiperazine **35** was obtained from **34**; it could be *O*-deprotected under acidic conditions then anomerized to the thermodynamically favoured C-2 epimer with strong base.[28] See also reference 3 for a general route to anomeric α-amino acids.



Reagent: i, Br_2, NaOAc, MeOH

Scheme 6

U.v.-irradiation of the *N*-(2-deoxypentosyl)-succinimide **36** resulted in the 1,2-fused bicyclic derivative **38** following initial intramolecular abstraction of H-2, whereas similar treatment of the 2-deoxyhexosyl derivative **37** resulted in the 1,5-bridged tricyclic derivative **39** as a consequence of initial intramolecular abstraction of H-5 (Scheme 7).[29] Addition of chlorosulfonyl isocyanate to certain *O*-benzyl protected glycals (four examples) resulted in β-lactams such as **40**.[30] Reaction of the *N*-tosyl derivative **41** with methanol caused cleavage of the C1-N bond to give **43**, but reaction of derivatives having less electronegative substituents on nitrogen, i.e. as in **42**, led to amide bond cleavage to give esters **44** (Scheme 8).[31]

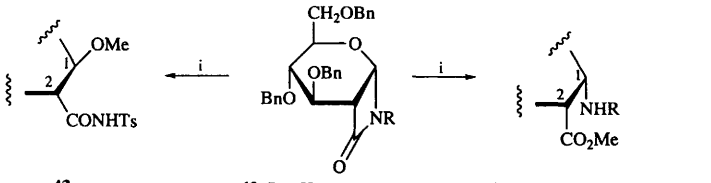


38   **36** R = H   **39**

37 R = $CH_2OTbdms$

Reagent: i, *hv*

Scheme 7

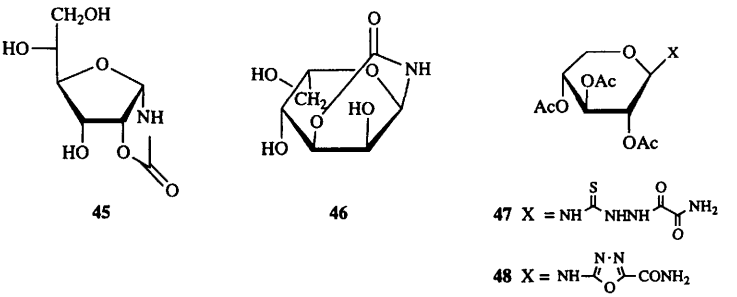


43 **40** R = H; **41** R = Ts; **42** R = Ac, CO_2Et, $CONH_2$ **44** R = Ac, CO_2Et, $CONH_2$

Reagent:i, MeOH

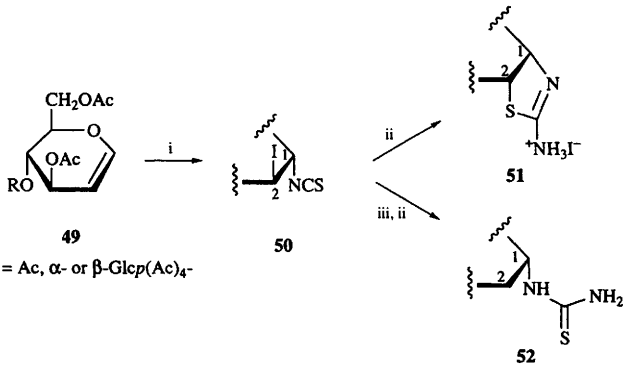
Scheme 8

1.3 N-Glycosyl-carbamates, -isothiocyanates, -thioureas and Related Compounds. — Further examples have been reported of the production of 1,2-*cis*-cyclic carbamates by treatment of free aldoses with potassium cyanate in acidic aqueous buffer. While D-allose gave only the 1,2-*cis*-furanoid carbamate **45**, L-gulose gave four products namely the 1,2-*cis*-furanoid and -pyranoid carbamates, the 1,3-*cis*-pyranoid carbamate **46**, as well as the 1,2-*cis*-furanoid carbamate with the β-L-*ido*-configuration as a product of C-2 epimerization.[32]



45 **46** **47** X = $NH{-}C(=S){-}NHNH{-}C(=O){-}NH_2$ **48** X = $NH{-}C_2N_2O{-}CONH_2$

Anomeric mixtures of 2-deoxy-D-*arabino*-hexopyranosyl isothiocyanate triacetate, tribenzoate or tri-*p*-nitrobenzoate were obtained by reaction of the corresponding α-glycosyl bromide with KSCN in the presence of 18-crown-6.[33] The *N*-(β-D-xylopyranosyl)-derivative **48** of 2-amino-5-carbamoyl-1,3,4-oxadiazole, and likewise its L-enantiomer, were synthesized by reaction of the corresponding α-xylopyranosyl bromide with AgSCN and $H_2NNHCOCONH_2$ and cyclization of the resulting products, e.g. **47**.[34] 2-Deoxy-2-iodo-glycosyl isothiocyanate **50**, produced from D-glucal derivatives **49**, could be converted into the 1,2-fused 2-aminothiazolines **51** on reaction with ammonia, or into the 2-deoxy-glycosyl thioureas **52** by radical reduction followed by reaction with ammonia (Scheme 9).[35]



49
R = Ac, α- or β-Glc*p*(Ac)$_4$-

50

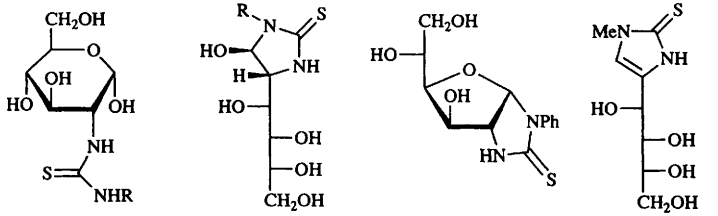
51

52

Reagents:i, I_2, KSCN, SiO_2; ii, NH_3, C_6H_6; iii, Bu_3SnH, AIBN

Scheme 9

2-Deoxy-2-thioureido-sugars, e.g. **53** (R=Bz or CO_2Et) could be synthesized by direct condensation of amino-sugars with benzoyl or ethoxycarbonyl isothiocyanate, whereas similar reactions with aryl or alkyl isothiocyanates led to alditol-1-yl substituted heterocycles, e.g. **54** by way of **53** (R=Ph or Me). These monocyclic products further cyclize in dilute acetic acid to give **55**

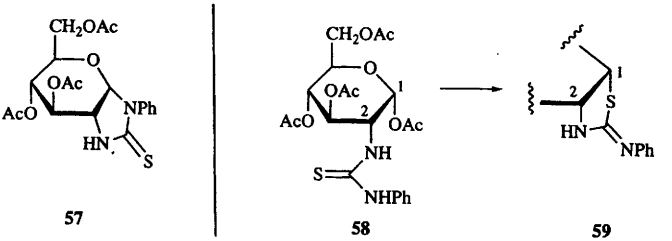


53 R = Bz, CO_2Et, Ph, or Me

54 R = Ph or Me

55

56



57

58

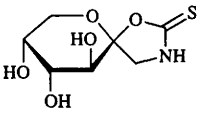
59

Reagents: i, $SnCl_4$, CH_2Cl_2

Scheme 10

accompanied in the case of R=Me by **56**. The pyranoid analogue **57** could be obtained, along with some of the monocyclic product analogous to **56**, by acetic acid treatment of the 3,4,6-tri-*O*-acetyl-**53** (R=Ph). These cyclization reactions involved the nitrogen rather than the sulphur atom of the thiourea, paralleling the chemistry seen for the 2-deoxy-2-ureido-analogues. In contrast, the Lewis acid catalyzed cyclization of **58** gave the 1,2-fused 2-iminothiazolidine **59**, which could be de-*O*-acetylated (Scheme 10).[36]

1-Deoxy-2,3:4,5-di-*O*-isopropylidene-1-isothiocyanato-β-D-fructopyranose has been prepared, and on *O*-deprotection in aqueous acid gave the cyclic thiocarbamate **60**.[37] The glucofuranosyl cyclic thiocarbamate **61** could be *S*-benzylated (to give **62**) and converted to **63** on treatment with a large excess of morpholine (Scheme 11).[38]



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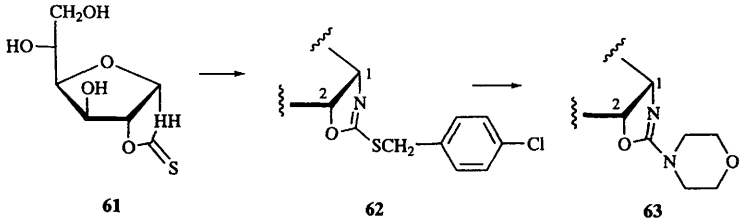


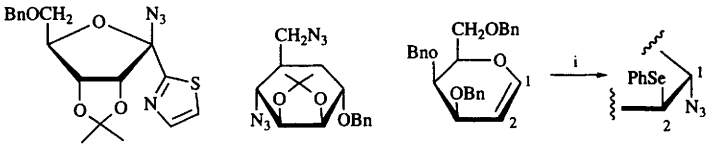
61 **62** **63**

Scheme 11

2 Azido-sugars

Glycosyl azides were obtained directly from free sugars by reaction with Ph_3P, N-chlorosuccinimide and LiN_3 in DMF at 5°C. Thus D-glucopyranosyl azide was obtained from glucose as a 14:1 β:α-mixtures in 70% yield. D-Mannose yielded a 3:1 mixture of α- and β-pyranosyl azides but 2-(benzyloxycarbonylamino)-2-deoxy-D-glucose gave the corresponding 6-chloro-6-deoxy-derivative as the only product.[39] A one-pot procedure involving 1,2-cyclic sulphite intermediates has also been described for making the same compounds. Thus reaction of D-glucose with *N,N'*-thionyldiimidazole in DMF at low temperature then lithium azide gave β-D-glucopyranosyl azide, isolated as the tetraacetate in 70% yield.[40]

New catalysts [$SnCl_4$ with $AgClO_4$, or $Yb(OTf)_3$] have been used to effect high yield (>95%) syntheses of peracylated β-glycosyl azides from the corresponding β-glycosyl acetates on reaction with trimethylsilyl azide.[41] The azide **64**, suitable for constructing (+)-hydantocidin, was similarly obtained from the corresponding ketosyl acetate derivative (by reaction with Me_3SiN_3, Me_3SiOTf).[3] 2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl azide was obtained in high yield from the corresponding methyl 1,2-orthoacetate derivative (with Me_3SiN_3, BF_3 OEt_2).[1]



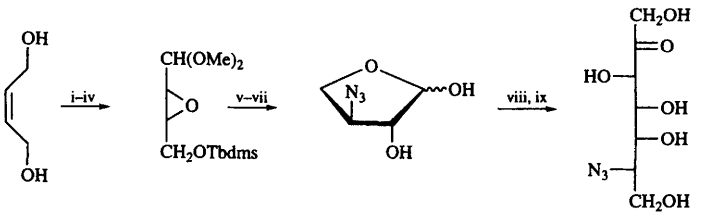
64 **65** Reagent: i, PhSeCl, NaN_3, DMSO

Scheme 12

Sodium azide in dichloromethane can be explosive, and diazidomethane is the culprit. For this reason, the use of tetramethylguanidinium azide in non-halogenated solvents has been advocated. The conversion of tetra-*O*-acetyl-α-D-glucopyranosyl bromide into the corresponding β-azide with this reagent in acetonitrile or nitromethane was quantitative.[42] **A synthesis of 6-amino-1,4,6-trideoxy-1,4-imino-D-mannitol from the diazide 65 was abandoned when the diazide detonated in a ground glass joint.**[7]

Addition of phenylselenyl azide to glycals under free radical conditions [PhSeSePh, NaN_3, $(AcO)_2IPh$] leads to phenyl 2-azido-2-deoxy-1-seleno-glycosides (Vol. 27, p.132). Further examples have now been published, and the use of the products as glycosyl donors investigated.[43-45] Notably, however, under polar reaction conditions, 2-phenylselenyl-2-deoxy-glycosyl azides can be formed, as exemplified in Scheme 12.[46]

Azido-sugars are frequently prepared by reaction of epoxides with azide ion. 3-Azido-3-deoxy-L-threose **68** was synthesized from *cis*-but-2-ene-1,4-diol **66** *via* the Sharpless asymmetic epoxidation product **67**, and was converted into 6-azido-6-deoxy-L-*galacto*-heptulose **69** by an enzyme-catalyzed aldol condensation (Scheme 13). 3-Azido-3-deoxy-L-erythrose, and thence 6-azido-6-deoxy-L-*gluco*-heptulose were obtained in a similar way *via* 4-*tert*-butyldiphenylsilyoxy-*trans*-but-2-enal. These and two other azido-heptulose isomers made from the enantiomeric 3-azido-3-deoxy-tetroses, were converted to α- and β-1-homonojirimycin and -homomannonojirimycin on hydrogenation.[47] Ethyl 3-azido-2,3-dideoxy-D-*erythro*-pentopyranoside and its 3-*C*-methyl analogue **71**, R=H or Me, were synthesized from crotonaldehyde or 3-methyl-2-

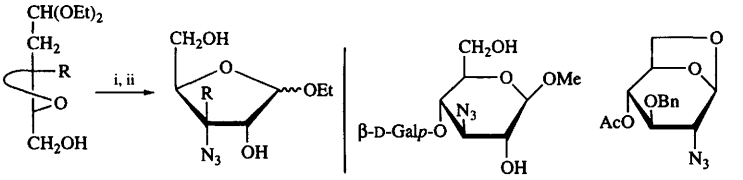


66 **67** **68** **69**

Reagents: i, TbdmsCl, BuLi, ii, Bu^tO_2H, $Ti(OPr^i)_4$, L-(+)-diethyl tartrate; iii, $Pr_4N.RuO_4$; iv, $(MeO)_3CH$, H^+; v, NaN_3; vi, H_3O^+; vii, BuNF; viii, $HOCH_2COCH_2OPO_3H_2$, fructose 1, 6-bisphosphate aldolase; ix, phosphatase

Scheme 13

butenal derived epoxides **70**, respectively, selective epoxide ring opening at C-3 being effected with a tri-isopropoxytitanium(IV) reagent (Scheme 14).[48] C-3 Modified methyl β-lactosides such as **72** were conveniently obtained by 3′,4′-*O*-isopropylidenation of methyl β-lactoside, formation of a D-*allo*-2,3-epoxide (i, TbdmsCl; ii, Ph_3P, DEAD), and regio-selective epoxide ring opening at C-3.[49] Syntheses of branched-chain amino-sugars *via* azido-intermediates are covered in Chapters 14 and 24.



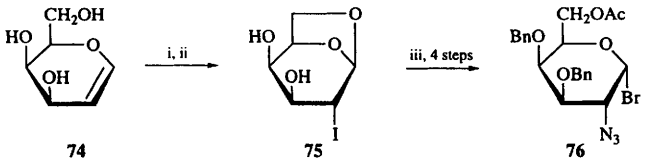
70 R = H or Me **71** R = H or Me **72** **73**

Reagents: i, $Ti(OPr^i)_3N_3$; ii, EtOH, HCl

Scheme 14

3-Azido-2,3-dideoxy-D-*threo*-pentose has been synthesized from 2,3-*O*-isopropylidene-D-glyceraldehyde by ultrasound-promoted indium mediated allylation (which gave the D-*erythro* adduct stereoselectively), introduction of azide by displacement of a mesylate with inversion, and oxidative cleavage of the terminal alkene (OsO_4, KIO_4).[50] The 1,6-anhydro-2-azido-2-deoxy-D-glucose derivative **73**, a versatile intermediate for the preparation of glucosamine-containing oligosaccharides, was synthesized from 4-*O*-acetyl-1,6-anhydro-2,3-*O*-*endo*-benzylidene-D-mannopyranose by reductive cleavage of the benzylidene acetal (BH_3.MeCN, $AlCl_3$), and displacement of a 2-O-triflate by azide with inversion.[51]

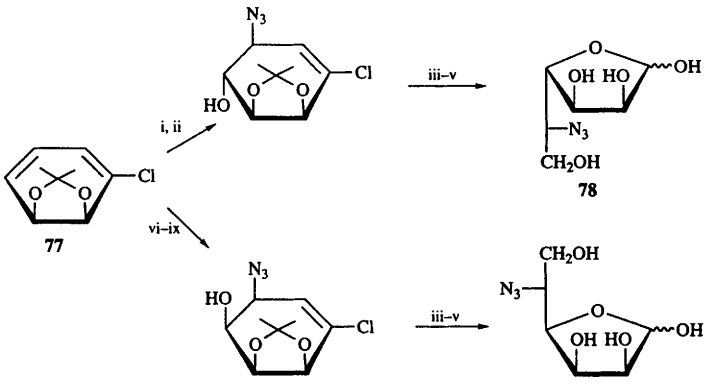
Phenyl 2-azido-2-deoxy-1-thio-β-D-glucopyranose, -α-D-mannopyranose and -β-D-galactopyranose have been obtained from peracetylated amino-sugars by thioglycosidation ($PhSSiMe_3$, ZnI_2), *N,O*-deacetylation and reaction with triflyl azide (2-NH_2→2-N_3; see Vol.25, p.125). Pent-4-en-1-yl 2-azido-2-deoxy-β-D-glucopyranoside was obtained similarly.[52] The 2-azido-2-deoxy-D-galactopyranosyl donor **76** has been synthesized from D-galactal **74** by iodocyclization to **75** and reaction with azide ion, which presumably proceeds by way of a *D-talo*-2,3-epoxide intermediate (Scheme 15), and used in the construction of *C*-glycosides.[53] 5-Azido-5-deoxy-D-talose and -D-mannose, **78** and **79** respectively, have been prepared from the *O*-isopropylidene derivative **77** derived from a product of microbial oxidation of chlorobenzene, and by different functionalisation of the more electrophilic double bond followed by ozonolytic cleavage of the chlorinated double bond (Scheme 16).[54]



74 **75** **76**

Reagents: i, $(Bu_3Sn)_2O$; ii, I_2; iii, LiN_3, DMF

Scheme 15



Reagents:i, MCPBA; ii, NaN_3; iii, O_3; iv, $NaBH_4$, –50 °C; v, H_3O^+; vi, NBS, H_2O; vii, NaOH; viii, LiBr; ix, NaN_3

Scheme 16

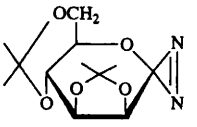
A new strategy for the synthesis of *O*-glycopeptides involves incorporation of a *O*-(2-azido-

2-deoxy-D-galactopyranosyl)-serine or -threonine unit into a peptide, and conversion of the sugar 2-N_3 to 2-NHAc (by use of CH_3COSH) in the last step.[55] The construction of the activated *O*-glycosyl amino acid is covered in Chapter 3.

A commercially available polystyryldiphenylphosphine has been used to convert 3′-azido-3′-deoxy-nucleosides into the corresponding 3′-amino-3′deoxy-nucleosides, by formation and hydrolysis of phosphine imine intermediates.[56] The formation of heterocyclic compounds on photolysis of glycosyl azides is covered in Section 6, and the formation of unsaturated sugars by radical elimination of vicinal phenyl selenide and xanthate azides from appropriate saturated compounds is covered in Chapter 13.

3 Diazirino- and Diazo-derivatives

The diazirino-mannose derivative **80** has been synthesized from the corresponding mannonolactone oxime (i, MsCl; ii, NH_3, MeOH; iii, I_2, Et_2O).[57] The use of this and other diazirino-sugars in the synthesis of *O*- and *C*-glycosides is covered in Chapter 3. α-D-Glucopyranosyl-phenyldiazomethane **81** has been synthesized as a mechanism-based α-glucosidase inhibitor.[58]



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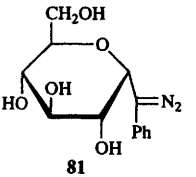


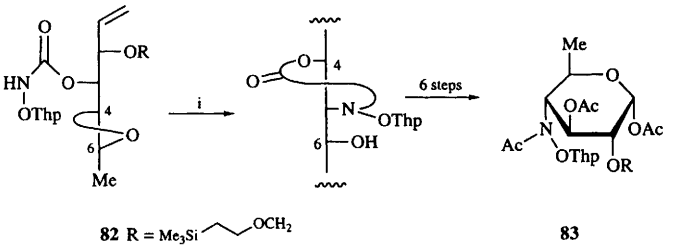
81

4 Oximes, Hydroxylamines and Nitriles

The crystal structure of a 2-oximino-sugar derivative is reported in Chapter 22.

The derivative **83** of the hydroxylamino-sugar residue of calicheamicin has been synthesized from the epoxide **82**, a product of asymmetric epoxidation and chiral allylboronate chemistry, by intramolecular opening of the epoxide ring, and oxidative cleavage (with O_3) of the terminal alkene (Scheme 17).[59] The mono- and disaccharide analogues **84** and **85** of this hydroxylamino-sugar were also obtained by displacement of a 4-triflate with inversion by either *O*-methylhydroxylamine or the anion of an *N*-ethoxycarboxyl *O*-glycosylhydroxylamine, respectively. These and analogues in which the nitrogen atom of the hydroxylamine unit is replaced by carbon, have been used in studies of the conformation about the glycosidic linkage in calicheamycin oligosaccharides.[60] Bicyclic

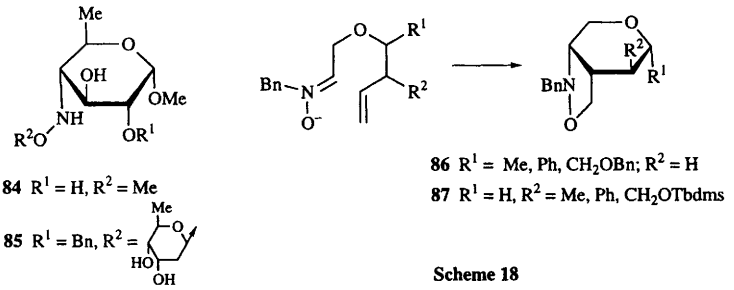
derivatives such as **86** and **87**, of interest as analogues of muramic and neuraminic acids, were the major products from dipolar cycloaddition of acyclic precursors (Scheme 18).[61] Spiro-tricyclic isoxazolidine nucleoside derivatives, formed in a similar fashion, are covered in Chapter 20.



82 R = Me_3Si–OCH_2 **83**

Reagents :i, DBU

Scheme 17



84 R^1 = H, R^2 = Me

85 R^1 = Bn, R^2 =

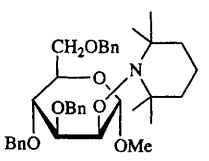
86 R^1 = Me, Ph, CH_2OBn; R^2 = H

87 R^1 = H, R^2 = Me, Ph, $CH_2OTbdms$

Scheme 18

The iodine atom in a 2-deoxy-2-iodo-glycoside can be replaced by a hydroxyl group by radical deiodination in the presence of 2,2,6,6-tetramethylpiperidine-*N*-oxide, resulting in adducts such as **88** and its C-2 epimer, the N-O bond in which can then be reductively cleaved (Zn, HOAc).[62]

2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl cyanide was obtained in high yield by reaction (with Me_3SiCN, $BF_3.OEt_2$) of the 3,4,6-tri-*O*-acetyl-β-D-mannopyranosyl 1,2-(methyl orthoacetate).[1] 2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl cyanide has been made from D-glucose by a rather lengthy (13 step) route from D-glucose involving the sequential displacement of mesylate groups from a 3,5,6-tri-*O*-mesyl-D-glucose derivative by attack of O-2 (at C-5), benzoate ion (at C-6) and water (at C-3).[63] Glycosyl azides, e.g. **89**, have been converted *via* aldonolactone *N*-bromoimines, e.g. **90**, into aldononitriles, e.g. **91** (Scheme 19).[64]



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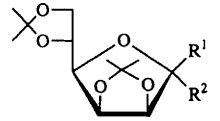
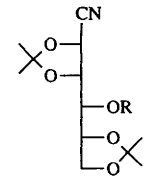




89 $R^1 = N_3$, $R^2 = H$ (i)

90 R^1, $R^2 =$ =NBr (i)

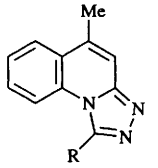
ii, iii → 91 R = H, Bn, Bz or Tbdps

Reagents: i, NBS; ii, Zn/Ag graphite or C_8K;
iii, H_2O, BnBr, BzCl or Tbdps-Cl

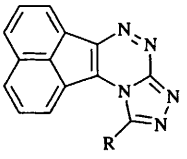
Scheme 19

5 Hydrazones, Hydrazines and Related Heterocycles

The *N*-(1-azido-napthalene-5-sulphonyl)-hydrazone derivative of lactose was prepared for photoaffinity labelling of a lectin from the conger eel.[65] Aldose *N*-methyl-*N*-(4-phenyl- and -*p*-substituted phenyl-thiazol-2-yl)hydrazones have been prepared and appear to have acyclic sugar residues.[66] Tri- and penta-cyclic derivatives such as **92** and **93** were obtained by condensation of free sugars with *N*-(4-methylquinolin-2-yl)hydrazine or a tetracyclic heteroaromatic hydrazine, respectively, followed by cyclization (catalyzed by $FeCl_3$ in EtOH).[67,68]

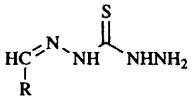


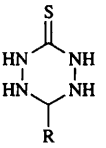
92

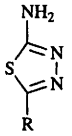


93

R = D-*gluco*-pentitol-1-yl



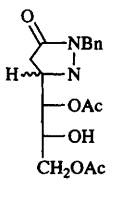




94 95

Thiosemicarbazone derivatives of glucose, galactose and mannose exist in DMSO solution as tautomeric mixtures of pyranose and acyclic forms, and that of fructose also contains furanose forms. The thiocarbohydrazone derivatives of glucose and galactose also exhibit ring-chain

tautomerism, but in addition form hexahydro-1,2,4,5-tetrazine-3-thione tautomers, e.g. **94**.[69,70] A number of 5-(alditol-1-yl)-3-amino-1,2,4-thiadiazole derivatives, e.g. **95**, have been made by cyclization of aldose thiosemicarbazones (i, $FeCl_3$; ii, Ac_2O, Py) or aldonoyl thiosemicarbazides ($ZnCl_2$, AcCl, Ac_2O).[71] Conjugate addition of *N*-benzylhydrazine to 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enono-1,5-lactone led to the *C*-3 epimeric D-*ribo*- and D-*arabino*-derivatives **96**, whereas the D-*threo*-analogue gave D-*xylo*-isomers only, but as a mixture of regioisomers wherein the *N*-benzyl group was on the nitrogen atom attached to C-1 or to C-3.[72]



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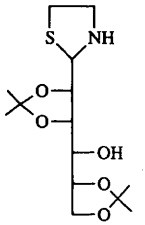

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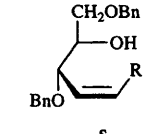
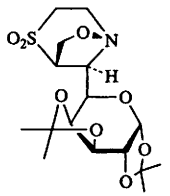
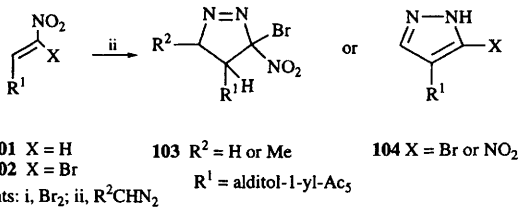


98 R =

99 R = CH=N



100



101 X = H
102 X = Br

103 R^2 = H or Me
R^1 = alditol-1-yl-Ac_5

104 X = Br or NO_2

Reagents: i, Br_2; ii, R^2CHN_2

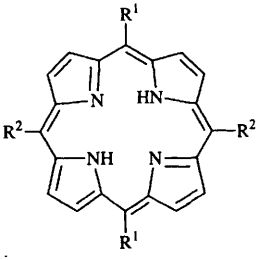
Scheme 20

6 Other Heterocycles

Base-catalysed condensation of 2,3-*O*-isopropylidene- or 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose, or 2,3-*O*-isopropylidene-D-ribose with 2-aminoethanethiol gave acyclic thiazolidine derivatives, e.g. **97** (which in this case is a single isomer of undefined stereochemistry at C-1). 2,3,4,6-Tetra-*O*-benzyl-D-glucose gave a 2:3 mixture of isomeric thiazolidine derivatives, and if a stronger base (NaOMe) was employed to catalyse the reaction, alkenes **98** and **99** were produced.[73] The cyclo-adduct **100** was the predominant isomer formed by condensation of the corresponding 6-aldehydo-D-galactose 6-oxime derivative with divinyl sulphone, the reaction proceeding by formation and intramolecular dipolar cycloaddition of a nitrone intermediate. Similar results were

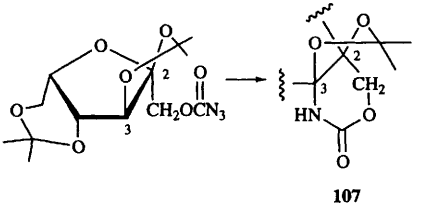
obtained with a methyl 5-aldehydo-D-ribofruanoside.[74]

Addition of bromine to D-*gluco*- or D-*galacto*-nitro-olefins **101** gave the brominated products **102** by an addition-elimination process. Condensation with diazomethane or diazoethane gave bromonitropyrazolines **103**, except in the case of D-*gluco*- **102** and diazomethane from which the two pyrazoles **104** were formed (Scheme 20).[75] Water-soluble tetra-*C*-(alditol-1-yl)porphyrins e.g. **105** were easily prepared by Lewis acid-catalyzed condensation of aldehydo-sugar derivatives (e.g. 2,3:4,5-di-*O*-isopropylidene-D-arabinose) with pyrrole, followed by *O*-deprotection.[76] Stepwise condensation of pyrrole with an aldehydo-sugar derivative followed by an aromatic aldehyde led to eight di-*C*-(alditol-1-yl)porphyrins such as **106**.[77]



105 $R^1 = R^2$ = D-*arabino*-tetritol-yl

106 R^1 = 4-F, R^2 = BnO, OBn, OH, CH_2OBn

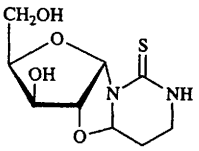


107

Scheme 21

The oxazolinone **107**, a new recoverable chiral auxiliary that gives a high level of asymmetric induction in model aldol reactions and Diels-Alder cycloadditions (in which the reactant is connected to the auxiliary by *N*-acylation), has been synthesized from L-gulonic acid. The key step in its synthesis was the thermal intramolecular nitrene insertion shown in Scheme 21.[78] The formation of oxazolinethiones on hydrolysis of isothiocyanato-sugar derivatives is covered in detail in Chapter 9, section 3.3. Base-catalysed reaction of 3,5-*O*-isopropylidene-D-xylofuranosylamine with β-isothiocyanato-alkanals led to tricyclic derivatives such as **108**, considered as cyclonucleoside analogues.[79]

4,5-Dihydroisoxazole derivatives, e.g. **110**, could be obtained from iodo-tosylates such as **109** as shown in Scheme 22. They have potential for production of chain extended compounds, e.g. **111**, as the nitro-group can be displaced by carbanionic reagents.[80] Addition of diazomethane to 3′-deoxy-3′-methylene-nucleosides yields 3′-*spiro*-pyrazoline derivatives which can be converted to 3′-*spiro*-cyclopropane analogues with loss of nitrogen.[81]



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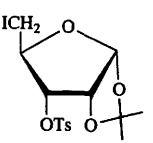

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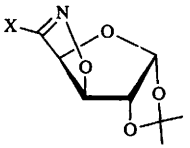
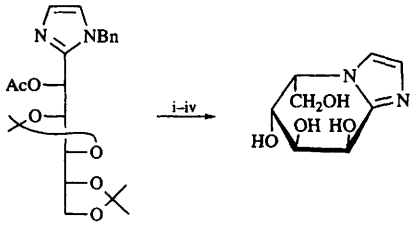


ii → **110** X = NO_2
111 X = $C{\equiv}CCH_2OBn$

Reagents:i, $NaNO_2$, PrONO,DMSO; ii, $LiC{\equiv}CCH_2OBn$

Scheme 22

The imidazole-fused deoxynojirimycin analogue **113** and its C-2 epimer were obtained by cyclization of **112** and its C-2 epimer (Scheme 23). The latter epimers were the major and minor products, respectively, from addition of lithiated *N*-benzylimidazole to 2,3:4,5-di-*O*-isopropylidene-D-arabinose followed by acetylation.[82]



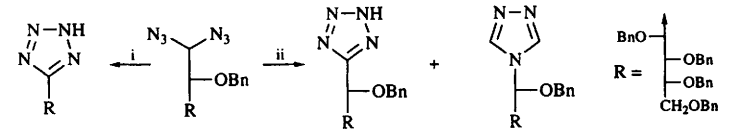
112 **113**

Reagents: i, H_3O^+; ii, TrCl; iii, Tf_2O, Py; iv, H_2, Pd/C, H_3O^+

Scheme 23

Thermoysis of the acyclic 1,1-diazido-1-deoxy-D-glucose derivative **114** produced the chain-shortened *C*-(D-*arabino*-tetritol-1-yl)-tetrazole **115**, whereas photolysis produced a mixture of the *C*- and *N*-(D-*gluco*-pentitol-1-yl)-tetrazoles **116** and **117** with all carbon atoms retained (Scheme 24). Similar products were obtained for the corresponding D-mannose and D-arabinose 1,1-diazides, and a mechanism for these reactions was proposed.[83] The identity of ring-expanded, fused tetrazole derivatives formed on photolysis of a D-glucosylidene 1,1-diazide derivative (Vol.17, p.138, ref.74) has been independently confirmed.[84] Photolysis of methyl 1-azido-D-glucopyranoside tetraacetate gave mixtures of the *O*-methyl-oximes **118** and the ring expanded products **119** and **120**, the proportions depending on the anomeric configuration in the starting material.[85]

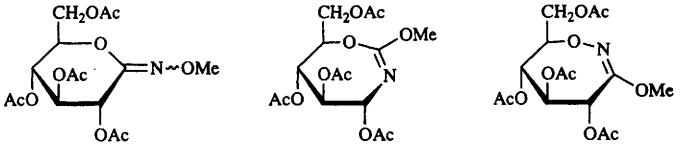
The synthesis of tetra-*O*-benzoyl-D-lyxononitrile and its conversion to a (D-*lyxo*-tetritol-1-



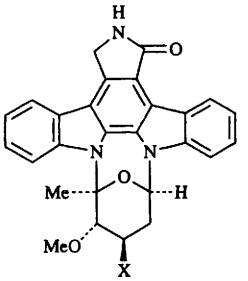
115 **114** **116** **117**

Reagents:i, Δ ; ii, *hν*

Scheme 24

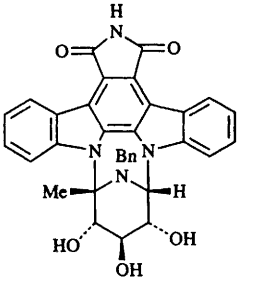


118 **119** **120**



121 X = NHMe

122 X = $\overset{+}{N}Me_3$ I^-



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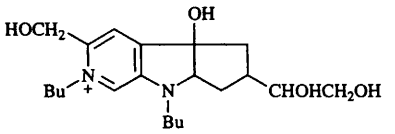
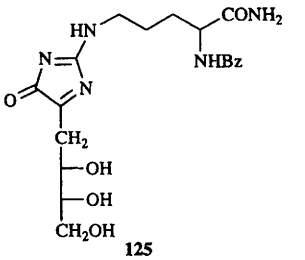


124



125

yl)-tetrazole derivative on reaction with sodium azide have been reported.[86]

Staurosporine **121**, a protein kinase C inhibitor, has been characterised by X-ray crystal structure determination of the quaternized derivative **122**.[87] The aza-analogue **123** was synthesized

by sequential condensation of D-*xylo*-1,5-pentodialdose with butylamine and benzotriazole then the dianion of the appropriate pentacyclic bis-indole.[88]

The new fluorescent pyrrolopyrimidinium compound **124** has been formed by Maillard reaction of 3-deoxyglucosone with n-butylamine,[89] and likewise the novel imidazolone **125** from its reaction with *N*-benzoyl-arginine.[90] The synthesis of cyclic guanidinium derivatives incorporating 1,3-diamino-1,3-dideoxy-tetritol moieties as glycosidase inhibitors is detailed in Chapter 9, section 3.7.

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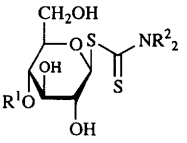
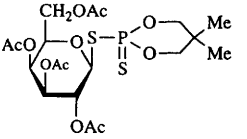
11
Thio- and Seleno-sugars

Glycosyl dithiocarbamate derivatives **1**, obtained by reaction of the corresponding acetobromo sugars with the sodium salt of *N,N*-diallyl- or *N,N*-diethyl-dithiocarbamate and subsequent deacetylation, are potential anticarcinogens and antimutagens.[1] Reaction of fully acetylated mono- and di-saccharides with *O,O*-dialkylphosphorothioic acid in the presence of $BF_3.OEt_2$ gave *S*-glycosylphosphorodithioates, such as compound **2**, in high yield.[2] Reaction of *O*-peracetylated 1-thioglucose with benzoquinones, followed by



R^1 = H, β-D-Gal*p*, or β-D-Glc*p*
R^2 = Et or All

1



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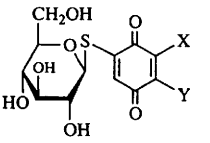
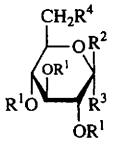


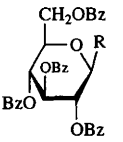
X, Y = H, Cl

3

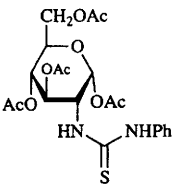
in situ oxidation and deacetylation, furnished the irreversible glycosidase inhibitors **3**; a number of bis- and tetrakis-(glucosylthio)quinones have also been prepared.[3] Thioglycosides **4** and thioethers **5** of D-glucose have been prepared to enhance the bioavailability of cysteamine.[4] Protected glycosyl thiocyanates and primary thiocyanato sugars reacted with Grignard reagents furnishing thioglycosides and primary thio sugars, respectively (*e.g.*, **6**→**7**).[5]



R^1 = H or Ac
4 R^2 = $S(CH_2)_2NHCO_2Bn$,
R^3 = H, R^4 = OAc
5 R^2 = H, R^3 = OMe,
R^4 = $S(CH_2)_2NHCO_2Bn$



6 R = SCN
7 R = SEt



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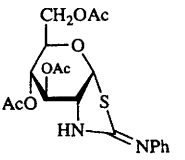
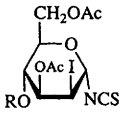
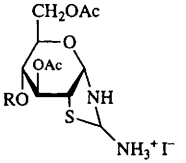
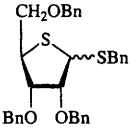


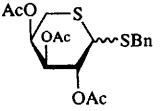
9

The acetylated 2-deoxy-2-thioureido sugar **8** (see Vol. 20, Chapter 9, Ref. 54) underwent Lewis acid-catalyzed cyclization *via* sulfur to give thiazoline **9**, in contrast to the corresponding 2-deoxy-2-ureido sugar which cyclizes *via* nitrogen (see Chapter 10).[6] Addition of iodine and potassium thiocyanate to a number of glycals afforded 2-deoxy-2-iodo-glycosyl isocyanates, e.g. **10**, which were transformed into 1,2-fused aminothiazolines **11** on exposure to ammonia.[7] Two papers describing the addition of phenylselenyl azide to glycals are covered in Chapter 10, as is the condensation of *O*-protected aldoses with 2-aminoethane thiol, and the photobromination of 1-*S*-benzhydroximoyl-1-thioglucose derivatives to yield spirooxathiazoles is referred to in Chapter 16.







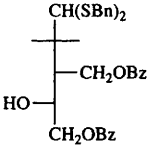


R = Ac, α- or β-D-Glc*p*(OAc)$_4$

10 **11** **12** **13**

Cyclization by displacement of a sulfonate group by a C-1 thioacetal sulfur atom, a convenient method for making 1,4-dithiofuranosyl and 1,5-dithiopyranosyl derivatives (see Vol. 25, Chapter 11, Scheme 4; Vol. 26, Chapter 11, Ref. 7) has been applied to the preparation of compounds **12**[8] and **13**.[9] A similar cyclization allowed the preparation of the branched dithiosugar **15**, a precursor of 2′,3′-dideoxy-3′-*C*-hydroxymethyl-4′-thionucleosides, from dithioacetal **14**.[10] The first synthesis of 1,5-dithio-D-glucopyranose peracetate has been reported; it has been used to prepare thio-analogues of glucosinolates.[11]

An improved route to diastereomerically pure sulfoxides involved esterification of diacetoneglucose with alkyl- or aryl-sulfinyl chlorides in the presence of a base. By using either pyridine or



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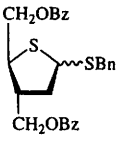
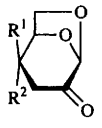
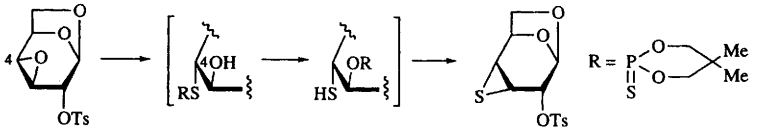


15



16 R^1 = H, R^2 = S$(CH_2)_n$ Me
17 R^1 = S$(CH_2)_n$ Me, R^2 = H
n = 7 or 9

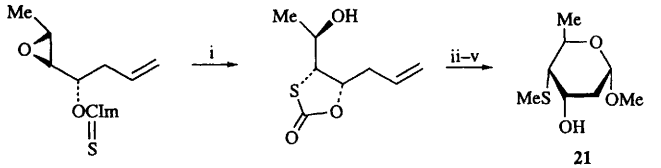


18 **20**

Reagent: $RS^- NHEt_3^+$ **19**

Scheme 1

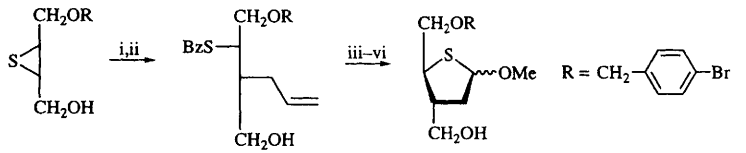
ethyldiisopropylamine, either isomer at sulfur was available selectively; they were both converted to the corresponding 3-thio D-glucose 3-sulfoxide derivatives.[12] Cathodically promoted Michael-like addition of long-chain alkyl thiols to levoglucosenone furnished the thermodynamic *erythro*-adducts **16** at high currents and the previously unknown kinetic *threo*-adducts **17** at low currents.[13] Treatment of 1,6:3,4-dianhydro-2-*O*-tosyl-β-D-galactopyranose (**18**) with the phosphorodithioate **19** gave the new 3,4-epithio derivative **20**; the reaction is thought to proceed *via* a transphosphorylation, as shown in Scheme 1.[14]



21

Reagents: i, $PhNH_2$, THF, then aq. HCl; ii, O_3, Me_2S; iii, MeOH, H^+; iv, LiOH; v, MeI

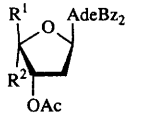
Scheme 2



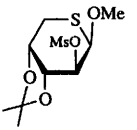
Reagents: i, AllMgBr; ii, BzCl; iii, OsO_4; iv, $NaIO_4$; v, NaOMe; vi, HCl, MeOH

Scheme 3

A new synthesis of the thiosugar **21** of esperamycin from non-carbohydrate starting materials relied on a novel method for the intramolecular delivery of a sulfur nucleophile as shown in Scheme 2,[15] and a new approach to branched-chain 4-thiofuranosyl derivatives involved regioselective opening of an episulfide, as shown in Scheme 3.[16] Selenation of deoxyadenosine derivative **22** *via* aldehyde **23** gave the C-4′-modified nucleosides **24** and **25** which were incorporated into oligonucleotides for radical cleavage studies.[17]



22 $R^1 = CH_2OH$, $R^2 = H$
23 $R^1 = CHO$, $R^2 = H$
24 $R^1 = CH_2OH$, $R^2 = SePh$
25 $R^1 = SePh$, $R^2 = CH_2OH$



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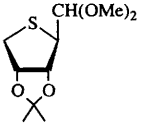

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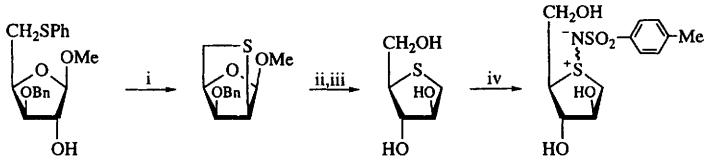


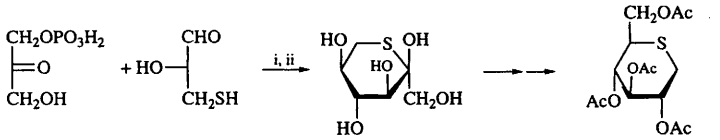
28 **29** **30**

Reagents: i, I_2, TPP, Im; ii, $NaBH_3CN$; iii, Na, NH_3; iv, Chloramine T

Scheme 4

The known 5-thio-D-arabinose derivative **26** (see Vol. 25 Chapter 11, Ref. 15) has been converted to the biotin precursor **27** by use of a ring-contraction similar to that undergone by its *ribo*-analogue (see Vol. 20, Chapter 11, Ref. 4).[18] Cyclization between C-2 and S-5 of the known xylose derivative **28** has been effected under iodination conditions (Scheme 4); hydrolysis/reduction and debenzylation gave anhydrothioalditol **29** which was iminated with chloramine T to furnish iminothiosugar **30**, a potential transition-state analogue glycosidase inhibitor.[19]

5-Thioglucose has been reported to inhibit root-growth in certain plant species.[20] 5-Thio-L-allose has been prepared in 11 steps and 16% overall yield by use of Vogel's "naked sugar" approach.[21] The aldolase-based route to hexoses and higher carbon sugars has been applied to the synthesis of thiosugars; as an example, the rabbit muscle aldolase-catalysed condensation of dihydroxyacetone phosphate (**31**) and (*R*)-3-thioglyceraldehyde (**32**), formed *in situ* from its *S*-acetyl diethyldithioacetal, to give 6-thio-L-sorbose (**33**) is shown in Scheme 5; *O*-acetylation and anomeric deoxygenation by chemical means converted **33** to 1,5-anhydro-5-thio-D-glucitol peracetate (**34**).[22] Attempts to prepare an abequosyl donor

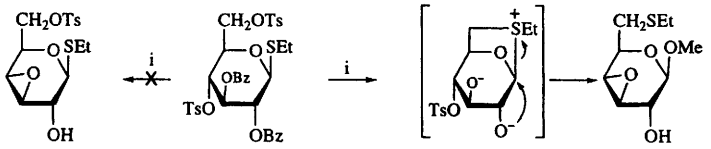


31 **32** **33** **34**

Reagents: i, Rabbit muscle aldolase; ii, phosphatase

Scheme 5

from dibenzoate ditosylate **36** by way of epoxide **35** failed because on treatment with sodium methoxide in methanol displacement at C-6 by sulfur took place, as shown in Scheme 6, so that the methyl 6-thio-β-D-galactopyranoside derivative **37** was isolated instead in 60% yield.[23] Methyl 2,3-anhydro-α-D-allopyranosides **39** with sulfur-bonded substituents at C-6 were readily obtained by reaction of bromide **38** with the appropriate nucleophiles.[24] Nine methyl α-D-glucosid-6-yl derivatives, *e.g.* **40**, of mercapto-purines and -pyrimidines have been synthesized as potential growth inhibitors of mammalian cells.[25]

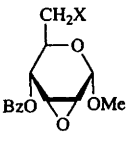


35 **36** **37**

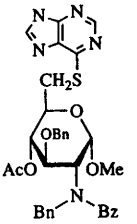
Reagents: i, NaOMe, MeOH

Scheme 6

The photorearrangement of carbocyclic 2-phenylthio-1,3-diols to give deoxy-thiosugars is covered in Chapter 12, the synthesis of 1,6-anhydro-2,3,4-trideoxy-3-phenylthio-D-*erythro*-hex-3-enopyranose in Chapter 13, sulfur-containing KDN derivatives in Chapter 16, and a synthesis of herbicidin which involves phenylthio intermediates is referred to in Chapter 24.



38 X = Br
39 X = $S(CH_2)_9Me$, SO_2Ph, *etc.*



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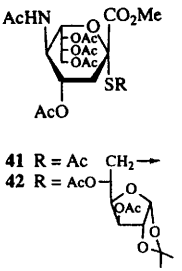
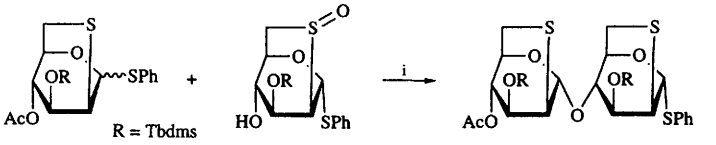


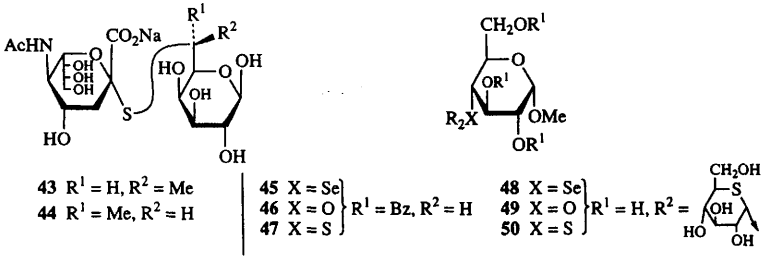
41 R = Ac
42 R = AcO

A new, highly stereocontrolled glycosidation method which employs 2,6-anhydro-2-thiosugars as glycosyl donors and their sulfinyl analogues as glycosyl acceptors has been developed; an example is given in Scheme 7.[26] Dithiosugar **13** (see above) was readily converted to the corresponding glycosyl bromide for use in the synthesis of 6-*O*-(5-thio-α-L-arabinosyl)-D-galactose.[9] Methyl and allyl 5′-thio-α-kojibioside and methyl 5′-thio-α-isomaltoside were synthesized by reaction of the phenylseleno glycoside or the

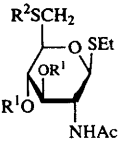


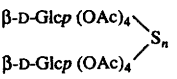
Scheme 7

trichloroacetimidate of 2,3,4,6-tetra-*O*-acetyl-5-thioglucose with the appropriate glucosyl acceptors.[27] 2-Thiokojibiose and 2-thiosophorose (as the β-peracetates) have been obtained by nucleophilic attack of the appropriate anomer of sodium 2,3,4,6-tetra-*O*-acetyl-D-glucosyl thiolate on 1,3,4,6-tetra-*O*-acetyl-2-*O*-triflyl-β-D-mannopyranose.[28] Similar techniques were employed in the synthesis of protected 2-thionigerose and 2-thioisomaltose.[29]



Treatment of the *O,S*-peracetate **41** with diethylamine in DMF caused selective *S*-deacetylation and allowed *in situ* reaction with primary bromides to give sulfur-linked disaccharides, *e.g.*, **42**.[30] The C-6 methylated, sulfur-linked sialoside analogues **43** and **44** have been synthesized, together with their *O*-linked analogues (see Chapter 16) to evaluate the correlation between conformation and biological activity.[31] The seleno sugar **45** was obtained by treatment of the corresponding methyl α-D-galactopyranosyl triflate with KSeCN and subsequent sodium borohydride reduction. Compound **45** and its oxygen and sulfur analogues **46** and **47**, respectively, were used as glycosyl acceptors in the preparation of the heteroanalogues **48-50** of methyl α-maltoside.[32] Condensation of Boc-protected 5-amino-5-deoxy-D-arabinose (see Chapter 9) with the 2-acetamido-1,6-dithiosugar **51** under acidic conditions gave, after deprotection, the trihetero-disaccharide glycoside **52**.[33] 2,3,4,6-Tetra-*O*-acetyl-1-thio-β-D-glucopyranose reacted with diisopropoxydi- and -nonasulfane to give the bis(β-D-glucopyranosyl)polysulfanes **53**.[34]





51 R^1 = Ac, R^2 = H

52 R^1 = H, R^2 =

53 *n* = 4 or 11

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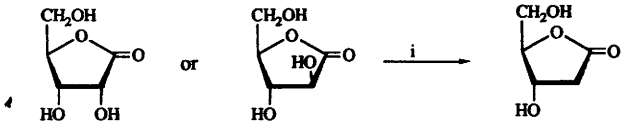
12
Deoxy-sugars

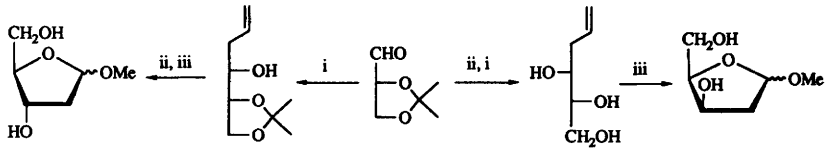
In a new variant of free radical deoxygenation, treatment of sugar and nucleoside *N*-phenylthioxocarbamates (ROCSNHPh) with tris(trimethylsilyl)silane or, for introduction of deuterium, with Bu_3SnD, gives the deoxycompounds in high yield. The substrates are derived from the hydroxycompound and phenyl isothiocyanate.[1] Unprotected aldonolactones can be deoxygenated in the α-position by use of SmI_2, as in the examples in Scheme 1.[2]



Reagents: i, SmI_2 (3 eq.), THF-H_2O

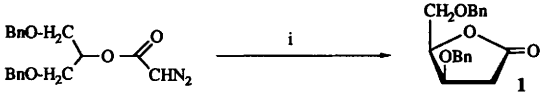
Scheme 1

Indium-mediated *C*-allylation of 2,3-dihydroxyaldehydes, promoted by ultrasound, can be directed to be diastereoselective in either sense, depending on whether the unprotected aldehyde or 2,3-*O*-isopropylidene derivative is used as substrate. Subsequent oxidative cleavage of the allyl



Reagents: i, CH_2=$CHCH_2Br$, In, ultrasound; ii, H_3O^+; iii, O_3, MeOH, then Ph_3P

Scheme 2



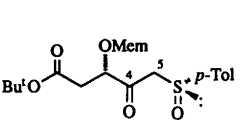
Reagents: i, dirhodium(II) tetrakis[methyl 2-pyrrolidone-5(*R*)-carboxylate], CH_2Cl_2

Scheme 3

group then gives a route to 2-deoxyglycosides as indicated in Scheme 2.[3] The intramolecular carbenoid insertion process shown in Scheme 3, carried out with a chiral rhodium catalyst,

proceeded with high diastereoselectivity in favour of the *threo*-product, and with 94% enantiomeric excess of the D-enantiomer **1**.[4] Asymmetric dihydroxylation of the *trans*-alkene **2**, using the ligand of appropriate structure, was the key to syntheses of methyl 2-deoxy-D-*threo*-pentofuranoside and of the L-enantiomer. The corresponding process applied to the *cis*-alkene gave *erythro*-products, but with poor e.e., as would be expected for asymmetric dihydroxylation of a *cis*-alkene.[5] Reduction of the β-keto sulfoxide **3** with DIBAL, followed by Pummerer rearrangement and Raney nickel desulfurization, gave the derivative **4** of 2-deoxy-D-*erythro*-pentonic acid. The L-*threo*-epimer of **4** was similarly prepared from the precursor epimeric at sulfur.[6] An enzymatic preparation of 2-deoxy-α-D-*arabino*-hexopyranosyl phosphate is mentioned in Chapter 7.

2



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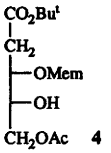
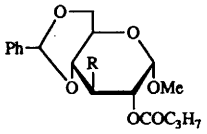


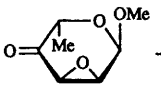
4

The radiolysis of 2-deoxy-D-ribose in the absence of oxygen and a radio-protectant gives malondialdehyde as one of the products.[7]

A route to 3-deoxy-D-*ribo*-hexose (3-deoxy-D-glucose) has been developed in which the monoester **5** was made by regioselective acylation using a lipase, and free radical deoxygenation was then used to obtain the 3-deoxyderivative **6**.[8] Photoreduction of α,β-epoxyketones has also been used to prepare 3-deoxysugar derivatives; when the epoxyketone **7**, derived from 3,4-di-*O*-acetyl-6-deoxy-L-glucal, was irradiated in acetonitrile containing triethylamine, methyl cimeruloside **8** was obtained.[9] The 3-deoxy-δ-lactone **9** was produced highly stereoselectively by hydrogenation of the 2-ene (Vol. 23, p. 139) over a palladium catalyst, and the related furanoid γ-lactone behaved similarly.[10]



5 R = OH
6 R = H



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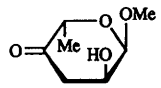
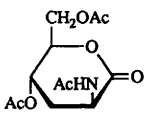


8

In a reinvestigation of the Duff degradation, treatment of the calcium salt of D-isosaccharinic acid with H_2O_2 and Fe^{3+} salts gave rise to 3-deoxy-D-*glycero*-pent-2-ulose.[11] Some carboxyl-reduced derivatives of Kdo (3-deoxyketoses) are mentioned in Chapter 3, and some 2,6-and 3,6-dideoxy-6-fluorosugars are discussed in Chapter 8.

Free radical deoxygenation methods have been used in syntheses of allyl 3-deoxy- and 4-deoxy-β-D-*xylo*-hexopyranosides (deoxygalactose derivatives),[12] derivatives of 3- and 4-deoxy-L-rhamnose,[13] and of 4-deoxy-*N*-acetylmannosamine.[14]

A convenient large-scale synthesis of the 1,6-anhydro-4-deoxysugar **10** has been described, using reduction of the D-*galacto*-3,4-epoxide by diborane generated from $NaBH_4$ and $BF_3.Et_2O$. Using $NaBD_4$, ~92% incorporation of deuterium at C-4 was possible.[15] Regioselective reductive opening of the epoxide **11** with Cp_2TiCl in the presence of 1,4-cyclohexadiene as a radical trap gave the 4-deoxyfructose derivative **12**.[16]



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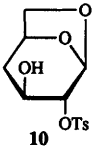

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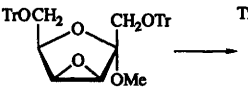
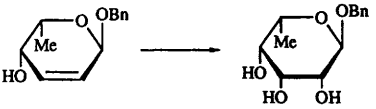
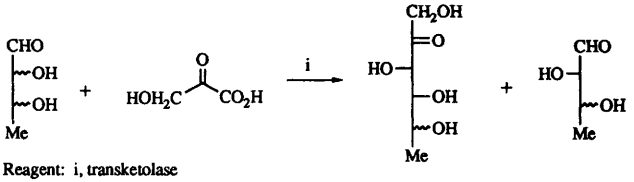


11 **12**



13 **14**

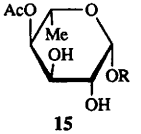
The 6-deoxy-L-talose derivative **14** was the major product of osmium tetroxide hydroxylation of the alkene **13**, itself prepared from di-*O*-acetyl-L-rhamnal by allylic rearrangement followed by Mitsunobu inversion at C-4.[17] 6-Deoxy-D-fructose and 6-deoxy-L-sorbose were obtained as a separable mixture from the transketolase-catalysed reaction of hydroxypyruvate with 2,3-dihydroxybutyraldehyde (mixture of isomers) (Scheme 4).[18]



Reagent: i, transketolase

Scheme 4

The steroidal glycoside hapaioside, from a marine sponge, contains a rare 6-deoxy-β-L-altropyranoside unit **15** glycosidically linked to *O*-3 of a 19-norpregnane structure,[19] whilst the new monosaccharide L-dianose (**16**) has been isolated from a Chinese medicinal plant.[20]



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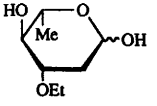

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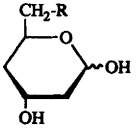
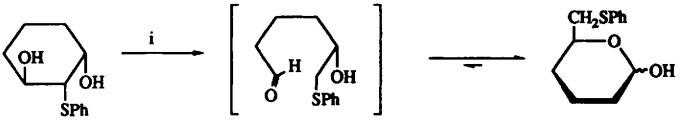


17

Some 2,4-dideoxyhexoses of type **17** (R = H, OMe, Cl, N_3) have been made by condensation of aldehydes RCH_2CHO with acetaldehyde, catalysed by 2-deoxyribose-5-phosphate aldolase; in these novel enzymatic aldol reactions, acetaldehyde adds to the substituted aldehyde to give a 3-hydroxy-4-substituted butyraldehyde which then adds another acetaldehyde unit.[21]

Racemic 5-*O*-acetyl-2,3-dideoxypentofuranosyl chloride has been prepared by radical chlorination of tetrahydrofurfuryl acetate.[22]

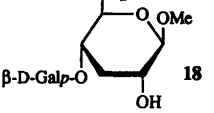
Some carbocyclic 2-phenylthio-1,3-diols have been converted photochemically to phenylthio-substituted deoxysugars, as in the case shown in Scheme 5.[23]



Reagents: i, h ν, 350 nm, $Ph_2C{=}O$, PhSH

Scheme 5

As in previous years, there have been reports of specifically-deoxygenated analogues of biologically-significant oligosaccharides. Two groups have independently prepared L-fucosyl donors deoxygenated at each of C-2, C-3, and C-4,[24,25] and these were used to make analogues of sialyl Lewis X with modified fucose units, the modifications being deleterious for E-selectin binding.[24,26] The 3-, 4- and 6-deoxyderivatives of methyl α-D-galactopyranoside have been prepared by Barton-type deoxygenation of appropriately protected compounds, and used to make analogues of α-L-Rha*p*-(1→2)-α-D-Gal*p*-OMe, the immunodeterminant of the O-specific polysaccharide of *Shigella dysenteriae* type 1, with the galactose unit specifically deoxygenated.[27] A recombinant *N*-acetylglucosaminyl transferase I has been used to add a β-D-GlcNAc residue to an analogue of the branched trimannose core unit of *N*-linked glycoproteins in which the α-(1→6)-linked mannose unit is deoxygenated at C-2.[28] Methyl β-lactoside specifically deoxygenated at C-3 (**18**) has been prepared by regioselective hydride reduction of a 2,3-D-*allo*-epoxide.[29]



18

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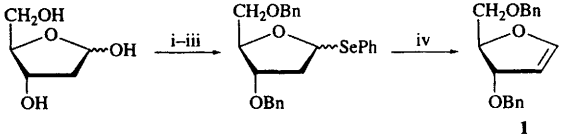
13
Unsaturated Derivatives

1 Glycals

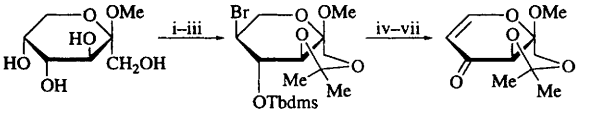
New routes for synthesizing furanoid glycals have appeared. Thus, reaction of thymidine or 5'-*O*-*t*-butyldiphenylsilyl-derivatives with 1,1,1,3,3,3-hexamethyldisilazane in the presence of ammonium sulfate causes elimination of the base and afford the 3,5-di- and 3-mono-trimethylsilyl glycals in high yield.[1] A mild method for the preparation of D-*erythro*-configured furanoid glycals from 2-deoxyribose, involved the mild oxidation-elimination of a 1-phenylseleno group, as the key step (Scheme 1). The D-*threo*-derivatives are prepared in a similar manner after *C*-3 epimerization of a 5-*O*-silyl protected phenyl 2-deoxy-1-seleno-D-*erythro*-pentofuranoside by treatment with trifluoromethylsulfonic anhydride then potassium nitrite.[2] The benzylated D-*erythro*-glycal **1** has also been prepared by treating 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribose first with Ph_3P-CCl_4 to produce the glycosyl chloride followed by elimination with lithium in liquid ammonia (which also removes the trityl group) then *O*-benzylation under standard conditions.[3]



1

Reagents: i, HCl–MeOH; ii, BnBr, NaH; iii, PhSeH, BF_3•Et_2O;
iv, Bu^tOOH, $Ti(OPr^i)_4$, Pr^i_2EtN

Scheme 1



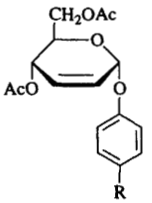
2

Reagents: i, Ph_3P–CBr_4; ii  , TsOH; iii, TbdmsCl; iv, NaSePh, DMF;
v, $NaIO_4$; vi, TBAF; vii, tetra-*n*-propyl perruthenate

Scheme 2

In the area of pyranoid glycals, Scheme 2 illustrates the use of D-fructose as precursor to glycal **2**, a useful intermediate in the preparation of chain-extended sugars.[4]

The Claisen rearrangement of 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosides (**3**, R = H, Me, OMe or Cl) to glycals **4** have been shown to proceed much more slowly than the corresponding reactions of the β-anomers.[5]



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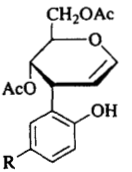

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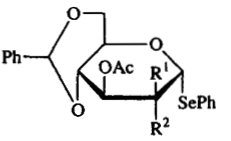
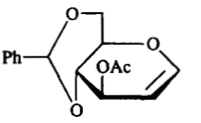


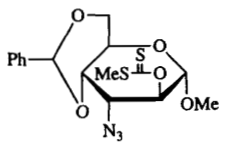
5 $R^1 = H, R^2 = N_3$
or $R^1 = N_3, R^2 = H$



6

The radical induced β-eliminations of vicinal phenyl selenide- or xanthate-azides to produce glycals and 2,3-unsaturated derivatives have been reported. Thus treatment of **5** with tributyltin hydride afforded a high yield of glycal **6** and similar treatment of azido-xanthate **7** gave **8** as the main product.[6]

Treatment of the iodo-alcohol **9** with PCC then lutidine affords the D-*arabino*-1-en-3-ulose **10** which spontaneousley dimerises to the glycal derivative **11**.[7]



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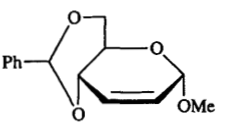

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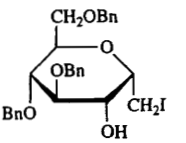

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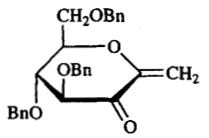

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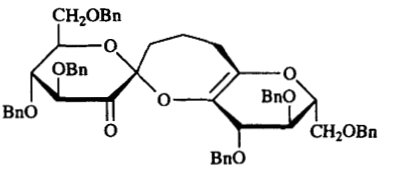
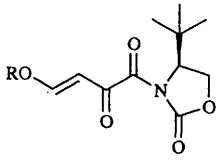


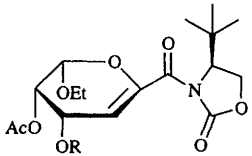
11

The preparation of 3,4-di-*O*-acetyl-6-*O*-tosyl-D-galactal from D-galactose by two one-pot procedures involving sequential tosylation-acetylation followed by bromination-reduction has been reported.[8]

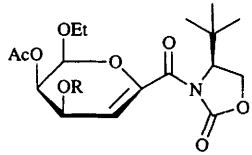
The *endo*-selective hetero Diels-Alder reaction of chiral oxazolidones **12** with (*Z*)-1-acetoxy-2-ethoxyethene yields the 1-substituted glycals **13** as the major products when catalysed with dimethylaluminium chloride, and **14** as the major products when catalysed with trimethylsilyl triflate. Compounds **13** (R = Et)and **14** (R = Et) were subsequently converted into ethyl β-D-mannopyranoside and ethyl β-L-mannopyrannoside, respectively.[9,10]



12 R = Et or Bz

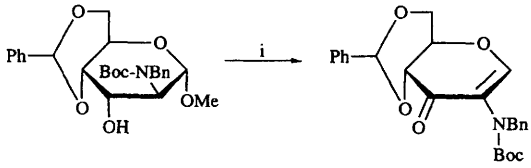


13 R = Et or Bz



14 R = Et or Bz

A new general method for the preparation of 2-aminoglycal derivatives is illustrated in Scheme 3 and involves oxidation of the 3-OH group of 2-(*N*-acyl-*N*-alkyl) amino glycosides.[11]



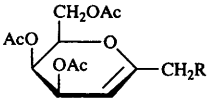
Reagents: i, PCC, CH_2Cl_2

Scheme 3

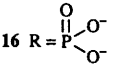
Conversion, by several standard synthetic transformations, of 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl cyanide into the (bromomethyl)glycal **15** has been reported, the glycal bond being formed during reduction of the CN group to an intermediate aldehyde. The product was further converted by a Michaelis-Arbuzov reaction into phosphonate **16** as a precursor for glycosyltransferase inhibitors. The paper records a further example of this chemistry with 2,3,4-tri-O-acetyl-β-L-fucopyranosyl cyanide as starting material.[12]

Treatment of methyl 2-deoxy-β-D-*erythro*-pentopyranoside with *t*-butyldiphenylsilyl chloride in the presence of silver nitrate followed by reaction with triflic anhydride gave methyl 3-*O*-Tbdms-2,4,5-trideoxy-α-D-*glycero*-pent-4-enopyranoside which on further reaction with *t*-butyllithium then tributyltin chloride affords stannylated glycal **17**. In a similar way methyl 2-deoxy-α-L-*erythro*-

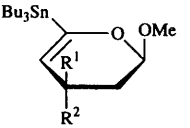
pentopyranoside gives the glycal **18**. Compounds **17** and **18** were further converted into the 3(*R*) and 3(*S*) enantiomers of 3-hydroxyleukotriene B4, respectively.[13]



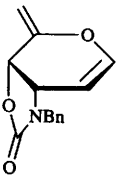
15 R = Br



16 R = $P(=O)(O^-)O^-$



17 R^1 = H, R^2 = OTbdps
18 R^1 = Tbdps, R^2 = H



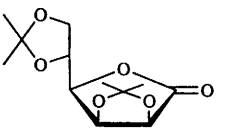
19

Glycal related dienes like **19**, prepared by base treatment of the corresponding 6-*O*-mesyl glycals have been described as substrates for epoxidation with dimethyldioxirane, and are useful precursors for making the protein kinase C inhibitor, staurosporine.[14]

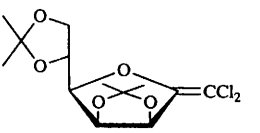
The [2+2]cycloadditions of chlorosulfonyl isocyanate to various glycals are mentioned Chapter 10 and 14. The isolation of new secoiridoid glycosides containing glycal fragments and the use of a quinol glycal for the preparation of bis *C*-arylglycosides as models for the antibiotic kidamycin are covered in Chapter 3. The use of galactal and lactal in the preparation of complex branched oligosaccharides will be found in Chapter 4. An improved synthesis of 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl bromide including a high yielding preparation of tri-*O*-acetyl-D-galactal is mentioned in Chapter 8.

2 Other Unsaturated Derivatives

Treatment of lactones such as **20** with Ph_3P-CCl_4 affords an easy way to "*exo*"-glycals like **21** in high yields.[15]



20

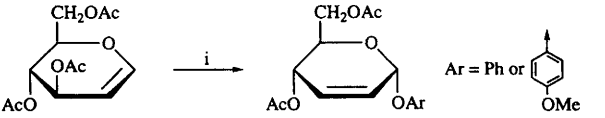


21

Unprotected glycals have been reported to react better with allyltrimethylsilane in the presence of trimethylsilyl triflate than do the corresponding *O*-acetylated derivatives to produce 2,3-

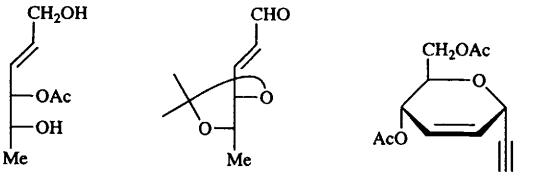
unsaturated allyl α-*C*-glycosides.[16]

2,3-Unsaturated phenolic glycosides have been prepared (Scheme 4) and used for the synthesis of the enantiomer of the natural product (+)-phomopsolide B. The same methodology applied to di-*O*-acetyl-L-rhamnal as starting material gave an intermediate used for the synthesis of osmundalactone.[17] In studies also related to the synthesis of (+)-phomopsolide B, the same group found that subjecting unsaturated alcohol **22** (prepared in two steps from di-*O*-acetyl-D-rhamnal) to sequential Mitsunobu reaction using benzoic acid as nucleophile, deacylation, acetal formation and oxidation of the remaining primary hydroxyl group gave unsaturated aldehyde **23**, but only in ~25% ee. This was thought to be a result of a possible acetyl migration during the synthetic and/or purification steps. An alternative multistep synthesis of **23** was therefore found using the known (Vol. 9, p. 92, ref. 398) 4,6-di-*O*-acetyl-2,3-dideoxy-aldehydo-D-*erythro*-(*E*)-hex-2-enose.[18]



Reagents: i, ArOH, 5 mol % $BF_3 \cdot Et_2O$, – 10°C, toluene

Scheme 4



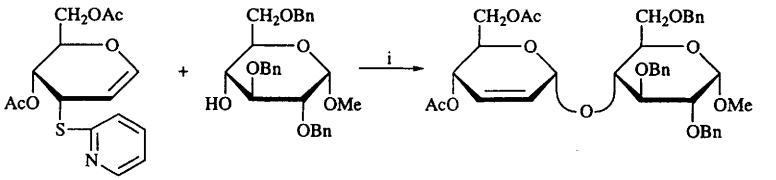
22 **23** **24**

Both L-rhamnal and 6-*O*-*t*-butyldimethylsilyl-D-glucal can be caused to react with substituted phenols (*p*-OMe and *p*-NO_2) under Mitsunobu conditions affording α-L-*O*-linked- and α-D-*O*-linked-2,3-unsaturated glycosides, respectively.[19]

Tri-*O*-acetyl-D-glucal reacts with bis(trimethylsilyl)acetylene in the presence of $SnCl_4$ followed by reaction with TBAF to afford unsaturated *C*-glycoside **24**, an intermediate directed

towards the synthesis of the marine toxins brevetoxin and ciguatoxin.[20]

3-Thio-glycal derivatives act as useful donors in a palladium-activated coupling with acceptor alcohols (Scheme 5). 2,3-Unsaturated thioglycosides are also donors.[21]

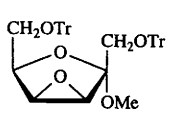


Reagents: i, $Pd(CH_2CN)_2Cl_2$–AgOTf

Scheme 5

The selective generation of free radicals from epoxides like **25** with bis(cyclopentadienyl)titanium(III) chloride affords the 2,3-unsaturated compounds **26**.[22] See also Chapter 18 for the intramolecular trapping of such radicals with a terminal alkene to afford chiral cyclopentane derivatives.

Treatment of 1,6-anhydro-3,4-dideoxy-β-D-*threo*-hex-3-enopyranoside with thionyl chloride in pyridine gave the 2,3-unsaturated D-*erythro*-chloride **27** which, on reaction with *O* or *S* nucleophiles, gave rearranged derivatives **28**.[23]



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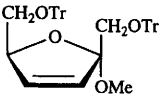

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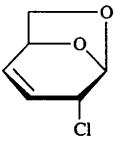

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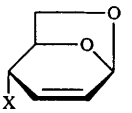


X = SPh, OR

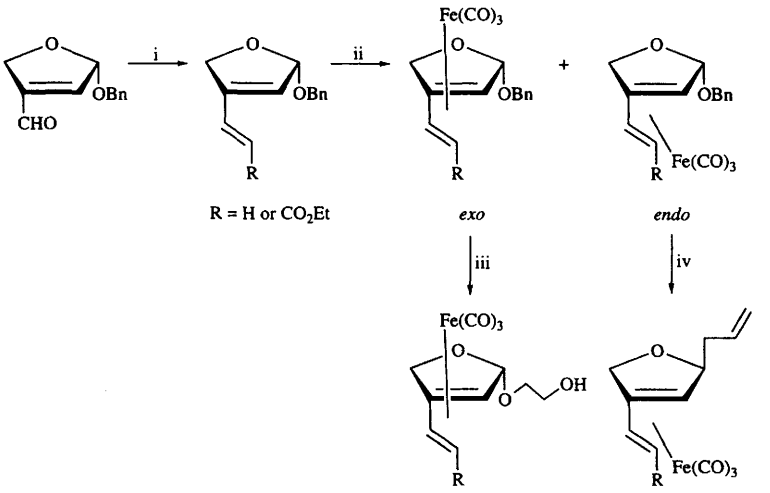
28

Reaction of the unsaturated alkyne **29** (derived from tri-*O*-acetyl-D-glucal) with diphenylphosphine in the presence of AIBN gave the vinyl phosphine **30** together with a product derived from intramolecular cyclisation onto the 2,3-double bond (See Chapter 14).[24]

The synthesis of iron(III) carbonyl complexes of dienes as precursors in the selective preparation of *O*- and *C*-gycosides is illustrated in Scheme 6.[25,26]

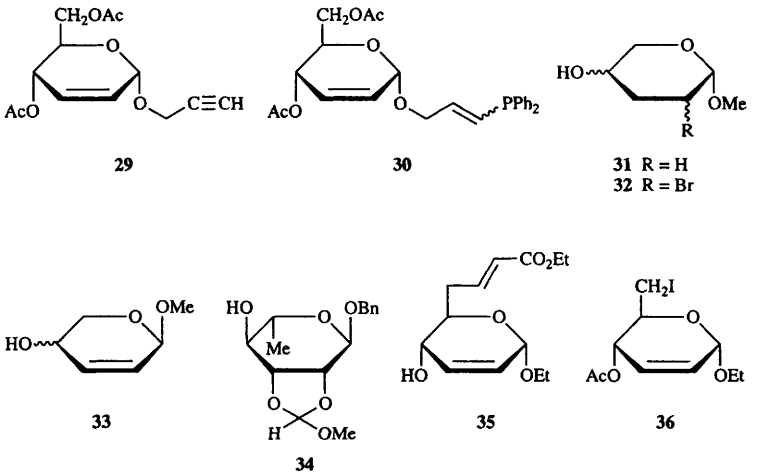
The regioselective bromination of racemic **31** with bromine in MeOH in the presence of concentrated HCl has been reported to give the bromide **32** (see also S. Yasuda *et al.*, *Tetrahedron*

Lett., 1969, 4397 for similar work) which on treatment with sodium methoxide affords unsaturated compound **33**.[27]



Reagents: i, $Ph_3P{=}CH_2$, THF, – 90 °C or $Ph_3P{=}CHCO_2Et$, THF, 50 °C; ii, $Fe_2(CO)_9$; iii, HO⌒⌒OH, $BF_3{\cdot}Et_2O$; iv, ⌒⌒Tms, $EtAlCl_2$

Scheme 6



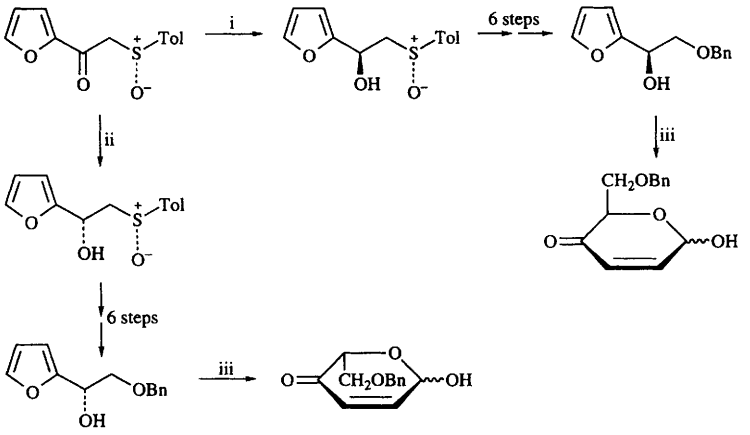
29 **30** **31** R = H, **32** R = Br

33 **34** **35** **36**

Pyrolysis of orthoester **34** (readily available from L-rhamnose) with acetic anhydride led to a good yield of benzyl 4-*O*-acetyl-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside by an Eastwood-like olefination process.[28]

A facile synthesis of the uronate **35** by treating iodide **36** with *Z/E* ethyl 3-(tributylstannyl)prop-2-enoate in the presence of AIBN followed by de-acetylation has been described. A much lengthier route to **35** using Wittig chemistry was also mentioned[29] (see Vol. 27 Chapter 13, ref. 35 for related work).

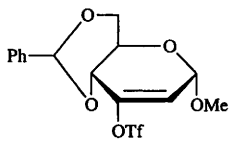
A "furan approach" to D- and L-hexose precursors is illustrated in Scheme 7.[30]



Reagents: i, DIBAL; ii, DIBAL, $ZnCl_2$; iii, Br_2, CH_3CN, H_2O

Scheme 7

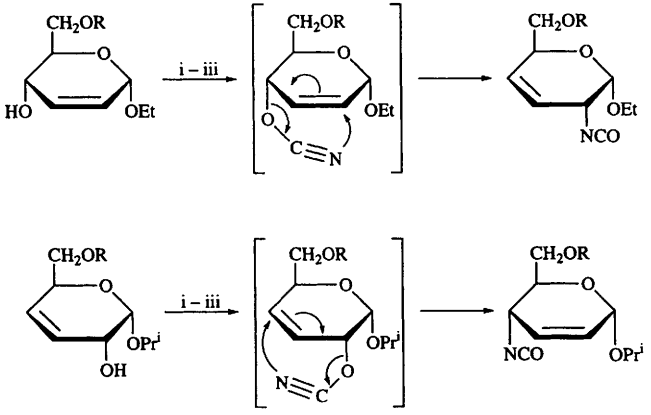
The vinyl triflate **37** is readily formed from methyl 2,3:4,6-di-O-benzylidene-α-D-mannopyranoside by treatment with *n*-butyllithium then *N*-phenyltrifluoromethanesulfonimide ($PhNTf_2$).[31] (See Chapter 14 for its use in preparing branched-chain sugars)



37

The preparation of 2,3-unsaturated sugars from dimethyl-L-(+)-tartrate as intermediates for preparing the *C*-27 to *C*-36 subunit of halichondrin B is mentioned in Chapter 24 and the synthesis of 2,3-unsaturated 4,6-di-*O*-pent-4-enyl acetals is covered in Chapter 6. The intramolecular cyclisation of radicals on the aglycon part of 2,3-unsaturated glycoside derivatives onto the double bond is noted in Chapter 14, and a one pot synthesis of unsaturated glycosyl haloacetylenes from glycosyl (trimethylsilyl)acetylides is mentioned in Chapter 3.

Tri-*O*-acetyl-D-glucal and 2-acetoxy-tri-*O*-acetyl-D-glucal have been transformed by standard methods into a range of 2,3- and 3,4-unsaturated compounds, respectively. These intermediates formed the basis for the synthesis of 2-amino-D-hex-3-enopyranoside or 4-amino-D-hex-2-enopyranoside derivatives in which the key step is a [3,3]sigmotropic rearrangement of an allyl cyanate to an allyl isocyanate (Scheme 8). The resulting isocyanates could be trapped with pyrrolidine or trimethylaluminium to provide allylic ureas or allylic acetamides, respectively.[32]

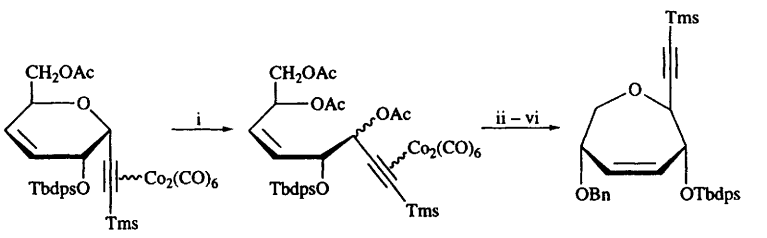


R = Tbdms

Reagents: i, CCl_3CONCO; ii, K_2CO_3/MeOH; iii, TPP, CBr_4, Pr^i_2NEt

Scheme 8

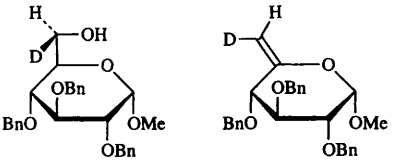
The conversion of cobalt complexed alkynyl *C*-glycosides into oxepane derivatives by ring opening through acetolysis and ring closure by the Nicholas reaction (step (v) of Scheme 9, attack by *O*-8 on *C*-3) has been described (Scheme 9).[33] A method for epimerising *C*-glycosyl alkynes from α- to β-anomers *via* cobalt hexacarbonyl complexes is covered in Chapter 3.



Reagents: i, Ac_2O, TfOH; ii, Bu^i_2AlH; iii, Et_3SiCl, base; iv, $BnOC(=NH)CCl_3$, TfOH; v, TfOH; vi, I_2

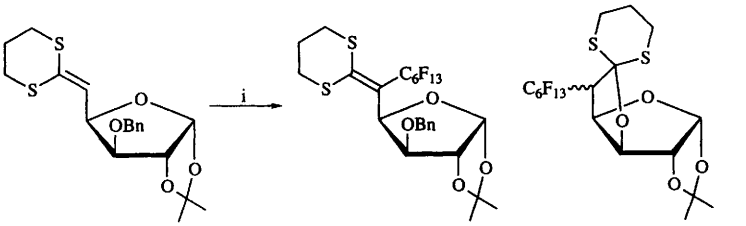
Scheme 9

Treatment of the deuterated alcohol **38** sequentially with *N*-(2-nitrophenylseleno)phthalimide, then hydrogen peroxide gave the *exo*-glycal **39** which was used to study the stereochemistry at *C*-6 during the Ferrier cyclization to a deoxyinososе derivative.[34]



38 **39**

The synthesis of a perfluoroalkyl dithioketene acetal is shown in Scheme 10. If *O*-3 in the precursor is left unprotected the internal adduct **40** is formed instead.[35]



40

Reagents: i, $C_6F_{13}I$, $Na_2S_2O_4$, DMF, H_2O, $NaHCO_3$

Scheme 10

The synthesis of benzyl 5,6-dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hex-5-enopyranoside from benzyl 5,6-di-*O*-methanesulfonyl-2,3-*O*-isopropylidene-α-D-mannofuranoside (prepared in four steps from mannose) has been reported.[36]

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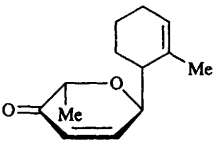
14
Branched-chain Sugars

1 Compounds with a  Branch-point

The aldol condensation between unprotected *glycero*-tetrulose and formaldehyde yields small quantities of 3-*C*-(hydroxymethyl)tetrulose in addition to the expected main products, *threo*- and *erythro*-3-pentuloses.[1]

An *O*-atom, in the α-position with respect to the carbonyl group of various protected keto-sugars, directs the nucleophilic addition of sulfur ylides ($Me_2S^+CH_2^-$ or $Me_2S^+(O)CH_2^-$) from the same side (*syn* attack) yielding spiro-epoxides with high stereoselectivity in a similar way to that reported for cyclopentanone compounds (Vol. 27, p. 212, ref. 77).[2] In contrast, bromomethyllithium gave products derived by nucleophilic attack in the opposite sense (*anti*-addition). Other epoxide compounds have been prepared having branching groups at *C*-4, from α,β-unsaturated-keto-*C*-glycosides such as **1**, also by treatment with dimethylsulfoniummethyl ylide.[3] (See Vol. 25, p. 52, ref. 216 and 217 for the preparation of **1**).

A non-carbohydrate synthesis of the 4-fluoromethyl compound **2** as a useful intermediate in the. peparation of 4'-fluoromethyl-2',3'-dideoxynucleosides has been reported. It uses (-)-(*S*)-*p*-tolylmethylsulfoxide to introduce chirality.[4]



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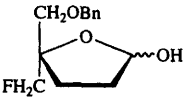


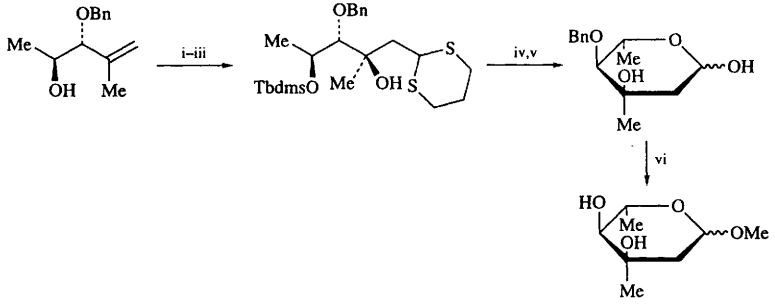
2

The synthesis of methyl L-mycaroside, in which the key step is an acyloin rearrangement of a α-hydroxy acetal has been disclosed (Scheme 1).[5]

Expanded details of an earlier paper (see Vol. 26, p. 155, ref 10) on the preparation of a sugar enediyne compound has been reported.[6]

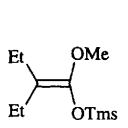
The reaction of aldonolactones such as 2,3:5,6-di-*O*-isopropylidenemannolactone with silyl

ketene acetal **3** affords moderate yields of the dimer **4**. Compound **4** could also be formed by reaction of the lactone with LDA and TmsCl, but in lower yields.[7]



Reagents: i Bu^tOOH, $VO(acac)_2$; ii, TbdmsCl, imidazole; iii, 1,3-dithiane, BuLi; iv, $HgO/HgCl_2/H_2O$–CH_3CN; v, TBAF; vi, MeOH, H_2, Pd/C

Scheme 1



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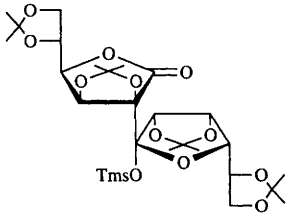
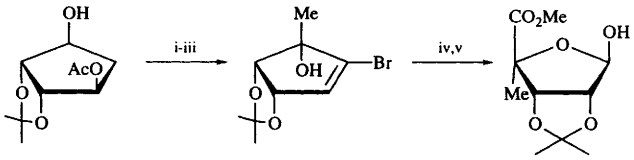


4

The conversion of a chiral cyclopentane derivative (prepared from cyclopentadiene by a process involving selective de-esterification with a lipase) as a useful precursor to the nucleoside *S*-(4'-*C*-methyladenosyl)-L-homocysteine has been reported (Scheme 2).[8]



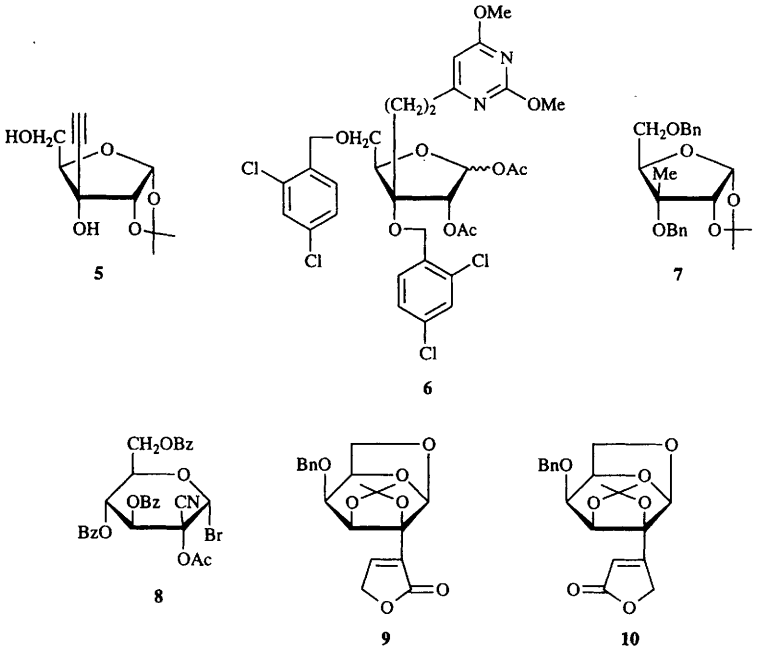
Reagents; i, PDC; ii, Br_2, Et_3N; iii, MeMgBr; iv, O_3, Py, MeOH; v, Me_2S

Scheme 2

The known acetylenic alcohol **5** (see J. Terashima *et. al.*, *J. Chem. Soc., Chem. Commun.*, 1992, 289) has been converted through standard chemical transformations into branched-derivative **6** as an intermediate in the synthesis of 2'-*O*-methyl-6,3'-ethanouridine.[9]

Sequential addition of methylmagnesium bromide, TBAF then sodium hydride-benzyl bromide to 6-*O*-*t*-butyldimethylsilyl-1,2-isopropylidene-α-D-*erythro*-pentos-3-ulofuranose gave nucleoside precursor **7**.[10]

3,4,6-Tri-*O*-benzoyl-α-D-*arabino*-hexos-2-ulopyranosyl bromide is readily converted into the cyanohydrin derivative **8** by treatment with trimethylsilyl cyanide then acetic anhydride.[11]

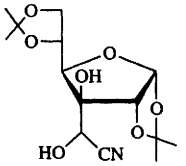


The isomeric butenolides **9** and **10** (see Vol. 27, p. 330, ref. 51a) have been converted into complex spirocyclic systems as potential inhibitors of squalestatin 1.[12]

The known branched-sugar, **11** (J.M. Tronchet *et al.*, *Helv. Chim. Acta*, 1972, **55**, 2820) has been transformed by several standard steps into the branched-chain lactone **12** as an intermediate for the preparation of the tricarboxylic acid **13**, a squalestatin analogue.[13]

Protected ascorbic acid derivatives can be *O*-allylated at the 2- or 3-position to give ethers

which on heating undergo Claisen rearrangements (Scheme 3).[14]



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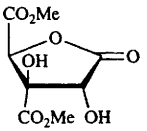

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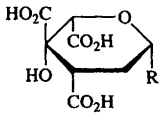

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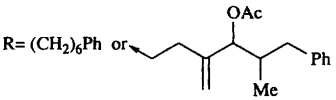
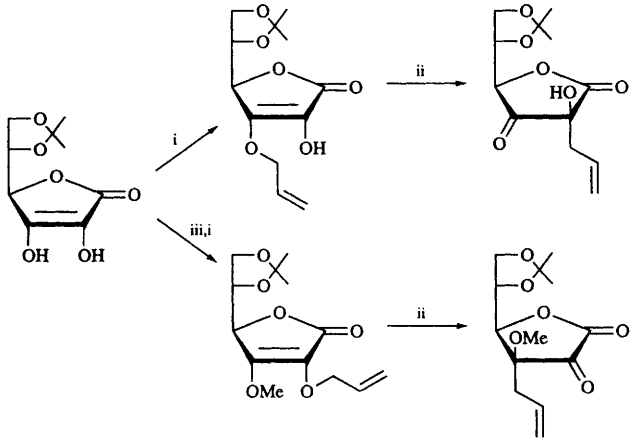




Reagents: i, Br/K_2CO_3; ii, reflux, toluene; iii, MeI/K_2CO_3

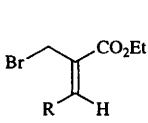
Scheme 3

Reaction of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexos-3-ulopyranoside with (*Z*)-ethyl-2-bromomethyl-2-alkenoates **14**, in the presence of zinc-silver graphite, produce spiro-compounds **15**.[15]

See Chapter 16 for the synthesis of 2-*C*-methyl-D-erythrono-1,4-lactone and 2-*C*-methyl-L-threono-1,4-lactone by asymmetric aldol reaction.

Reaction of 3-keto compound **16** (made in four steps from L-xylose) with ethyl acrylate in

the presence of samarium diiodide affords spirocyclic compound **17**, as a useful intermediate for the synthesis of rigid diacylglycerol derivatives.[16]



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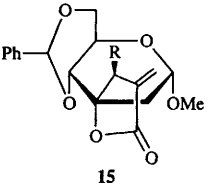

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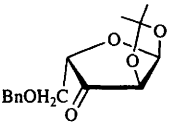

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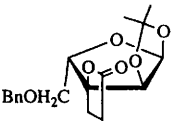

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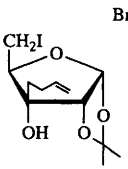

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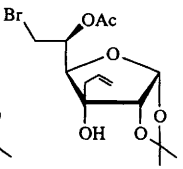

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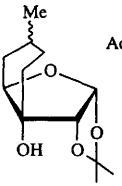

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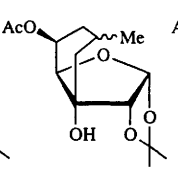

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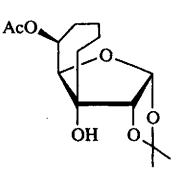
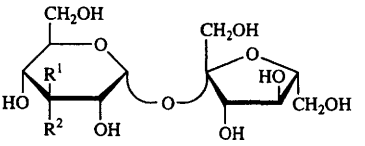


21a

The synthesis of polyfunctionalized cyclohexanes by 6-*exo*-free radical cyclization have been reported.[17] In this way iodo-alkene **18** and bromo acetate **19**, on treatment with tributyltin hydride and AIBN, afford products **20** and **21**, respectively. In addition, **21a** was formed as a minor product from **19**.

Microbial oxidation of sucrose with *Agrobacterium tumefaciens* gives keto derivative **22** which on protection of the hydroxyl groups with TmsCl then addition of Grignard reagents and deprotection give branched-compounds **23**.[18]



22 $R^1, R^2 = O$

23 $R^1 =$  , , $CH_3(CH_2)_9$, $CH_3(CH_2)_{11}$

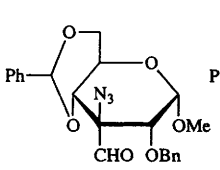
$R^2 = OH$

2 Compounds with a  Branch-point

The addition of dichloromethyl lithium to 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-*ribo*-hexos-3-ulopyranoside and to methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-*arabino*-hexos-2-ulopyranoside affords intermediate spiro-chloroepoxide derivatives which, on addition of sodium azide, give azidoaldehydes **24** and **25**, respectively.[19]

A ready method for generating oxycarbinyl radicals for radical cyclization reactions involves adding di-*t*-butyl hyponitrite to refluxing solutions of precursors. For example the 6-bromide **26** gives a radical which is intramolecularly trapped by the nitrile group to give an imine from which the product **27** is obtained on hydrolysis.[20]

See Chapter 16 for the preparation of a branched-chain 1,4-lactam starting from 2,2-dimethyl-5-nitro-1,3-dioxane.



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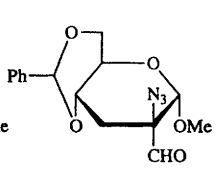

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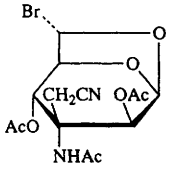

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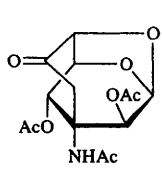
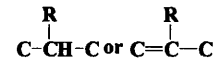


27

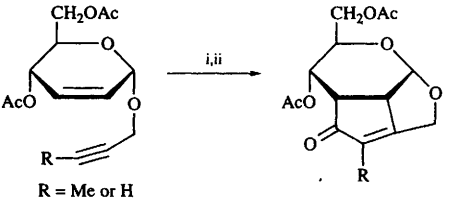
3 Compounds with a  Branch-point

4-*O*-Benzyl-2-deoxy-2-*C*-hydroxymethyl-D-glucose has been prepared as a useful intermediate for the synthesis of the potent glucosidase inhibitor, isofagomine by reaction of vinylmagnesium bromide on 1,6:2,3-dianhydro-4-*O*-benzyl-β-D-mannopyranoside followed by ozonolysis, hydride reduction and hydrolysis of the anhydro linkage.[21]

The synthesis of bis-annulated pyranosides by use of the Pausen-Khand reaction is exemplified in Scheme 4. Other examples are described starting from 2-*O*-propargyl-3,4-unsaturated derivatives.[22]

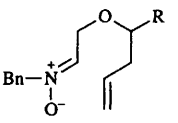
The synthesis of carbohydrate-like azabicyclo[4.3.0]nonanes as models for the amino-sugars

muramic acid and neuraminic acid has been reported. For example, heating the *N*-oxide **28** affords **29** as the major product.[23]

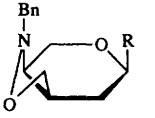


Reagents: i, $Co_2(CO)_8$; ii, NMNO

Scheme 4



28 R = Me, Ph, CH_2OBn

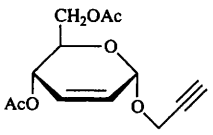


29 R = Me, Ph, CH_2OBn

Heating the olefinic acetylene **30** with diphenylphosphine in the presence of AIBN gives vinyl phosphine **31**.[24]

The *endo*-isomers **32** are the major products when unsaturated bromides **33** (R= Me, Et, ^{i}Pr) are treated with tributyltin hydride-AIBN. With **33** (R = Ph), the *exo*-isomer predominates. The same paper also describes the addition of *p*-toluenesulfonyl bromide to compounds **34** (R = Ac or Bn) to give access to branched-derivatives **35**.[25]

The diastereoselective conjugate addition of dialkyl- or diaryl-copper lithiums or radicals derived from alkyl halides, with tributyltin hydride-AIBN, to enone systems, is illustrated in Scheme 5.[26]



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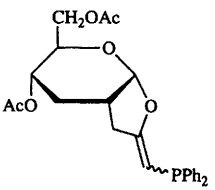

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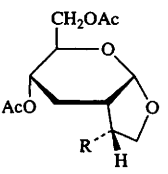

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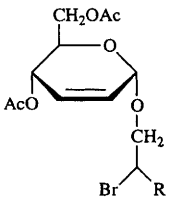

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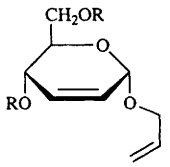

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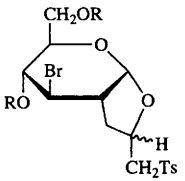

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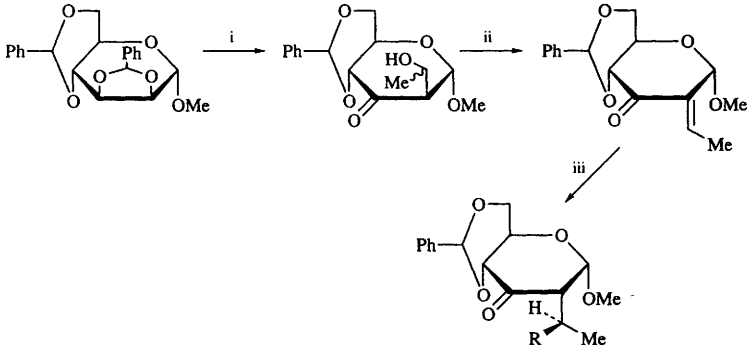
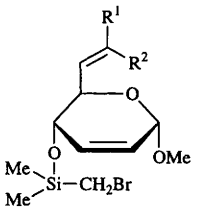


Reagents: i, BuLi then MeCHO; ii, MsCl, Py; iii, R_2CuLi or RI(Br), $Bu^n{}_3SnH$, AIBN

Scheme 5

The fine tuning of chemoselectivity during the intramolecular cyclization of various tethered radicals derived from 4-*O*-substituted-α-D-*erythro*-oct-2,6-dienopyranoside has been studied. For example reaction of compound **36** (R^1 = $CH_2OTbdms$, R^2 = H) with tributyltin hydride-AIBN gave, after oxidation and acetylation, the 5-*exo*-trig.-derived product **37** while reaction of **36** (R^1 = H, R^2 = CO_2Et) under the same conditions gave the 6-*exo*-trig. compound **38**. Radical addition therefore occurred at *C*-3 and *C*-6 in the respective cases.[27]



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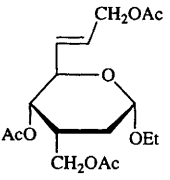

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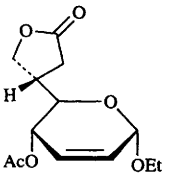
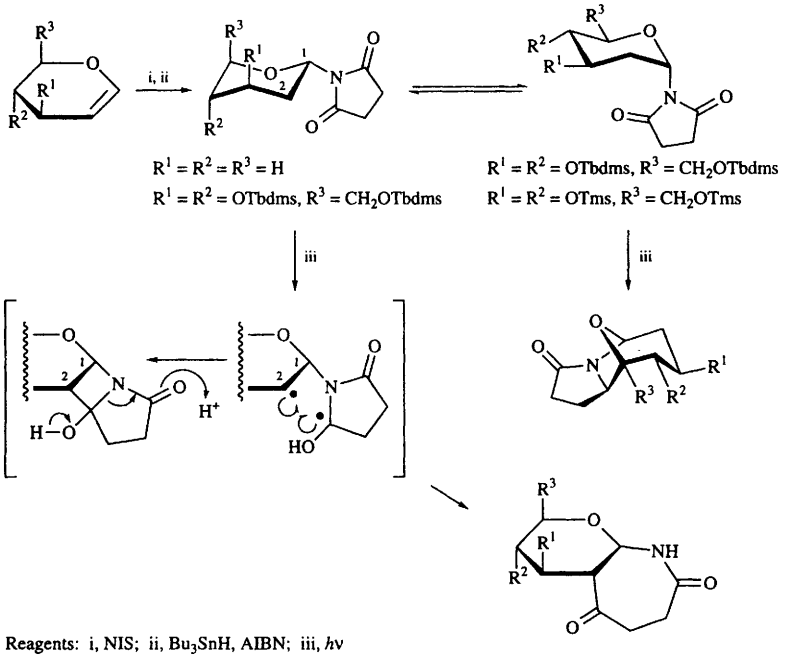


38

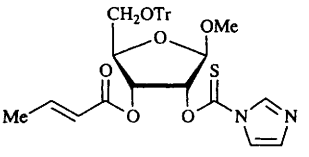
Glycals react with NIS followed by reduction with tributyltin hydride-AIBN to produce glycosylsuccinimides (Scheme 6). Depending on the type of monosaccharide and protecting group chosen, a conformational preference exists from which different products (novel bicyclic 2,5-azepanediones or [5.3.1.$0^{2,6}$]undecanamides) are produced upon treatment of the glycosylsuccinimides with uv light.[28]



Reagents: i, NIS; ii, Bu_3SnH, AIBN; iii, *hν*

Scheme 6

Reaction of the vicinal imidazolylthiocarbonyl α,β-unsaturated esters **39** with tributyltin hydride-AIBN, followed by reaction with isobutylamine and aluminium trichloride, affords branched-chain derivative **40**.[29]



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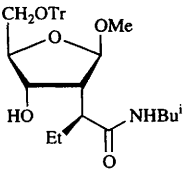
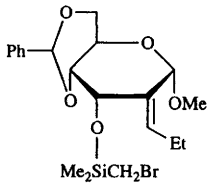


40

In a study on the radical cyclization of α-silyl radicals derived from allylic silyl ethers, *eg* **41** the reaction has been shown to proceed with 6-*endo*-addition affording *cis*-fused ring derivative **42** in high yield. In cases where a *trans* ring is formed (*eg* from the *C*-3 epimer of **41**) the yields are much lower.[30]

The reaction of *N*-methylindole with the aziridino lactone **43** in the presence of boron trifluoride etherate gives branched-chain derivative **44**.[31] In contrast, reaction of the aziridino acetal **45** in the same way gives **46**. The regioselectivity of ring opening was rationalized by comparing the LUMO coefficients and atomic charge distributions using MNDO methods.



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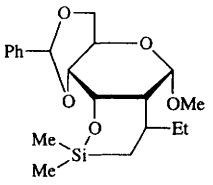

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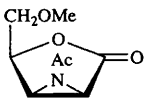

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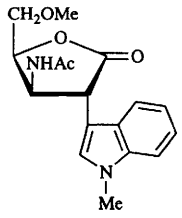

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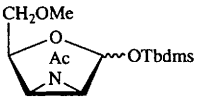

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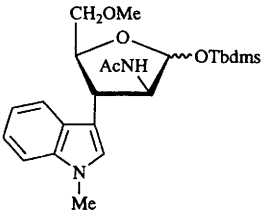


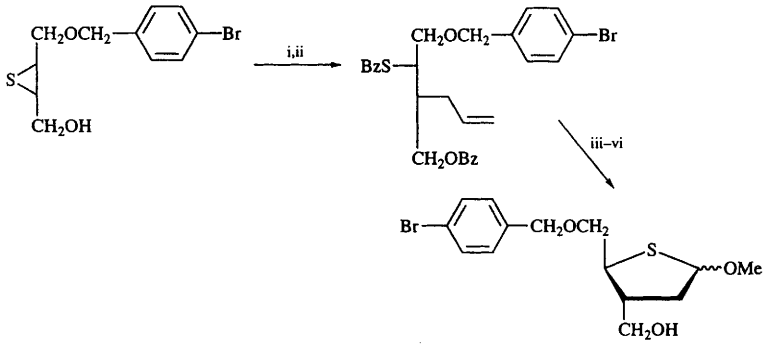
46

The synthesis of 3-(2-cyanoethyl)-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose has been reported from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose by oxidation of the 3-hydroxyl group, Wittig reaction, hydrogenation then conversion of the resulting 3-*C*-2-hydroxyethyl group to a 2-cyanoethyl group. This was followed by selective de-acetalation of the 5,6-*O*-isopropylidene group and treatment with periodate.[32]

Full details of previously reported work (Vol. 26, p. 242, ref. 159 and Vol. 25, p. 173, ref. 43) on the photocatalysed addition (by *C*-*C* bonding) of alcohols to 2,3-unsaturated 1,4-lactones as intermediates for branched-chain nucleosides has appeared.[33]

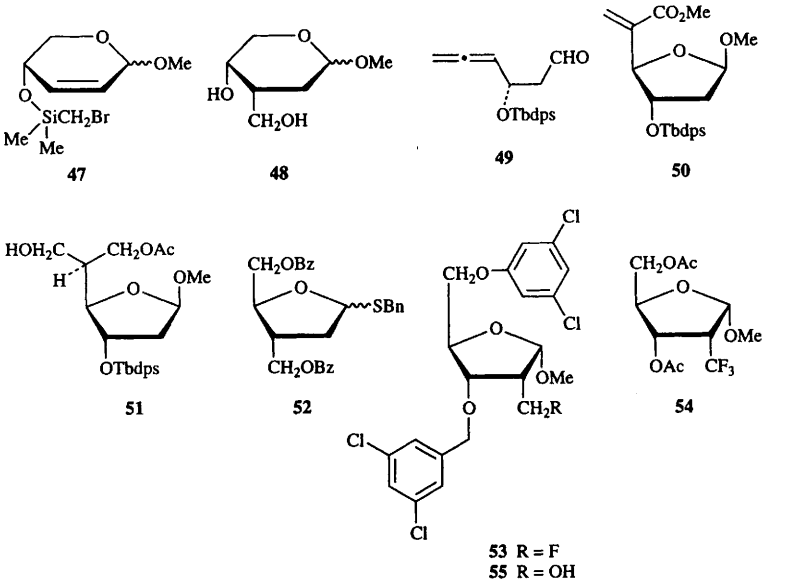
Reaction of the (bromomethyl)dimethylsilyl allyl ether **47** (prepared in three steps from 3,4-di-*O*-acetyl-D-xylal) with tributyltin hydride followed by potassium fluoride and hydrogen peroxide

gives branched-derivative **48** as an intermediate for nucleoside synthesis.[34] (See also Vol. 27, p. 169, ref. 24 and 25 for a similar process).



Reagents: i, MgBr; ii, BzCl; iii, OsO_4/NMNO; iv, $NaIO_4$; v, NaOMe; vi, HCl/MeOH

Scheme 7



Chiral allene **49** undergoes a palladium(II)-mediated acetalization-cyclization-methoxycarbonylation in the presence of acid and water scavengers to afford compound **50** (see Vol.

27, p. 176, ref. 46), needed to prepare a nucleoside analogue. Further reaction of **50** with DIBAL then acetic anhydride followed by borane-THF complex with oxidative work-up, gave **51**.[35]

A new approach to branched-chain 4-thiofuranosyl derivatives is outlined in Scheme 7.[36]

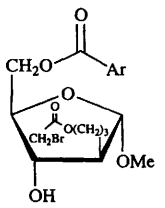
The 4-thio-compound **52**, as an intermediate for the synthesis of a nucleoside analogue, has been prepared from 5-*O*-benzoyl-3-*C*-[(benzoyloxy)methyl]-2,3-dideoxy-L-*threo*-pentose dibenzyldithioacetal by reaction with chlorodiphenylphosphine, iodine and imidazole. These reagents generated a leaving group at *C*-4 while permitting migration of an *S*-benzyl group from *C*-1 to *C*-4.[37]

The synthesis of the 2-*C*-branched derivatives **53** and **54**[38] and of **55**,[39] starting with Jones' oxidation of methyl-3,5-di-*O*-(3,5-dichlorobenzyl)-α-D-ribofuranoside and subsequent standard chemistry, have been reported.

Addition of allylmagnesium chloride to methyl 2,3-anhydro-α-D-*ribo*-furanoside, followed by hydroboration and standard chemistry, gave the protected *C*-2 branched compound **56** (Ar = 1-naphthyl).[40]

The preparation of nucleoside derivatives with branching at *C*-3 is mentioned in Chapter 20 and the peparation of *C*-3 branched sugar lactones is covered in Chapter 16.

Further examples of [2+2]cycloadditions of isocyanates to glycals to form β-lactam derivatives have been reported[41] (See Vol. 27, p. 170, ref. 28). When strongly electron-withdrawing isocyanates such as tosylisocyanate are used, subsequent methanolysis results in the formation of 2-carbonyl-2-deoxy glycosides. Such intermediates have been used to make pseudo-glycopeptides like **57**.[42] In contrast, methanolysis of β-lactam derivatives derived from glycals with isocyanates containing less electron-withdrawing groups favour products of type **58**, the result of an addition-elimination type of mechanism.[43]



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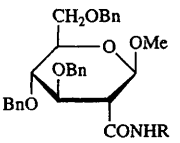
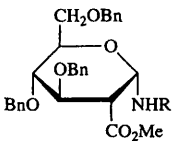
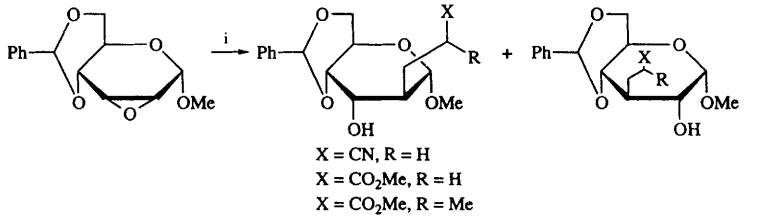


57 R = CH_2CO-L-LeuOMe
R = $CH_2CONHCH_2CO_2Me$



58 R = Ac, CO_2Et, $CONH_2$

Bis(cyclopentadienyl)titanium(III) chloride is a useful reagent for the radical deoxygenation of epoxides giving rise to intermediates that can be trapped by Michael acceptors (Scheme 8).[44]



X = CN, R = H
X = CO_2Me, R = H
X = CO_2Me, R = Me

Reagents: i, Cp_2TiCl, THF

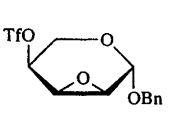
Scheme 8

The displacement with inversion of the protected sugar derivatives bearing a 4-*O*-triflate group with cyanide or diethyl malonate anions to produce 4-*C*-branched-chain sugars has been described.[45]

The addition of anions derived from β-dicarbonyl compounds to epoxy-triflate derivatives like **59** in the presence of added base affords adducts **60**.[46] (R = alkyl, aryl or carboxyalkyl, X = alkoxy).

The Diels-Alder addition of dienes to levoglucosenone gives products **61** as intermediates useful for the preparation of functionalized cyclohexane derivatives.[47]

The reaction of perfluorinated iodohexane with the thioketene acetal **62** in the presence of sodium dithionite afford the branched-sugar **63**.[48] See Chapter 13 for a different course of the reaction of compounds when the *C*-3 hydroxyl group of **62** is protected.



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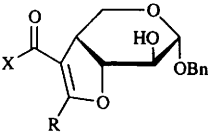

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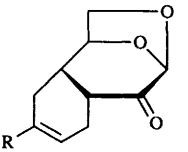

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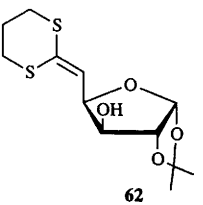

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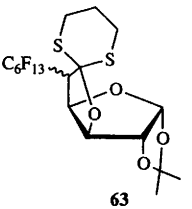


63

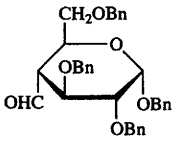
Swern oxidation of benzyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside then sequential reaction with Tebbé reagent, hydroboration and Swern oxidation affords aldehyde **64** as an intermediate in the preparation of *C*-bridged lactose derivatives.[49]

The branched lactose derivative **65** has been prepared by Wittig reaction then hydrogenation-hydrogenolysis of the corresponding benzyl protected 3-keto compound.[50]

The synthesis, in five standard chemical transformations, of the *C*-2 methyl derivative **66** from aldehyde **67** has been reported.[51]

The unsaturated triflate **68** has been prepared and cross-coupled under palladium catalysis to a variety of vinylic- and acetylenic-tributytin compounds to give products **69**.[52]

Reaction of the unsaturated compound **70** with thionyl chloride in pyridine gives the allylic chloride **71** as a useful intermediate for preparing *C*-2-alkoxymethylhex-2-enopyranosides.[53]



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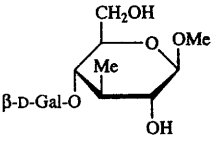

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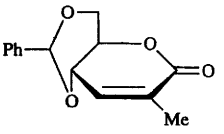

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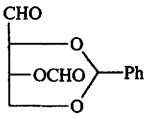

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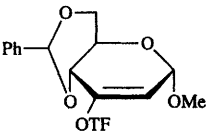

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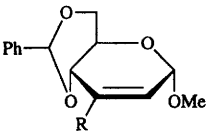
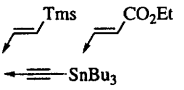
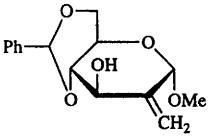


69 R =





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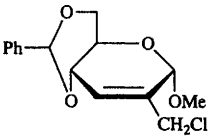


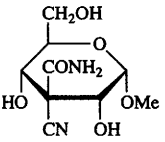
71

4 Compounds with a C-C(R)-C or C=C(R)-C Branch-point

Full details on the addition of silyl ketene acetals to lactones and α-ketolactones have been reported.[54] (See Vol. 27, p. 178, ref. 50 for a preliminary report).

The synthesis of the 3-*C*-carbonyl-3-*C*-cyano compound **72** has been described following the addition of 2-cyanoacetamide to the dialdehyde obtained by periodate oxidation of methyl α-D-glucopyranoside.[55]

The (*Z*)- and (*E*)-unsaturated lactones **73** and **74** have been prepared as analogues of diacyl glycerols and found to be more inhibitory of [^{3}H-20]-phorbol-12,13-dibutyrate binding to protein kinase C than the corresponding saturated derivatives.[56]



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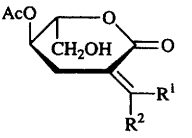

73 $R^1 = H$, $R^2 = C_{13}H_{27}$

74 $R^1 = C_{13}H_{27}$, $R^2 = H$

Further examples of the synthesis of derivatives of (2*R*,3*S*)-3-isopropylmalic acid as potential inhibitors of isopropylmalate dehydrogenase by the carbohydrate template method described in Vol. 27, p. 177, ref. 49 have been reported.[57]

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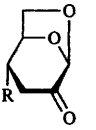
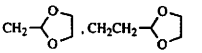
15
Aldosuloses and Other Dicarbonyl Compounds

1 Aldosuloses

A dehydrogenase from an *Arthrobacter* species oxidizes 1,6-anhydro-β-D-glucopyranose into 1,6-anhydro-β-D-*ribo*-hexopyranos-3-ulose.[1] Alternative conditions (Ph_3P, NCS, DMSO, then Et_3N) to the Swern oxidation for the oxidation of hydroxy groups to carbonyls have been proposed, but without obvious advantages.[2]



1 R = Me, Et, CH_2CH_2Ph,



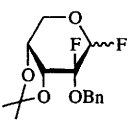
The synthesis of highly complex natural products from levoglucosenone has been reviewed;[3] asymmetric induction in the addition of carbanions to levoglucosenone has been further investigated,[4] while the conjugate addition of free radicals to levoglucosenone has afforded adducts **1**.[5] The synthesis of some conjugated α-D-hexenopyranosulosides from D-glucose by standard procedures has been outlined.[6]

Methyl β-L-*threo*-D-*galacto*-nonos-8-ulopyranoside has been prepared by the enzymic chain extension of a galactodialdose derivative using dihydroxyacetone phosphate as substrate.[7] The reaction of the 2-benzyloxy-2-fluoro-glycosyl fluoride **2** with benzyl alcohol (catalysed by Cp_2HfCl_2, AgOTf) affords either the *C* glycoside **3** or the *O*-glycoside **4** depending on the conditions used.[8]

2 Other Dicarbonyl Compounds

An enzymatic synthesis of the antibiotic cortalcerone **5** has used the co-immobilized enzymes pyranose-2-oxidase catalase and aldos-2-ulose dehydratase.[9] The synthesis of 6-deoxyheptos-5-

ulosurono-7,4-lactones (e.g. **6**) by chain extension of pentos-1,5-dialdose derivatives has been reported[10] and the diulose Ascopyrone T **7** has been reduced by several bacteria to 1,5-anhydro-4-deoxy-D-*erythro*-hex-3-ulitol.[11] The chain-extended dialdose **8** has been prepared by use of a Wittig condensation between two monosaccharide derivatives.[12] See Chapter 2 for the synthesis of some C_{19} and C_{21} dialdoses and other chain-extended compounds.



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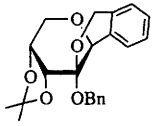

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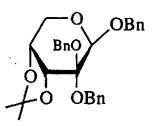

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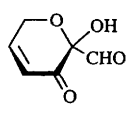

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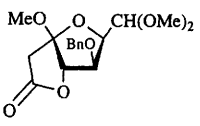

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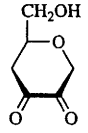

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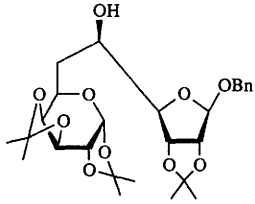

8

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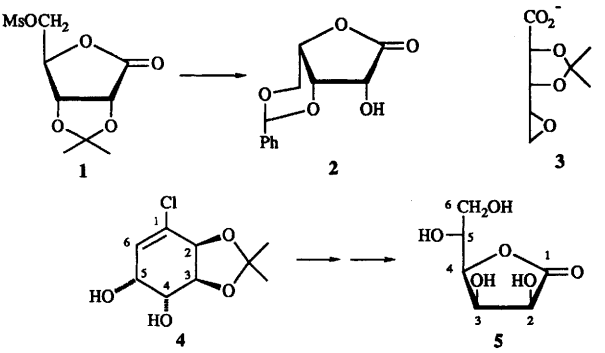
16
Sugar Acids and Lactones

1 Aldonic Acids and Aldonolactones

An extensive review on the use of aldonolactones in synthesis has appeared, covering amongst other topics *O*-substitution, deoxygenation, reaction with nucleophiles, β-eliminations, and the use of aldonolactones in preparing other classes of compounds such as iminoalditols.[1]

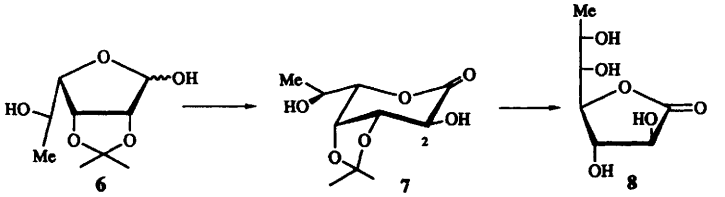
A review on the use of tetrapropylammonium perruthenate (TPAP) as a catalytic oxidant in conjunction with NMNO includes examples of its use in preparing fully *O*-protected aldonolactones by oxidation of hemiacetals,[2] and other workers have also favourably compared the use of TPAP as opposed to other oxidants in similar oxidations leading to *O*-benzyl- and *O*-allyl-aldonolactones.[3] A kinetic study has been carried out on the electrochemical oxidation of carbohydrates to aldonic acids.[4]

When the D-ribonolactone derivative **1** was treated with aqueous KOH followed by acid, L-lyxonolactone, isolated as the benzylidene derivative **2**, was formed. ^{13}C-N.m.r. studies indicated the presence of the *ribo*-epoxide **3** as an intermediate in the basic medium, and similar chemistry was used to convert D-lyxonolactone to L-ribonolactone.[5] Microbial dihydroxylation of chlorobenzene, followed by acetonation and further dihydroxylation using permanganate, gave **4**; on ozonolysis, followed by work-up under conditions of catalytic hydrogenation and subsequent



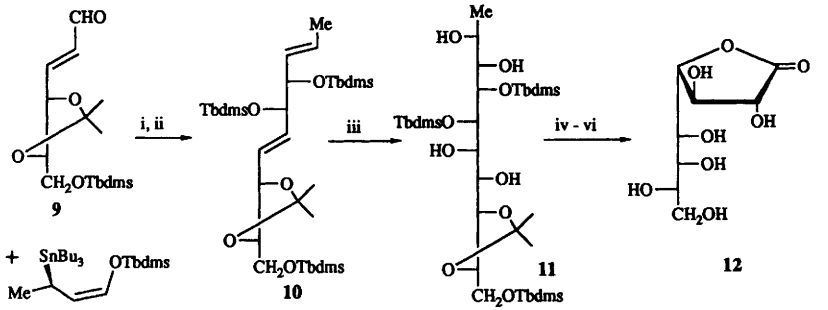
treatment with TFA, D-mannonolactone **5** was obtained.[6] Treatment of the L-rhamnose derivative **6** (Scheme 1) under Kiliani conditions gave a 3:1 predominance of the L-*glycero*-L-*galacto*-lactone **7** over the C-2 epimer. Reaction of **7** with TFA gave the γ-lactone **8**, convertible to its

5,6-*O*-isopropylidene derivative; an analogous series of reactions were carried out on the minor L-*glycero*-L-*talo*-epimer.[7]



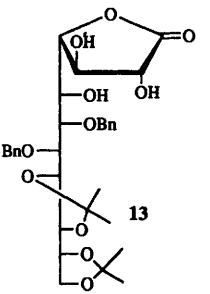
Scheme 1

In an inventive approach to higher-sugar lactones (Scheme 2), Marshall and Beaudoin treated the tartrate-derived enal **9** with the chiral allyl stannane shown to give the *threo*-adduct **10**, after further silylation of the initially formed alcohol. This bis-allylic ether was hydroxylated with high *erythro*-selectivity to **11**, convertible to the octonolactone **12**. A similar sequence was used to extend di-*O*-isopropylidene-*aldehydo*-D-arabinose to the C_{11}-lactone **13**, an intermediate previously used in a synthesis of hikizimycin.[8]



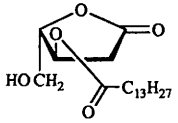
Reagents: i, $BF_3.Et_2O$; ii, TbdmsOTf; iii, OsO_4, NMNO; iv, H_5IO_6; v, PCC; vi, TsOH

Scheme 2



Unprotected aldono-1,4-lactones can be deoxygenated in the α-position by treatment with samarium diiodide in aqueous THF.[9]

There have been further reports from Marquez' laboratory concerning conformationally restricted diacylglycerol derivatives related to aldonolactones (see also Vol. 27, p. 183-4). Ester **14** has been described, along with various related structures,[10] and the α,β-unsaturated system **15** and its reduced analogue have been made from L-xylose (sugar carbons indicated) with inversion of stereochemistry at C-3, the same precursor being used to prepare compound **16**.[11] Data has been given concerning the ability of various 3-*O*-acyl-2-deoxy-L-ribonolactones to compete with phorbol dibutyrate in a protein kinase C assay.[12]



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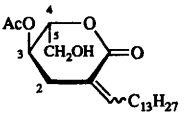

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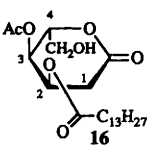

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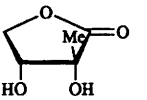
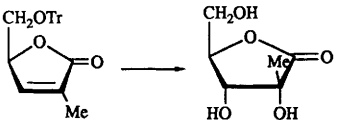
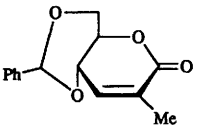


17

Some papers describing branched aldonolactones have appeared. 2-*C*-Methyl-D-erythronolactone (**17**) and its C-2 epimer (L-*threo*-) have been separately prepared by asymmetric aldol condensations mediated by chiral Sn(II) Lewis acids,[13] and 2-*C*-methyl-D-ribonolactone (**19**) has been made by stereoselective hydroxylation ($KMnO_4$, crown ether) of the unsaturated compound **18**, available from isopropylidene-D-glyceraldehyde by a Wittig sequence.[14] Similar chemistry carried out on 2,4-*O*-benzylidene-3-*O*-formyl-*aldehydo*-D-erythrose gave rise to the unsaturated lactone **20**.[15] An efficient large-scale route has been developed to convert D-ribonolactone into the demethylated analogue of **18**; subsequent conjugate addition of various alkyl- and aryl -copper species then led to 3-*C*-alkyl/aryl-2,3-dideoxy-D-*erythro*-pentono-1,4-lactones (**21**).[16]



18 **19**



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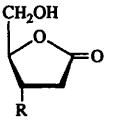
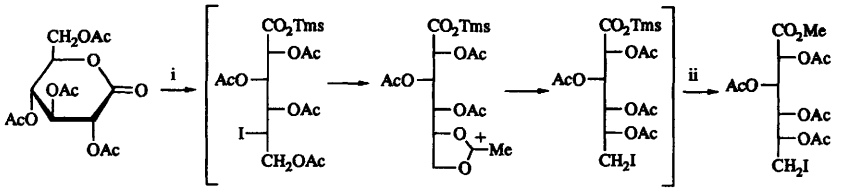


21

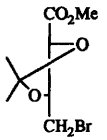
Treatment of peracylated sugar lactones as shown in Scheme 3 gives terminally-iodinated methyl aldonates. The suggested sequence of events is indicated; 1,4-lactones behaved similarly, as did *O*-pivaloyl or *O*-benzoyl derivatives, and work-up with ethanol gave ethyl esters.[17] Methyl 4-bromo-4-deoxy-L-threonate (**22**) has been prepared by oxidative degradation of L-ascorbic acid, and introduction of bromine using TPP-carbon tetrabromide.[18]

There have been reports on new routes to 2-amino-2-deoxyaldonic acids (polyhydroxylated α-aminoacids). One approach to compounds of this type is illustrated by the



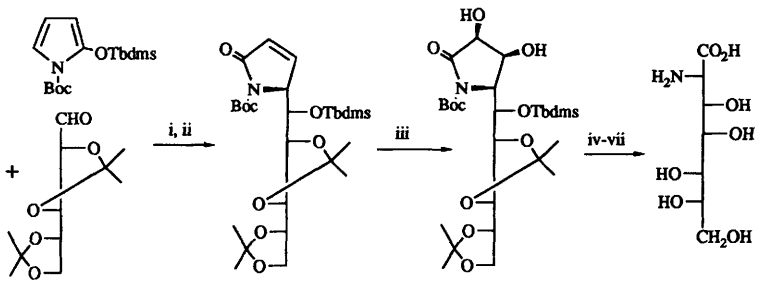
Reagents: i, TmsI, CH_2Cl_2; ii, MeOH

Scheme 3



22

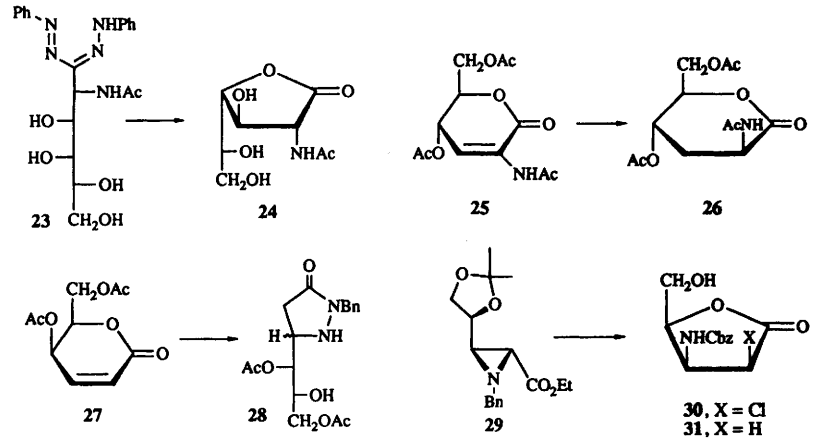
sequence in Scheme 4, and various other similar examples were presented.[19,20] Interestingly, the initial condensation is *threo*-selective as shown if $SnCl_4$ is used as Lewis acid, but reverses to *erythro*-selectivity if boron trifluoride etherate is employed instead.[20] Treatment of the previously-described products such as **23**, from reactions of formazans with ammonia (Vol. 17, p.



Reagents: i, $SnCl_4$; ii, TbdmsCl; iii, $KMnO_4$; iv, LiOH; v, $NaIO_4$; vi, RuO_2, $NaIO_4$; vii, H_3O^+

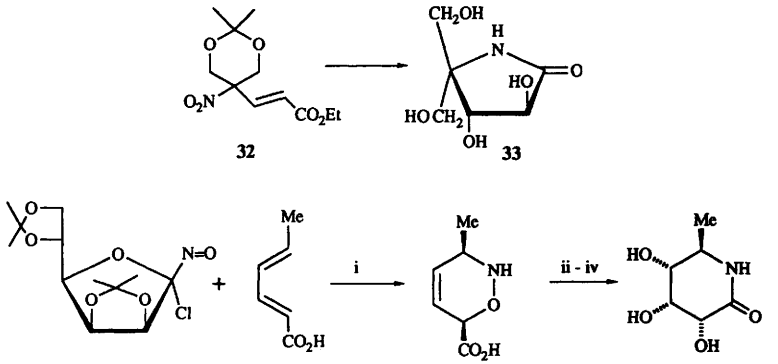
Scheme 4

110), with TFA in ethanol gives 2-acetamido-2-deoxyaldonolactones such as **24**.[21] When D-glucosaminic acid is treated with acetyl chloride in pyridine, a mixture of **25** and the equivalent 1,4-lactone is produced (Vol. 23, p. 139); catalytic hydrogenation of either of these lactones proceeded highly stereoselectively from the α-face, so that **26** was obtained from **25**. The 4,6-*O*-benzylidene compound related to **25** was also reduced with the same high selectivity. The overall process involves a net inversion of configuration at C-2 of D-glucosaminic acid.[22] Some papers on compounds which incorporate an α-amino acid function at the anomeric position of a sugar are covered in Chapter 10.



Reaction of *N*-benzylhydrazine with the D-*threo*- unsaturated lactone **27** gave a mixture of epimers **28**; the D-*erythro*-isomer of **27**, on the other hand, gave two products, both of D-*ribo*-stereochemistry, but differing in the position of the *N*-benzyl group.[23]

When the known aziridine **29** was hydrogenated for a short time, the *N*-benzyl group was removed; subsequent treatment with Cbz chloride in pyridine, followed by HCl in dioxane, gave the product **30**. Hydrogenation of **29** for a prolonged period caused both debenzylation and hydrogenolysis to give the β-amino acid, convertible to the lactone **31**.[24]



Reagents: i, mix in EtOH; ii, CbzCl; iii, OsO_4, NMNO; iv, H_2, Pd/C

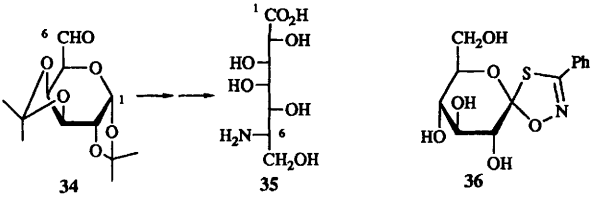
Scheme 5

Hydroxylation of **32**, made by base-catalysed reaction of the 5-nitro-1,3-dioxane with methyl propiolate, followed by partial reduction and acid hydrolysis, gave the racemic γ-lactam **33**.[25] An interesting *de novo* asymmetric synthesis of the lactam of 5-amino-5,6-dideoxy-D-

allonic acid involves the use of a chiral chloronitroso compound derived from D-mannose, as outlined in Scheme 5.[26]

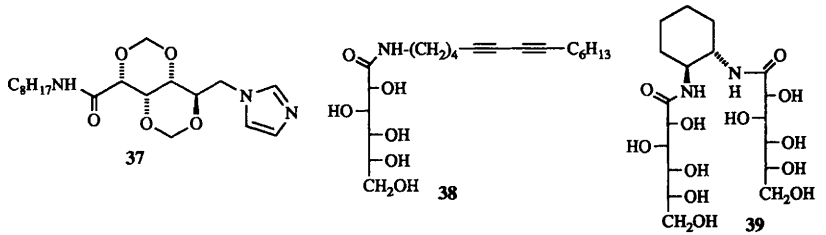
Addition of the Grignard reagent $PhMe_2SiCH_2MgCl$ to the D-*galacto*-aldehyde **34**, followed by oxidative desilylation, were key steps in a synthesis of destomic acid (**35**).[27]

Full details of the synthesis of the spiro-oxathiazole **36** have been presented (see Vol. 27, p. 184).[28]



34 **35** **36**

Aldonolactones continue to be used as precursors for amphiphilic molecules. Gluconolactone has been converted into the derivative **37**, which in Tris buffer solution at pH 8.5 forms long fibres and hollow tubuli, whilst its copper complexes form helices of 330 nm diameter.[29] Aldonamides such as **38** have been made by interaction of various sugar γ-lactones with the diacetylenic amine,[30] whilst interaction of D-glucono-1,5-lactone with 1,2-di-amino-cyclohexane gave a diastereomeric mixture from which the (*S*,*S*)-isomer **39**, a double-headed amphiphile, was obtained by crystallization.[31]



37 **38** **39**

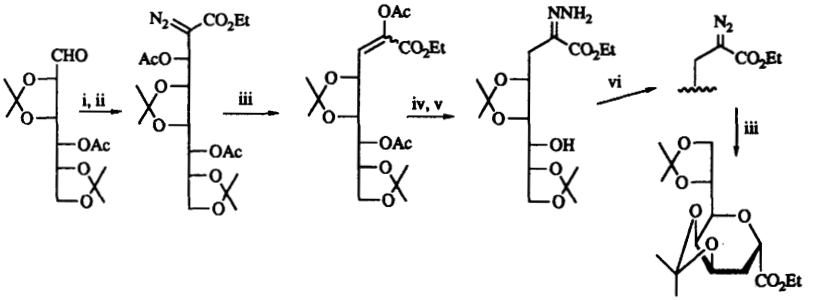
An AB block copolymer of poly(γ-benzyl L-glutamate) and poly(ethylene oxide) has been made with a lactonamide group at the terminus. This polymer caused adhesion of rat hepatocytes which have galactose-specific lectins on their cell surfaces.[32]

The interaction of magnesium ions with gluconate in solution has been studied by ^{13}C n.m.r. relaxation measurements, and it was concluded that the main sites of interaction of the magnesium ions were at *O*-1 and *O*-6 of the sugar chain.[33] Iron(II) complexes of lactonic acid in aqueous solution have been studied potentiometrically.[34]

A paper on benzylidene and isopropylidene acetals of pentonolactones is mentioned in Chapter 6.

2 Anhydroaldonic Acids

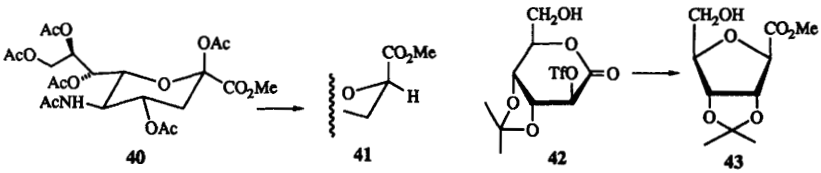
An interesting new route to 2-deoxy-Kdo is illustrated in Scheme 6. Although not relevant to the overall synthesis, it is noteworthy that the epimer shown was produced highly stereoselectively in the initial addition of ethyl diazoacetate. The final intramolecular insertion reaction was also stereoselective.[35]



Reagents: i, CHN_2CO_2Et; ii. Ac_2O; iii, $Rh_2(OAc)_4$; iv, N_2H_4; v, MeOH, KOH; vi, MnO_2

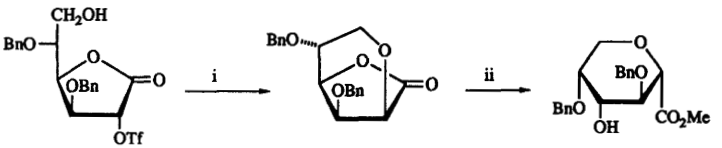
Scheme 6

Treatment of the NeuNAc derivative **40** with SmI_2 in ethylene glycol and THF gave stereoselectively the product **41** with an axial carboxymethyl group. The same selectivity was found in the reduction of the equivalent Kdo derivative, leading to 2-deoxy-β-Kdo.[36]



40 **41** **42** **43**

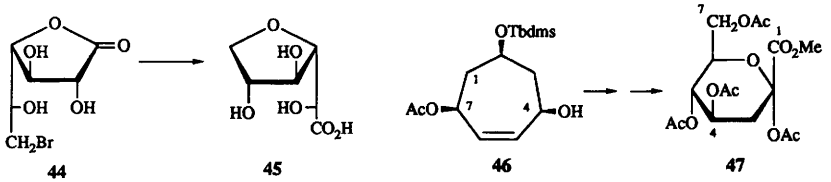
The triflate **42** underwent ring-contraction when treated with potassium carbonate in methanol to give the 2,5-anhydro-D-allonate **43**, whilst a derivative of 2,6-anhydro-D-mannonic



Reagents: i, DMF, heat; ii, HCl, MeOH

Scheme 7

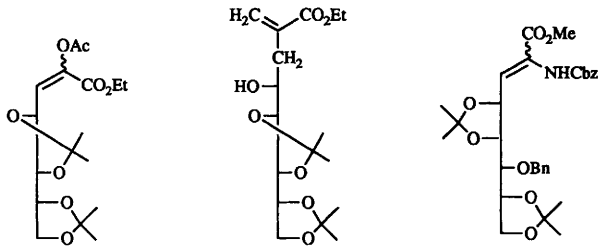
acid was prepared as indicated in Scheme 7.[37] 3,6-Anhydro-D-galactonic acid (**45**) is formed in high yield when the 6-bromo-compound **44** is heated in water.[38]



44 **45** **46** **47**

3 Ulosonic Acids

Syntheses of 3-deoxy-2-ulosonic acids have again been the subject of a number of reports. The cycloheptene derivative **46** was made by enzymic desymmetrization of the *meso*-compound and employed in a multistep synthesis of the derivative **47** of 3-deoxy-D-*arabino*-heptulosonic acid (Dah), dihydroxylation being used to establish the required chirality at C-5 and C-6 of the sugar relative to that at C-4.[39] If, in the chemistry of Scheme 6, the final rhodium-catalysed reaction was replaced by MCPBA oxidation, Kdo could be obtained. Application of the earlier stages of



48 **49** **50**

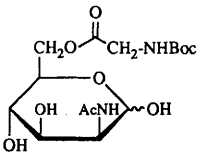
Scheme 6 to di-*O*-isopropylidene-*aldehydo*-D-arabinose gave **48**, convertible by hydrolysis to Dah.[40] Whitesides' group have now extended their earlier work on the synthesis of 3-deoxy-2-ulosonic acids using organoindium chemistry (Vol. 27, p.187-8); if di-*O*-isopropylidene-*aldehydo*-D-arabinose is used in indium-mediated reaction with ethyl 2-(bromomethyl)acrylate, then the adduct **49** of *erythro*-stereochemistry predominates, and this can be converted to Kdo by ozonolysis followed by hydrolysis.[41] In the earlier work, use of unprotected sugars had given mostly adducts of *threo*-stereochemistry. The D-*gluco*-epimer of Kdo has been made by an approach used some time ago for the synthesis of Kdo itself (Vol. 15, p.154).[42] In another new Kdo synthesis, a Wadsworth-Emmons reaction on a long-established *aldehydo*-D-mannose derivative gave **50**, which was coverted to Kdo by a two-stage hydrogenation procedure. One-carbon extension of D-mannose by Henry reaction and Nef oxidation, followed by a similar Wadsworth-Emmons sequence gave rise to 3-deoxy-D-*glycero*-D-*galacto*-nonulosonic acid

(Kdn).[43] Dondoni's group have extended their earlier work on the use of a thiazolyl phosphorane as a masked C_3 synthon for making 3-deoxy-2-ulosonic acids (Vol. 25, p. 187), and have now described this approach as applied to Dah, Kdn and 4-*epi*-Kdn.[44]

A paper has described interesting studies on the use of sialic acid aldolase with unnatural substrates to make various 3-deoxy-2-ulosonic acids. When the aldolase is used to catalyse the reaction of D-arabinose with pyruvate, both 4-*epi*-Kdo, the product of the enzyme's normal stereoselectivity, and Kdo, the product of inverted selectivity, are produced. Use of a large excess of arabinose increased the proportion of Kdo. Similarly, condensation of pyruvate with L-xylose, D-altrose and D-ribose gave isomeric mixtures, and use of L-xylose in excess gave a good yield of 7-*epi*-Kdo, the product of inverted stereoselectivity. With L-allose as substrate, just the 'normal' product, 7,8-di-*epi*-Kdn, was obtained. Relationships between the enzyme stereoselectivity and the conformation and C-3 stereochemistry of the substrate were discussed.[45]

Various aspects of the chemistry of Kdn have been described, including the preparation of the 8,9-*O*-isopropylidene derivative of the methyl ester-β-methyl glycoside, and a 1,7-lactone derived from this.[46] A paper on nucleoside analogues of Kdn is mentioned in Chapter 20.

In the area of sialic acid and its derivatives, a paper in Japanese has described the synthesis of the methyl ester-β-methyl glycoside of 5-*epi*-Kdn via condensation of D-glucose with oxaloacetic acid; formation of a 1,5-lactone allowed differentiation of *O*-5, so that Walden inversion could be carried out at C-5 to give NeuNAc.[47] The 7-deoxy- and 7-*O*-methyl derivatives of NeuNAc have been prepared from the appropriate *N*-acetylmannosamine derivatives using sialic acid aldolase and pyruvate,[48] whilst the *N*-acetylmannosamine ester **51** was converted in the same way to the 9-*O*-acylated sialic acid; removal of the Boc group was followed by attachment of the fluorescent dansyl unit. Ester **51** was itself made by selective acylation of *N*-acetylmannosamine using subtilisin.[49] Sialic acid aldolase was also used to convert various *N*-thioacylmannosamines to the corresponding (5-*N*-thioacyl)-sialic acids, although chemical thioacylation of sialic acid derivatives gave an alternative route. The same workers also reported 9-deoxy-9-thioacetamido-NeuNAc, made from a 9-azido-9-deoxyglycoside.[50]



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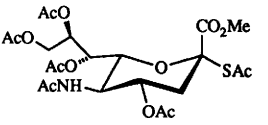
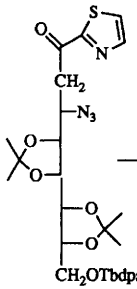


52

When the neuraminic acid derivative **52** was treated with diethylamine, selective *S*-deacetylation occurred, and the deacetylated material could be alkylated with various 6-bromo-6-deoxyhexose derivatives to give thioglycoside disaccharides.[51]

The azide **53** was prepared by *threo*-selective addition of Tms azide to the α,β-unsaturated ketone; the thiazole could be unmasked to give a carboxy group, thus leading to the regioisomer **54** of NeuNAc.[52]



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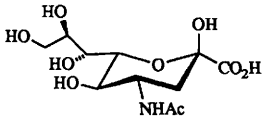

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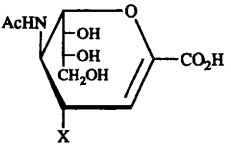
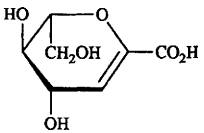


55 X = -NH-C(NH)NH$_2$
56 X = H

Synthetic details have now been given for the important guanidino-derivative **55**, a potent inhibitor of influenza virus sialidase,[53] and the 4-deoxycompound **56** has been made by elimination of acetic acid from a known intermediate (Vol. 25, p. 188); the truncated analogue **57** was also reported, made by a similar synthesis ($C_5 + C_2$) from di-*O*-isopropylidene-*aldehydo*-L-arabinose.[54] The 3-ene **58** has also been prepared from *N*-acetylmannosamine.[55] A route to reduced derivatives of NeuNAc by chain extension is mentioned in Chapter 2.



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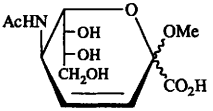

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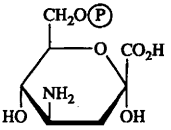


59

Full details have been given concerning the synthesis of the amino-analogue **59** of Dahp, an intermediate in the variant of the shikimate pathway leading to 3-amino-5-hydroxy-benzoic acid (see Vol. 26, p.170).[56]

Sialic acid has been attached, as an α-glycoside, to a spacer arm terminating in an acrylamide unit. Polymerization of this material with excess acrylamide gave a material which inhibited haemagglutination induced by influenza virus.[57]

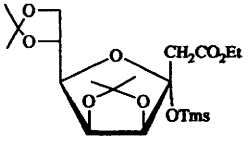
There has been an expanded account of the synthesis of 3-ulosonic acid derivatives such as **60** by fluoride-catalysed reaction of aldonolactones with silyl ketene acetals.[58]

Treatment of 2,3-*O*-isopropylidene-D-erythronolactone (**61**) with reagents **62** (R=Me, Et) in the presence of Zn/Ag intercalated into graphite led to the formation of the 4-ulosonic acid derivatives **63**.[59]

4 Uronic and Aldaric Acids

A study has been reported on the electrocatalytic activity of a μ-oxo-bridged Ru(III) dication towards the oxidations of methyl glycosides to the corresponding uronides.[60] Catalytic oxidation

over Pt/C was used to convert methyl α-D-fructofuranoside to the uronic acid **64**, whilst treatment of the same starting material with periodate followed by sodium chlorite gave the salt **65**.[61] Oxidation using PDC, followed by methylation with diazomethane was effective in the synthesis of **66** from the methyl glycoside.[62]



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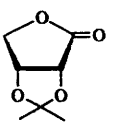

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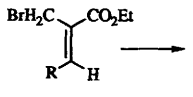

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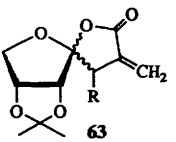

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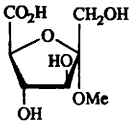

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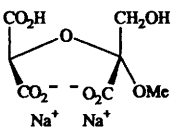

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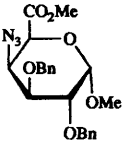
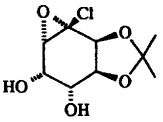


66

The epoxide **67** is produced by further oxidation of the diol **4**, and on treatment of it with two equivalents of $NaIO_4$, 2,3-*O*-isopropylidene-D-erythuronolactone (**68**) is obtained.[63] Sequential treatment of branched lactones of type **21** with alkali, $NaIO_4$, and acetic anhydride gave teturonolactones **69**.[64]



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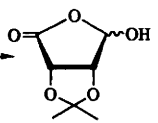

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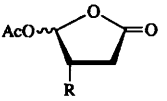

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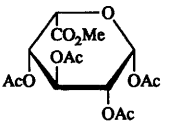
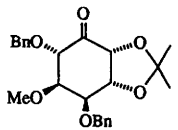
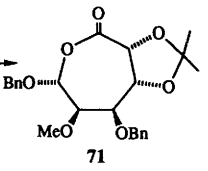


70

A direct route to the L-iduronic acid derivative **70** involves isomerization of the corresponding D-glucuronate by photobromination followed by reduction with tributylstannane, which gives a 3:1 preponderance of the L-*ido*-epimer.[65]





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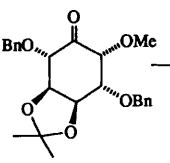
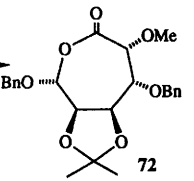




72

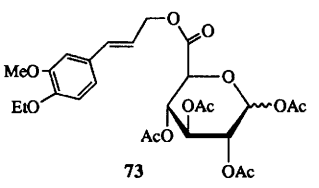
Various uronolactones have been prepared by regioselective Baeyer-Villiger oxidations of polyhydroxycyclohexanone derivatives, all made from L-quebrachitol. The formation of **71** and

72 are typical, and the migratory aptitude observed in these studies related to the α-substituent in the order OBn>OMe>ketal oxygen>>acyloxy.[66]

D-Glucuronic acid, α-linked to a glycerol unit, has been found as a constituent of ardiscrenolide E, a triterpenoid pentasaccharide from a Chinese shrub.[67] Both the phenolic and acyl β-D-glucuronides of salicylic acid, and the phenolic β-D-glucuronide of salicyluric acid (*N*-salicylyl-glycine) have been isolated from human urine by preparative h.p.l.c; their stability in aqueous solution, and towards glucuronidase, was assessed.[68]

Some long chain alkyl β-D-glycosides of D-glucofuranosidurono-6,3-lactone have been prepared by acid-catalysed glycosidation; the glucuronides were also reduced to alkyl β-D-glucofuranosides.[69]

A series of glucuronic esters such as **73** have been prepared as models for the linkages between lignin and carbohydrate in wood. They were shown to cleave oxidatively with DDQ and TFA.[70] Various amino acids, in both the D- and L-series, have been linked to D-galacturonic acids to give compounds of type **74**, which were used for making high molecular weight glycopolymers.[71]



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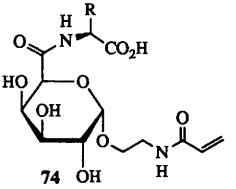
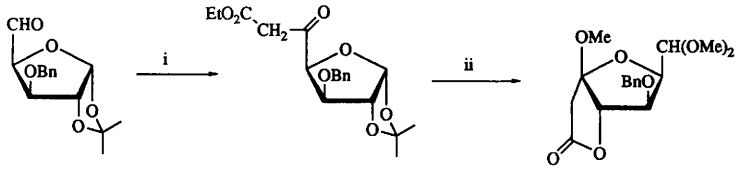


74

Scheme 8 indicates the use of sugar β-ketoesters in the synthesis of 6-deoxy-heptulosurono-7,4-lactones; analogous reactions were also carried out on starting aldehydes with D-*ribo*- and D-*lyxo*-stereochemistry.[72]

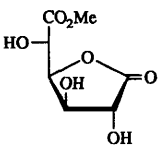


Reagents: i, CHN_2CO_2Et, BF_3; ii, MeOH, H_2SO_4

Scheme 8

In work on the synthesis of chiral polyamides, treatment of D-glucaric acid with methanol and acidic resin gave a mixture from which the crystalline 1,4-lactone **75** could be obtained by seeding. When ethanol and acidic resin were used, followed by seeding, the 6,3-lactone **76** could be crystallized. Either of these, on heating under reduced pressure, gave the dilactone **77**, and all three compounds could be converted into poly(alkylene-D-glucaramides) on treatment with 1,n-polymethylene diamines.[73] The same group has shown that treatment of D-glucaric acid with

acidic methanol gives a mixture of **75**, the methyl analogue of **76**, and dimethyl D-glucarate, and this mixture again gave dilactone **77** on thorough drying under vacuum. The equilibria between the various species was studied in both acidic and basic methanol.[74]



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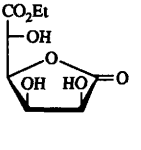
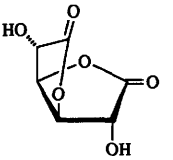


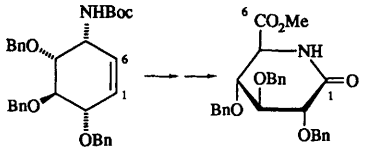
76



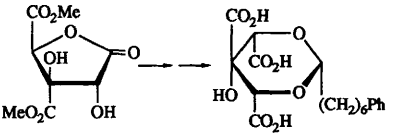
77

The cyclohexene **78** is available from D-glucose by means of Ferrier rearrangement followed by a Mitsunobu inversion. When cleaved by ozonolysis in methanol, followed by removal of the Boc group using TFA, an acyclic dimethyl ester was obtained, which on heating in THF at reflux gave the lactam **79**. The parent deprotected compound can be regarded as an oxidation product of nojirimycin.[75]

The branched aldarolactone **80** has been prepared from di-*O*-isopropylidene-D-glucose, and, by treatment with $Ph(CH_2)_6CH(OMe)_2$ in the presence of methanol, trimethyl orthoformate and HCl, followed by demethylation, this was converted to the 2,4-acetal **81**, a monocyclic analogue of squalestatin.[76]



78 **79**

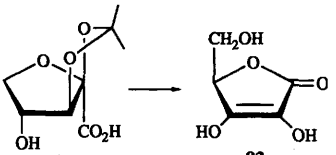


80 **81**

5 Ascorbic Acids

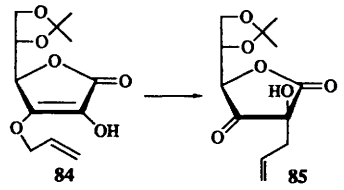
The conformation of L-ascorbic acid has been studied by molecular mechanics methods.[77]

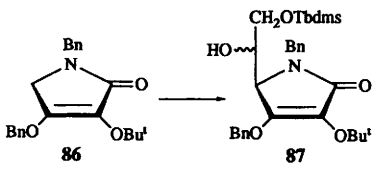
In a four-step synthesis of D-erythroascorbic acid (**83**), D-xylose was isomerized enzymically to D-xylulose; this was isopropylidenated and oxidised catalytically to give **82**, which with acidic methanol gave **83**.[78]



82 **83**

The *O*-allyl ether **84** of L-ascorbic acid underwent Claisen-type rearrangement on heating in toluene to give stereoselectively the branched structure **85**. A similar sequence from a 2-*O*-allyl ether gave a structure with a *C*-allyl group at C-3, again with α-selectivity.[79]





The enolate of **86** on treatment with Tbdms-oxyacetaldehyde gave **87** as a 1:1 mixture of diastereoisomers; deprotection on oxygen then gave racemic *N*-benzylated 4-aza-analogues of ascorbic and isoascorbic acids.[80]

Various mono- and bis-hydrazones of dehydro-L-ascorbic acid have been reported.[81]

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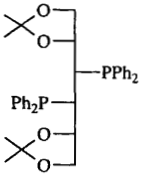
17
Inorganic Derivatives

1 Carbon-bonded Phosphorus Derivatives

1,2-(S)-Bis(diphenylphosphino)butane-4-ol has been synthesized from L-ascorbic acid and used to prepare chiral hydrogenation catalysts,[1] while the hexitol derivative **1** has been prepared for similar purposes,[2] and the synthesis and spectroscopic studies of methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-diphenylphosphinyl-α-D-altropyranoside have been reported.[3]

The phase transfer-catalysed synthesis of carbohydrate 1,2-epoxyphosphonates (e.g. **2**) has been achieved,[4] and the *C*-glycoside phosphonate **3** has been described.[5] The related phosphonate **4** has been synthesized from D-mannose as an analogue of L-*myo*-inositol 1,4,5-trisphosphate[6] and the glycosyl phosphonate **5** has been prepared as an analogue of KDO.[7] Some glycal methylphosphonates (e.g. **6**) have been synthesized as precursors to potential glycosyltransferase inhibitors (see Chapter 13 for details of synthesis),[8] and some 2′,3′-dideoxy-3′-*C*-phosphononucleosides are mentioned in Chapter 20.



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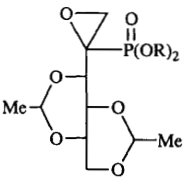

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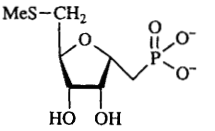

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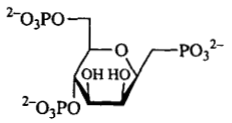

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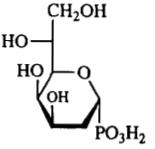

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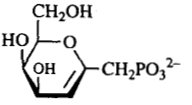
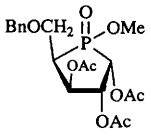


6

The synthesis of 6-amino-5,6-dideoxy-5-hydroxyphosphinyl-D-glucopyranose has been described[9] as have the synthesis of racemic forms of **7-10**,[10] and 1,2,3,4,6-penta-*O*-acetyl-5-deoxy-5-phenylphosphonothioyl-α and -β-D-glucopyranose have been prepared by standard techniques.[11]

Treatment of 2,3,5-tri-*O*-benzyl-D-arabinose with dibenzylphosphite and DBU has afforded mixtures of the cyclic phosphonate esters **11** - **14** termed phostones. Other similar compounds were also prepared as well as the disaccharide analogues **15** and **16**.[12] An alternative approach to phostones such as **11** - **14** has also been described.[13]



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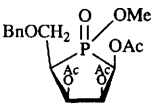

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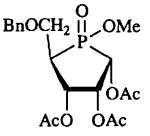

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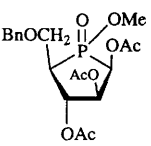

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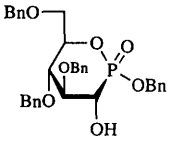

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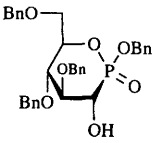

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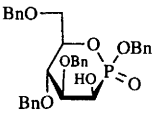

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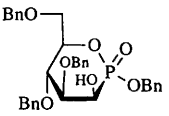

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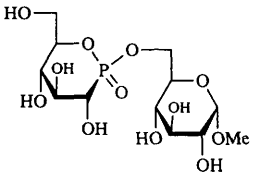

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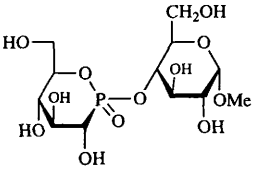


16

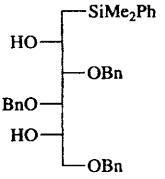
2 Other Carbon-bonded Derivatives

The organosilyl derivative **17** was the exclusive product when 2,3,5-tri-*O*-benzyl-*L*-arabinose was treated with phenyldimethylsilylmethyl magnesium chloride,[14] whereas organoiron compound **18** was an intermediate in the synthesis of some hepturonic acid derivatives.[15] Some organomercury compounds were characterized during a study of the stereochemical integrity of the Ferrier carbocyclization reaction,[16] and the hexacarbonyldicobalt complexes **19** and **20** have been prepared

from the corresponding alkynyl glycosides.[17] Some α and β C-1-Sn compounds have been synthesized by way of C-1 carbene derivatives.[18] Other stannylated derivatives are covered in Chapter 13.

3 Oxygen-bonded Derivatives

Rhodium chelates of some vicinal bis-diphenylphosphinite sugar derivatives have been used in asymmetric catalytic hydrogenation,[19,20] and a further study of similar compounds concluded that ee's were dramatically improved when electron donating aryl phosphinite esters were used.[21] The synthesis and properties of the 1,3,6-phosphite of 2,4-di-*O*-methyl-β-D-glucopyranose has been described,[22] and 1:1 complexes have been observed between octyl α- and β-D-gluco-, manno-, and galacto-pyranosides and the phosphonates **21** and **22**.



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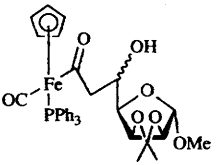

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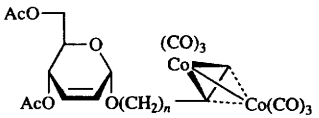
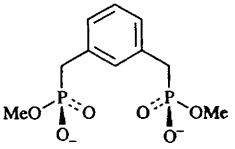


19 $n = 1$
20 $n = 2$

21



22

The formation of borate esters of a number of mono- and di-saccharides in aqueous solutions has been studied using ^{11}B and ^{13}C n.m.r. spectroscopy,[24] and another study of the complexation of carbohydrates with borate ions has utilized thermospray m.s.[25] A bis-arylboronic acid that is a glucose-selective fluorescence sensor has been prepared and evaluated and is apparently suitable for the detection of physiological glucose levels,[26] while *trans*-3,3′-stilbene diboronic acid has been shown to give a large increase in fluorescence on complexation with disacharides.[27]

Aqueous solutions of Fe(III) complexed with D-fructose have been studied by ^{13}C n.m.r.[28] and crystalline Fe(III) complexes with D-glucose and D-fructose have been isolated.[29] The site specificities of interactions of Cu(II) with some aldopento-pyranoses and -pyranosides in aqueous DMSO have been studied.[30] A systematic examination of the relative stabilities of the complexes formed between polyhydroxy compounds (sugars and alditols) and trivalent lanthanide cations in aqueous solution has been performed using thin layer ligand-exchange chromatography. The t.l.c. results were compared with thermodynamic complexation constants determined previously by calorimetry with good linear correlations.[31]

The ^{119}Sn n.m.r. spectra of a number of dialkylstannylene acetals derived from carbohydrate terminal 1,2-diols have been studied. Most of the compounds displayed spectra consistent with the presence of single symmetric dimers, and it was concluded that the regioselectivity of reactions of the stannylene acetals with electrophiles is dependent on the position of the dimer equilibrium and on the rates of reaction of individual dicoordinate oxygen atoms within the dimers.[32] The formation of tungstate complexes with alditols has been studied by ^{183}W n.m.r. spectroscopy, and a novel complex formed with D-*glycero*-D-*galacto*-heptitol has been characterized.[33] Some sugar complexes of vanadium of the type $[VO(sugar)_2]^{2-}$ have been prepared for the first time in non-aqueous media. The complexes were stable for long periods and were not susceptible to hydrolysis in the pH range 2-12.[34]

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18
Alditols and Cyclitols

1 Alditols

1.1 Acyclic alditols.-Studies of the vitreous transition in maltitol glasses[1] and the thermal behaviour of four commercially available hexitols during crystallization and vitrefication[2] have appeared. Reports on the water sorption and solubility of polyols[3], and on the kinetics of mercury-mediated electroreduction of glucose, galactose and lactose[4] have also been published.

The syntheses of both saturated and unsaturated alditols and aldoses by the Lewis-acid catalysed addition of (γ-alkoxyallyl)stannanes to α-alkoxyaldehydes, a process similar to that reported earlier, (Vol. 25, p. 200, ref. 12) have been described.[5,6]

The regioselective complexation of D-mannitol, -galactitol, -xylitol, -ribitol and -erythritol with bis(phosphine)platinum(II) carbonate complexes has been studied, and conformational analyses of the products by ^{1}H n.m.r have been performed.[7] Also a study on the preferred conformations of hex-1,5-dien-3,4-diols, which includes reference to hydroxylation reactions, suggesting an approach to hexitol and higher alditol syntheses has been reported.[8]

Optical, rheological and spectroscopic methods have been used to examine the gel formed from 1,3:2,4-di-*O*-isopropylidene-D-glucitol and ethylene glycol.[9]

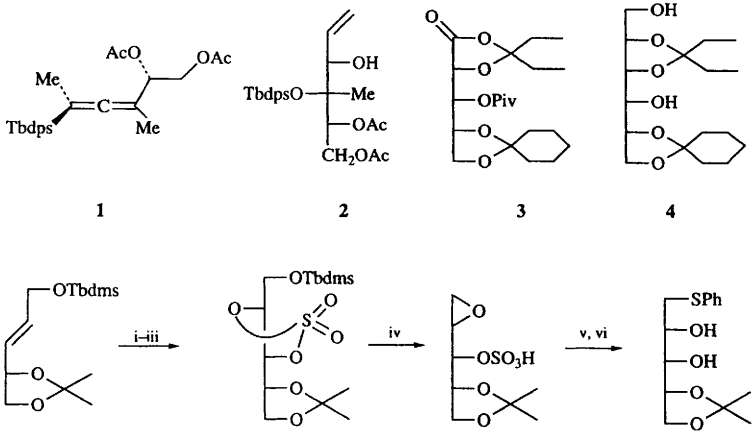
The synthesis of a family of D- and L-octitols, as g.l.c-m.s. standards, using a Wittig reaction and 2,3,4,5,6-penta-*O*-benzyl-*aldehydo*-derivatives of D-altrose, -idose, -talose and -gulose has been described.[10] (See Vol. 27, p. 201, ref. 14 for related work).

The chiral allene **1**, after treatment with MCPBA, DBU (to effect a $C \rightarrow O$ migration of the silyl group) then sodium borohydride-cerium(III) chloride gives **2** as a precursor to branched alditol and aldose derivatives.[11]

Dimethyl L-(+)-tartrate has been converted in six steps and 63% overall yield into 3-(*p*-methoxybenzyloxy)-1,2-*O*-(3-pentylidene)-L-*threo*-tetritol on a kilogram scale.[12]

α-Hydroxyacid-acetals such as **3** on Tebbé methylenation followed by hydroboration with oxidative work-up, afford 2,3-*erythro*-alditols such as **4**.[13]

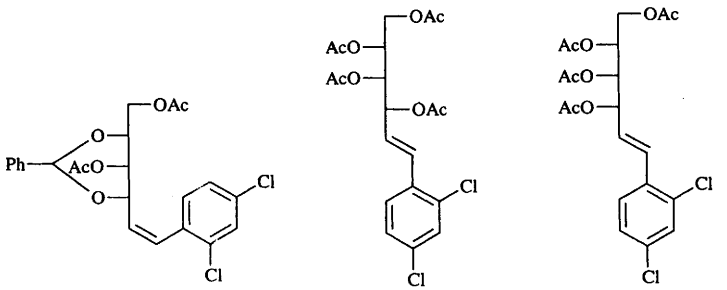
The synthesis of *erythro*-diols by Sharpless asymmetric dihydroxylation of *t*-butyldimethylsilyl-protected allylic alcohols, followed by cyclic sulfate formation and fluoride induced Payne-like rearrangement, is illustrated in Scheme 1.[14]



Reagents: i, AD-mix-β; ii, $SOCl_2$; iii, $RuCl_3$, IO_4^-; iv, TBAF; v, PhSNa; vi, H_3O^+

Scheme 1

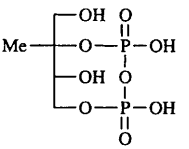
Acetolysis (H_2SO_4-Ac_2O) of the (*Z*)-L-*ribo*-hex-5-enitol derivative **5** unexpectedly affords the (*E*)-D-*lyxo*-hex-5-enitol **6** and the (*E*)-L-*ribo*-hex-5-enitol **7** as the major products.[15]



5 **6** **7**

Lyophilization of the bacterial-derived cyclic cyclopyrophosphate **8**, then treatment with hydrofluoric acid, gives the tetrol **9**.[16]

The preparation of fluorescent labelled glucitol, mannitol, maltitol and maltotriol derivatives by reaction of the corresponding free sugars with 2-amino-6-carboxyethyl pyridine or 2-amino-6-cyanoethyl pyridine, followed by reduction of the imine with borane, has been reported.[17]



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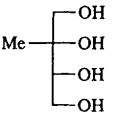
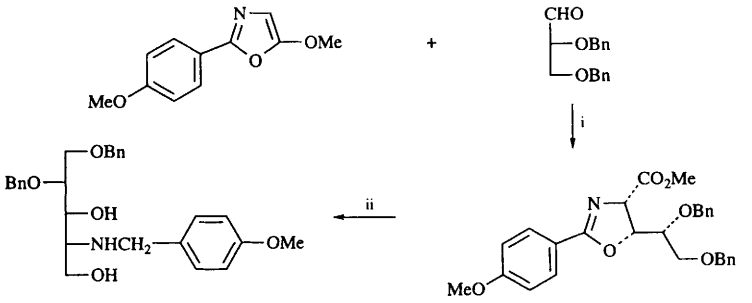


9

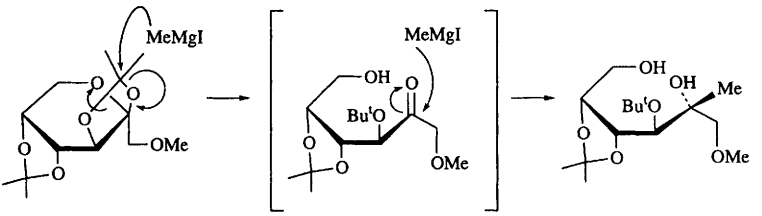
Scheme 2 illustrates a formal [3+2]cycloaddition of a 5-alkoxyoxazole and an α-alkoxyaldehyde, the product of which, on reduction, affords the illustrated 2-amino-2-deoxypentitol derivative.[18]



Reagents: i, $SnCl_4$; ii, LAH

Scheme 2

Treatment of a 1-*O*-methyl-D-fructose acetal with an excess of methylmagnesium iodide gives a branched-chain hexitol compound in high yield as shown in Scheme 3.[19]



Scheme 3

Coupling of a 3-stannylprop-1-enyl glycoside with isomeric 2-methyl-3-silyloxypropanals offers an ingenious route to 1,2,4-trideoxy 4-*C*-methylhex-1-enitols. This chemistry is discussed in Chapter 3.

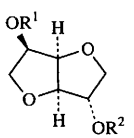
The X-ray crystal structures, n.m.r solution conformations and origins of the inadequacies of molecular mechanics calculations in predicting the geometries of various 1,3,5,7-tetraoxadecalins derived from D-threitols are covered in Chapters 21 and 22

1.2 Anhydro-alditols.-D-Glucitol, on reaction with pyridinium hydrochloride, gives rise to mixtures of the 1,4-anhydride and 1,4:3,6-dianhydride, the proportions of which vary according to the temperature used.[20] The dehydration of D-galactitol under similar conditions was also studied.

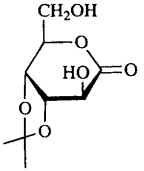
A useful strategy for the selective substitution of dianhydroglucitols utilizing a titanium-mediated hydride reduction of 1,4:3,6-dianhydro-2,5-di-*O*-nitro-D-glucitol has appeared. Thus reduction of the latter with titanium(III) borohydride [$Ti(BH_4)_3$] affords the monoester **10**, and with diisopropyloxytitanium(III) borohydride [$(^iPrO)_2 TiBH_4$]the isomeric compound **11** is produced.[21]

A complex mixture of mono- and di-anhydrohexitols is produced on dehydrating D-glucitol with methanesulfonic acid in refluxing xylenes. From it, 2,5-anhydro-L-iditol can be isolated by formation of a crystalline di-*O*-isopropylidene intermediate.[22]

Treatment of the D-altrono-δ-lactone acetal **12** with triphenylphosphine-diethylazodicarboxylate affords the corresponding 2,6-anhydride from which, after reduction of the lactone function with lithium borohydride followed by acid hydrolysis of the acetal, 2,6-anhydro-D-altitrol (1,5-anhydro-D-talitol) **13** is produced.[23]



10 $R^1 = H$, $R^2 = NO_2$
11 $R^1 = NO_2$, $R^2 = H$



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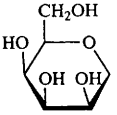
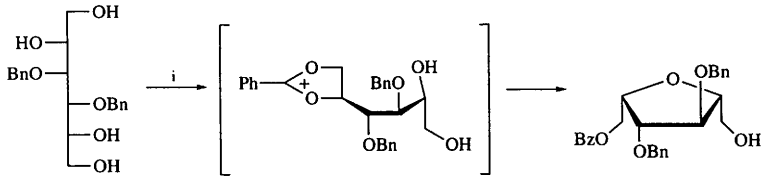


13

Heating 6-bromo-6-deoxy-D-galactono-1,4-lactone or -D-galactitol in water yields 3,6-anhydro-D-galactonic acid and 1,4-anhydro-L-galactitol (3,6-anhydro-D-galactitol) respectively.[24]

The conversion of certain polyol derivatives into anhydroalditols by a one-pot method is depicted in Scheme 4.[25]

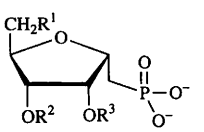


Reagents: i, $PhC(OMe)_3$, cat. TfOH, CH_2Cl_2–MeOH

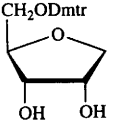
Scheme 4

A synthesis of the phosphonate **15** as an analogue of 5-methylthioribose-1-α-phosphate, has been achieved by sequential treatment of the known phosphonate **14** (R.W. McClard *et al.*, *Bioorg. Chem.*, 1990, **18**, 165) with H_2/Pd-C, tosyl chloride-pyridine and potassium methylthiolate followed by hydrolysis of the acetal.[26]

The anhydroalditol **16** has been prepared by two routes; one involving the tributyltin hydride-AIBN reduction of an isopropylidene protected furanosidic phenylthionocarbonate followed by hydrolysis; the other involving tributyltin hydride-dibenzoyl peroxide reduction of a benzoate protected phenylthioglycoside followed by saponification.[27] Compound **16** was incorporated into hammerhead ribozyme.



14 R^1 = OTr, R^2, R^3 = CMe_2
15 R^1 = SMe, R^2 = R^3 = H

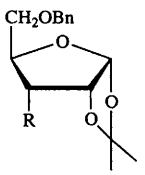


16

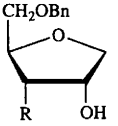
Reductive cleavage (triethylsilane-trimethylsilyl triflate) of the isopropylidene derivatives **17** gives anhydro-sugars **18**. The OH-2 groups in **18** have been further converted to mesylates and displaced with purine bases or azide (further converted into a pyrimidine ring) to lead to nucleoside analogues.[28]

Addition of the Grignard reagent derived from (chloromethyl)dimethylphenylsilane ($Ph(Me_2)SiCH_2MgCl$, see also ref. 57 below for use of this reagent) to 2,3,5-tri-O-benzyl-α/β-L-arabinose affords the L-glucitol derivative **19**. Treatment of **19** with boron trifluoride etherate,

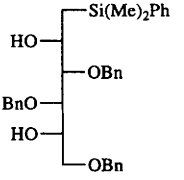
followed by protodesilylation with sodium borohydride in acetic acid, then hydrogenolysis, gave 2,5-anhydro-L-glucitol. With sulfuric acid as catalyst **19** gives 2,5-anhydro-L-mannitol as the main product [29] In both cases an unwanted Peterson elimination reaction was observed, but this could be prevented by using a Grignard reagent containing a phenyldiisopropylsilane moiety. In this case, L-glucitol derivatives were now the main products formed when either boron trifluoride etherate or sulfuric acid was used.[30]



17 R = OH, CH_2OH



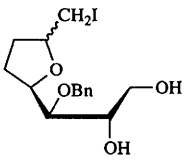
18 R = OH, CH_2OH



19

The 2,5-anhydro-1-iodooctitol **20** is formed, as indicated from **21**, by a complex carbocation rearrangement reaction upon treatment of the isopropylidene protected alkene with iodonium dicollidine perchlorate, then sodium borohydride.[31]

The multistep synthesis of the anhydrodeoxyiodothioanhydro-L-talitol compound **22**, as a precursor for the synthesis of thio-analogues of α-glucosidase inhibitors, has been described.[32]



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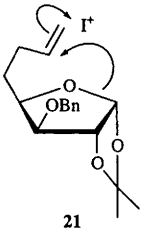
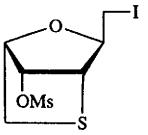


21



22

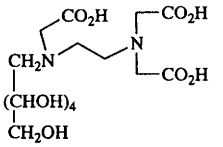
A set of *N*-alkyl-2,5-diamino-2,5-dideoxy-1,4:3,6-dianhydroalditols have been prepared from the corresponding 1,4:3,6-dianhydroalditols, *via* carbonyl intermediates, as useful base catalysts for polyaddition reactions of isocyanates to afford polyurethanes and polyureas.[33]

1.3 Amino- and Imino-alditols.-The reductive amination of aldehydo-sugars with benzylamine in the presence of pyridinium borohydride in acetic acid-water-methanol has been reported to give good yields of *N*-benzylaminoalditols without significant formation of dimeric products.[34]

High pressure hydrogenation of D-galactose or D-mannose over a Pt-C catalyst in the presence of ethylenediamine, followed by carboxymethylation gives derivatives **23** as useful chelating agents for Cd(II) or Ca(II) ions.[35]

The preparations of aminoalditols **24** in a straightforward manner, starting from a protected D-glucitol derivative, have been reported as acyclic analogues of nojirimycin.[36]

Hapten **25** has been synthesized and antibodies raised which were found to catalyse *O*-glycoside hydrolysis. This suggests a new dimension to the study of the reactions of glycosides.[37]



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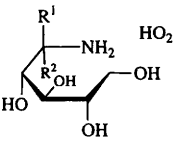
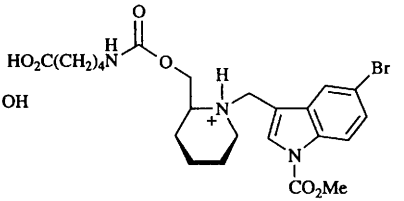


24 $R^1 = H, R^2 = CH_2OH$
$R^1 = CH_2OH, R^2 = H$



25

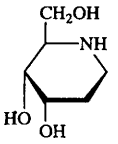
2,6-Dibromo-2,6-dideoxy-D-altrono-1,4-lactone can be converted into 1-amino-3,6-anhydro-1-deoxy-D-allitol by reaction with sodium borohydride followed by aqueous ammonia. The same starting dibromide, on treatment with potassium fluoride then aqueous ammonia, affords 3,6-dideoxy-3,6-imino-D-gluconic acid which can be reduced to 1,4-dideoxy-1,4-imino-L-gulitol *via* the 1,4-lactone.[38]

The leaves of *Merus bombycis*[39] and *Merus alba*[40] have been shown to contain, in addition to 1-deoxynojirimycin, several related compounds including 1,4-dideoxy-1,4-imino-D-arabinitol, 1,4-dideoxy-1,4-imino-D-ribitol, fagomine and several glycosylated (glucose, galactose) imino-alditols including the novel 3-*epi*-fagomine **26**.

Facile access to various *N*-alkyl-1,5-dideoxy-1,5-imino-D-arabinitols by reaction of 1,5-di-*O*-toluene-*p*-sulfonyl-2,3,4-tri-*O*-benzyl-D-arabinitol with various alkyl-amines followed by hydrogenolysis of the benzyl protecting groups has been reported. In an analogous way, ditosylate derivatives of benzyl protected L-arabinitol and D-ribitol starting materials affords the corresponding 1,5-dideoxy-1,5-imino-L-arabinitols and 1,5-dideoxy-1,5-imino-D-ribitols.[41]

A preparation of 1,5-dideoxy-1,5-imino-D-allitol from *N*-protected deoxynojirimycin which involves a microbial redox reaction at *C*-3 has been described, and the glycosidase inhibitory properties of the product were determined together with those of other imino-alditols isolated from the leaves of *Merus alba* (see also ref. 40 above).[42]

The synthesis of 1,5-dideoxy-1,5-[*N*-hydroxy(alkoxy)imino]-D-lyxitol derivative **27** has been achieved by treating 1-*O*-acetyl-2,3-di-*O*-cyclopentylidene-α-D-*lyxo*-pentodialdose-1,4-furanose with hydroxylamine or *O*-(*E*)-phenylprop-2-enylhydroxylamine ($PhCH{=}CHCH_2ONH_2$) followed by reductive cyclization.[43]



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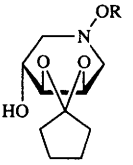
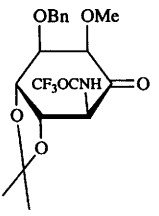


27 R = H or $CH_2CH{=}CHPh$

The synthesis of 5-amino-5,6-dideoxy-D-allose (see Hussein *et. al.*, *Tetrahedron* , 1993, **49**, 2123 for a synthesis of the L-compound) by way of a 1,2-oxazine formed by a Diels-Alder reaction using 2,3:5,6-di-*O*-isopropylidene-1-*C*-nitroso-D-mannofuranosyl chloride has appeared.[44] (See Vol. 22, p. 101, ref. 51 for a similar method using an achiral nitroso derivative and Vasella *et. al.*, Vol. 27, p. 216, ref. 96).

Monotosylation of 3,4-di-*O*-benzyl-D-mannitol, followed by azide displacement, gave the 6-azidodeoxy derivative which, on oxidation with bistributyltin oxide and bromine, afforded 6-azido-3,4-di-*O*-benzyl-6-deoxy-D-fructofuranose. This latter compound on hydrogenolysis gave 1-deoxymannojirimycin.[45]

An interesting synthesis of galactostatin and 1-deoxygalactostatin from L-quebrachitol has appeared in which the key step involves a Baeyer-Villiger oxidation of ketone **28** to the 7-membered lactone **29**. Several standard chemical transformations produce imino hydrogensulfite adduct **30** as the immediate precursor to the imino derivatives.[46]



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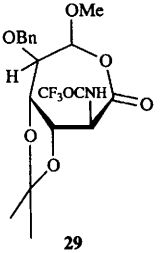

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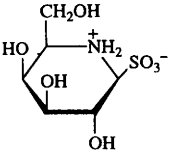
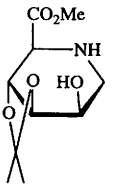


30

Full details (see Vol. 24, p. 197, ref. 34) on the synthesis of racemic *arabino*- and *altro*-1,5-imino sugars by double osmylation of 1,2-dihydropyridines has been reported.[47]

D-Glucono-δ-lactone has been transformed in several steps to the protected pipecolic acid ester derivative **31** which, on reduction with lithium aluminium hydride, then hydrolysis, gives 1-deoxymannojirimycin. Hydrolysis only of **31** provided the iduronidase inhibitor 2,6-imino-D-mannonic acid. [48]

A racemic synthesis of deoxymannojirimycin has been described from the lactam **32**, which was prepared from a non-carbohydrate source.[49]



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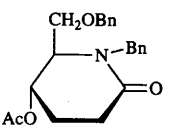

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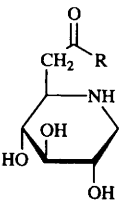


33

Expanded details have been provided for the synthesis of mannojirimycin and other aza-sugars by use of the *Pseudomonas putida* oxidation product of chlorobenzene (see Vol. 27, p. 208, ref. 52, p. 183, ref. 6 and p. 182, ref. 5)[50]

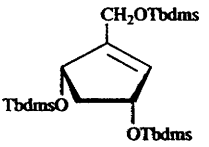
A short synthesis of *N*-butyl-1-deoxynojirimycin from D-glucose has been reported in which the key step involves a microbial oxidation of *N*-butylglucosamine with *Gluconobacter oxydans*.[51]

1-Amino-1-deoxy-D-glucitol has been used as starting material for the preparation of 6-azido- and 6-amino-analogues [52] or 7-carbonyl homologues [53] (**33**, R = Me, Ph, NH_2, OH) of 1-deoxynojirimycin.

Ozonolysis of the chiral cyclopentene **34** (prepared in several steps from cyclopentadiene), followed by reductive amination and hydrogenolysis affords 1,3-dideoxynojirimycin **35**[54]

N-Hydroxymethyl-1-deoxynojirimycin has been reported to delay starch degradation in germinating wheat seedlings.[55]

Subjecting azidofuranoses **36** and **37** to aldol reaction with dihydroxyacetone phosphate in the presence of rabbit muscle fructose-1,6-bisphosphate aldolase, followed by treatment with phosphatase then hydrogenation, gives homomannojirimycin **38** and homonojirimycin **39**, respectively.[56]



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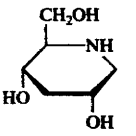

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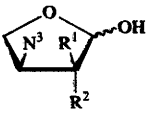
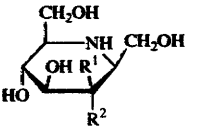
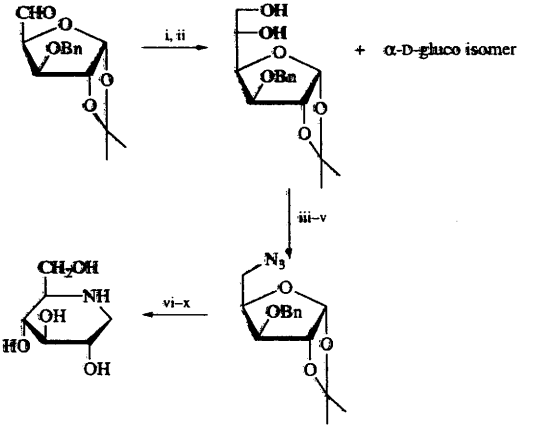


36 $R^1 = H, R^2 = OH$
37 $R^1 = OH, R^2 = H$



38 $R^1 = OH, R^2 = H$
39 $R^1 = H, R^2 = OH$

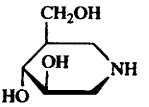
Addition of the Grignard reagent formed from (chloromethyl)dimethylphenylsilane (see also ref. 29 above for use of this reagent) to 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdose-1,4-furanose has been described as part of a route to deoxynojirimycin (Scheme 5).[57]



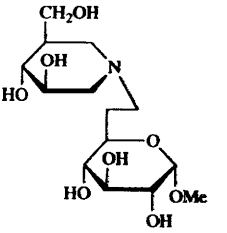
Reagents: i, $Ph(Me)_2SiCH_2MgCl$; ii, CH_3CO_3H, NaBr, NaOAc; iii, $SOCl_2$; iv, $NaIO_4$, $RuCl_3$; v, LiN_3; vi, LAH; vii, CbzCl, $NaHCO_3$; viii, BnOH, $BF_3{\cdot}OEt_2$; ix, H_2/Pd/C, Bu^tOH, AcOH; x, Ion exchange (^-OH)

Scheme 5

Isofagomine **40** has been prepared from 1,6:2,3-dianhydro-4-*O*-benzyl-β-D-mannopyranose by reaction with vinylmagnesium bromide, ozone, sodium borohydride then hydrolysis to give 4-*O*-benzyl-2-deoxy-2-*C*-hydroxymethyl-D-glucose which was further treated with sodium periodate, aqueous ammonia then hydrogenolysed to give **40**.[58] The same group has also incorporated **40** into **41** as a transition state mimic for isomaltose hydrolysis.[59]



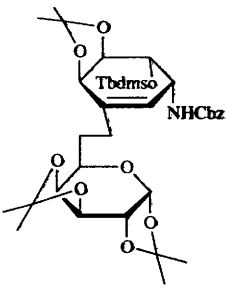
40



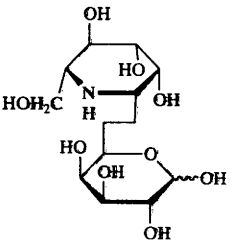
41

Various mixtures of 2-*O*-, 3-*O*- and 4-*O*-α-D-glucopyranosyl *N*-(benzyloxycarbonyl)-1-deoxynojirimycin are produced on glucosidation of *N*-(benzyloxycarbonyl)-1-deoxynojirimycin with a range of glucosidases.[60]

A Suzuki-type cross coupling reaction between a cyclitol-derived vinyl bromide and a D-galactose derived alkylborane affords the carbadisaccharide **42**. Ozonolysis of the cyclitol double bond and standard chemical transformations give the aza-*C*-disaccharide **43** as an analogue of 6-*O*-β-D-mannopyranosyl-D-galactose.[61]



42

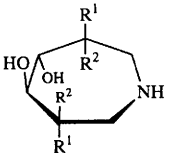


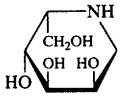
43

2,3-Di-*O*-benzyl-*N*-benzyloxycarbonyl-6-*O*-*tert*-butyldiphenylsilyl-1,5-dideoxy-1,5-imino-D-glucitol has been prepared as an acceptor and coupled to a phenyl 2-azido-1-thio-D-glucopyranoside

in order to prepare an aza analogue of the basic disaccharide unit found in heparin as a potential inhibitor of heparanase.[62]

Double nucleophilic attack of benzylamine on the *C*-2-symmetric 1,2:5,6-dianhydro-3,4-di-*O*-benzyl-D-mannitol, followed by hydrogenolysis, gave 1-deoxynojirimycin together with the 7-membered ring product **44**.[63] In a similar way 1,2:5,6-dianhydro-3,4-di-*O*-benzyl-L-iditol gave the 6- and 7-membered ring analogues **45** and **46**.

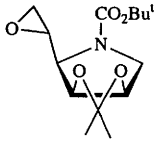


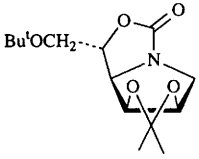


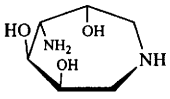
44 $R^1 = OH, R^2 = H$
46 $R^1 = H, R^2 = OH$

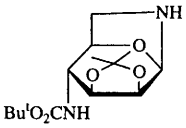
45

Acid catalysed opening of the epoxide **47** in the presence of benzylamine afforded 6-benzylamino-1,4,6-trideoxy-1,4-imino-D-mannitol as product, whereas in the absence of benzylamine the rearranged *tert*-butyl ether **48** was the major isolate. The same paper also describes the preparation of the 7-membered ring product **49** by reacting bicyclic hemiaminal **50** (prepared in six steps from benzyl-4-azido-4-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside) with sodium cyanoborohydride followed by hydrolysis.[64]









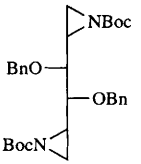
47 **48** **49** **50**

A short route to *N*-benzyl-1-deoxynojirimycin by a double reductive amination of D-*xylo*-hexos-5-ulose (5-*keto*-D-glucose) with benzylamine has been described. In a similar way reductive amination with various amines and D-*threo*-hex-2,5-diulose (5-*keto*-D-fructose) gives 2,5-anhydro-2,5-iminoalditols.[65]

Reaction of the L-*ido*-bis aziridine **51** with sodium azide and tetrabutylammonium iodide affords the pyrrolidine **52**, whereas reaction of **51** with thiophenol and sodium hydroxide affords pyrrolidine

53.[66]

6-Deoxy-L-galactose-1-phosphate aldolase-catalysed reaction of dihydroxyacetone phosphate with 2-azido-3-hydroxypropanal, followed by a phosphatase and hydrogenation, gives the 2,5-dideoxy-2,5-imino-alditol **54** as an α-galactosidase inhibitor.[67]



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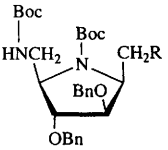
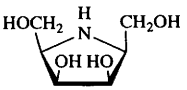


52 R = N_3
53 R = SPh

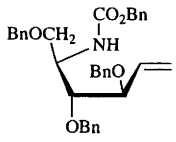


54

The synthesis of 2,5-dideoxy-2,5-imino-D-mannitol from 2,3,5-tri-*O*-benzyl-D-arabinose in which the key step is a mercury(II)-catalysed cyclization of amidoalkene **55**, followed by reaction with iodine to give bicyclic product **56**.[68]

Cleavage of the acetonide group of the acyclic α-aminoaldonic acid derived **57** with an acid resin, followed by hydrogenolysis, affords 2,5-dideoxy-2,5-imino-D-mannitol.[69]

Conversion of the piperidine derivative **58** to the pyrrolidine compound **59** on treatment with lithium azide has been described, and subsequently used in a synthesis of 1-acetamido-1,2,5-trideoxy-2,5-imino-D-glucitol, an *N*-acetylglucosaminidase inhibitor.[70]



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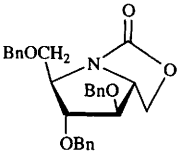

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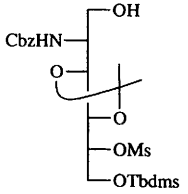

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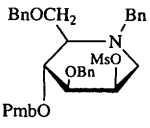

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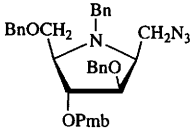


59

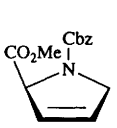
Excellent yields of polyhydroxypyrrolidines are produced by reductive elimination-amination

of 6-deoxy-6-bromoglucopyranosides in the presence of amines under ultrasound irradiation.[71]

Full details on the preparation of 2-acetamido-1,2,4-trideoxy-1,4-imino-D-galactitol have appeared (see Vol. 27, p 208, ref. 55). In addition the synthesis of 2-acetamido-1,2,4-trideoxy-1,4-iminoglucitol is also described.[72]

A synthesis of 1,4-dideoxy-1,4-imino-D-ribitol from the 3,4-dehydroproline derivative **60** has been reported.[73]

The dihydroxyproline compound **61** has been identified as a constituent of an adhesive protein from the mussel *Mytilus edulis*.[74]



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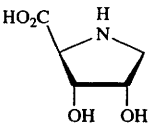

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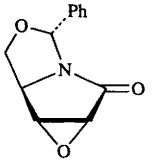


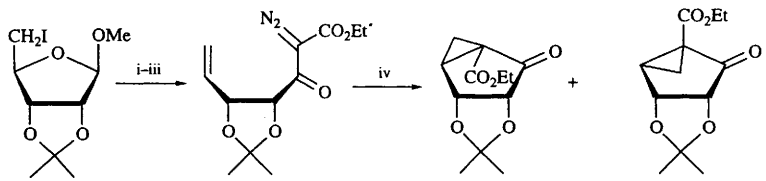
62

Reaction of the epoxypyrrolidine **62** with trifluoroacetic acid followed by acetic anhydride-pyridine then lithium aluminium hydride produces 1,4-dideoxy-1,4-imino-D-arabinitol.[75]

The preparation of deoxynojirimycin derivatives incorporating an imidazole ring is mentioned in Chapter 10 and quaternary 2,5-imino-hexitol derivatives are covered in Chapter 24.

2 Cyclitols

2.1 Cycloheptane, Cyclopentane, Cyclobutane and Cyclopropane Derivatives.- The synthesis of bicyclo[3.1.0]hexan-2-ones from a D-ribose derivative is depicted in Scheme 6.[76]



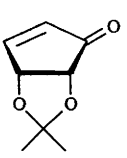
Reagents: i, Zn/EtOH; ii, N_2CHCO_2Et, $SnCl_2$; iii, TsN_3; iv, CuI

Scheme 6

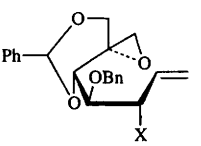
The same group has also prepared 4α-aminocyclopentane-1α,2β,3β-triol as an intermediate in the synthesis of carbocyclic nucleosides by way of an intramolecular cycloaddition of a nitrone-alkene derivative.[77]

Addition of bromomethyllithium to the cyclopentenone **63** effects a cyclopropanation of the double bond, whereas the saturated cyclopentanone equivalent reacts at the carbonyl group producing epoxide derivatives.[78] (See also Vol. 27, p. 212, ref. 77 for related work).

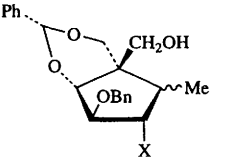
The radical cyclization of epoxy-alkenes using cyclopentadienyltitanium chloride (Cp_2TiCl) in THF has been described for the conversion of **64** into **65**.[79]



63



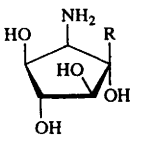
64 X = H or OBn



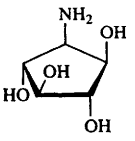
65 X = H or OBn

Coupling of the novel cyclitols **66-68** with tetra-*O*-benzyl-α-D-glucopyranosylisothiocyanate affords intermediate thioureas which on treatment with mercury (II) oxide undergo a rearrangement to the cyclic isoureas **69** after deprotection (illustrated with cyclitols **66** and **67** only).[80] In a similar way, the same group have converted a series of aminocyclopentanols by reaction with phenylisocyanate into the corresponding *N*-phenyl cyclic isourea derivatives and assessed their glycosidase activity.[81]

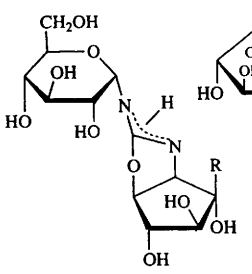
The synthesis of the (1→4) linked "trehazoloid" drivative **70** as an analogue of the potent α,α-trehalase inhibitor trehazolin, using a similar method of forming the cyclic isourea as described above, has been described.[82]



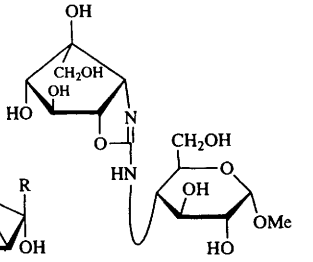
66 R = H
67 R = Me



68



69 R = H or Me



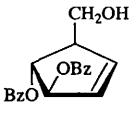
70

A full paper citing proof for the correct structure of trehazolin is mentioned in Chapter 19.

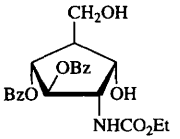
A synthesis of the insecticidal compound allosamidine (plus isomer) and aglycone allosamizoline has been reported. The key step in the formation of the allosamizoline involved the oxyamination of cyclopentene **71** with osmium tetroxide and sodio ethyl *N*-chlorocarbonate in the presence of mercury(II) trifluoroacetate to afford **72** together with regioisomers.[83] See also Chapter 19 for other syntheses of allosamizoline.

The Diels-Alder reaction of 1-(methylthio)-cyclopent-2,4-diene with (*R*)-(-)-mandelohydroxamic acid gave an intermediate oxazine which on treatment with mercury-amalgam afforded cyclopentene derivative **73** as a useful intermediate for the preparation of mannostatin A and its derivatives.[84]

In an alternative synthesis of mannostatin analogues, radical cyclization of dithioacetal **74** with tributyltin hydride-AIBN gave products **75**.[85] See also Chapter 24 for an improved synthesis of (+)-mannostatin A.



71



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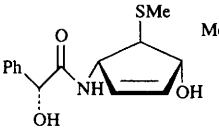
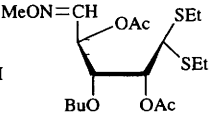


73



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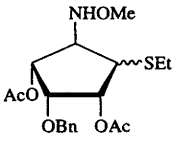

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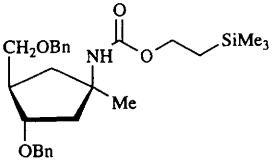
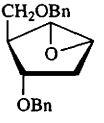


76



77

Full details (see Vol. 27, p. 213, ref. 80) on the synthesis of carba-α-D-arabinofuranose and of intermediate cyclopentane derivatives suitable for preparing nucleoside analogues have been reported.[86]

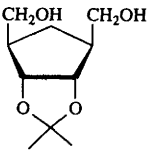
The aminocyclopentanol derivative **76** has been prepared, as an intermediate to 1'-methylcarbocyclic thymidine, from the cyclopentadiene derived epoxide **77** by several standard chemical transformations.[87]

The cyclopentane tetrol derivative **78** (from norbornadiene) has been resolved with horseliver alcohol dehydrogenase or with a lipase to provide ultimately the useful carbocyclic nucleoside building block **79**.[88]

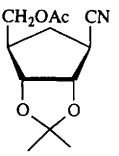
Norbornadiene and cyclopentadiene have both been converted into carbocyclic nucleoside precursor **80** through cyclopentene-ester-amide or ester-acid intermediates, respectively. Asymmetry was introduced by use of naproxen esterase.[89]

The preparation of the aminocyclopentene **81** as a carbocyclic nucleoside precursor has been reported. The approach started from D-glucono-γ-lactone and the key step involved a Diekmann cyclization of an adipate diester.[90]

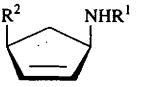
Racemic 6-oxabicyclo[3.1.0]hexan-3-*endo*-ol has been transformed into the cyclopentane derivative **82** as a precursor to the phosphonate isostere of carboxylic 5-bromovinyldeoxyuridine monophosphate.[91]



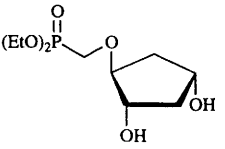
78



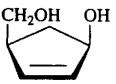
79



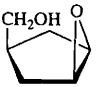
80 R^1 = Ac, R^2 = CO_2Me
81 R^1 = H, R^2 = CH_2OH



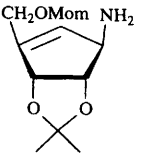
82



83



84



85

Full details have been reported (see Vol. 27, p. 213, ref. 78 for preliminary account) on the preparation of the diacetate of racemic cyclopentenol **83**.[92] The same group has also reported the synthesis of both enantiomers of **83** by reaction of *meso*-epoxyalcohol **84** with two equivalents of butyllithium in the presence of (1*S*,2*R*) or (1*R*,2*S*)-norephedrine.[92,93] Compound **83** is an important intermediate for preparing the carbocyclic nucleoside, carbovir.

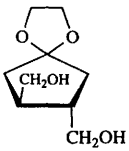
Two routes to the neplanocin A precursor **85** have been developed; one involving a multistep synthesis from methyl 2,3-di-*O*-isopropylidene-β-D-ribofuranoside; the other from a functionalized cyclopentane dicarboxylic acid-ester (see Vol. 25, p. 263, ref. 177).[94]

The carbocyclic nucleoside precursors **86** have been prepared from a known hydroxycyclopentanedicarboxylic ester (see H.-J. Gais *et. al.*, *J. Org. Chem.*, 1989, **54**, 5115).[95]

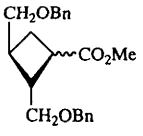
A non carbohydrate route to the cyclopentanone diol **87** in five steps from diethyl maleate has been described. Sequential reaction of **87** with benzyl bromide-sodium hydride, methanolic

hydrochloric acid, sodium methoxide-methylformate, tosyl azide-triethylamine and hν-methanol gave the cyclobutane derivative **88** as an intermediate for preparing 4-membered *C*-nucleosides.[96]

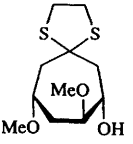
86 $R^1 = R^2 = Bz$, X = H, Y = OH
$R^1 = R^2$ Bz, X = OH, Y = H
$R^1 = R^2 =$  , X = OH, Y = H



87

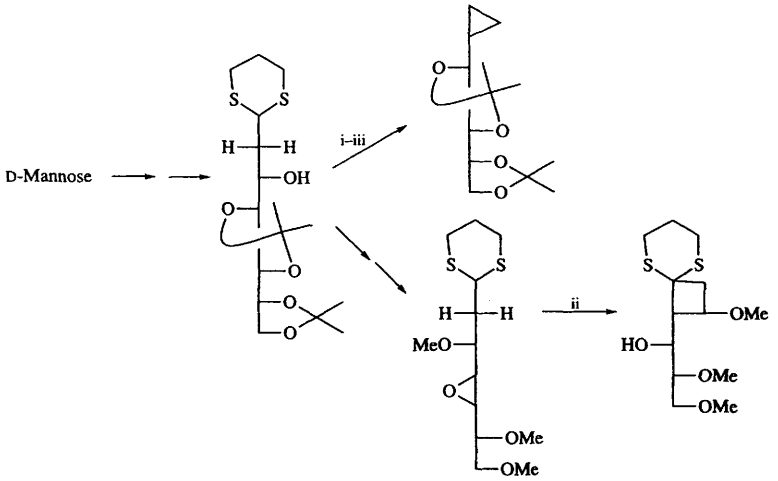


88



89

Scheme 7 illustrates a new route to cyclobutane and cyclopropane rings derived from D-mannose.[97] The preparation of larger rings has also been reported, including cycloheptane **89**.[98]



Reagents: i, TsCl, Py; ii, Bu^nLi; iii, Raney Ni,

Scheme 7

2.2 Inositols and Other Cyclohexane Derivatives.-A review on inositol liquid crystals, particularly *O*-alkylated derivatives of *myo*-, *scyllo*- and *chiro*-inositols has appeared.[99]

Three polyaza cleft molecules (non-carbohydrate) have been investigated as binding receptors for various tri-deoxycyclitols.[100]

The synthesis of validatol and 4-*epi*-validatol in which the cyclitol ring is formed by

cyclization of a dithiane anion onto a terminal epoxide in a related way to work described in refs. 97 and 98 above has been reported.[101]

The conformational preferences of inositols determined by employing *ab initio* calculations have been reported.[102]

The total synthesis of surugatoxin, a complex marine natural product containing a *myo*-inositol ring[103] and of neosurugatoxin which contains a β-D-xylopyranosyl-*myo*-inositol[104] have appeared.

A new synthesis of 1,4,6-tri-*O*-benzyl-*myo*-inositol using a regioselective benzylation of 1,2-*O*-isopropylidene-4,6-di-*O*-benzyl-*myo*-inositol[105] and the regioselective *O*-alkylation of *myo*-inositol derivatives with alkyl halides under solid-liquid phase transfer catalysis[106] have been described.

Acylation of *myo*-inositol or its 1,2-acetal derivatives with chloroacetyl chloride, chlorobutanoyl chloride or nicotinoyl chloride gives tetra-acetate or hexa-acetate derivatives with antiischemic activity.[107]

An improved preparation of 1,2-*O*-isopropylidene-*myo*-inositol directly from *myo*-inositol with 2,2-dimethoxypropane-H^+ in DMSO has been achieved.[108] Also described is a synthesis and resolution *via* camphanate esters of racemic 1,4-di-*O*-benzyl-isopropylidene *myo*-inositol.

Alkylation, acylation, sulfonylation and silylation of 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol or 1,2:5,6-di-*O*-isopropylidene-*myo*-inositol take place mainly at the *O*-3 position.[109]

1,2:5,6-Di-*O*-cyclohexylidene- and 1,2:3,4-di-*O*-cyclohexylidene-*myo*-inositol have been kinetically resolved with lipases,[110] 1,4,5,6-tetra-*O*-benzyl-*myo*-inositol has been resolved *via* a (1*S*)-(-)-camphanic ester of the 2,3-*O*-dibutylstannylene derivative.[111] Resolution of carbohydrate-derived *myo*-inositol diastereomers by HPLC has also been reported.[112]

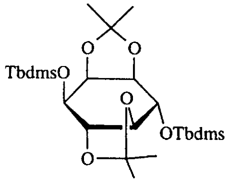
The *myo*-inositol derivative **90** has been made by a samarium diiodide-induced reductive coupling of dialdehyde **91** followed by reaction with 2,2-dimethoxypropane-H^+.[113]

Swern oxidation of 2,3,4,5-tetra-*O*-benzyl-L-iditol (prepared from L-sorbose), followed by treatment with samarium diiodide afforded 3,4,5,6-tetra-*O*-benzyl-D-*myo*-inositol.[114]

Reaction of *meso*-2,5-di-*O*-benzoyl-*myo*-inositol with (2*S*,2'*S*)2,2'-dimethyl-3,3',4,4'-tetrahydro-6,6'-bi-2H-pyran gives the "dispoke" compound **92** from which 1D-1,2,5,6-tetra-*O*-benzyl-*myo*-inositol can be made.[115] 1L-1,2,5,6-Tetra-*O*-benzyl-*myo*-inositol can be prepared in a similar way by using (2*S*,2'*S*)2,2'-diphenyl-3,3',4,4'-tetrahydro-6,6'-bi-2H-pyran, which forms the intermediate regioisomeric "dispoke".

The absolute configuration of (+)-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol, which seems to have caused some confusion in the literature, has been confirmed as 1D.[116]

The protected racemic *myo*-inositol compound **93** can be alkylated with benzyl bromide or allyl bromide in the presence of silver(I) oxide to give **94** which are thought to arise due to formation of a complex which leads to loss of the axial benzoate protecting group.[117]



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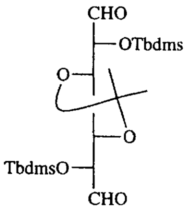

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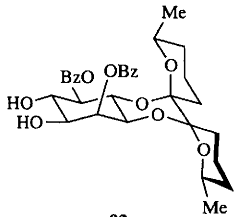

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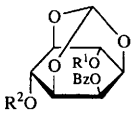
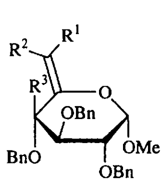
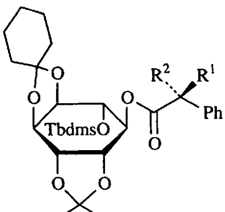


93 $R^1 = Bz$, $R^2 = H$
94 $R^1 = R^2 = Bn$ or All

2,3,6-Tri-*O*-benzyl-D-*myo*-inositol has been achieved from a protected α-D-*xylo*-hex-5-enopyranoside by way of a Ferrier reaction. In a similar way the branched-chain sugar **95** was used as starting material for the synthesis of (-)-laminitol and mytilitol.[118] On the mechanism of the Ferrier reaction, it has been observed that there is loss of stereochemistry at *C*-6 in the deuterated eno-pyranoside **96** during the formation of the carbocyclic ring.[119]



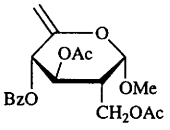
95 $R^1 = R^2 = H$, $R^3 = Me$
96 $R^1 = R^3 = H$, $R^2 = {}^2H$



97 $R^1 = H$, $R^2 = OH$
98 $R^1 = OH$, $R^2 = H$
99 $R^1 = OH$, $R^2 = CH_2C(O)Bu^t$ (Ph)

The α-hydroxy esters **97** and **98** have been prepared by reduction of the corresponding α-keto ester (formed by reaction of benzoylformic acid chloride with 1L-3-*O*-(*t*-butyldimethylsilyl)-1,2:5,6-di-*O*-cyclohexylidene-*chiro*-inositol) with K- or L-selectride, respectively.[120] The same group have also added various nucleophiles [*eg.* CH_2=C(^{t}Bu)(OTms) or CH_2=C(Ph)(OTms)] to the α-keto esters in the presence of tin(IV) tetrachloride to give products **99**.[121]

Several papers have appeared directed towards the synthesis of the β-glucosidase inhibitor, cyclophellitol and its derivatives. In one case a Ferrier reaction on branched-chain sugar **100** has been used to construct the cyclohexane ring;[122] in another, quinic acid has been used as starting material.[123,124] (See Vol. 26, p. 199, ref. 93 and Vol. 25, p. 209, ref.62 for similar work). Radical cyclizations of iodo-acetylene **101** with tributyltin hydride-AIBN affords a bicyclic drivative which, on treatment with dichlorodicyanoquinone (DDQ), sodium borohydride and *t*-butyldimethylsilyl chloride affords cyclitol **102**, which can be used to make cyclophellitol.[125]



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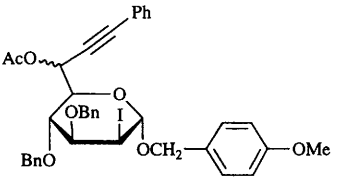

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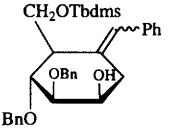
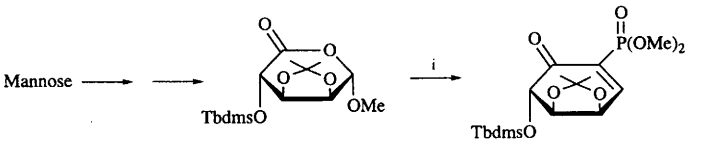


102

Scheme 8 illustrates a modified Fujimoto-Belleau approach to the synthesis of mannose derived cyclitols.[126]

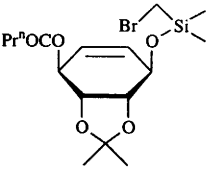


Reagents: i, $(MeO)_2P(O)Me$, Bu^nLi

Scheme 8

A preliminary report[127] and a full paper[128] on the synthesis of carba-*allo*-, *gulo*-, *manno*- and *talo*-pyronosides have appeared. Two general methods have been used. For example, the Stork

radical cyclization of bromomethylsilyl ether **103** with tributyltin hydride-AIBN followed by treatment with potassium fluoride and hydrogen peroxide gives the protected carba-β-L-*gulo*-pyranoside **104**. Alternatively a [2,3]Wittig rearrangement of an allyl tributylstannylmethyl ether, eg. **105** with butyllithium affords carbocycle **106** which can be further elaborated into carba-α-D-mannopyranose.



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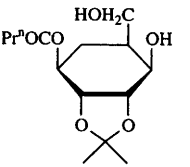

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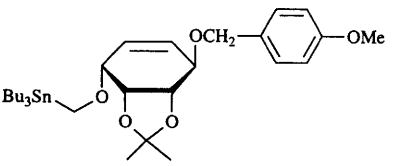

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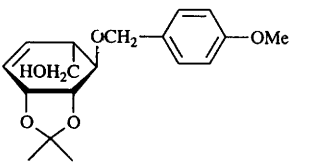
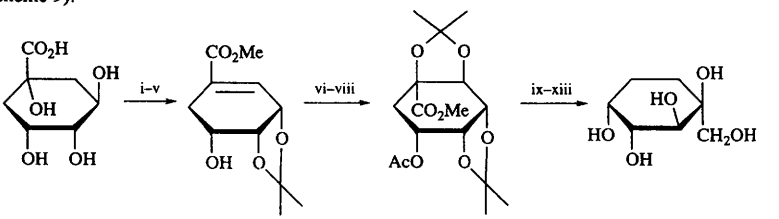


106

An interesting synthesis of carba-β-D-fructopyranose has been reported from quinic acid (Scheme 9).[129]

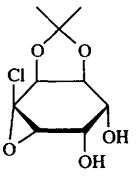


Reagents: i,  , H$^+$; ii, NaOMe, MeOH; iii, PCC; iv, $NaBH_4$; v, Me_2CO, H$^+$; vi, Ac_2O, Py; vii, OsO_4; viii,  ; ix, DIBAL; x, TbdmsCl; xi, PhOC(S)Cl, Py; xii, Bu_3SnH; xiii, H_3O^+

Scheme 9

Full details on the synthesis of carba-α- and β-D-glucopyranose and the carba-aminosugar validamine from D-glucurono-6,3-lactone have been reported.[130] (See Vol. 27, p. 216, ref. 95 for preliminary work).

The microbial oxidation (*Pseudomonas putida*) of halogeno benzenes continues to be a useful source of cyclitols. Thus, *neo*-inositol has been synthesized from the epoxide **107**, which in turn has been prepared by an interesting oxidation of 1-chloro-5,6-*cis*-isopropylidenedioxycyclohexa-1,3-diene using potassium permanganate.[131] Epoxide **107** has also been transformed into pyrazines like **108** on reaction with ammonia. The same cyclohexa-1,3-diene takes part in a Diels-Alder reaction with dienophiles like benzoquinone to afford *endo*-adducts.[132] A full account of the synthesis of (+)-lycoricydine by way of an acylnitrosyl cycloaddition with 1-bromo-5,6-*cis*-isopropylidenedioxycyclohexa-1,3-diene has been reported (See Vol. 26, p. 202, ref. 118 for a preliminary account).[133]



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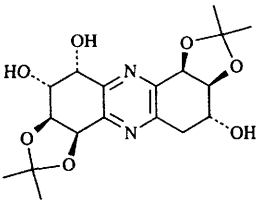

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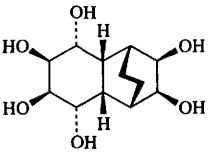


109

The preparation of racemic bicyclic analogues of conduritol A such as **109** has been achieved by cycloaddition of benzoquinone to 1,3-cyclohexadiene followed by hydride reduction and dihydroxylation.[134] The same paper also describes the synthesis of six isomeric conduritols A-F by modifications of existing routes, and tests them for their ability to modulate the release of insulin from isolated pancreatic cells.

The synthesis of conduritol E by a Sharpless dihydroxylation of 1,2-*O*-benzylidene-*cis*-cyclohexa-3,5-diene-1,2-diol (made from benzene by microbial oxidation) has been reported[135] together with a paper correcting the original asssignments in reference. 135.[136]

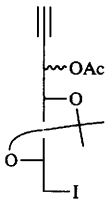
(+)-Conduritols C and (-)-C[137] and E and F[138] have been synthesized from D-galactose and D-mannose, respectively, using the Ferrier reaction to form the carbocyclic ring.

A short route to toxocarol by way of photooxygenation of cyclohexa-1,3-diene[139] and one to racemic conduritol B[140] from benzoquinone by reaction with one equivalent of bromine, hydride

reduction, acetylation, displacement of bromide with silver or potassium acetate followed by deacetylation have been described.

The iodoacetylenes **110** (derived from tartaric acid) undergo a 6-*endo*-dig. radical cyclization on treatment with tributytin hydride-AIBN. Deacetylation and oxidation to cyclohexenone **111** was then carried out.[141]

1,4-Additions of Grignard reagents to epoxyalkene **112** in the presence of copper(I) iodide have been reported.[142]



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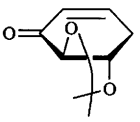

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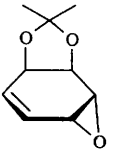

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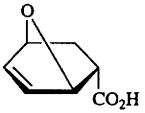


113

The preparation of a glycosylceramide derived from 2,3:4,6-di-*O*-isopropylidene-β-valienamine as an analogue of glucosylceramide[143] and of some carbaglycosylamides[144] as glycolipid analogues have been described.

A synthesis of validamine and isomers has been achieved by a stereocontrolled nucleophilic epoxidation of polyhydroxylated cyclohexenyl sulfones obtained from (phenylsulfonyl)-7-oxabicyclo[2.2.1]heptane, itself derived from compound **113**.[145]

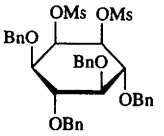
myo-Inositol has been converted into racemic 1,2-diamino-1,2-dideoxy-*myo*-inositol by way of a displacement reaction of dimesylate **114** with sodium azide.[146]

Racemic conduramines have been prepared from pyrrole, the key step being treatment of bicyclic derivative **115** with hydride then strong base to give **116**.[147]

The preparation of the *muco*-nucleocyclitol **117** has been described.[148] (See Vol. 26, p. 202, ref. 119 for related work).

The preparations of Schiff bases between primary amine groups in the aminocyclitol kasugamine and various chromophoric aldehydes have been effected and their c.d. spectra recorded.[149]

In the shikimic acid area, the conversion of D-glucose into the industrially important compound adipic acid using mutant enzymes derived from the shikimate pathway has been reported.[150]



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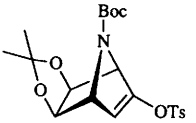

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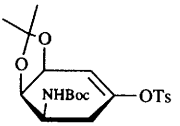

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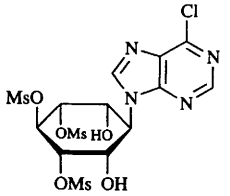

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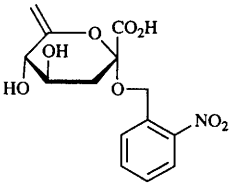

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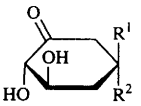


119 $R^1 = CO_2H$, $R^2 = OH$
120 $R^1 = OH$, $R^2 = CO_2H$

Photoconversion of **118** into cyclitols **119** and **120** has been observed.[151] However only product **119** is formed when **118** is treated with 3-dehydroquinate synthase prompting the question does the enzyme catalyse **118** to **119** or just provide a conformational template to prevent formation of **120**?

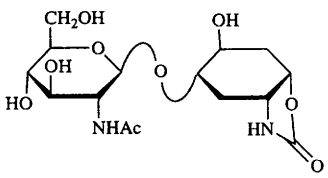
The use of the time-resolved rotational echo double resonance (REDOR) solid state n.m.r. experiment has been used to look for intermediate dipolar coupling in the transient enzyme-intermediate complex of 5-enolpyruvylshikimate-3-phosphate synthase.[152]

The synthesis of carbadisaccharide **121** which is related to the D-allobiose disaccharide of allosamidine and hence to carbocyclic analogues of the insecticide, have been described. The aminocyclitol unit was constructed using a Ferrier reaction.[153]

The cyclitol derived glycoconjugate analogue **122** has been prepared by Lewis acid promoted coupling of alcohol **123** with epoxide **112** followed by dihydroxylation and removal of the protecting groups.[154]

The cysteinyl *myo*-inositol drivative **124** has been isolated from a *Streptomyces* species.[155]

See Chapter 21 for an n.m.r. study on a series of carbadisaccharides.



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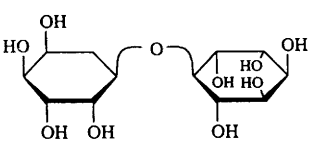

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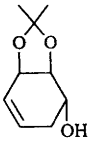

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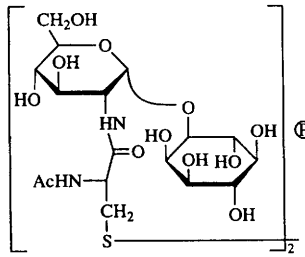

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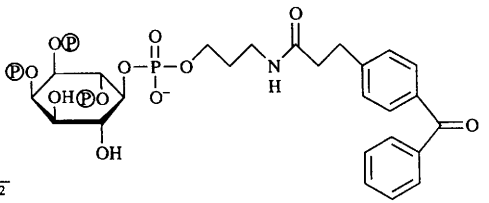


125

2.3 Inositol Phosphates and Derivatives.-The synthesis of D-*myo*-inositol 3,4,5,6-tetrakisphosphate as previously reported (Vol. 26, p. 206, ref. 154) was in fact of the enantiomer.[156]

A novel inositol phosphate, L,L-di-*myo*-inositol-1,1'-phosphate has been isolated from *Pyrococcus woesei* and its structure confirmed by synthesis.[157]

The synthesis of enantiomerically pure *myo*-inositol phosphates by resolution methods continue to be reported (see also section 2.2). By this approach, D-*myo*-inositol 1,5,6-trisphosphate *via* a camphor dimethylacetal[158] and both enantiomers of *myo*-inositol 1,3,5-trisphosphate[159] as well as benzyl protected derivatives of 1D-*myo*-inositol 2,4,5-trisphosphate[160] (see also Vol. 26, p. 206, refs. 157-159 for related work) by way of camphamate esters, have been prepared. Kinetic resolution of *myo*-inositols using lipases have led to D-*myo*-inositol 1,4,5-trisphosphate,[161] D-*myo*-inositol 1,4,6-trisphosphate,[162] D- and L-*myo*-inositol 1,4,5,6-tetrakisphosphate[163] and D-*myo*-inositol 1-phosphate[164].

The synthesis of racemic *myo*-inositol 1,4,5-, 2,4,6- and 1,3,5-trisphosphate by a regioselective benzoylation of a *myo*-inositol 1,4-di-*O*-benzoate derivative has appeared.[165]

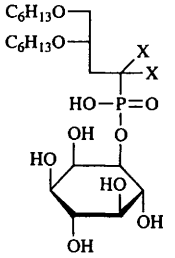
The synthesis of *myo*-inositol tetrakisphosphate derivative **125** as an affinity probe for *myo*-inositol 1,2,6-trisphosphate receptors, has been prepared using an advanced intermediate reported in Vol. 25, p. 208, ref. 54.[166]

Compound **126** has been prepared as an isosteric and isopolar inhibitor of a phosphatidylinositol-specific phospholipase C (PI-PLC) from *Bacillus cereus*.[167]

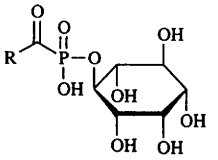
The acylphosphonyl derivative **127**, as an inhibitor of PI-PLC has also been reported.[168] (See also Vol. 27, p. 203, ref. 154 for related work). A short synthesis of *myo*-inositol 3,4,5-trisphosphate 1-glycerophosphate[169] and of D-2-deoxy-3-fluoro (and 3-chloro) -*myo*-inositol 1-glycerophosphate[170] derivatives have also been reported.

The synthesis of 3-*O*-alkylated (Me, Et, ^{n}Pr) *myo*-inositol 1,4,5-triphosphate as potent receptor ligands and enzyme inhibitors[171] and of 3-amino-3-deoxy-*myo*-inositol 1,4,5-triphosphate as a pH dependent partial antagonist at the *myo*-inositol 1,4,5-trisphosphate receptor of neuroblastoma cells[172] have been described.

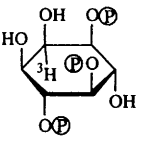
2-Substituted (eg aminobenzoyl) *myo*-inositol 1,3,4,5-tetrakis- and 1,3,4,5,6-pentakis-phosphate[173] and the tritiated derivative **128**[174] have been prepared, the latter by reduction of the corresponding benzyl protected inosose with potassium borotritiide followed by hydrogenolysis.



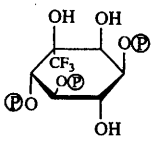
126 X = H or F



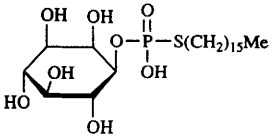
127 R = n-$C_{17}H_{35}$, n-$C_{15}H_{31}$



128



129



130

The incorporation of a bulky axial group into the 3-position of *myo*-inositol 1,4,5-trisphosphate derivative **129** leads to a small decrease in the Ca^{2+} binding and releasing activity compared with that of D-*myo*-inositol 1,4,5-trisphosphate, whereas 1L-*chiro*-inositol 1,2,3,5-tetrakisphosphate is more than seven hundred fold less active.[175]

The syntheses of D-3-modified (Cl, Br, OMe) *myo*-inositol 1,4,5 trisphosphates as probes for the D-1,4,5 IP_3/D-1,3,4,5-IP_4 functional interface have been described.[176] In the case of the halogeno derivatives, the known (A.P. Kozikowski *et. al.*, *Cancer Chemother. Pharmacol.*, 1991, **29**, 95) D-3-deoxy-3-halogeno-*myo*-inositols were the starting materials and methylation of the known (J.P. Vacca *et. al.*, *J. Am. Chem. Soc.*, 1987, **109**, 3478) D-4-*O*-benzyl-3-*O*-camphanoyl-1,2:5,6-di-*O*-cyclohexylidene-*myo*-inositol provided access to the 3-*O*-methyl derivative.

The preparations of some 2-amino-2-deoxy-α-D-glucopyranosyl-*myo*-inositol 1- and 1,2-cyclic phosphates have been reported.[177] (see Vol. 26, p. 24, ref. 63 for similar work).

A number of phosphorothioate and thiophosphate derivatives of *myo*- and *chiro*-inositols have appeared. Thus, 1D-[178] and racemic-[179]*myo*-inositol 1,4,5-trisphosphate 3-phosphorothioate, 1L-*myo*-inositol 1,4,5-trisphosphorothioate,[180] 1L-*chiro*-inositol 1,4,6-trisphosphorothioate[181] and the thiophosphate analogue **130** of phosphatidylinositol[182] have been described.

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19
Antibiotics

1 Amino-Glycosides and Aminocyclitol Derivatives

Molecular modelling studies of the ABC ring system of calicheamycin γ_1^I oligosaccharide has been reviewed,[1] a convergent total synthesis of calicheamycin γ_1^I, using a previously reported tetrasaccharide precursor, has been described,[2] and the three dimensional structure of the DNA-calicheamycin complex has been probed by construction of models involving the thiosugar-thiobenzoate-rhamnose moiety of calicheamycin.[3]

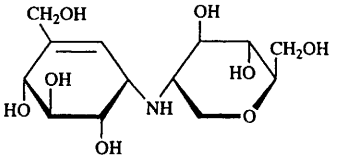
A total synthesis of (±)-allosamizoline from a symmetrical trisubstituted cyclopentene has been reported,[4] and a synthesis of allosamidin and its (1→3) linked isomer includes a review of the preparation of the starting aminocyclitol and disaccharide moieties.[5] The synthesis of allosamizoline and allosamidin and isomers is also mentioned in Chapters 3 and 18.

Chiral β-lactams prepared from a 6-imino-D-galactose derivative have been used as synthons for 6-*epi*-lincosamine.[6]

A series of azido- and fluoro-analogues of sannamine and sporamine have been prepared from cyclohexane diepoxides derived from benzene.[7]

A 2,6-dideoxy-2-methylamino-D-galactose thioglycoside has been used to prepare a neocarzinostatin analogue for apoprotein bonding studies.[8]

Salbostatin **1**, a trehalose inhibitor, has been isolated from *S. albus*, ATCC 21838.[9]



1

Syntheses have been reported for trehazolin,[10] the β-anomer of trehazolin[11] and of 5-epi-trehazolin,[12] the required azido-cyclopentitol intermediates being made in multistep procedures from D-glucose.

Full details of the synthesis of trehazolin analogues have been published (see Vol. 27, Chap.

19, ref. 99), [13] and such syntheses are also referred to in Chapter 18.

Further GlcNAc-GalUA disaccharide analogues of moenomycin A have been synthesized from allyl glucoside precursors, and proved to be biologically inactive.[14] (See also Vol. 27, Chap. 19, ref. 16).

Dibekacin has been converted to 2″-amino-2″-deoxy-arbekacin and five analogues, some showing potent antibacterial activity.[15] ^{1}H and ^{13}C N.m.r. studies on aminoglycoside antibiotics have been reported, which served to confirm the conformations of *N*-demethylclindamycin and some cyclic derivatives.[16]

A review on semi-synthetic antibiotics invulnerable to enzymes of resistant bacteria includes references to aminoglycoside derivative.[17]

The synthesis of purpurosaminide C derivatives is mentioned in Chapter 9.

2 Anthracycline and Other Glycosylated Polycyclic Antibiotics

A new anthracycline antibiotic, cororubicin, obtained from a *micromonospora* strain, contains a 2-deoxyfucose-decilonitrose-diginose trisaccharide unit.[18] Arugomycin has a similar structure with an additional tetrasaccharide substituent on the aglycon (See Vol. 17, Chap. 19, p. 176-7).

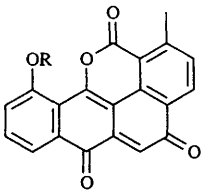
4′-Deoxy-3′-homo-daunosamine analogues of anthracyclines containing 3-aminomethyl-2,3,4,6-tetradeoxy-α-L-hexosyl compounds have been synthesized, giving products with potent cytotoxic activity.[19]

The glycosidic component of a pregnane glycoside obtained from the bark of *Marsdenia condurango* is an important contributor to its cell differentiation inducing ability. It contains a 6-deoxy-3-*O*-methyl-β-D-allose·β-D-oleandrose-β-D-cymarose trisaccharide unit.[20]

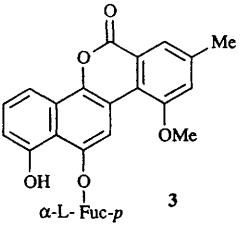
A saponin isolated from the Zimbabwean plant *Phytolacca dodecandra*, shown to have molluscicidal activity, contains a β-Gal(1→3)-β-Glc disaccharide unit.[21]

Chrymutasins, novel antitumour antibiotics from a mutant strain of *S. chartreusis*, have the general structure **2**, with disaccharide or trisaccharide substituents.[22] BE-12406A **3**, a new antibiotic from a streptomyces strain, has been synthesized.[23]

A new naphthoquinone antibiotic, 3′-O-α-D-forosaminyl-(+)-griseusin A, obtained from *S. griseus*, has the structure **4**.[24] Another streptomyces strain (sp. KB10) has yielded the *C*-glycosides menoxymycins A **5** and B which has an acyclic ester group in place of the lactone ring.[25]



2 R = Fucosyl-Fucosyl,
Digitalosyl-Fucosyl,
or
Digitalosyl-Fucosyl-Fucosyl



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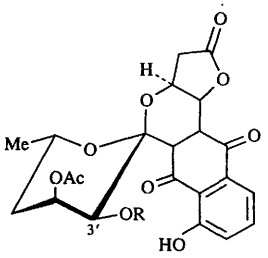
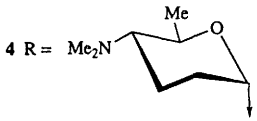
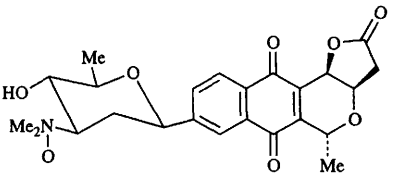




4 R = Me_2N



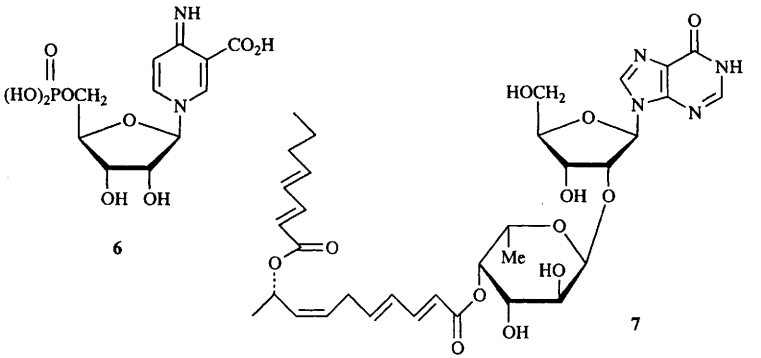
5

A total synthesis of both enantiomers of the *C*-glycoside antibiotic gilvocarcin M utilizes an O→C glycoside rearrangement. The natural enantiomer was synthesized from D-fucose.[26] The total synthesis of aryl *C*-glycoside antibiotics has been reviewed.[27]

The synthesis of benzanthracycline analogues of 4-demethoxydaunorubicin is mentioned in Chapter 3.

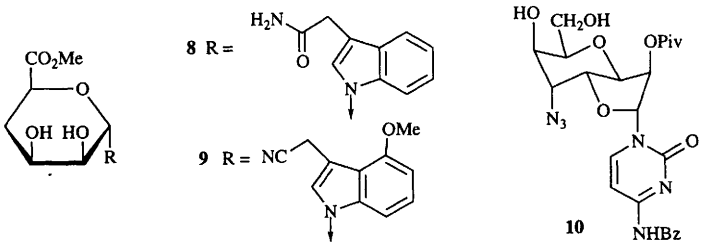
3 Nucleoside Antibiotics and Related Compounds

Conventional syntheses have been reported for 5-(bromoethynyl)-2′-deoxyuridine [28] and for oxanosine and its 5-thio analogue.[29] Clitidine 5′-mono-phosphate **6**, a toxic pyridine nucleotide, has been isolated from a Japanese toadstool, which had previously yielded the corresponding nucleoside.[30] 3′-*O*-(β-D-Galactopyranosyl)-ara-C and 3′-*O*-[β-D-galactopyranosyl-(1→4)-*O*-(β-D-galactopyranosyl)]-ara-C have been isolated from the culture filtrate of *Sporobolomyces singularis*.



6 **7**

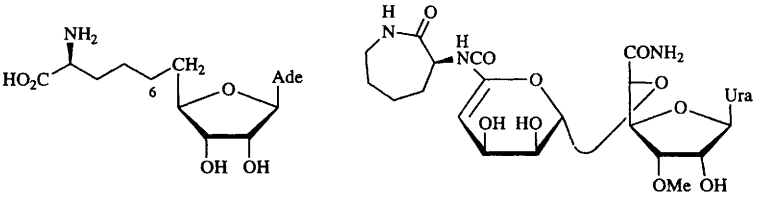
The same yeast can also be used to prepare 3′-O-β-D-galactosyl derivatives of adenosine and inosine.[31] Further details of the structure of adenophostins A and B have been reported.[32] (See Vol. 27, Chap. 19, ref. 52). The cytotoxic and antimicrobial nucleoside shimofuridin A **7** has been isolated from a marine tunicate.[33] References to AZT derivatives and to 2′-deoxy-2′-fluorouridine derivatives are made in Chapter 20.



8 R = **9** R =

10

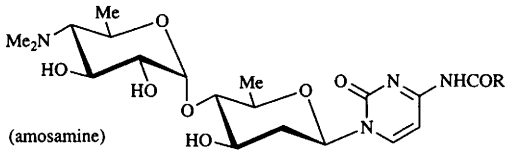
Total syntheses of thymine polyoxin C[34] and polyoxin J[35] have been reported. Syntheses have also been reported for neosidomycin **8** and the related antibiotic SF-2140 **9**, thereby confirming their structures.[36]



11 **12**

The octosyl nucleoside **10** has been made as an intermediate for preparing ezomycin A_1,[37]

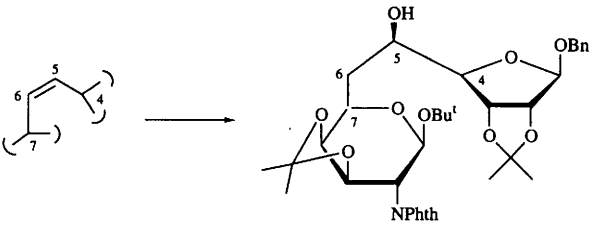
6-deaminosinefungin **11** and 6-(*S*)-methyl-6-deaminosinefungin have been synthesized by conventional methods,[38] and a *talo*-nucleoside has been used to prepare capuramycin **12**.[39]



13

Spectral methods have been used to characterize cytoaminomycins A-D **13**, new anticoccidal agents obtained from *S. amakusaensis*; they differ from oxyplicacetin, and each other, only in the amide residue of the pyrimidine ring.[40]

Full details of the synthesis of tunacamycin have been published[41] (See Vol. 27, Chap. 19, ref. 79), and the syntheses of the tunicamine derivative **14**,[42] and a related deaminotunicaminylur-acil compound,[43] utilize stereoselective hydroboration of a Wittig product to introduce the hydroxy group at C-5 (Scheme 1).



14

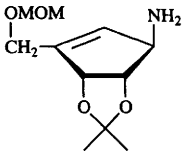
Scheme 1

Improved syntheses of showdomycin and 2′-deoxyshowdomycin have been described, and the paper includes an X-ray single crystal structure for 1-benzyl-2′-deoxyshowdomycin.[44] The pH dependence of the ^{13}C chemical shifts of formycin has been investigated, and conformational conclusions drawn.[45]

The biosynthesis of aristeromycin from neplanocin A has been studied, particularly the stereochemistry of the reduction step, in which the 4-*pro-R* hydrogen atom of NADPH becomes the 6′-β-hydrogen in the antibiotic.[46]

Syntheses have been recorded for neplanocin A using two alternative routes to the

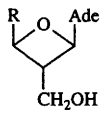
aminocyclopentenol intermediate **15**,[47] while another route uses a cyclopentenone precursor,



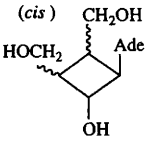
15

which was also used to make other purine analogues of neplanocin A.[48] The same cyclopentenone precursor has also been used to prepare (6′*R*) and (6′*S*)-6′*C*-methyl-3-deazaneplanocin A.[49] 2-Chloro- and 2-fluoroneplanocin A have also been prepared, the latter showing marked antibiotic activity.[50]

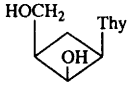
Analogues of oxetanocin A to have been synthesized are the alkylphosphonic acid derivatives, **16**,[51] and carbocyclic analogues **17**[52] and **18**[53]. Other analogues of oxetanocin are mentioned in Chapters 18 and 20.



16 R = $CH(OH)PO(OH)_2$, $(CH_2)_2PO(OH)_2$, $(CH{=}CHPO(OH)_2$, $(CH_2)_3PO(OH)_2$



(±)-**17**

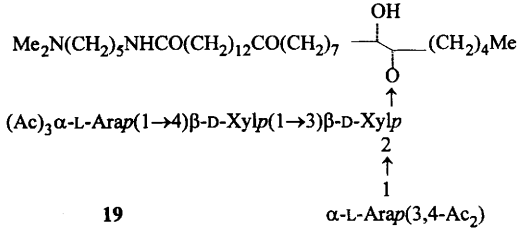


18

4 Miscellaneous Antibiotics

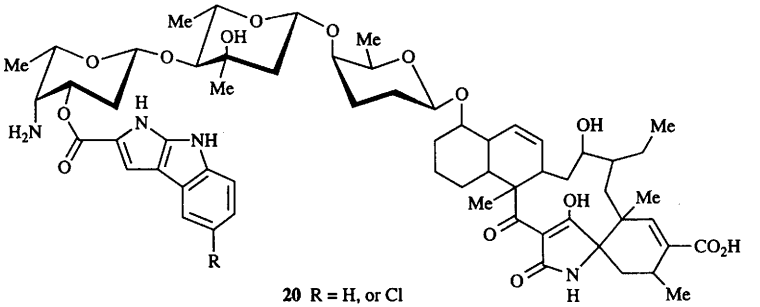
Orthosomycin antibiotics have been extensively reviewed.[54]

Erylusamines, a complex of interleukin receptor antagonists isolated from the marine sponge *Erylus placenta*, contain a branched tetrasaccharide with varying acetylation attached to a fatty alcohol aglycone, *e.g.* erylusamine E **19**, the most potent component.[55] Related antibiotics of the



19

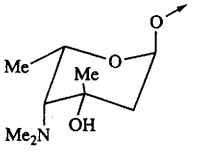
glykenin family produced by *Basidiomycetes* sp. have been separated by a combination of chromatographic techniques.[56]



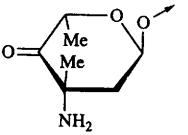
20 R = H, or Cl

Pyrroindomycins **20** are new potent antimicrobial antibiotics produced by *S. rugosporus*. The absolute configuration of the compound is unknown.[57]

A new thiopeptide antibiotic, glycothiohexide α, isolated from the broth of a "*Sebekia*" sp., contains the amino-sugar 4-dimethylamino-3-*C*-methyl-2,4,6-trideoxy-α-L-*lyxo*-hexopyranoside



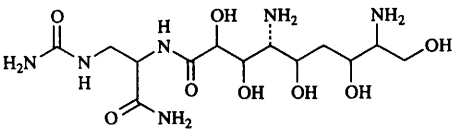
21



22

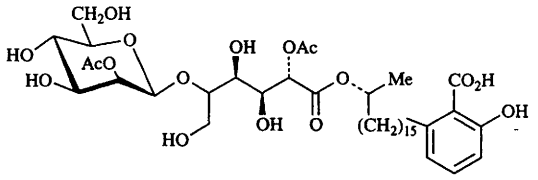
21 glycosidically linked to a bicyclic peptide core, and is a close relative of nosiheptide and antibiotic S-54832A.[58] Balkimycin is another new vancomycin group glycopeptide antibiotic, containing D-glucose and dehydrovancosamine **22**, the latter being hydrated in solution.[59] A new antifungal antibiotic, cepacidine A, produced by *Pseudomonas cepacia*, is a glycopeptide containing a single xylopyranosyl unit.[60]

Aldecalmycin, a new antimicrobial from *S.* sp. MJ147-72F6, has been characterized as a β-D-glucopyranoside of a complex *trans*-decalinol.[61,62]



23

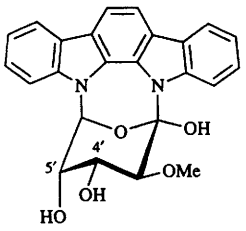
The antibiotic zwittermicin A **23**, isolated from *Bacillus cereus* UW 85, with alkali, yielded the γ-lactam of a 4,8-diamino-4,6,8-trideoxynononic acid.[63] Caloporoside **24**, a new inhibitor of



24

phospholipases C from *Caloporus dichrous*, contains a 2-*O*-acetyl-β-D-mannopyranosyl unit unusually 1,5-glycosidically attached to a 2-*O*-acetyl-D-mannonic ester derivative.[64]

A new protein kinase inhibitor, 4'-demethylamino-4',5'-dihydroxystaurosporine (MLR-52)



25

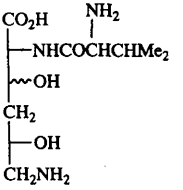
25, obtained from a *streptomyces* strain, appears formally to be a derivative of 4-*O*-acetylyxuronic acid.[65]

N-Methylstreptothricin D has been isolated from a *Streptomyces* strain (SNU 8810-111).[66]

A mutant strain of *S. chartreusis* has produced a complex of antibiotics, chrymutasins, which are analogues of chartreusins, with the same disaccharide or trisaccharide chains of fucose and/or digitalose, but with modified aglycons.[67]

The synthesis of the trimeric cyclic saccharide antibiotic anthrobacilin A has been reported.[68]

The structure of antibiotic Tü1718B has been examined by synthesis of the epimers **26**.[69]



26

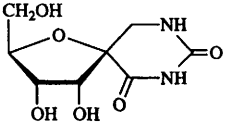
The allyl ether of the aglycon of hygromycin A has been synthesized.[70](See Vol. 26, Chap. 19, p. 219). Another synthesis of hygromycin A and related compounds has been reported.[71]

Matteuorienates A and B, potent inhibitors of aldose reductase, are *C*-flavone glucoside dicrotalic acid esters.[72]

Antiviral, cytotoxic and anti-ATPase activities of 14 synthetic digitoxigenyl glycosides have been correlated with each other.[73] The synthesis and antimicrobial properties of methyl-3-*O*-alkyl-D-glucopyranosides have been described.[74] Carbohydrate *N,N*-bis(2-chloroethyl)phosphoramidates have been prepared, and some showed antitumour activity.[75]

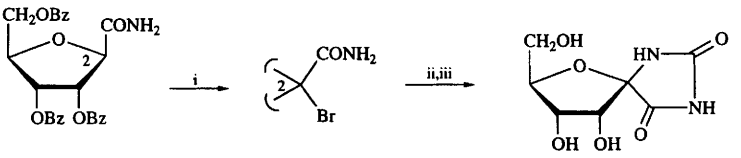
An improved, three-step synthesis of *N*-butyl-1-deoxynojiromycin from D-glucose has been described, involving an enzymic oxidation of N-butylglucamine.[76] A synthesis of *N*-[^{11}C]methyl-1-deoxynojirimycin and its *manno* epimer has been reported in a study of glycosidase inhibition.[77] 1,3,4-Trideoxy-3-fluoronojirimycin and its *manno* epimer have been characterized and stereochemically distinguished by mass-analyzed ion kinetic energy spectroscopy.[78]

Trifluoroacetamide analogues of siastatin B have been prepared, and show anti-tumour activity.[79] The synthesis of mannostatin A and its derivatives is mentioned in Chapter 18, and an improved synthesis of (+)-mannostatin A is referred to in Chapter 24.



27

The uracil analogue **27** of hydantocidin has been synthesized, but it showed no herbicidal activity.[80] A direct enantioselective synthesis of (+)-hydantocidin **28** has been described, utilizing a 2,5-anhydrohexonamide precursor (Scheme 2).[81]



28

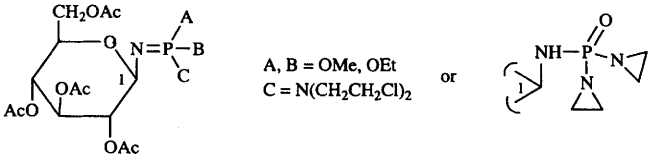
Reagents: i, NBS, Bz_2O_2, CCl_4; ii, AgOCN, $MeNO_2$; iii, LiO_2H, THF, H_2O

Scheme 2

A 2D n.m.r. procedure has been used to determine the orientation of sugar units in macrolide antibiotics[82] and other references to conformations of macrolide antibiotics are given in Chapter 21.

A synthesis of validamine and related carbasugars from 7-oxabicyclo[2,2.1]heptane derivatives has been described.[83]

The synthesis of 2,3,4,6-tetra-*O*-acetyl-1-β-D-glucosaminophosphonic acid derivatives containing cytotoxic groups was effected from the corresponding glucosylazide and gave compounds such as **29**.[84]



29

Bis-*C*-aryl glycosides as model kidamycins are mentioned in Chapter 3, and amino acid analogues of 3-deoxyprumycin are referred to in Chapter 9. Cyclophellitol and its diastereomers are covered in Chapter 18, and the synthesis of intermediates for antibiotics is mentioned in Chapter 24.

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20
Nucleosides

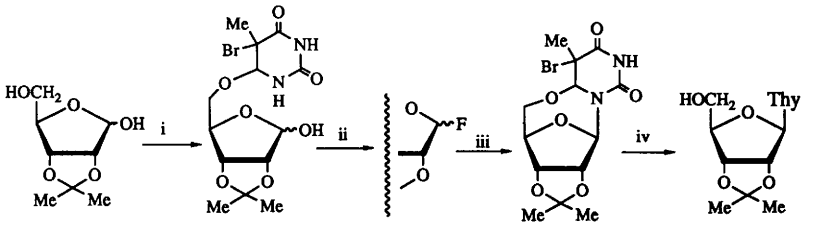
1 General

De Clercq has reviewed the antiviral activity spectrum as related to the target of action for different classes of nucleoside analogues,[1] and the potential of boron-containing pyrimidines, nucleosides and oligonucleotides in neutron-capture therapy has been discussed.[2] A memorial tribute to the life and work of R.K. Robins has been given, along with a bibliography of Robins' publications.[3]

2 Synthesis

As regards synthetic methods, a full account has been given of the use of methyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl carbonate in condensations with silylated heterocycles in the presence of silver salts and diphenyltin sulfide (see Vol. 27, p. 242),[4] and similar condensations can also occur with high β-selectivity in the presence of tin(II) chloride in acetonitrile.[5] Thp derivatives of heterocycles have been used in Vorbrüggen-type couplings, β-D-ribofuranosyl derivatives of purines, pyrimidines, imidazoles and pyrazoles being made in this way.[6]

An interesting intramolecular coupling procedure for the synthesis of thymidine is outlined in Scheme 1; the presence of allyl trimethylsilane in the key coupling step was necessary to remove TfOH formed in the reaction.[7] The application of this procedure for making 2'-deoxynucleosides is discussed in Section 4 below.



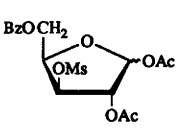
Reagents: i, thymine, NBS; ii, DAST; iii, CH_2=CH-CH_2Tms, TmsOTf; iv, Zn, HOAc

Scheme 1

In a route to nucleosides uniformly-labelled with ^{13}C in the sugar unit, [U-$^{13}C_6$]-glucose was converted to mesylate **1**; displacement with Bu_4NOBz, followed by standard coupling and deprotection, then gave the labelled ribonucleosides.[8] Various methods have been used to make

[5-$^2H_2$]-, [4-^{2}H]-, [1-^{2}H]-, and [(5*R*)- and (5*S*)-^{2}H]-D-ribose from the unlabelled sugar, and from these the corresponding deuteriated cytidines and, by deoxygenation, 2'-deoxycytidines were prepared.[9] The deuteriated ribose derivative **2** was prepared from the unlabelled material by periodinane oxidation followed by $NaBD_4$ reduction, and hence 2'-deuteriated adenosine and uridine were made.[10]

Pyrimidine α-nucleosides have been prepared from the oxazoline **3** (from D-ribose and NH_2CN), by elaboration of the pyrimidine ring, initially as a 2,2'-anhydronucleoside; 2'-deoxy-α-nucleosides could also be prepared by modification of this sequence.[11]



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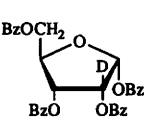

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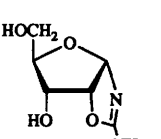

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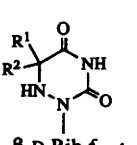
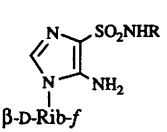


4

Conventional condensation procedures have been used to prepare β-D-ribofuranosyl derivatives of 2-pyrimidinone,[12] 4-chloro-2-pyrimidinone,[13] some 5-alkyl-6-aza-5,6-dihydrouridines of type **4**,[14] and 5-amino-4-sulfonamidoimidazoles **5**, where, in the case of R=H, cyclization gave the imidazothiadiazine dioxide analogue **6** of adenosine.[15] Two groups have described base sugar condensations to give the benzimidazole-2-thione **7**,[16,17] which could be *S*-alkylated,[17] and the structure **8** has been assigned to the minor product formed in the synthesis of the 5,6-dichlorocompound ('DRB').[18] 8-Aza-3-deazaadenosine (**9**), and its 2'- and 3'-deoxyanalogues,[19] 1,3-dialkylxanthine 7-ribosides,[20] and β-D-ribofuranosyl derivatives of 4-amino-imidazo[4,5-*d*]pyridazin-7-one (**10**),[21] thieno[3,2-*d*]pyrimidine -2,4-diones **11** and the N^3-ribosylated products,[22] various heterocondensed pyrimidinones,[23] and of an imidazo [4,5-*e*][1,3]-diazepine **12**[24] have also been prepared by base-sugar condensation.



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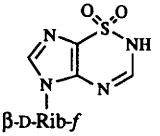

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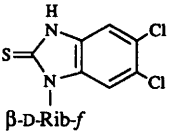

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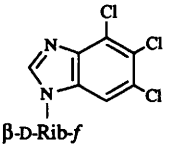

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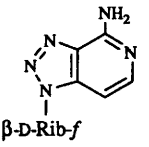

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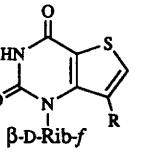

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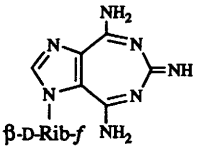
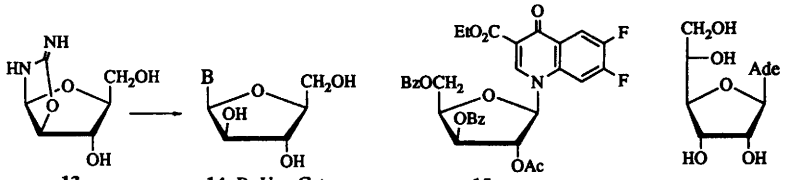


12

L-Arabinose was converted into the oxazoline **13** and hence into the L-enantiomers **14** of ara-U and ara-C.[25] The β-D-xylofuranosylquinolone **15** was prepared by base-sugar coupling,[26] glycofuranosyl analogues of spongosine have been described,[27] and α-L-talofuranosyladenine **16** and the corresponding pyranosyl analogue have been prepared.[28]

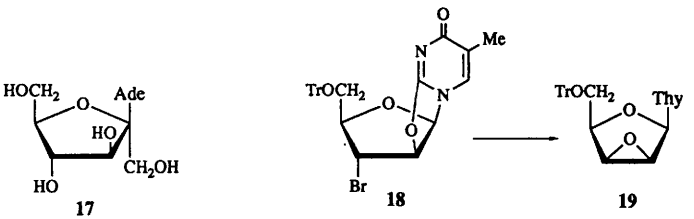


13 **14**, B=Ura, Cyt **15** **16**

When 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose was linked with adenine under Mitsunobu conditions, the β-D-fructofuranosyl nucleoside **17** could be obtained after deprotection with reasonable stereoselectivity, whereas use of *O*-benzoyl protection gave only the α-anomer.[29] Various 1'-*C*-substituted thymine ribonucleosides have been prepared by the same approach as reported earlier for the *C*-methyl compound (Vol. 26, p.226).[30]

Perbenzylated pyranosyl trifluoro- and trichloracetates have been linked with silylated bases in the presence of $SnCl_4$,[31] whilst condensation of pyridine-2-thiones with acetobromoglucose and -galactose has been used to make 1-(β-D-glycopyranosyl)pyridinethiones (deaza-pyrimidines).[32-34]

There has been an extended report on the characterization of α-*N*-glycosides of 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (Kdn) (see Vol. 25, p.244).[35]

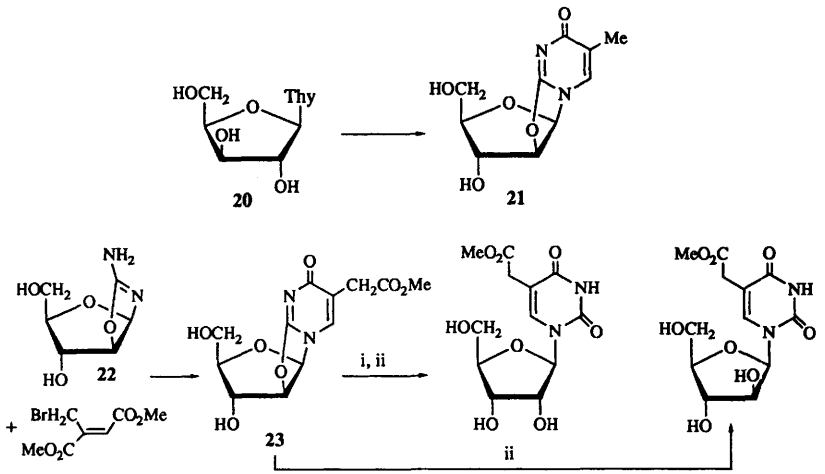


17 **18** **19**

3 Anhydro- and Cyclo-nucleosides

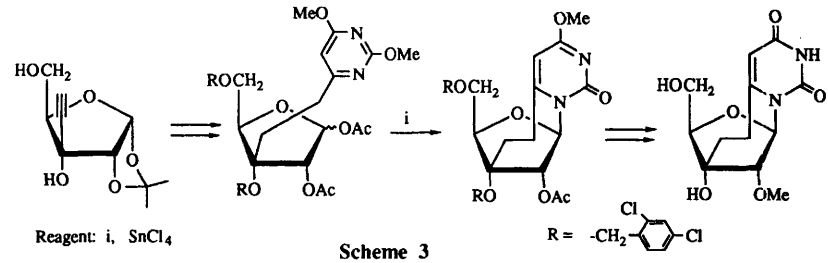
There has been a fuller account given of the formation of the 2,2'-anhydro-system **18** from the 2',3'-ene by treatment with *N*-bromoacetamide (see Vol. 26, p. 227). Treatment of **18** with NaOH in acetone formed the D-*lyxo*-epoxide **19**.[36] When the xylose-derived nucleoside **20** was treated with diphenyl carbonate and $NaHCO_3$, the 2,2'-anhydronucleoside **21** was obtained, and it was proposed that the mechanism of this process proceeded through the 3',5'-cyclic carbonate and the 2',3'-*ribo*-epoxide as intermediates. Treatment of **21** with pyridinium bromide followed by hydrogenolysis gave thymidine.[37] The oxazoline **22** can be used as a precursor of various 5-substituted 2,2'-anhydrouridine derivatives,[38,39] as in the case shown in Scheme 2. The

anhydronucleoside **23** could be converted to D-*ribo*- or D-*arabino*- configured nucleosides as indicated, and the 2'-deoxy-system could again be obtained by treatment with HBr followed by hydrogenolytic or free radical debromination.[39]



Scheme 2

Scheme 3 outlines a synthesis of 2'-*O*-methyl-6,3'-ethanouridine **24**, in which intramolecular glycosidation is a key step. The product **24** was incorporated into antisense oligonucleotides.[40]

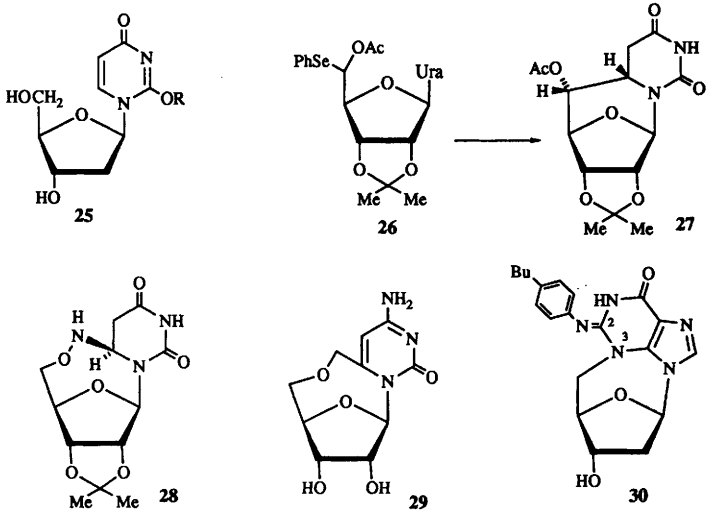


Scheme 3

The 2,5'-anhydride is presumed to be an intermediate in the conversion of 5'-*O*-tosylthymidine into 2'-*O*-alkylthymidines **25** on treatment with the appropriate alcohol ROH and DBU.[41]

When the Pummerer product **26** (Vol. 26, p. 239) was treated with tributylstannane, the cyclonucleoside **27** was formed as the major diastereomer,[42] whilst **28**, with the indicated

stereochemistry, was formed on cyclization of the 5'-*O*-aminonucleoside, itself made by Mitsunobu chemistry.[43] 5'-*O*, 6-Methanocytidine (**29**) has been prepared by extension of the route to the uridine analogue (Vol. 26, p.227), and its conformation was studied in some detail.[44]



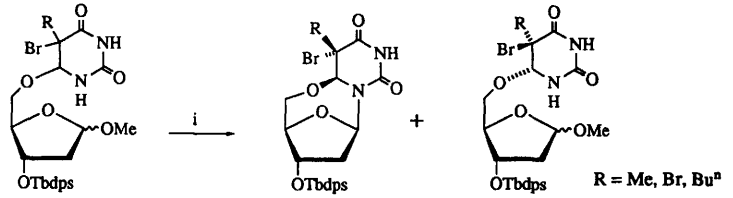
The tautomeric equilibrium in N^2-(4-*n*-butylphenyl)-2'-deoxy-3,5'-cycloguanosine has been the subject of study. In $CDCl_3$, the imino tautomer **30** is present, whilst in DMF or DMSO this exists as a slowly interconverting mixture with the N^2-amino-tautomer. N^2-(4-*n*-Butylphenyl)-2'-deoxyguanosine exists only in the N^2-amino form.[45]

Several applications of anhydronucleosides as intermediates in the synthesis of other types of nucleoside are mentioned later in this Chapter.

4 Deoxynucleosides

There have been further reports on stereocontrolled approaches to 2'-deoxynucleosides. When the intramolecular glycosylation indicated in Scheme 1 above was investigated in the 2'-deoxy-series it was found (Scheme 4) that only one diastereomer of **31** underwent ring closure, the other being recovered. Treatment of the cyclonucleosides **32** with zinc in acetic acid gave the appropriate 5-substituted deoxyuridines.[7] Condensation of the deoxyribose derivative **33** with silylated pyrimidines in the presence of NBS gives up to 10:1 selectivity in favour of the β-anomers.[46] Condensation of silylated purines and pyrimidines with methyl 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-ribofuranoside in the presence of 10 equiv. of tin(IV) chloride gives good yields of nucleosides with some α-selectivity. Use of less catalyst gave lower yields with acyclic byproducts also being formed.[47] Similar use of 1,3,5-tri-*O*-acetyl-2-deoxy-D-ribofuranose with silylated purines gave

the nucleosides, again with low to moderate α-selectivity, and 2'-deoxyribopyranosyl systems were similarly prepared.[48]

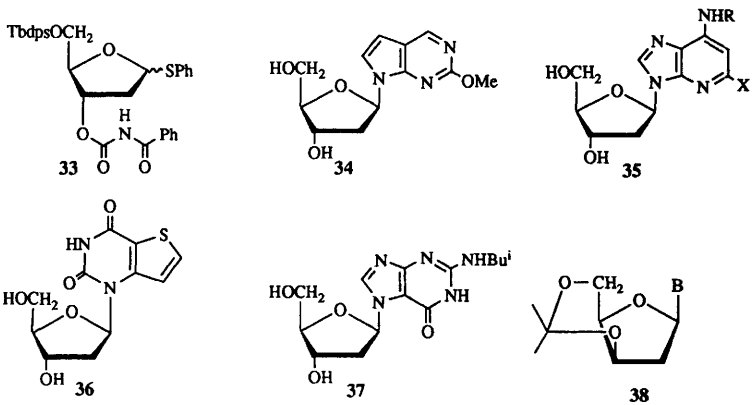


31 **32**

Reagent: i, $BF_3.Et_2O$

Scheme 4

Fairly conventional base-sugar condensations (usually sodium salt and α-glycosyl chloride) have been used to make 2'-deoxyribofuranosides of 4-acetyl-imidazolin-2-one (where the 5-acetyl regioisomer was obtained using Vorbrüggen-type coupling),[49] 5-ethyl-2-pyrimidinone,[50] 5-bromoethynyluracil,[51] various other 5-substituted and 5,6-disubstituted uracils,[52] 5-substituted-6-azauracils,[53] 2-amino-6-(methylthio)purine (deoxyribosylated at N-9),[54] 2-(methylthio)purine (deoxyribosylation at both N-7 and N-9) and 2-methoxy-7-deazapurine (i.e. **34**).[55] Various other deoxyribonucleosides of pyrrolo[2,3-*d*]pyrimidines have been similarly prepared,[56,57] as have imidazo [4,5-*b*]pyridines (1-deazapurines) of type **35** (R = H or alkyl, X = H, Cl),[58] the thieno[3,2-*d*]pyrimidine **36**,[59] and 1-(2-deoxy-β-D-ribofuranosyl)-4,6-dimethylindole, a hydrophobic nucleoside isostere.[60] The 7-(deoxyribosyl)guanine derivative **37** was prepared by conventional deoxygenation and incorporated into oligodeoxyribonucleotides.[61]

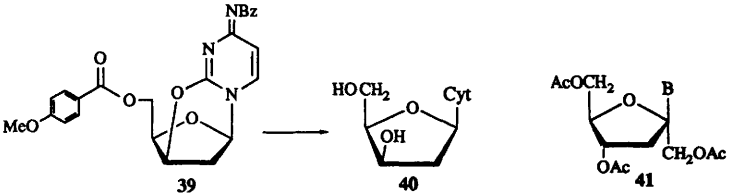


33 **34** **35**

36 **37** **38**

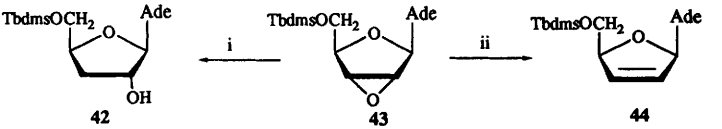
2'-Deoxy-β-D-*threo*-pentofuranosyl nucleoside derivatives of type **38** could be obtained by condensation of silylated heterocycles with the α-(phenylthio)glycoside, induced by NBS. With pyrimidines, good β-selectivity was found, whereas with purines longer reaction times were

required and the anomeric selectivity, although still acceptable, was rather less.[62] The anhydronucleoside **39** was obtained from N^4-benzoyl-2'-deoxycytidine under Mitsunobu conditions, and on base treatment gave D-*threo*-2'-deoxycytidine **40** for incorporation into oligodeoxynucleotides.[63] 3'-Deoxypsicofuranosyl nucleosides **41** were prepared with some β-selectivity by condensation of the *O*-acetylated methyl glycoside with silylated heterocycles under $SnCl_4$ catalysis.[64]



39 **40** **41**

There have been several reports on the synthesis of 3'-deoxyribonucleosides either by glycosylation[65-67] or by free radical deoxygenation procedures on suitable 2',5'-diprotected intermediates.[66,67]



42 **43** **44**

Reagents: i, Cp_2TiCl, 1,4-cyclohexadiene; ii, Cp_2TiCl, THF

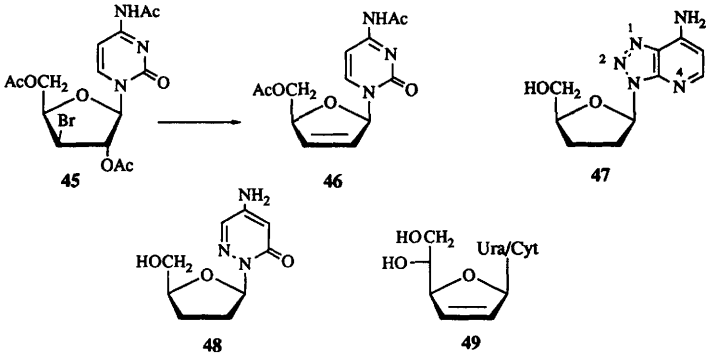
Scheme 5

The 3'-deoxyadenosine derivative **42** (Scheme 5) was the major regioisomer formed when the *ribo*-epoxide **43** was treated with Cp_2TiCl in the presence of a hydrogen-donor, whilst with THF as solvent, deoxygenation occurred to give the 2'-ene **44**.[68] Similar 2'-enes (d4 nucleoside derivatives) have also been made by treatment of *N*- and 5'-*O*-protected compounds with Garegg's I_2-PPh_3-imidazole reagent,[69] and a study has been carried out to improve the yield of the electrochemical reduction of **45** to give **46**.[70] The benzimidazole thione **7** has been converted into its 2'-ene by deoxygenation, with a 2,2'-anhydro-D-*arabino*- intermediate being involved, and the saturated 2',3'-dideoxynucleoside was also made by base-sugar condensation.[71]

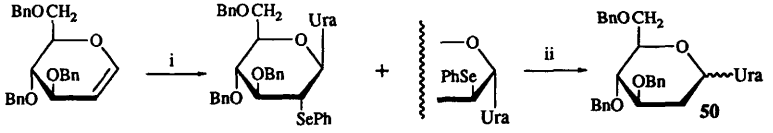
Various 2',3'-dideoxynucleosides have been prepared by the fusion method, without stereocontrol,[72] and the idea of intramolecular glycosylation using a thioglycoside (Vol.27, p.245) has been extended to a synthesis of dideoxythymidine.[73] The 8-aza-1-deazaadenosine derivative **47** was produced, together with N^1- and N^2-substituted products, from base-sugar condensation using the 7-chloroheterocycle, whilst use of silylated 8-aza-1-deazaadenosine in the condensation gave the N^4-glycosylated products.[74] 2',3'-Dideoxyanalogues of 6,7-disubstituted lumazine nucleosides,[75] and of pyridazine nucleosides (e.g. **48**)[76] have been prepared conventionally.

The oxazoline **13** was used to prepare 2',3'-dideoxy-β-L-cytidine, which was more potent than the D-enantiomer against human hepatitis B virus.[77] The same group have also reported

various other L-dideoxynucleosides, both α- and β-, and 2',3'-dideoxy-5-fluoro-β-L-cytidine had good anti-HIV activity.[78] Other workers have also prepared α-L-2',3'-dideoxynucleosides; the pyrimidine examples were made, ultimately from D-glutamic acid, by Vorbrüggen-type couplings, whilst the purine derivatives were made from the L-thymidine analogue by enzymic transglycosylation using thymidine phosphorylase and purine nucleoside phosphorylase.[79]



The hexofuranosyl-2'-ene nucleoside **49**, and the saturated analogue, have been reported.[80] A route to 2'-deoxyhexopyranosyl uracils is indicated by the formation of **50** (Scheme 6); the mixture of adducts from the phenylselenylation was inseparable, but the final α,β-mixture could be resolved by h.p.l.c.[81] Compounds of type **51** have been prepared by extension of earlier work (Vol. 24, p.236-7).[82]



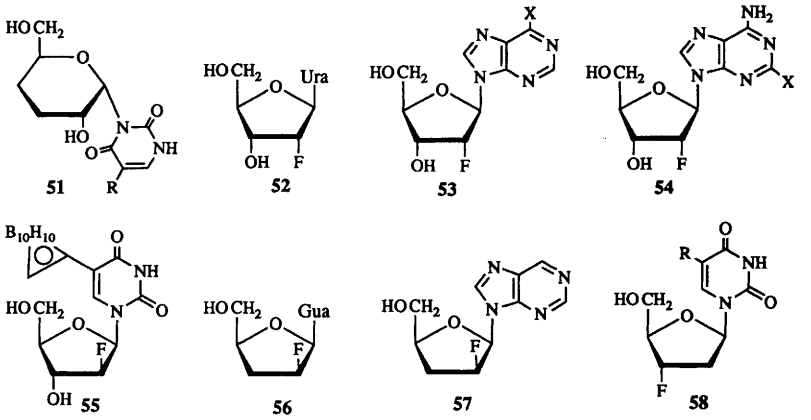
Reagents: i, PhSeCl, $(Tms)_2Ura$, then AgOTf; ii, Bu_3SnH, AIBN

Scheme 6

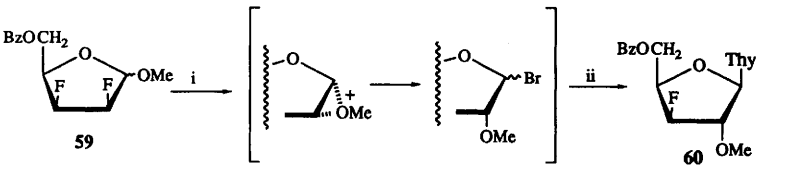
5 Halogenonucleosides

2'-Deoxy-2'-fluorouridine (**52**) and some N^3-alkylated analogues were prepared via the reaction of a 3',5'-*O*-protected arabinosyl nucleoside with DAST.[83] The same approach has also been used to make some 6-substituted purine nucleosides **53** (X=NH_2, NMe_2, SH, SMe)[84] and some 2-substituted -2'-deoxy-2'-fluoroadenosines **54** (X=OMe, SMe, I, F).[85] Compounds of type **54** (X=NH_2, F, Cl), and the guanosine analogue, have also been made using base-sugar coupling, and were found to be less cytotoxic than the corresponding arabinosyl analogues with the F 'up'.[86] Such 2'-deoxy-2'-fluoro-arabinofuranosyl nucleosides have been prepared by base-sugar coupling with 5-phenyl- and 5-benzyl-uracil and -cytosine, and their nitrated derivatives, as bases,[87] as has the carboranyl analogue **55** as a potential intracellular neutron-capture agent.[88] The guanosine

analogue **56** has been made using both xanthate deoxygenation and base-sugar coupling procedures, and the 6-amino- and 6-chloro-derivatives were also described.[89] The unsubstituted purinyl analogue **57** has also been described; it was a substrate for xanthine oxidase and thus a potential prodrug for the anti-HIV agent 2'-fluoro-*ara*-ddI.[90]



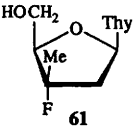
Intramolecular glycosidation using a thioglycoside (Vol. 27, p.) has been applied to a stereoselective synthesis of FLT (**58**, R=Me). Various other compounds of type **58** (R=CHO, NO_2, $NHCO_2Et$, $NHCOCHMe_2$) were prepared using coupling of the silylated heterocycle with a 5-*O*-protected methyl glycoside; β-nucleosides predominated, but acyclic products from cleavage of the endocyclic C-O bond were formed as by-products.[91] 3'-Deoxy-3'-fluoro-N^6-cyclopentyladenine has been prepared as an adenosine receptor agonist, DAST being used to introduce the fluorine.[92] When the difluorosugar derivative **59** (Chapter 8) was treated as indicated in Scheme 7, the nucleoside **60** was formed. The authors suggest that the combined effect of the two fluorines is to make the formation of a glycosyl cation very difficult, so that the rearrangement shown occurs during formation of the glycosyl bromide. Other attempts to make difluoronucleosides from **59** also failed.[93] The branched and fluorinated thymidine analogue **61** was made from a chiral acyclic epoxyalcohol, and converted to its triphosphate which was tested for DNA polymerase activity.[94]



Reagents: HBr, HOAc; ii, $(TMS)_2Thy$

Scheme 7

The 5'-fluorinated compound **62** was prepared by base-sugar coupling using the di-*O*-benzoyl methyl glycoside as the sugar component. Nucleoside **62** was only a minor product, with considerable amounts of the acyclic material from endocyclic C-O cleavage being obtained.[95] Some fluorinated thionucleosides are covered in Section 7 below.



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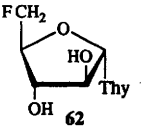
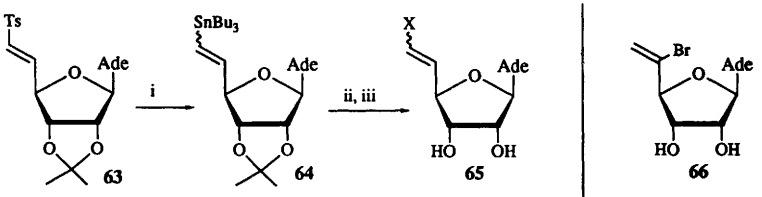


62

When the vinyl sulfone **63** (Vol. 25, p.254-5) was treated (Scheme 8) with tributylstannane, the separable alkenyl stannanes **64** were obtained. These could each be converted with retention of stereochemistry into the vinyl halides **65** (X=I or Br). The corresponding chlorides (with Cl_2) and fluorides (with XeF_2) could also be made, but not stereoselectively. The same paper also reported the synthesis of the alkenyl bromide **66**. Several of these compounds showed time-dependent inactivation of *S*-adenosylhomocysteine hydrolase.[96]



63 **64** **65** **66**

Reagents: i, Bu_3SnH, AIBN; ii, I_2 or Br_2; iii, H^+

Scheme 8

6 Nucleosides with Nitrogen-substituted Sugars

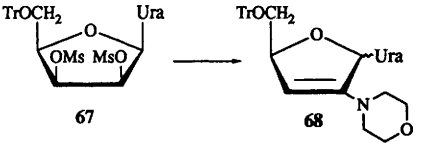
A commercially available polystyryl diphenylphosphine has been recommended for the reduction of azidonucleosides; a polymer-bound phosphine imine is initially generated, from which the aminonucleoside can be liberated on hydrolysis.[97] Further studies have also been reported on the electrochemical reduction of azidonucleosides.[98]

An improved synthesis of 2'-azido-2'-deoxyuridine has been described, in which 2,2'-anhydrouridine is treated with the lithium azide-tetramethyl ethylene diamine complex, generated *in situ*.[99]

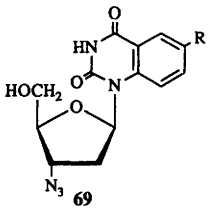
When the D-*lyxo*-dimesylate **67** is treated with secondary amines, enaminonucleosides such as **68** are produced. The products are anomeric mixtures, and the intermediacy of the 3'-deoxy-2'-ketonucleoside is proposed.[100]

Intramolecular glycosylation using a thioglycoside as donor (see Vol. 27, p. 245) has been applied to the synthesis of AZT.[73] Base-sugar condensation was used to prepare some AZT analogues of type **69**.[101] The 3'-amino-2',3'-dideoxy-β-D-ribofuranosides of adenine and guanine

(**70**) can be prepared by enzymic transglycosylation from the thymine or uracil analogues using a strain of *E. coli*.[102] Tri-*O*-acetyl-D-glucal was used as a precursor for the piperazino-substituted thymidine analogue **71** and its α-anomer, using an approach used earlier for introducing other nitrogen-containing substituents at C-3' (see Vol. 26, p. 234-5 and Vol. 25, p. 253).[103] 3'-(2-Tetrazolyl)-2',3'-dideoxythymidine has been prepared from a 2,3'-anhydronucleoside,[104] whilst the hydantoin nucleoside **72**, and the 5'-amino-2',5'-dideoxy-structure, were made by heterocycle-sugar condensation.[105]



67 **68**



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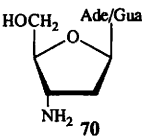

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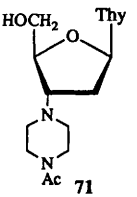

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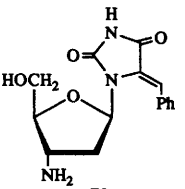
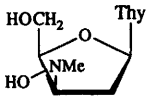
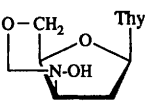


72

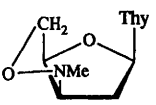
The N-hydroxyamino compound **73**, and its demethylated analogue, have been prepared by reduction of a nitrone and an oxime respectively. DDQ oxidation of **73**, silylated at *O*-5', gave an *N*-methylene nitrone, which on desilylation formed the bicycle **74**.[106] Alternatively, an intramolecular Mitsunobu reaction on **73** gave the isoxazolidine **75**, and the regioisomeric structure **76** was formed from the 3'-*O*-amino-compound under Mitsunobu conditions.[107]



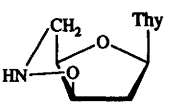
73



74



75

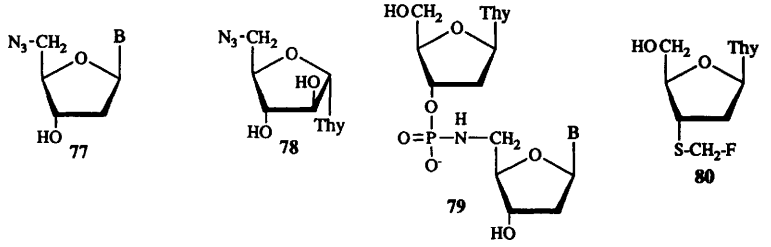


76

5'-Azido-2',5'-dideoxynucleosides of type **77**, and the α-anomers, and the α-nucleoside **78**, have been prepared by condensation of silylated bases with methyl glycosides of the protected sugars.[95]

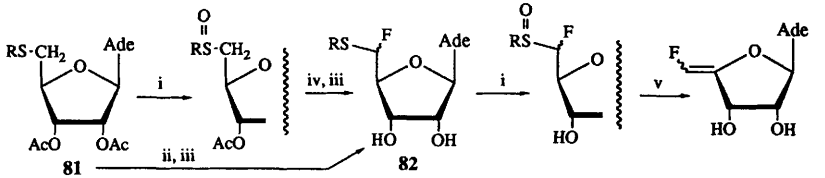
Phosphoramidate-linked dinucleotide analogues **79** have been obtained by the reaction of 5'-azido-nucleosides with the dimethyl sugar phosphite in a Staudinger-type reaction followed by *in situ* Michaelis-Arbusov reaction. Regioisomers with oxygen and nitrogen reversed were similarly obtained from an AZT derivative.[108]

Uses of aminodeoxynucleosides in making neutral isosteric analogues of the internucleotidic link are discussed in Section 13 below, and a study of the X-ray and solution conformations of the anti-HIV agent 4'-azidothymidine is mentioned in Chapters 21 and 22.



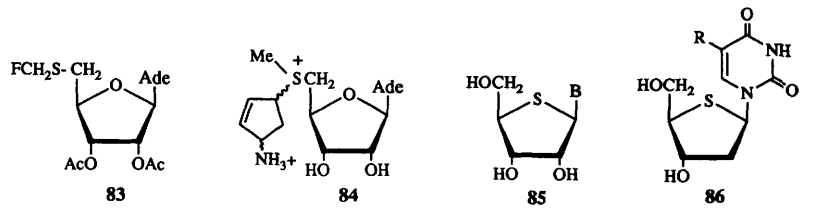
7 Thio- and Seleno-nucleosides

The fluoromethyl sulfide **80** has been prepared by treatment of 5'-*O*-benzoyl-3'-deoxy-3'-methylsulfinylthymidine with DAST, followed by debenzoylation.[109] Similar Pummerer-type reactions at the 5'-position are amongst the chemistry described in an extensive paper from M.J. Robins and his colleagues, which discusses the reactions indicated in Scheme 9 (R=Ph, *p*-MeO-C_6H_4-, *p*-Cl-C_6H_4), some of which have been discussed in briefer reports in earlier years. Compounds **82** undergo hydrolysis to adenosine 5'-aldehyde, and act as time-dependent inactivators of *S*-adenosylhomocysteine hydrolase. In the case of **81** (R=Me), application of either method of fluorination leads to a mixture of the two products **82** (R=Me) and the fluoromethyl compound **83**,[110] although other workers have reported that use of XeF_2 in CH_2Cl_2 at -60°C gives just **83**.[111]



Reagents: i, MCPBA; ii, XeF_2, CH_2Cl_2; iii, NH_3, MeOH; iv, DAST, $SbCl_3$; v, $EtNPr^i_2$, diglyme, Δ

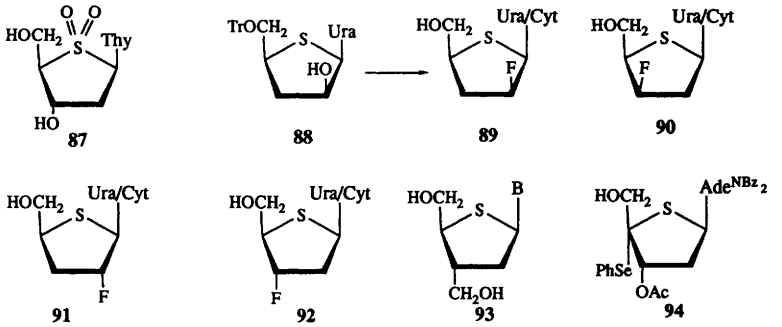
Scheme 9



All four diastereomers of the *S*-adenosylmethionine (SAM) analogue **84** have been separated. All showed similar K_i values towards SAM decarboxylase from *E. coli*.[112] A convenient procedure for the synthesis of 5'-deoxy-5'-methylthioadenosine from the parent nucleoside has been described.[113]

There have been further reports of 4'-thionucleosides (sulfur-in-ring analogues). The Montpellier group have described routes to **85** (B = Ade, Cyt) and the α-anomers, from D-ribose, with two inversions at C-4 of the sugar,[114] and a similar approach was used by others to make **85** (B = 2-chloroadenine) and its 2'-deoxyanalogue, the latter by conventional deoxygenation.[115] There has been a report on the synthesis of 2'-deoxy-systems **86** (R = H, Me, CF_3), the cytosine analogue, and their α-anomers, by silyl condensations, and the L-enantiomers were also made.[116] The sulfone **87** has been prepared by MCPBA oxidation, but was biologically inactive, possibly due to the high glycosidic torsion angle (85.5°, determined by X-ray crystallography), which is so large that the compound is unlikely to be a kinase substrate.[117]

Some fluorinated 4'-thionucleosides have also been reported. 4'-Thiouridine was converted *via* a 2,2'-anhydrosystem into **88**, which on treatment with DAST gave after deprotection the products **89** of fluorination with retention of configuration. Similar retentive fluorination occurred at C-3' to give products **90**, and sulfur participation was invoked to explain these findings.[118] The products **91** and **92** with fluorine 'down' could be prepared by opening the appropriate anhydronucleoside with fluoride ion.[119]



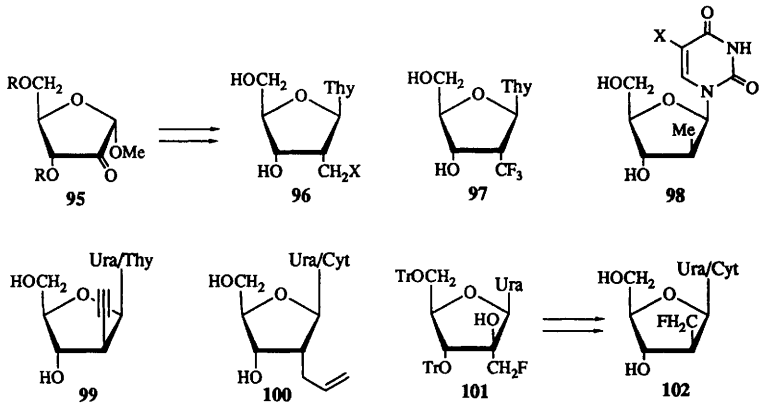
The branched 4'-thionucleosides **93** (B=Ade, Thy, Cyt) have been prepared, along with their α-anomers by silyl condensation using a sugar unit prepared from non-carbohydrate materials by asymmetric synthesis.[120]

The 4'-phenylselenyl compound **94** has been made by reaction of the 5'-aldehyde with PhSeCl in the presence of Et_3N, followed by hydride reduction, but unfortunately the 4'-epimer of **94** was the major product. Phosphoramidite methods were used to incorporate **94** into oligonucleotides, and the PhSe group was used to generate 4'-radicals, leading to cleavage of the oligonucleotide.[121]

8 Nucleosides with Branched-chain Sugars

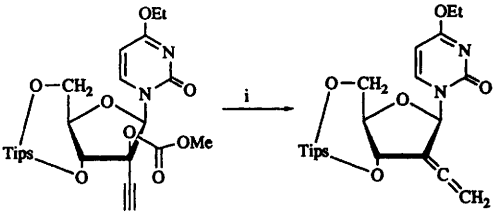
The ketone **95** (R=dichlorobenzyl) was converted by Wittig methylenation followed by 'top-face' hydroboration into a precursor of nucleosides of type **96** (X = OMe, OAc, $NHCOCF_3$), which

were converted to phosphoramidites for inclusion in oligonucleotides.[122] The nucleoside **96** (X=F) was also prepared by conversion of **95** into the fluoromethylene compound using a known protocol (see Vol. 25, p. 256-7), hydrogenation, and conventional linkage to silylated thymine. The trifluoromethyl compound **97** was accessible by addition of a CF_3^- synthon to **95**, and free radical deoxygenation with β-selective hydrogen abstraction, followed again by conventional attachment of the base.[123] Radicals at C-2' in preformed deoxyribonucleosides tend to react with α-stereoselectivity; thus compounds of type **98** (X=H, F, Cl, Br, I, with the last of these showing good anti-HIV activity),[124] and **99**[125] were made by deoxygenation (methoxalyl ester method) of the adducts of the 3',5'-*O*-Tips-2'-ketonucleosides with MeMgBr and TmsC≡CLi respectively. Catalytic reduction of a protected 2'-methylene derivative gave rise to a mixture of **98** (X=H) and the D-*ribo*- compound, both of which were subsequently deoxygenated at C-3', whilst the α-allylated compounds **100** were produced stereoselectively by generation of a radical at C-2' in the presence of allyl tributylstannane (see also Vol. 27, p. 253-4).[126] The fluoromethyl-branched structure **101** was made stereoselectively from the 2'-ketone by reaction with trimethylsulfoxonium methylide and opening of the resultant epoxide with KF-HF. Deoxygenation gave the products **102** with β-oriented CH_2F groups, the cytidine analogue having potent cytotoxicity.[127]



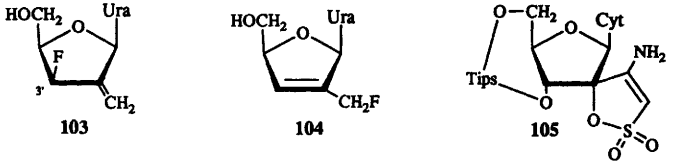
The reaction indicated in Scheme 10 was the key step in the synthesis of the 2'-allenyl analogue of cytidine, and the adenosine derivative was made similarly, these compounds representing the first examples of allenyl nucleosides.[128]

There has been a fuller account given of the reactivity of pyrimidine 2'-deoxy-2'-methylene nucleosides and their use in making 3'-amino-2',3'-dideoxy-2'-methylene nucleosides (see Vol. 26, p. 240-241).[129] Reaction of 2'-deoxy-2'-methylene-5'-*O*-trityluridine with DAST gave, after deprotection, the fluorinated systems **103** and **104**; the 3'-epimer of **103**, together with **104**, was produced when the epimeric starting material was used, and cytidine analogues were prepared from the uridine derivatives.[130]

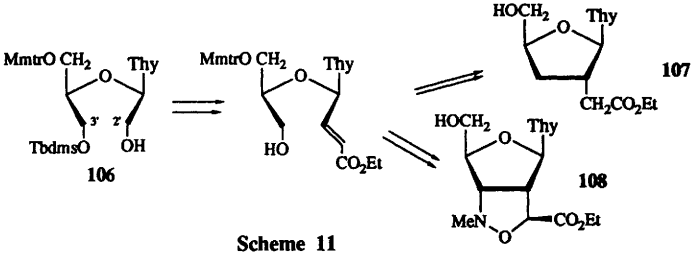


Reagents: i, HCO_2NH_4, Bu_3P, Pd_2(dibenzylideneacetone)$_2$, DMF

Scheme 10



The spirocyclic nucleoside **105** has been made by cyclization of a cyanomesylate;[131] similar chemistry carried out at C-3' has been mentioned in previous Volumes, and see also refs. 147 and 148 below.



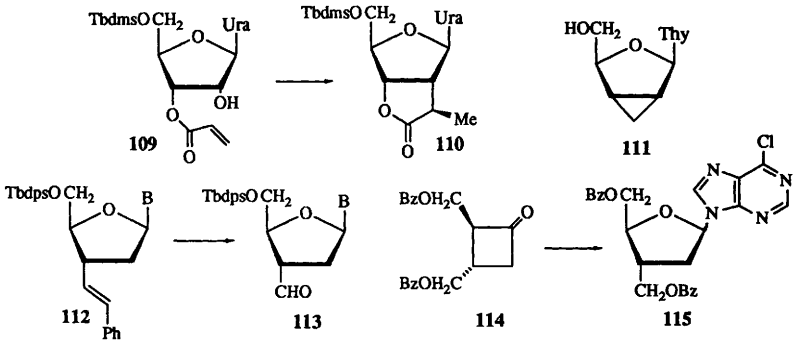
Scheme 11

The seconucleoside derivative **106** could be used as outlined in Scheme 11 to make branched structures **107** using free radical addition to the enoate, and **108** by intramolecular nitrone cycloaddition. The 2'-*O*-Tbdms derivative was produced together with **106**, and thus could be used to make analogous structures branched at C-3'.[132] In somewhat similar fashion, the acrylate **109**, produced regioselectively using stannylene chemistry, cyclised to **110** on generation of a radical at C-2'. Again, the 2'-*O*-acryloyl compound led to compounds with the lactone fused in the opposite sense.[133]

The cyclopropanothymidine **111** has been prepared using a method previously employed for the cytidine analogue (Vol. 23, p. 218).[134]

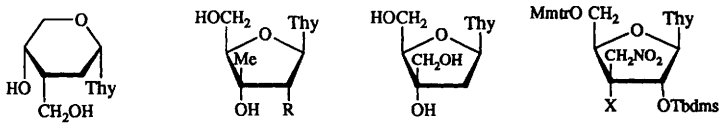
There has also been considerable activity in the synthesis of systems branched at C-3'. Interaction of a radical at C-3' with β-tributylstannyl styrene gives adducts **112** which can be cleaved oxidatively to aldehydes **113**, of use for making antisense systems (Section 13).

Reduction of **113** (B=Thy) and deprotection led to 3'-deoxy-3'-hydroxymethylthymidine, a potent antiviral and antitumour agent,[135] and similar work was done in the deoxyadenosine and deoxyguanosine systems.[136] Photolysis of the chiral cyclobutanone **114** in the presence of 6-chloropurine gave the nucleoside **115**, in a novel approach to this system.[137] A full account has been given of the use of the photoaddition of methanol to butenolides as a route to 2',3'-dideoxy-3'-hydroxymethyl nucleosides (see Vol. 26, p. 242).[138]



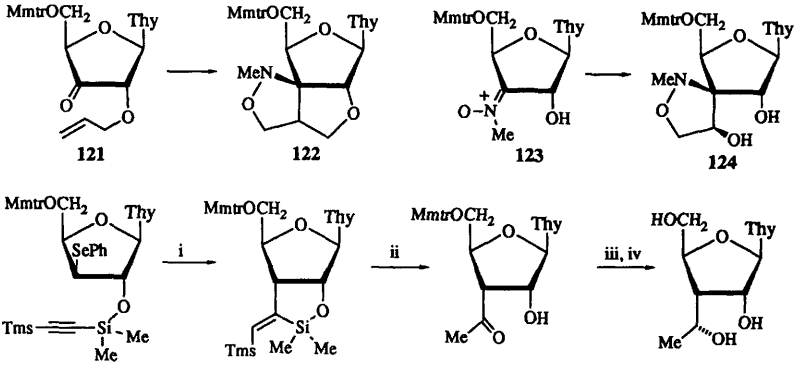
The pyranose nucleoside **116** has been prepared by a sequence involving intramolecular delivery of the hydroxymethyl unit from *O*-4, using a silicon tether.[139]

In a study on the effect of 2'- and 3'-alkyl substitution on oligonucleotide hybridization and stability, the 3'-*C*-methyl compounds **117** and **118** were prepared, the methyl group being introduced stereoselectively by Grignard addition to a 3-ketosugar prior to base-sugar coupling.[140] 3'-*C*-(Hydroxymethyl)thymidine (**119**) the first example of this type of nucleoside has been synthesized by α-selective dihydroxylation of the 5'-*O*-Dmtr-3'-methylene-nucleoside, and was converted into a phosphoramidite for incorporation into oligonucleotides.[141] The same α-stereoselectivity was observed on the addition of nucleophiles to the 3'-nitroalkene to give the products **120** [X = -CH(CO_2Me)$_2$, -NHCH$_2$CO$_2$Me, -CH$_2$NO$_2$].[142]



The tricyclic system **122** was formed by intramolecular cycloaddition when **121** was treated with *N*-methylhydroxylamine. When the nitrone **123** was treated with vinyl dimethylchlorosilane, a tricyclic cycloadduct was formed, which on oxidative desilylation (H_2O_2, KF, $KHCO_3$) gave the spiro-isoxazolidine **124**. Analogous regioisomers could be formed starting

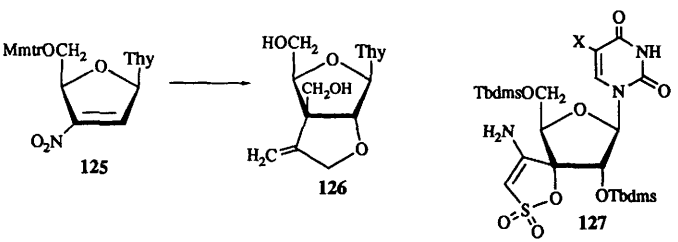
from 2'-nitrones.[143] A silicon tether was similarly involved in the chemistry of Scheme 12; in this situation, the cyclization in the reverse sense worked equally well to give the 2'-*C*-branched bicycle, but the desilylation could in some cases be accompanied by loss of the base.[144]



Reagents: Bu_3SnH, AIBN; ii, H_2O_2, KF, $KHCO_3$; iii, $NaBH_4$; iv, HOAc, H_2O

Scheme 12

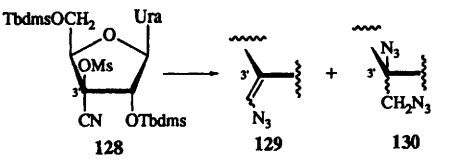
When the nitroalkene **125** was subjected to the three-step procedure of Michael addition of propargyl alcohol, Henry reaction, and intramolecular radical cyclization, the bicyclic structure **126** was obtained.[145]



Further compounds of type **127** (X=F, Br, I, CF_3) have been described; in the cases of X=Br and I, the yield was lowered by the formation of a cyclization product by interaction of the amino group with C-6 of the pyrimidinedione.[146] Similar analogues with 1,2,3-triazole bases have also been prepared.[147]

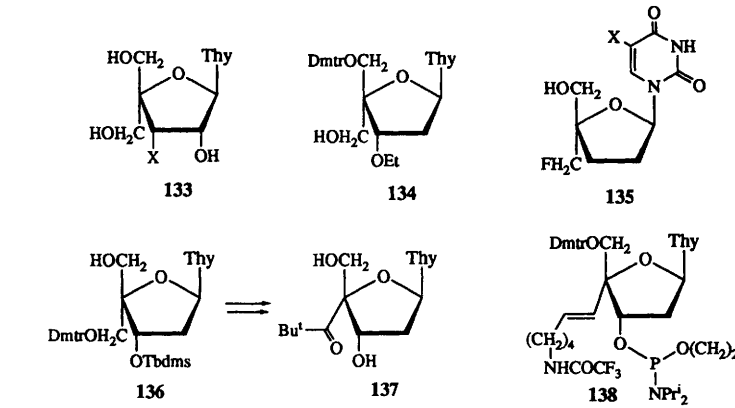
Full details have been given of the conversion of 3-uloses via their *O*-mesyl cyanohydrins to vinyl azido compounds (Vol. 26, p. 129), and this work was extended to the case of the nucleoside derivative **128**, which gave the vinyl azides **129** and the diazides **130**.[148]

The 3'-spirocyclopropanes **131** were prepared by cycloaddition of diazomethane to the 2',5'-di-*O*-benzoyl-3'-deoxy-3'-methylenenucleosides, followed by photolytic extrusion of nitrogen and deprotection. The 4',5'-spirocyclopropane **132** was similarly made from a protected 4'-ene.[149]



128 **129** **130** **131** **132**

A number of papers have described 4'-branched systems, including compounds **133** (B = Ade, Cyt, Ura; X = H, N_3, NH_2),[150,151] and some related 2',3'-epoxides.[151] The Czech group have described routes to 1-(4-*C*-azidomethyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine, 1-(2,3-dideoxy-4-*C*-methyl-β-D-*glycero*-pentofuranosyl)thymine and its 2',3'-dehydro-derivative,[152] and **134** has been prepared and converted to a phosphoramidite for incorporation into modified oligonucleotides.[153] The 4'-fluoromethyl compounds **135** (X=Me, F), and the α-anomers, were made by Vorbrüggen-type coupling; the sugar unit was prepared by asymmetric synthesis from non-carbohydrate precursors (Chapter 14).[154] A 4-*C*-methyl-D-ribofuranose unit also discussed in Chapter 14 was used to make the 4'-*C*-methyl derivative of *S*-adenosylhomocysteine.[155]



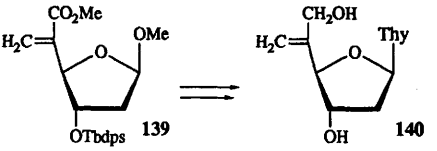
133 **134** **135**

136 **137** **138**

The known thymidine derivative **136** (Vol. 26, p. 243) was converted into the *t*-butyl ketone **137**. This was incorporated into a deoxyoligonucleotide and used to generate a radical at C-4', which in turn led to chain cleavage.[156] In a related study mentioned above,[121] 4'-phenylselenyl nucleosides were employed in a similar way, but application of the selenium method was not possible for pyrimidine nucleosides, since the synthetic method used for the synthesis of compounds of type **94** gave only the wrong diastereomer in these cases.

The compound **138** has been prepared from 3'-*O*-Tbdms-4'-hydroxymethylthymidine; it was incorporated into oligonucleotides, and the side-chain aminogroup was used to attach a biotin unit.[157]

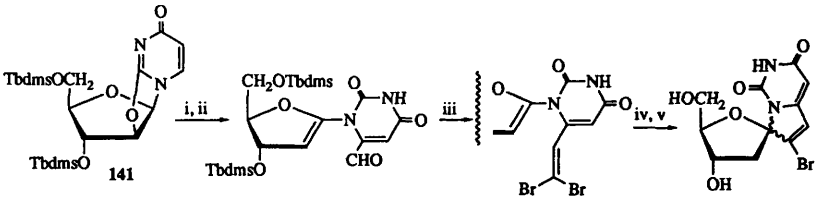
The enoate **139** has been prepared from a chiral acyclic allene by a Heck-type reaction (Chapter 14), and was used to make the thymidine analogue **140**.[158]



9 Nucleosides of Unsaturated Sugars and Uronic Acids

Some papers discussing 2',3'-didehydro-2',3'-dideoxynucleosides were mentioned in Section 4, along with their saturated analogues.

Treatment of the anhydronucleoside **141** (Scheme 13) with LDA led to lithiation at C-6, as well as opening of the anhydro ring to give a 1'-ene. The lithioderivative could be formylated and converted to a spiro-system as indicated (for some similar earlier work, see Vol. 26, p.244).[159]



Reagents: i, LDA; ii, HCO_2Me; iii, Br_2CPPh_3; iv, Bu_3SnH, AIBN; v, Bu_4NF

Scheme 13

Diacetyl-L-rhamnal underwent a Ferrier-type reaction with silylated uracil and thymine to give the 2',3'-unsaturated nucleosides.[160]

The Gif group have used their methods for decarboxylative generation of a free radical to effect the conversion of **142** to **143** in ~30% overall yield.[161]

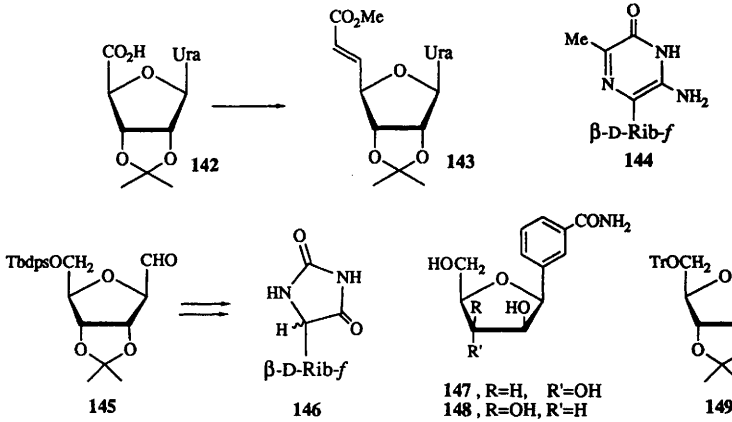
N-Glucuronides of 5-fluorouracil and its 2-*O*-alkyl derivatives (N^3-glycosylated) have been reported,[162,163] and N^6-benzyladenosine-5'-uronamides[164] and their 2-substituted derivatives[165] have been synthesized as A_3-selective adenosine agonists.

10 *C*-Nucleosides

Although synthetic details were not described in the preliminary communication, the pyrazinone *C*-nucleoside **144** has been reported, and incorporated into oligonucleotides to investigate non-standard hydrogen bonding.[166]

The aldehyde **145** has been made by reduction of the nitrile with DIBAL, and was used as a precursor for the hydantoin analogue **146** of showdomycin, obtained as a mixture of diastereoisomers.[167] A full account has been given of the use of a similar aldehyde to produce an

imidazole analogue of 2'-deoxy-ribavirin (see Vol. 25, p.259),[168] and details of the synthesis of *C*-nucleosides by coupling of anomeric free radicals with heterocycles (see Vol. 25, p. 260 and Vol. 26, p. 246) have also been reported.[169]

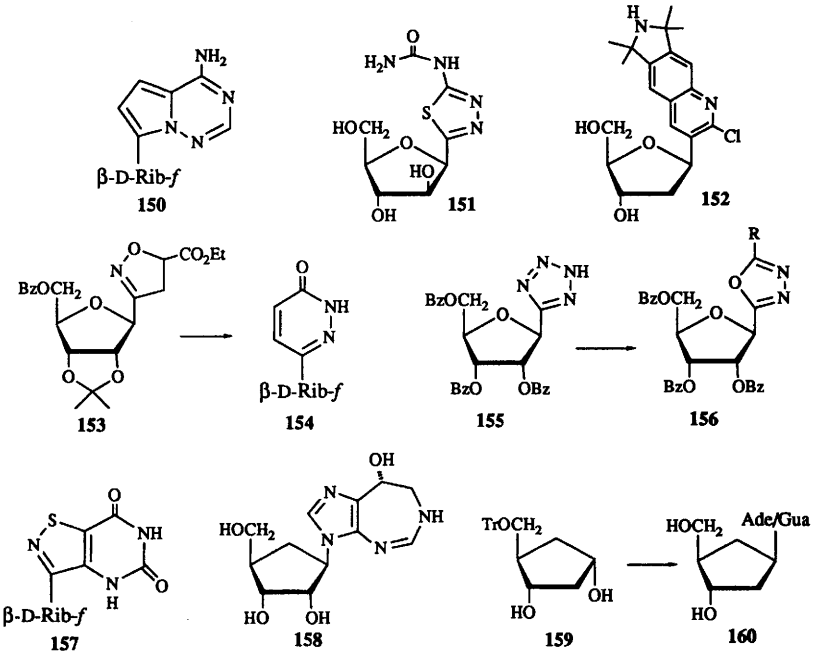


The D-*arabino*- and D-*lyxo*-furanosyl pyridine *C*-nucleosides **147** and **148** have been made using condensations of a lithiated pyridine with *aldehydo*-sugars, followed by cyclizations of mesylates,[170] an approach used previously by the same team to make other pyridine *C*-nucleosides. Various *C*-ribosylated heterocycles of the type **149** (Het=2-furyl, 2-thienyl, 2-benzofuryl, 2-benzothienyl, 2-indolyl and 2-pyridyl) have been synthesized by the interaction of lithiated heterocycles with 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranose, followed by cyclization under Mitsunobu conditions. α-Products tended to predominate in most cases but an 8:1 selectivity for the β-product was found for 2-indolyllithium.[171] Reaction of pyrryl magnesium bromide with 2,3,5-tri-*O*-benzyl-D-ribofuranose, followed by acid-catalysed cyclization, were key steps in a route to the 4-aza-7,9-dideaza-analogue **150** of adenosine; this procedure was stereoselective for the β-nucleoside, and the correct solvent was important for obtaining *C*-alkylation in the Grignard reaction.[172] Acid-catalysed cyclizations of alditol precursors were also used to prepare 4-α- and -β-D-erythrofuranosylimidazole,[173] the 1,3,4-thiadiazole **151**,[174] and 1-phenyl-3-(α- and β-D-threofuranosyl)-pyrazolo[3,4-*b*]quinoxaline.[175] Cyclization of an open-chain mesylate was used in a synthesis of the spin probe **152** and its α-anomer.[176]

An attempt to prepare the β-D-glucopyranosyl analogue of **15** led instead to glycosylation of the heterocycle at C-8.[26]

Protected ribofuranosyl 1,3-dipoles have been used as intermediates in some novel *C*-nucleoside syntheses. Thus, isoxazoline **153** was obtained by cycloaddition of the nitrile oxide, generated in situ from the nitromethyl compound and PhNCO, with ethyl acrylate; cleavage of the N-O bond with $Mo(CO)_6$ and subsequent reaction with hydrazine led to the pyridazinone *C*-

nucleoside **154**.[177] When the *C*-glycosylated tetrazole **155** (Vol. 21, p.211) was *N*-acylated, extrusion of nitrogen occurred to give a nitrile imine which underwent intramolecular cyclization to 1,3,4-oxadiazoles **156** (R = CH_3 or OEt).[178] Cycloaddition of (2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-nitrile sulfide, generated *in situ* (Vol. 18, p. 200), with DMAD was the key to syntheses of isothiazolo[4,5-*d*]pyrimidines such as **157**, and the inosine analogue.[179] An alternative approach to such compounds reported last year (Vol. 27, Chapter 20, Scheme 11) has now been extended to the synthesis of the guanosine analogue.[180]



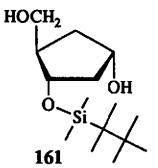
11 Carbocyclic Nucleoside Analogues

The literature until the end of 1993 on the synthesis of carbocyclic nucleosides has been reviewed.[181]

The racemic form of carbocyclic coformycin (**158**), a natural product, and three related analogues have been prepared using Pd(0)-catalysed coupling of the diazepinone with an allylic acetate in the key step.[182] Full details have been reported on the syntheses of (ψ-β-D-arabinofuranosyl)adenine (cyclaradine) and the uracil analogue (see Vol. 27, p. 260).[183]

In a new approach to carbocyclic 2'-deoxyribonucleosides, intermediate **159**, produced in chiral form by enzymic resolution, was converted to its bicyclic sulfate by interaction with $SOCl_2$ followed by oxidation; the sulfate was then linked with an appropriate base unit to give the analogues **160** of 2'-deoxy-adenosine and -guanosine together with the 2,6-diaminopurine

derivative.[184] Other workers have reported a new route to the intermediate **161**, suitable for making carbocyclic 2'-deoxynucleosides,[185] and some new carbocyclic 3'-deoxypurine ribonucleosides, including **162**, have been described.[186]



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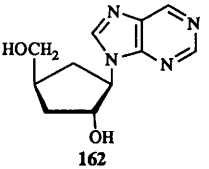

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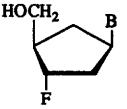
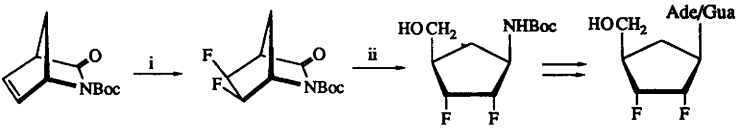


163

There has been a full and extended report on the synthesis of 2',3'-dideoxy-3'-fluoro-carbocyclic nucleosides **163** (involving all five common nucleobases) (see Vol. 24, p.241),[187] whilst racemic dideoxydifluoro-compounds **164** have been prepared as outlined in Scheme 14.[188]



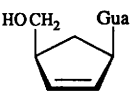
Reagents: i, F_2; ii, $NaBH_4$, MeOH

164

Scheme 14

π-Allylpalladium intermediates again feature strongly in reports on the synthesis of carbovir (**165**) in enantiopure form[189] or as the racemate,[190,191] and the racemic 7-deaza-analogue of carbovir has also been reported, along with the adenine and inosine compounds; the adenine and guanine derivatives were active against HIV.[192] The 6'-hydroxylated compound (±)-**166** has also been synthesized.[193]

When the carbocyclic anhydronucleosides **167** were treated with LiCl in DMF, followed by detritylation, the 3',4'-didehydro-systems **168** were obtained.[194]



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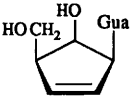

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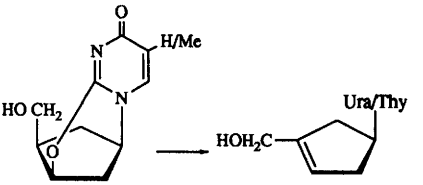
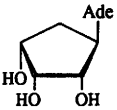


167 **168**

The 'unnatural' (+)-enantiomer of 5'-nor-aristeromycin (see Vol. 27, p. 235) has been prepared, using Pd(0) chemistry to introduce the base,[195] and similar chemistry was also used to make the epimer **169** of nor-aristeromycin.[196] Other workers have reported the synthesis of **170** and its three stereoisomers; in this work, as in a number of reports in this area, enzymic

desymmetrization of *cis*-1,4-dihydroxy-2-cyclopentene was used to obtain the chiral carbocyclic units, with Mitsunobu inversions being used where necessary.[197]



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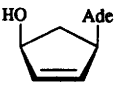
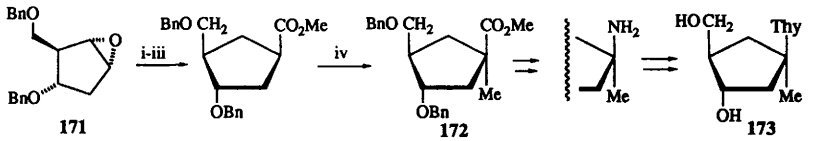


170

There have been a number of reports on branched carbocyclic nucleosides. 1'-Methyl carbocyclic thymidine (**173**) has been prepared from the known chiral unit **171** (Scheme 15), which is itself available from cyclopentadiene. The alkylation gave a 2:1 selectivity in favour of the desired epimer **172**. When incorporated into oligonucleotides, the analogue gave somewhat

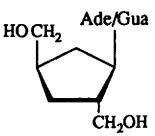


171 **172** **173**

Reagents: i, KCN, $LiClO_4$; ii, radical deoxygenation; iii, TsOH, H_2O, then MeOH, H^+; iv, LDA, MeI

Scheme 15

less stable duplexes with complementary RNA than did the wild type.[198] The hydroxymethyl-substituted compounds **174** have been made from a suitable chiral carbocycle,[199] and the 3'-branched analogue **175** has been prepared in racemic form, as a system that is potentially self-polymerizable to give oligonucleotide analogues.[200] The *meso*-compounds **176** have also been described, with the base being coupled to the cyclopentane using Mitsunobu chemistry. The method was somewhat less successful in the pyrimidine series, with *O*-alkylated products being obtained in some cases.[201]



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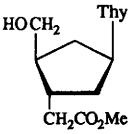

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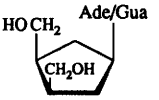

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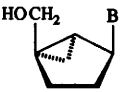
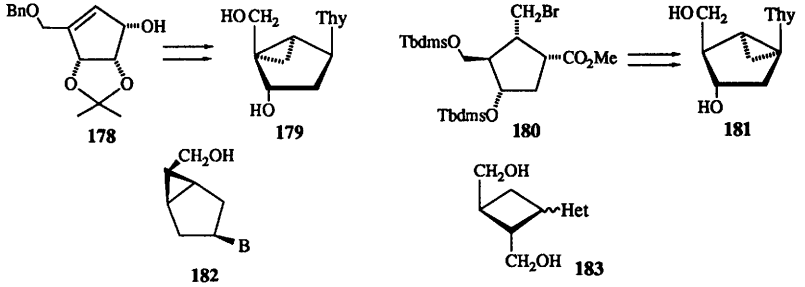


177

There has been an extended account of the synthesis of racemic cyclopropanes of type **177**, where Simmons-Smith cyclopropanation, followed by Mitsunobu coupling, were used to obtain the correct relative stereochemistry.[202] A similar approach was used in Altmann's laboratory to convert the chiral unit **178**, derived from D-ribonolactone, into the thymidine analogue **179**. This compound was shown by X-ray analysis to adopt a 2'-exo- conformation, and this led to increased stability of RNA/DNA duplexes when **179** was incorporated into

oligodeoxynucleotides.[203] On the other hand, the isomeric structure **181**, made from the homochiral precursor **180** by a sequence involving intramolecular alkylation, Curtius reaction, and construction of the thymine unit, adopts a 3'-exo-conformation and oligonucleotides incorporating **181** form less stable duplexes with complementary RNA or DNA.[204] Bicyclic analogues of type **182** have also been described.[205]



A Barton-type radical decarboxylation was used to generate a cyclobutyl radical which was captured by heterocycles to give carbocyclic *C*-nucleosides of type **183**;[206] reference 169 above describes similar chemistry in pentofuranosyl compounds.

Some other papers describing potential synthons for carbocyclic nucleosides are mentioned in Chapter 18, and some phosphonates of carbocyclic nucleosides are discussed in the next Section.

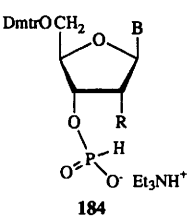
12 Nucleoside Phosphates and Phosphonates

As regards developments in methodology for oligonucleotide synthesis, an effective route to 3'-H-phosphonates **184** (R=H or OTbdms) has been developed, involving the interaction of the 3'-hydroxy compound with diphenyl H-phosphonate in the presence of pyridine, followed by hydrolysis with aqueous triethylamine.[207] 2'-Deoxynucleoside-3'-*O*-phosphoramidites have been produced containing two novel phosphite protecting groups, namely the 2-(trimethylsilyl)ethyl[208] and the 2-(diphenylmethylsilyl)ethyl groups,[209] the latter of which could be removed under mild conditions using aqueous ammonium hydroxide. The dimethoxybenzoin phosphate **185**, made by reaction of the homochiral benzoin with the 3'-*O*-phosphoramidite followed by oxidation, could be obtained by chromatography as a single diastereoisomer. The protecting group could be removed photochemically to give a diester.[210]

O-3'-Cyanoethyl *N,N*-diisopropylphosphoramidites have been made, and incorporated into oligoribonucleotides, in the cases of 5-fluorouridine,[211] an N^4-modified cytidine,[212] pseudouridine[213,214] and pseudoisocytidine.[214]

In the area of modified internucleosidic links, the use of the selenium-containing system **186** in the synthesis of oligonucleoside phosphorothioates has been preferred to the earlier sulfur analogue since the P-Se bond is more labile in reaction with the 5'-OH group of the other

nucleoside component.[215] The allyl group has been employed for the protection of internucleosidic links during the synthesis of phosphorothioates.[216] [^{35}S]-Labelled phosphorothioates can be made by reaction of internucleosidic phosphites with labelled 3*H*-1,2-benzodithiole-3-one-1,1-dioxide,[217] and *S*-alkylphosphorothioates **187** were prepared as potential prodrugs by *S*-alkylation. They could be hydrolysed back to the phosphorothioate by treatment with human serum or porcine liver esterase.[218]



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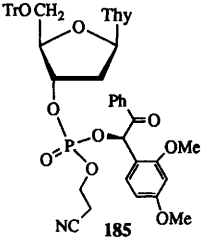

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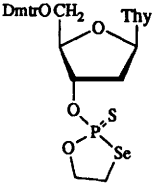

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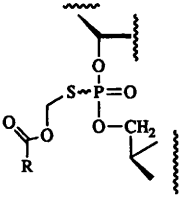

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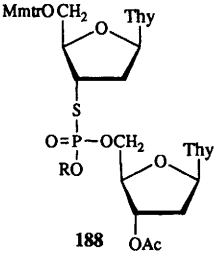

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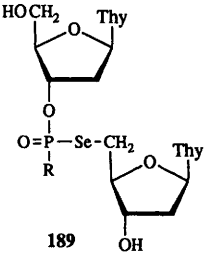

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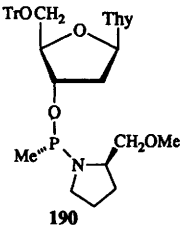


190

Some protecting-group chemistry of relevance to oligonucleotide synthesis is discussed in Section 14 below.

Dithymidine phosphorothiolate triesters of type **188** have been made by reaction of a 5'-phosphite with a 3'-disulfide in an Arbusov-type process.[219]

There has been a full account of the synthesis of phosphoroselenoates and phosphorothioselenoates using the selenium-transfer reagent 3*H*-1,2-benszothia-selenol-3-one (Vol. 26, p.250),[220] whilst 'Se-in-chain' analogues of type **189** (R = OH, OMe, Me) have been made by Se-C bond formation using 5'-bromo-5'-deoxythymidine as an alkylating agent.[221]

A method has been developed for the synthesis of diastereomerically-pure isomers of dinucleoside methylphosphonates,[222] and P-chiral building blocks such as **190** have been reported as intermediates for diastereoselective synthesis of nucleoside methylphosphonates.[223] Dinucleoside phenylphosphonates have been prepared using 6-nitrobenzotriazol-1-yloxy tris(dimethylamino)phosphonium hexafluorophosphate as coupling agent.[224]

A route has been developed for the synthesis of phosphoramidates of type **191**, involving condensation of 5'-dialkyl H-phosphonates with 3'-amino-2',3'-dideoxynucleosides, in the presence of CCl_4.[225] Similar linkage of a dinucleoside H-phosphonate with $MeONH_2$ in CCl_4

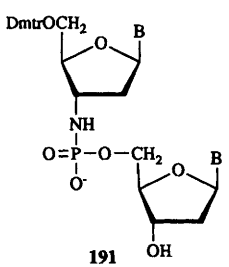
gave a route to the *N*-methoxyphosphoramidate **192**, which was incorporated into oligonucleotides.[226]

Complexes such as **193**, between nucleoside phosphites and tungsten hexacarbonyl have been characterized.[227]

A synthesis has been developed for deoxynucleosidyl 5'-phosphorodifluoridates such as **194**. These will react with 3'-OH nucleosides to give dinucleosidyl phosphorofluoridates such as **195**. These compounds can also be made by treatment of dinucleosidyl phosphoroimidazolides with benzoyl fluoride. After deprotection, compounds of type **195** can be hydrolysed to 5'-nucleosidyl phosphorofluoridates by snake venom phosphodiesterase, and to 3'-phosphorofluoridates using spleen phosphodiesterase.[228]

Rapid and efficient solution-phase syntheses have been described for di(deoxynucleoside) phosphates additionally phosphorylated at either *O*-5' or *O*-3'.[229]

The oligomerisation of the imidazolyl phosphate **196** in the presence of montmorillonite clay has been studied,[230] and variations in the amine have been investigated by the synthesis of various other activated adenosine monophosphates in which the imidazole is replaced by other heterocycles.[231]



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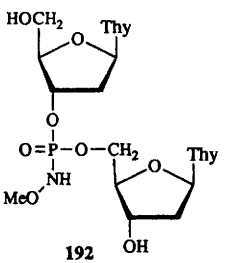

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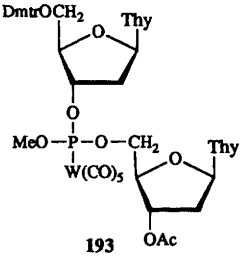

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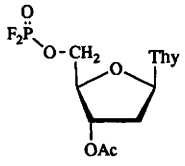

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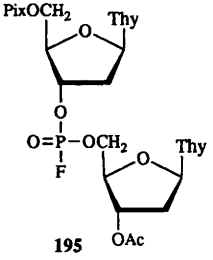

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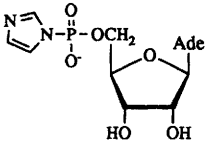

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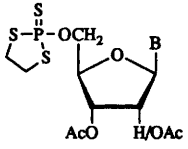


197

Adenosine 5'-phosphorothioate can be prepared by the acidic hydrolysis of the 5'-phosphorothiomorpholidate, but the 5'-phosphorodithiomorpholidate gives adenosine by P-O cleavage on acid treatment, so this approach cannot be used to make dithioanalogues of nucleoside phosphates.[232]

Some thymidine 5'-triphosphates having a long chain aminoalkoxymethyl side-arm at *O*-3' have been made, and shown to be terminators of DNA synthesis catalysed by a thermostable DNA

polymerase.[233] 2'-Deoxy-5-styryluridine, its 2',3'-dideoxyderivative, and the 3'-azido-2',3'-dideoxy-compound have been converted to their triphosphates, which were examined for their effects on reverse transcriptase.[234]

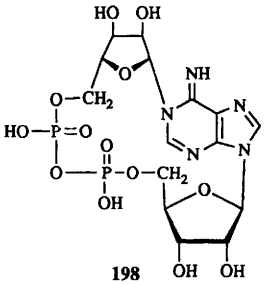
A new one-pot synthesis of the P^1-methylphosphonyl analogues of thymidine triphosphate and AZT triphosphate has been developed,[235] and the P^1, P^2-methylene analogue of the DNA polymerase inhibitor N^2-(*p*-*n*-butylphenyl)-2'-deoxyguanosine has been synthesized.[236]

Treatment of (2'-deoxy)nucleoside derivatives of type **197** with pyrophosphate anion, followed by aqueous ammonia, gives access to (deoxy)nucleoside 5'-*O*-(1,1-dithiotriphosphates) (see Vol. 25, p. 267 for earlier work).[237]

Nicotinamide mononucleotide has been prepared from NAD by specific hydrolysis of the pyrophosphate bond using Zr^{4+} ion as catalyst,[238] whilst NAD labelled with radioactive or stable isotopes,[239] and the trifluoroacetyl analogue of NAD ($COCF_3$ replacing $CONH_2$)[240] have been synthesized enzymically. Sih's laboratory has reported both enzymic[241] and chemical[242] routes to the NAD metabolite cyclic ADP-ribose (cADPR, **198**).

Dinucleoside triphosphates such as GpppG have been prepared by the reaction of the nucleoside monophosphate (2 moles) with S,S'-bis(4-chlorophenyl) phosphorodithioate, in the presence of silver(I) ions.[243] Although subsequent methylation of one guanine unit can give rise to the cap structure (m^7GpppG), dimethylation is a problem, and a better route to such cap structures involves a stepwise but 'one-pot' procedure in which a nucleoside-5'-phosphate reacts firstly with the reagent **199**, with displacement of the PhS unit, and then m^7GMP is added.[244,245]

An analogue of UpU has been prepared in which 2'-thiouridine is present as the 5'-residue.[246]



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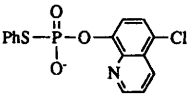

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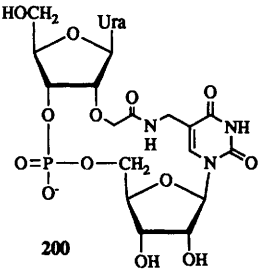


200

A dinucleotide analogue has been described in which an imidazole unit is linked via a spacer arm to C-8 of the adenine of the TpA dinucleotide. This compound, designed as a ribonuclease mimic, self-hydrolyses at a rate 62 times greater than the unmodified structure.[247] The cyclic dinucleotide **200** has been made, in a sequence involving initial amide bond formation, followed by linking the phosphate, as a mimic of a tRNA U-turn having a sharp bend.[248] Bisubstrate analogues of protein kinase C have been reported, in which adenosine 5'-phosphates with differing numbers of phosphate groups are linked to peptides via a serine hydroxyl function.[249] A novel CMP-NeuNAc analogue has been reported, which has an additional

NeuNAc unit α-(2→8) linked to the CMP-NeuNAc molecule; this was made for investigation as a substrate for sialyl transferases.[250]

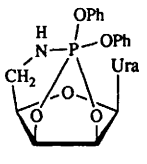
A conjugate between ara-C monophosphate and mitomycin C has been made and evaluated against leukaemias.[251]

Various phosphate-based prodrugs have been described. Bis(pivaloyloxymethyl)-2'-deoxy-5-fluorouridine-5'-monophosphate has been made as a prodrug of 2'-deoxy-5-fluorouridine (FdU),[252] and a number of 5'-phosphonates of 3'-deoxy-3'-fluorothymidine have been prepared by DCC-induced coupling of the phosphonic acid and the nucleoside. The same paper also reports 5'-phosphorofluoridates of various 2',3'-dideoxynucleosides, of AZT and of 3'-deoxy-3'-fluorothymidine.[253] Diaryl phosphates of AZT have been described,[254] and there have been reports of phosphodiesters[255] and phosphotriesters[256] involving AZT and steroids. Phosphoramidates between AZT and 3'-deoxy-3'-fluorothymidine monophosphates and phenylalanine and tryptophan methyl esters have been made, with the phosphoramidites as intermediates.[257]

When 5'-azido-5'-deoxy-β-D-lyxofuranosyluracil was treated with triphenyl phosphite, the phosphinimine produced underwent intramolecular cyclization to give the novel 5-coordinate phosphorus species **201**.[258]

Some unsaturated pyranosyl ketonucleotides have been prepared by phosphorylation of the primary alcohol.[259]

In the area of nucleoside phosphonates, the *C*-phosphonosugar unit **202** has been prepared by addition of dimethyl phosphite to the 3-ketosugar followed by radical deoxygenation, both reactions occurring with β-selectivity. The 3'-deoxy-3'-*C*-phosphononucleosides **203** (R=H or OH) were then made fairly conventionally from **202**.[260] The mimics **204** of nucleoside 5'-monophosphates were produced from a known sugar unit (*Tetrahedron Lett.*, 1992, **33**, 1839) by base-sugar condensation.[261]



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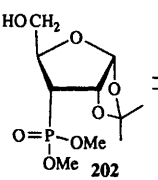

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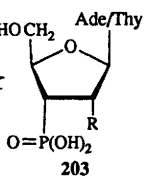

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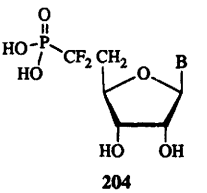
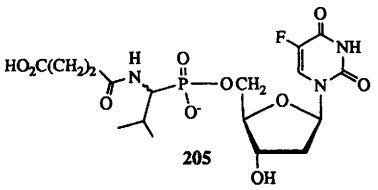


204

In an interesting study on antibody-catalysed prodrug activation, the phosphonate **205** was prepared by Mitsunobu condensation of the phosphonic acid with the 3'-*O*-Tbdms derivative of FdU. This hapten was linked to keyhole limpet hemocyanin and bovine serum albumin via the carboxylate group. The monoclonal antibodies specific for **205** were found to catalyse the hydrolysis of 5'-*O*-(*N*-acetyl-D-valyl)-FdU, an FdU prodrug that was not hydrolysed by endogenous esterases, and a combination of **205** and antibody was as effective as FdU itself in preventing the growth of *E.coli in vitro*.[262]

The pentopyranosyl analogue **206** of d4T monophosphate has been reported, with β-D-xylopyranosylthymine as a key intermediate and with a Mitsunobu inversion at C-4'.[263]



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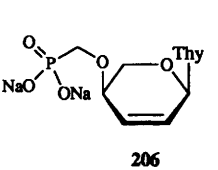

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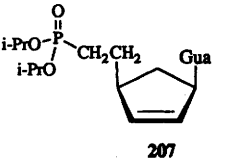

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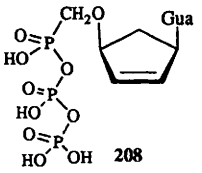

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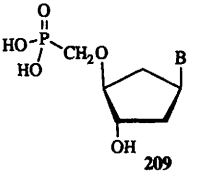

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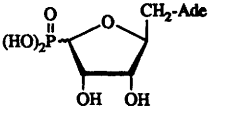


210

There have been reports on phosphonates of carbocyclic nucleosides. The di-isopropyl phosphonate **207** related to carbovir monophosphate has been prepared, using Pd(0) chemistry to link heterocycle and carbocycle.[264] Following from earlier work with racemic material, the Exeter-Glaxo group have now used enzymic resolution to obtain the 'natural' form **208** of a phosphonate related to carbovir triphosphate, and also the enantiomer. Surprisingly, the 'unnatural' enantiomer showed greater activity in inhibition of HIV reverse transcriptase than did the 'natural' form.[265] Phosphonates of type **209** have been described as racemates, where B=5-(2-bromovinyl)uridine (i.e. related to carbocyclic BVDU),[266] and where B = Gua and 6-(methylthio)purine.[267]

Nucleotide analogues such as **210**, which are structurally related to the acyclonucleoside HPMPA, have been reported from Holy's laboratory.[268,269]

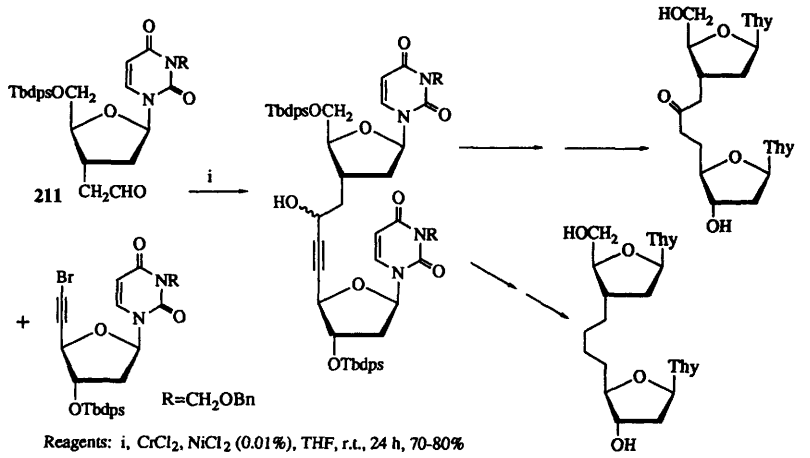
13 Oligonucleotide Analogues with Phosphorus-free Linkages

Increasing interest in the potential modulation of gene expression by antisense oligonucleotides has led to considerable activity in the synthesis of oligonucleotides in which internucleotidic phosphate links have been replaced by neutral isosteric units, and much elegant chemistry has been reported to achieve these targets.

Dinucleoside units linked by all-carbon chains have been prepared as outlined in Scheme **16**, the building block **211** being obtained by oxidative cleavage of a *C*-allyl group, itself put in place by reaction of a radical at C-3' with allyl tributyltin.[270]

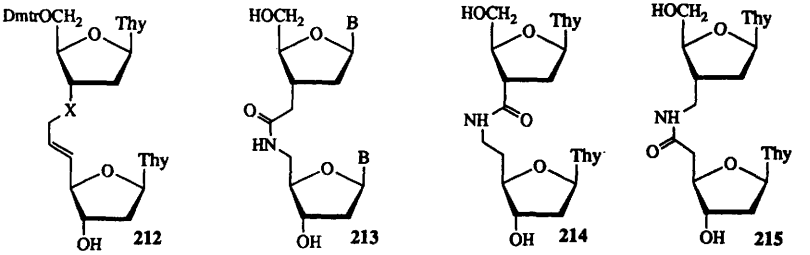
Matteucci's group have reported the synthesis of units **212** (X=O or S), by nucleophilic displacements on an allyl bromide; the saturated systems were also prepared. Incorporation of these units into oligonucleotides led to rather poorer hybridization than was found for all-

phosphodiester systems.[271] Workers at Sterling Winthrop have devised an alternative synthesis for the -O-CH_2-CH_2- system, with similar results.[272]



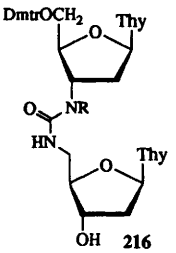
Scheme 16

Amides of type **213** (B = Thy or Cyt) have been prepared and incorporated into oligodeoxynucleotides.[273-275] De Mesmaeker and colleagues have compared complementarity data for several classes of oligonucleotides containing isosteres prepared in the Ciba-Geigy laboratory,[276] and they found that amides of type **213** could give positive changes in melting temperature as compared to the wild type.[273,274,276] Alternative amide structures **214**[277] and **215**[278] have also been reported by the Ciba-Geigy team, with intermediates **112** and **113** (B =Thy) being involved in both synthetic sequences.



Ureas **216** (R = H, Me),[279,280] carbamates such as **217**,[280-282] and the regioisomeric structure **218**[282] have all been described, and incorporated into oligodeoxynucleotides, with complementarity studies being reported. The carbamates were conveniently accessed using the

reaction of an amine (3'- or 5'-) with a *p*-nitrophenyl carbonate (5'- or 3'-),[281,282] and in the case of modification **217**, oligonucleotide analogues with up to three adjacent carbamate linkages were made.[281]



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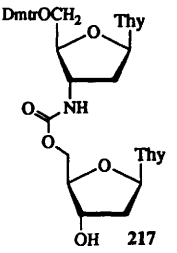

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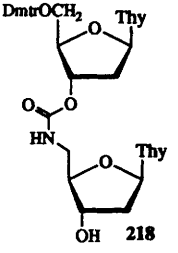
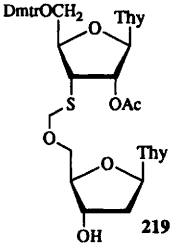


218

Fuller details have been given of the formation, and incorporation into oligodeoxynucleotides, of *N*-cyanoguanidine isosteres (see Vol. 26, p. 236-7),[283] and similar structures have been described in which an acyclonucleoside unit is involved at one end of the linkage.[284]

Earlier work on methylene acetal and monothioacetal links has been extended to the synthesis of **219**, containing a ribonucleoside unit,[285] and to systems **220** (X=O, S), which incorporate a propynyl substituent known to give high antisense binding in phosphorothioates.[286] Systems **221** (X=O,S) with 2',5'-acetal and monothioacetal links have now been reported as well; the *O,O*-acetal was made by activating a 2'-*O*-methylthiomethyl ether with bromine, in the presence of 3'-*O*-Tbdms-thymidine, whilst the *O,S*-acetal was derived by reaction of a 3'-deoxy-2'-thionucleoside with a 5'-*O*-chloromethylnucleoside. When incorporated into oligodeoxynucleotides, the sulfur analogue, in particular, caused considerable destabilization of duplex formation.[287]



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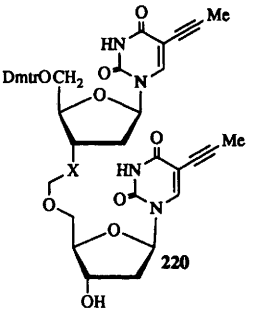

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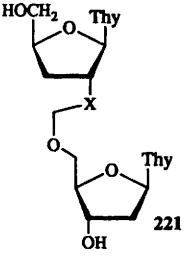
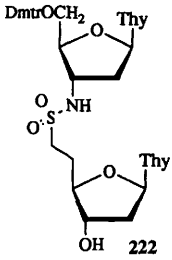


221

There has been a further report on the synthesis of a sulfonamide-linked dinucleoside **222**, incorporated into oligodeoxynucleotides,[288] and the structure **223**, with one atom less in the link, has also been made; it was found that the T_m of duplexes involving decamers with two such

replacement links were only slightly reduced relative to the all-phosphate system.[289] Finally, Cook's laboratory has described the synthesis of the interesting 'dimers' **224** (X=O and CH_2), in which the 5'-carbon has been replaced by oxygen. The 'bottom' unit was introduced in the form of **225**, which was obtained by lead tetraacetate oxidative decarboxylation of the uronic acid.[290]



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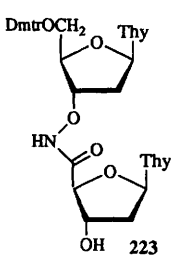

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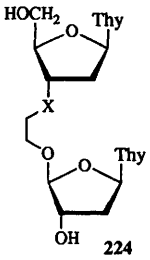

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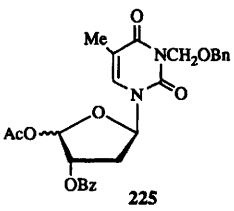


225

14 Ethers, Esters and Acetals of Nucleosides

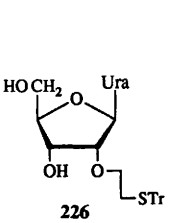
There have been a number of reports on stereoselective base-sugar condensation, leading to 2'-*O*-methyl-β-D-ribonucleosides, including 2'-*O*-methyluridine[291,292] and other 2'-*O*-methyl pyrimidine nucleosides,[292] 6-amino-2'-*O*-methylcytidine,[293] and 2'-*O*-methyl derivatives of both pyrimidine and purine ribonucleosides, made by highly β-selective condensation of silylated heterocycles with a sugar trichloroacetimidate.[294] It has been shown that placing a bulky substituted trityl group at *O*-5' of N^6-cyclohexyladenosine caused only a modest increase in the regioselectivity of 2'- versus 3'-*O*-methylation using methyl iodide or methyl sulfate.[295] 2'-*O*-Methyl-β-D-arabinofuranosylthymine has been made by Vorbrüggen-type coupling, but without stereocontrol; the product was incorporated into oligo-*ara*-nucleotides.[296]

High yielding preparations of 2'-*O*-allylribonucleosides have been described, by allylation of 3',5'-*O*-Tips derivatives. Again, phosphoramidites were made for incorporation into oligonucleotides.[297] The uridine derivative **226** was also made by alkylation of a Tips derivative.[298]

The removal of modified trityl and of pixyl groups has been carried out by the use of an acidic species generated by the reaction of diethyl oxomalonate with methanol, thought to be the hemiacetal formed by addition of methanol to the ketonic carbonyl. In the case of 2'-deoxy-purine nucleosides depurination occurred competitively.[299] Silver ion has been found to have a pronounced effect on the regioselectivity of tritylation of nucleosidic hydroxyl groups.[300]

As regards silyl ethers, tetrabutylammonium fluoride has been shown to catalyse the formation of 2',3',5'-tri-*O*-Tms uridine using Tms-imidazole as silylating agent.[301] In connection with the synthesis of oligoribonucleotides containing isoguanosine, silylation of the 2',3'-diol gave isoguanosine derivative **227** with good selectivity under certain conditions; it was shown that this 2'-*O*-silyl product was formed under conditions of kinetic control, and 2'- to 3'- migration of the silyl group could occur.[302] An efficient procedure for the formation of 3'-*O*-Tbdms-2'-

deoxynucleosides has been documented, involving silylation of the 5'-*O*-Dmtr-compound, followed by ditritylation.[303]



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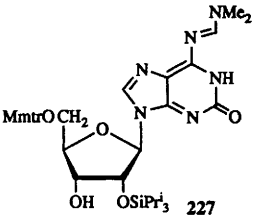

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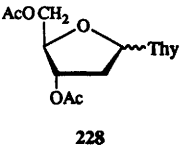


228

Triethylamine trihydrofluoride[304] and KF and 18-crown-6 in DMF[305] have been advocated as reagents for deprotection of nucleoside silyl ethers, including Tips derivatives, in the presence of acid- or base-labile protecting groups. A ^{1}H-nmr study has allowed the position of silylation to be defined for 2'- and 3'-*O*-silylated nucleosides.[306]

Conditions for phase-transfer catalysed acylation of the hydroxyl groups of nucleosides have been defined. Thymine and uridine under these conditions are benzoylated without modification of the bases.[307] When an anomeric mixture of diacetylated thymidines (**228**) is treated with wheat germ lipase or pig liver esterase, the pure β-anomer is formed as the only fully deacetylated product. The equivalent diacetylated pyranosyl nucleoside gives a 5:1 preponderance of the α-nucleoside with wheat-germ lipase.[308] When 3',5'-di-*O*-acetyl-2'-deoxy-adenosine or -guanosine are treated with citrus acetyl esterase, selective deacetylation at *O*-3' occurs. If however the base is *N*-phenylacetylated, then the selectivity of the enzyme is reversed and the 3'-*O*-acetyl product is produced. Using a penicillin acylase (EC 3.5.1.11), with the *N*-phenylacetylated starting materials, no *O*-acetyl cleavage occurs, but only removal of the *N*-protection.[309]

High yields and 5'-*O*-regioselectivity can be obtained in the acylation of ribonucleosides using subtilisin as catalyst if pyridine is used as solvent.[310] When the acetoxime esters of Cbz-glycine and Cbz-β-alanine were used as acyl donors, *Candida antarctica* lipase catalysed the formation of 5'-*O*-aminoacyl derivatives of ribo- and 2'-deoxyribonucleosides, whilst use of *Pseudomonas cepacia* lipase gave reaction at *O*-3' in 2'-deoxyribonucleosides (the same selectivities as observed in previous work; see Vol. 27, p. 266). The enzymes would not accept donors with α–branches, so other α-aminoacid derivatives could not be used.[311]

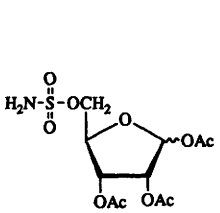
Some 5'-*O*-(α-aminoacyl) derivatives of ribavirin have been made using DCC coupling.[312]

The 5'-*O*-sulfamoylribose derivative **229** was used in modified Vorbrüggen couplings with various bases to make a range of 5'-*O*-sulfamoyl nucleosides related to the herbicidal natural product lead compound, 2-chloroadenosine 5'-sulphamate, but most of the analogues were toxic in a mammalian cell line.[313]

The structure **230** has been reported, and found to exist in 'open' and 'closed' forms; in the latter, the two uridine units are intramolecularly hydrogen-bonded to each other.[314]

The 2-(*p*-nitrophenyl)ethoxycarbonyl group has been used to protect *O*-2' of arabinofuranosyl nucleosides during their incorporation into oligonucleotides,[315] and the 2-

dansylethoxycarbonyl group has been used to protect the 5'-OH during solid-phase DNA synthesis as an alternative to the Dmtr group, and may have application in RNA synthesis, since it is acid-stable but easily deprotected by base.[316]



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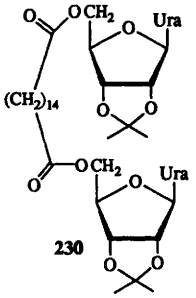

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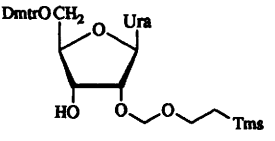


231

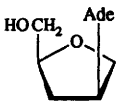
The 2-(trimethylsilyl)ethoxymethyl (Sem) group has been employed, as in the intermediate **231**, for protection of the 2'-OH during oligoribonucleoside synthesis.[317]

A paper on the glycosylation of ara-C is mentioned in Chapter 3.

15 Miscellaneous Nucleoside Analogues

There has been a further report on 'bicyclonucleosides' (see Vol. 27, p. 268-9) which discusses their incorporation into oligonucleotides and the resultant physical behaviour.[318]

Nair's group have given full details of the synthesis of iso-dideoxynucleosides (Vol. 26, p. 255); (-)-iso-ddA (**232**) was the most potent antiviral agent of the compounds reported.[319] The same laboratory has also given more details on the synthesis of the substituted analogues **233**,[320] and other workers have made similar systems, including branched compounds **234** which can be regarded as ring-expanded oxetanocin analogues, from D-glucose (sugar carbons indicated). Some of the compounds reported had good antiviral activity.[321] Some aza- and deaza-analogues of iso-ddA (in the opposite enantiomeric series), such as **235**, have also been described. The 8-aza-analogue **235** was converted to a phosphoramidate which had antiviral activity similar to iso-ddA, but the equivalent derivative of iso-ddA was better still.[322] Earlier chemistry in this area has been modified to include a Cannizzaro reaction so as to produce the branched systems **236** (B-Ade, Thy, Ura, Cyt), and their enantiomers.[323]



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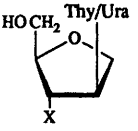
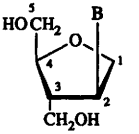


233 X=OH, N_3



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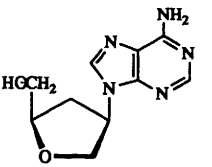

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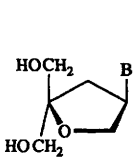

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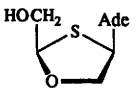

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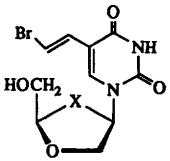

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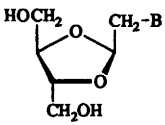
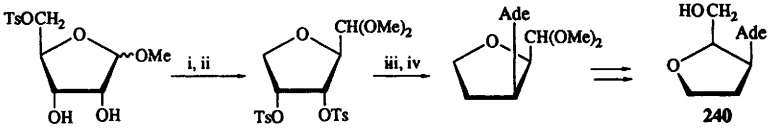


239

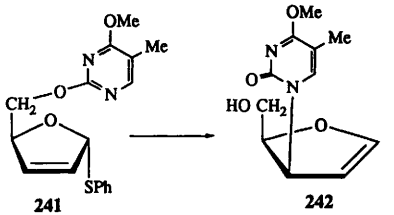
Dioxolane and oxathiolane systems continue to attract attention, given the powerful bioactivity associated with certain compounds in this class. The oxathiolane **237** (Vol. 27, p. 270) has been made in enantiomerically-pure form along with the cytosine and 5-fluorocytosine compounds, by chemistry which cleverly adapts chiral intermediates in the synthesis of the regioisomeric oxathiolanes (heterocycle attached next to oxygen) to the required targets. α-(*Trans*-) isomers were also made, as were the enantiomers.[324] The BVDU analogues **238** (X=O and S), their α-isomers, and the enantiomers of both series, have been produced by adaption of earlier routes, and that developed to make **237**. Oxathiolane **238** (X=S) was strongly active against HSV-2, whilst the enantiomer of **238** (X=O) had good activity against HSV-1.[325] Some phosphonoformate and phosphonoacetate esters of 3TC have been prepared,[326] and compounds **239** (B-Thy, Ade, Gua) have been made from tartaric acid, but did not show any anti-HIV activity.[327]

Scheme 17 outlines a route developed for the synthesis of a novel type of dideoxynucleoside analogue, the regioselective desulfonation being a key step. The enantiomer of **240** was also made from D-ribose by a multistep process.[328] A similar system **242** was formed, rather than the d4 nucleoside, when **241** was treated with Me_2S^+-SMe BF_4^-, followed by NaOH solution.[329]

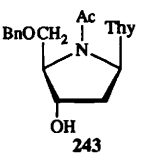


Reagents: i, TFA, MeOH; ii, TsCl, py; iii, LiBHEt$_3$; iv, adenosine, K_2CO_3, 18-crown-6

Scheme 17



241 **242**

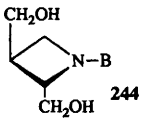


243

There has been a full account of the synthesis by Nair's group of dideoxyapiosyl nucleosides (Vol. 26, p.255), and of their homologues with -CH_2CH_2OH branches (Vol. 27, p. 269).[330]

The nitrogen-in-ring compound **243** has been made by a sequence involving base- 'sugar' condensation, and was incorporated into oligonucleotides.[331] Other groups have reported syntheses of 2',3'-dideoxy- systems similar to **243**,[332,333] and also a D-*ribo*-analogue, with a hydroxy group at C-2'.[333] Azetidinyl nucleoside analogues **244** (B=Ura, Thy, Cyt), related to oxetanocin, have been prepared, with diethyl L-tartrate as starting material, and with the pyrimidine ring being built up from an *N*-amino intermediate.[334,335]

The enantiomerically-pure cyclopropane **245** has been described,[336] as has the adenine analogue of opposite chirality, together with other similar racemic species,[337] and the analogue **246**, prepared by treatment of 1-cyanomethyluracil with LDA, followed by epibromohydrin.[338]



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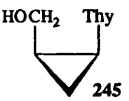

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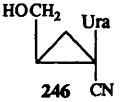


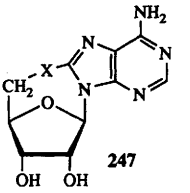
246 CN

Some phosphorus-in-ring structures related to nucleosides are mentioned in Chapter 17.

16 Reactions

β-D-Galactopyranosyl nucleosides have been converted, after appropriate protection, to the *seco*-nucleosides derived by cleavage of either the 2'-3' or the 3'-4'- bonds.[339]

Rates of hydrolysis have been measured for the N^1- and N^6-methyl derivatives of 2'-deoxyadenosine, and the half-life of the N^7-isomer, which could not be synthesized, was estimated.[340] The effect of substituents at C-8 on the rates of hydrolysis of 2'-deoxypurine nucleosides at pH 5.2 has also been studied. Electron-withdrawing substituents gave increased lability, with the effect of a methylsulfonyl group being particularly marked, which gives a basis for selective depurination of oligodeoxynucleotides.[341]



247

The kinetics of the acid-catalysed hydrolysis of the cycloadenosines **247** (X=O, S, NH) have been studied. The *S*- and *N*-bridged compounds are hydrolysed entirely by cleavage of the

base-sugar linkage, whereas the *O*-linked compound undergoes concurrent cleavage of the 5',8 cyclo-linkage. These observations were related to the different puckerings of the sugar rings in the threeanalogues.[342]

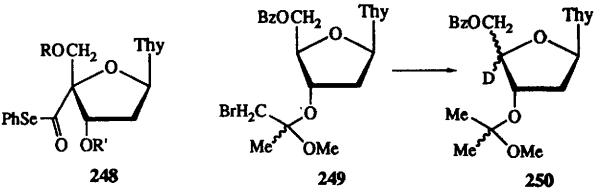
The rate constants for the acid-catalysed hydrolysis of various 1-substituted uracils and thymines have been determined. By comparison with data for equivalent adenine derivatives, it is suggested that the hydrolysis of 4-oxo-pyrimidine nucleosides proceeds by opening of the sugar ring.[343]

A detailed study of the gas-phase dissociation of some 2'-substituted nicotinamide arabinosides has been reported, which discusses data obtained both by LSIMS studies and theoretical calculation.[344]

The hydrolysis and interconversion of the dimethyl esters of 5'-*O*-methyluridine-2'- and -3'-phosphates has been studied over an acidic pH range; under more acidic conditions, the hydrolysis is faster than the interconversion, but this situation reverses at pH >3.[345]

Ceric ammonium nitrate (10^{-2} M) at pH 7 catalyses the hydrolysis of cAMP and cGMP, with half-lives of 7 and 15 seconds respectively. The rate is even faster in the presence of γ-cyclodextrin.[346]

A model study has been reported of relevance to the process of cleavage of oligonucleotide chains by generation of radicals at C-4' (see also refs. 121 and 156 above). When 4'-phenylselenyl deoxynucleosides, or acyl selenides of type **248**, were irradiated, C-4' radicals were generated, as indicated by trapping with PhSH. When a phosphate ester was present at O-3' [e.g. **248**, R'=PO(OPh)$_2$], photocurrent experiments gave evidence that the radical formed subsequently lost phosphate to give a radical cation.[347] Other workers have generated C-4' radicals by intramolecular hydrogen abstraction, as in the formation of **250** by treatment of **249** with Bu_3SnD.[348]



248 **249** **250**

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21
N.M.R. Spectroscopy and Conformational Features

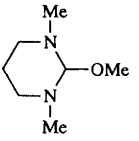
1 General Aspects

A precise procedure for the selective excitation of heteronuclear spin systems has been devised and applied to anomeric [1-^{13}C]D-glucose and maltotriose.[1] Steady-state reverse ^{1}H-^{13}C-n.O.e. and ^{1}H-detected INEPT-(R)NOESY (a new sequence) spectroscopy have been illustrated by use of [1-^{13}C] methyl α,β-D-glucopyranoside as model.[2]

Detailed *ab initio* calculations of the anomeric effect in tetrahydropyrans, 1,3-dioxanes and D-glucose indicated that the effect is due to hyperconjugation,[3] whereas ^{1}H- and ^{13}C-n.m.r. studies on 2-methoxy-1,3-dimethylhexahydropyrimidine (**1**) led to the conclusion that it arises primarily from electrostatic interactions.[4] Molecular mechanics calculations for systems containing O-C-C-O fragments have been reparameterized after the discovery that failure of MM3 force field as well as *ab initio* methods to reproduce the relative stabilities and geometries of the three diasteromeric 1,3:2,4-di-*O*-methylidenetetritols **2** was due to inadequate handling of the stereoelectronics in O-C-C-O units.[5,6] An n.m.r. titration method has been used to measure the shifts in the anomeric equilibria of *N*-(D-glucopyranosyl)imidazole and its per-*O*-acetate on protonation. The results revealed a small but significant preference of the protonated imidazole group for the axial position, contrary to what is expected on the basis of a strong reverse anomeric effect.[7]

A review on the conformational analysis of hydroxymethyl groups in hexopyranoses by ^{1}H-n.m.r. techniques has been published.[8] Magnitudes and signs of ^{13}C-^{1}H spin-coupling constants in specifically ^{13}C-labelled substrates were the basis of a new method for the conformational analysis of monosaccharides and nucleosides.[9] The ^{1}H spin-lattice relaxation times of anhydrous, polycrystalline α-D-glucose have been correlated with the jump motions of hydroxyl protons between equilibrium sites in hydrogen bonds and *trans/gauche* rearrangement of the CH_2OH group.[10] The findings that chemical shifts of hydroxyl protons are sensitive to stereochemical features but relatively independent of experimental conditions if referenced to water, prompted the suggestion that they might provide diagnostic information about the stereochemistry of simple carbohydrates.[11]

The reactions of the D-ribono-, D-xylono-, D-lyxono-, L-arabinono-, and 2-deoxy-D-*erythro*-pentono-lactone with acetone or benzaldehyde in acidic media, which involve complex equilibria, were investigated by extensive ^{13}C-n.m.r. experiments; structural and conformational assignments were



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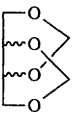

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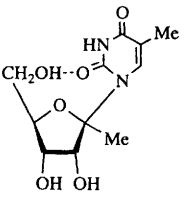


3

facilitated by theoretical calculations (MM2, PM3, AM1) and by X-ray crystallographic analysis of selected products.[12] Amadori compounds (1-amino-1-deoxy-D-fructose derivatives) prepared by reaction of D-glucose with various aliphatic amino acids, have been analyzed by ^{1}H- and ^{13}C-n.m.r. spectroscopy; in D_2O solution the β-pyranose forms predominated.[13] ^{1}H- And ^{13}C-n.m.r. studies on several primary sugar formamides, thioformamides, acetamides, and thioacetamides showed that in $CDCl_3$ the first two exist as Z/E mixtures about the N-C bond; for the last two compounds only the Z-rotamers were observed.[14] Primary sugar thioureas have been similarly examined.[15] ^{1}H-N.m.r. spin-lattice relaxation experiments have been used to investigate the molecular associations between water and sugars (glucose and sucrose,[16] galactose and maltose[17]), and the effect of alkali ions on these associations.[16,18] A molecular dynamics simulation model for studying the intricate interactions between mannose-binding protein (MPB), calcium ions, carbohydrates and water, based on crystallographic data of MPB complexed with mannose has been developed.[19]

2 Acyclic Systems

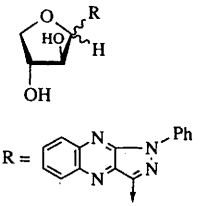
Conformational n.m.r. studies on *N*-octyl-D-hexonamides in DMSO revealed highly favourable and even fixed conformations, determined mainly by repulsive 1,3-*syn* interactions and attractive *gauche* interactions between neighbouring hydroxyl groups.[20]

3 Furanose Systems

On the basis of semiempirical molecular modelling data, the total unreactivity of the primary alcohol group in 1-(1-deoxy-β-D-psicofuranosyl)thymine (**3**) has been ascribed to hydrogen bonding with the base moiety as shown.[21] The ^{1}H- and ^{13}C-n.m.r. spectra of ribofuranose in D_2O have been fully assigned by use of 2D techniques.[22] The ^{13}C-n.m.r. spectra of methyl tri-*O*-acetyl-α- and -β-L-arabinofuranosides are referred to in Part 4 below. 2D ^{1}H NOESY techniques were used to ascertain the anomeric configuration of several purine deoxyribonucleosides and the chemical shift values allowed differentiation between 7- and 9-*N*-linked isomers.[23] The anomeric configurations of the *C*-nucleosides **4**, obtained in

two steps from a mixture of D-*glycero*-L-*manno* and D-*glycero*-L-*gulo*-heptose, have been determined by ^{1}H-n.m.r.spectroscopy.[24]

Conformationally restricted tetrahydrofuran derivatives **5** carrying various substituents at the 2-position have been synthesized for use in an investigation of the anomeric effect in furanosides.[25] Conformational analysis revealed that in contrast to their *O*-analogues, α- and β-*C*-arabinofuranosides, *e.g.* compound **6**, and α- and β-*C*-2-deoxyribofuranosides tend to have equatorial anomeric bonds.[26] The effect of changes in the torsion angle about the glycosidic bond in nucleosides on the ^{13}C chemical shifts of the base moiety has been demonstrated by an *ab initio* study with model compound **7**.[27]



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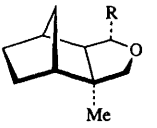

R = H, OBn, SBn, CH_2Bn, or Thy

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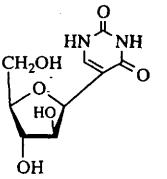

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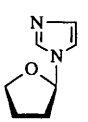
N.m.r. experiments in D_2O and DMSO-d_6 and molecular mechanics calculations have shown that di-(3-deoxy-β-D-*glycero*-pentulose) 1,2′:2,1′- dianhydride (**8**) is asymmetric with a marked difference in the flexibility of the two furanose rings.[28] Selective deuteration provided efficient markers in the conformational analysis of 2′-deoxyuridine and its 3′,5′-*O*-Tips derivative by ^{1}H-n.m.r.-, F.t.i.r.-, and Raman-spectroscopy.[29]

Factors which influence the pseudorotational North South equilibrium in nucleoside and nucleotide derivatives in solution, such as the electronegativity of the C-3-substituent,[30] the presence of a 2′-hydroxyl group,[31] and steric and stereoelectronic features of the base moiety[32] have been assessed by conformational n.m.r. analysis using the PSEUROT program. According to PSEUROT analysis, 4′-azidothymidine (**9**) is exceptional among antiretroviral nucleosides in assuming in solution the unexpected North conformation, with the N_3-group axially disposed.[33]



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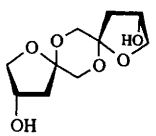

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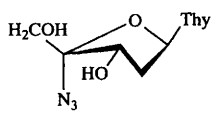

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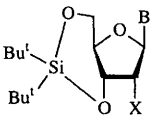
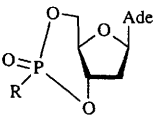


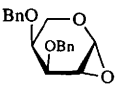
X = H or OH

10



R = Me or Bu

11



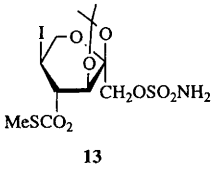
12

Conformational analysis by ^{1}H-n.m.r. spectroscopy has been carried out on 5-formylcytosine,[34] on sila-analogues **10** (nine examples) of 3′,5′-cyclic nucleotides,[35] and on bis-tetrahydrofurans related to annonaceous acetogenins (see Vol. 26, Chapter 24, structures **84**).[36] Various n.m.r. techniques have been applied to the conformational analysis of 1-(2′-deoxy-2′-fluoro-5-iodoribosyl)cytosine and its *arabino* isomer,[37] and of adenosine 3′,5′-cyclic alkylphosphonates **11**.[38]

4 Pyranose Systems

The ^{1}H- and ^{13}C-n.m.r. spectra of the simple aldohexopyranoses in D_2O have been fully assigned.[22] The ^{13}C-n.m.r. resonances of *N*-acetylneuraminic acid in D_2O at pH 7.0 and pH 10.0 have been unambiguously assigned with the help of ^{1}H-^{13}C correlation methods.[39] By use of similar techniques, all acetyl methyl resonances in the ^{1}H-n.m.r. spectra of 1,3-di-*O*-acetyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)glycerol and of the two diastereomeric 1-*O*-acetyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)glycerols have been assigned.[40] Co-crystallized anomeric mixtures of methyl D-xylopyranoside have been examined by high resolution solid state ^{13}C-n.m.r. spectroscopy.[41] The n.m.r. analysis of the four methyl α-D-mannopyranoside monophosphates is referred to in Part 6 of this Chapter.

Monte Carlo simulations, performed to study the effect of solvation on the anomeric equilibrium of 2-methoxytetrahydropyran, indicated a 2 kcal mol^{-1} stabilization of the equatorial over the axial anomer.[42] Energy surfaces have been computed for aldopyranosyl rings by use of MM3; the $^4C_1$ conformations of the model pyranosyl ring were dominant for both anomers of D-allose, D-galactose, D-glucose, D-mannose, and D-talose, as well as for the β-anomers of D-altro-, D-gulo-, and D-ido-pyranose, whereas equilibria between the $^4C_1$ and $^1C_4$ chair forms were predicted for α-D-altro-, α-D-ido-, and α-D-gulo-pyranose, with contributions from $^OS_2$ in the last two compounds.[43] The conformational analysis of (6*R*)-[6-^{2}H$_1$]-1,2:3,4-di-*O*-isopropylidene-α-D-galactose by n.m.r. spectroscopy and molecular modelling has been reported.[44]



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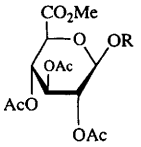
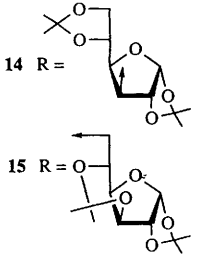




A quantitative and highly mathematical approach to describing the dynamics of overall motion of monosaccharides in solution has been developed on the basis of ^{13}C relaxation data, and applied to an analysis of the variable temperature ^{13}C spin-lattice relaxation times of 1,6-anhydro-β-D-glucopyranose which appears to tumble anisotropically in DMSO.[45] The chemical shift anisotropy of the anomeric protons in aqueous α- and β-D-glucopyranose has been studied by use of [1-^{13}C]glucose in ortho-ROSEY and SLOESY experiments.[46] ^1H-N.m.r. spectroscopy combined with molecular mechanics calculations showed that 1,2-anhydro-3,4-di-*O*-benzyl-β-L-arabinopyranose (**12**) (see Chapters 3 and 5 for synthesis) assumes a near $^5H_4$ conformation,[47] and that a twist form (^3S_O) prevails over possible chair forms for each of several 2,3-*O*-isopropylidene-α-L-sorbopyranose derivatives, such as the anticonvulsant sulfamate **13**.[48]

5 Disaccharides

The ^{13}C chemical shift tensors in single crystal sucrose have been assigned.[49] The molecular mobility of sucrose in aqueous solution has been studied by use of ^{13}C-n.m.r. relaxation methods,[50] and a short-time-scale molecular dynamics investigation of sucrose in water and DMSO concluded that the conformation in the two solvents is practically the same and similar to that in the crystal.[51] According to an n.m.r. study, *C*-sucrose (but not the natural *O*-sucrose) in methanol undergoes a conformational change on addition of Ca(II) ions.[52] The isoenergy surfaces for both anomers of isomaltose and gentibiose have been calculated on the basis of 46,656 conformers for each disaccharide as obtained by relaxed-residue conformational mapping with MM3.[53] A study of intra- and inter-molecular H-bonding in methyl β-cellobioside showed that in water O-3 is predominantly H-bonded to the solvent, whereas in DMSO it is bonded to O-5′.[54]

Conformational analyses by n.m.r. spectroscopy and/or computational methods have been carried out on a series of (1→6)-linked disaccharide methyl glycosides,[55] the disaccharide acetals **14** and **15**,[56] methyl 4-thio-α-maltoside,[57,58] methyl 4-thio-β-maltoside, the nitrogen-linked analogues of methyl α-maltoside and of methyl 6-deoxy-α-maltoside, and 4-*O*-α-D-glucopyranosyl-deoxynojirimycin,[58] methyl and allyl 5′-thio-α-D-kojibioside and methyl 5′-thio-α-D-isomaltoside,[59] several deoxy-halo-analogues of methyl β-lactoside,[60] the T and T_N antigenic determinants **16** and **17**,

respectively, as their crotyl glycosides,[61] the disaccharide constituents **18** and **19** of tumor-associated antigens, as their propyl glycosides,[62] the disaccharide glycosides **20**, **21**,[63] and **22**,[64] the antigenic determinant of blood group B (which is also the repeating unit of seaweed galactans),[65] the saccharide glycoside **23**, in free form and bound to *Aleuria aurantia* agglutinin,[66] digalacturonic acid **24** and its sodium salt in D_2O and DMSO-d_6,[57,67] and 12 *pseudo*-disaccharides containing D-glucopyranose and 5a-carba-D- or L-glucopyranose.[68]

16 α-D-Gal*p*NAc

17 β-D-Gal*p*-(1→3)-α-D-Gal*p*NAc

18 β-D-Gal*p*-(1→3)-β-D-Gal*p*

19 α-L-Fuc*p*-(1→2)-β-D-Gal*p*

20 β-D-Gal*p*-(1→3)-β-D-Xyl*p*-OBn

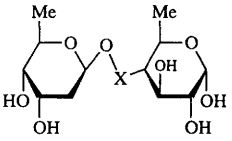
21 β-D-Gal*p*-(1→4)-β-D-Xyl*p*-OMe

22 α-D-Fuc*p*-(1→4)-β-D-Glc*p*NAc-OMe

23 α-L-Fuc*p*-(1→6)-β-D-Glc*p*NAc-OMe

24 α-D-Gal*p*U-(1→4)-α-D-Gal*p*U

The influence of the hydroxylamine glycosidic linkage in calicheamycins on the shape of their oligosaccharide moieties has been probed by force field calculations and n.m.r. experiments using models such as disaccharides **25**.[69] Computer graphics have been applied to the study of the interactions of sucralose and related chlorinated disaccharides with a helical proteinacious receptor model.[70]



25 X = CH_2 or NH

6 Oligosaccharides and Related Structures

A new, computer-aided, 3D heteronuclear n.m.r. technique (3D TOCSY HECTOR) for ^{1}H- and ^{13}C-chemical shift assignments has been applied to raffinose as model.[71] The structures of the four neutral trisaccharides **26-29** from goat colostrum have been elucidated by g.c. analysis of hydrolysis products and

26 α-L-Fuc*p*-(1→2)-β-D-Gal*p*-(1→4)-D-Glc

27 α-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→4)-D-Glc

28 β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→4)-D-Glc

29 β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→4)-D-Glc

30 β-D-Glc*p*NAc-(1→6)-β-D-Gal*p*-(1→4)-D-Glc

400 MHz ^{1}H-n.m.r. spectroscopy, and trisaccharide **30**, prepared by β-galactosidase digestion of lacto-*N*-novotetraose, has been characterized by 1D and 2D n.m.r. methods at 600 MHz.[72] The ^{1}H- and ^{13}C-n.m.r. spectra of α- and β-laminaripentaose peracetates and the corresponding dodecyl glycosides have been fully assigned,[73] as have the ^{13}C-n.m.r. spectra of agaro-tri- to -hexose.[74] 1- and 2-D n.m.r. techniques were used to fully analyze the pentasaccharide **31** of the Forssman antigen,[75] to characterize the heptasaccharide **32** obtained by keratase digestion of keratan sulfate,[76] and to examine the conformations of synthetic tetra- and hexa-saccharides which represent epitopes of the *O*-specific polysaccharide of *Shigella dysenteriae*.[77] The newly assigned ^{13}C-n.m.r. spectra of the methyl tri-*O*-acetyl-L-arabinofuranosides have been used to interpret the spectra of oligosaccharides **33** and **34**, obtained from the enzymic digestion of barley-hull arabinoxylan.[78] The complete structural description of branched oligosaccharide fragments of ribonuclease B, such as undecaose **35**, has been achieved by 300 MHz ^{1}H-n.m.r. spectroscopy, supported by laser desorption m.s.[79] ^{13}C-Filtered 1D TOCSY experiments allowed the stereospecific assignment of the exocyclic methylene protons in panose (**36**).[80] MM3 calculations and ^{13}C-n.m.r. spectroscopic data indicated that inulin oligomers do not adopt simple helical structures.[81]

α-D-Gal*p*NAc-(1→3)-β-D-Gal*p*NAc-(1→3)-α-D-Gal*p*-(1→4)-β-D-Gal*p*-(1→4)-β-D-Glc*p*

31

R-β-D-Glc*p*NAc(6S)-(1→3)-β-D-Gal*p*(6S)-R

3
↑
1
α-L-Fuc*p*

R = *β*-D-Glc*p*NAc(6S)-(1→3)-β-D-Gal*p*-(1→4)-

32

α-L-Ara*f*-(1→3)-β-D-Xyl*p*-[(1→4)-D-Xyl*p*]$_n$

33 n = 1 **34** n = 2

(D-Man*p*)$_9$-β-D-Glc*p*NAc-(1→4)-D-Glc

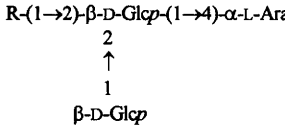
35

α-D-Glc*p*-(1→6)-α-D-Glc*p*-(1→6)-D-Glc

36

The ^{1}H-n.m.r. data of 20 oligosaccharides containing α-NeuAc linked (2→3) or (2→6) to α-D-Gal*p*NAc or β-D-Gal*p* residues in D_2O have been carefully analyzed. It was found that the chemical shift of H-6 of the NeuAc residue is characterisatic for the linkage type.[82]

Deviations from additivity of chemical shift values in the ^{13}C-n.m.r. spectra of a large number of branched trisaccharides, due to conformational differences between the disaccharide fragments of the trisaccharides under consideration and the respective unsubstituted disaccharides, have been reported.[83,84] A repulsive interaction between the methyl group of rhamnose and the hydroxyl groups of other sugar residues in the triterpenoid tetrasaccharide **37** has been identified from force field calculations as the cause of an appreciable difference in conformation between analogues **37** and **38** and the resulting absence of glycosylation shifts in **37**.[85]

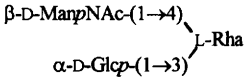


37 R = α-L-Rha*p*

38 R = β-D-Xyl*p*

The repeating unit **39** of the *O*-antigenic polysaccharide of *Aeromonas salmonicida*[86] and sialyl Lewis x[87] have been subjected to detailed conformational analysis by ^{1}H-n.m.r. spectroscopy including n.O.e. measurements and molecular mechanics, respectively. Molecular mechanics and dynamics calculations, as well as ^{1}H- and ^{13}C-n.m.r. data have been used to determine the solution conformations of trisaccharides formed from barley glucan.[88]

Extensive long-range ^{1}H spin-spin coupling, either by zig-zag pathways or "through space", has been observed in rigid cyclic systems, such as terpenoid tetrasaccharide glycosides,[89] and long-range ^{1}H-^{13}C coupling constants in peracetylated β-cyclodextrins have been measured by 1D inverse-detected methods; emphasis was put on interglycosidic heteronuclear couplings which are useful for conformational analysis.[90]



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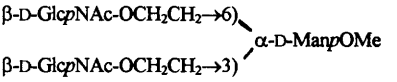


40

The site-specificity of the β-(1→4)-D-galactosyl transferase catalyzed galactosylation of biantennary acceptor substrates has been investigated by application of n.m.r. spectroscopic techniques to the spacer-modified trisaccharide glycoside **40** as model.[91]

4-*O*-Me-α-L-Dig*p*-(1→4)-α-L-Dig*p*-(1→3)-α-L-Dig*p* Dig = 2,6-dideoxy-*ribo*-hexose

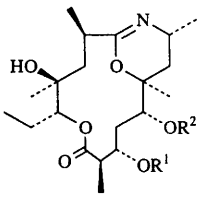
3
↑
1
α-L-Dig*p*

41

A study on the macrolide antibiotic kijanimycin, which contains the tetrasaccharide residue **41**, by n.m.r. spectroscopy and HSEA force field calculations on the carbohydrate moiety, showed that the α-(1→3)-linked digitoxose residues are severely restricted in their conformational freedom.[92] The predominant solution conformation of the synthetic intermediates, such as macrocycle **42**, of 15-membered azalides have been established by similar techniques.[93] Molecular dynamics studies on calicheamycins are referred to in Chapter 19.

7 N.m.r. of Nuclei other than ^{1}H and ^{13}C

The ^{1}H- and ^{19}F-n.m.r. spectra of 4-deoxy-4-fluoro-D-glucose and 6-deoxy-6-fluoro-D-galactose in D_2O, methanol-d_4, and DMSO-d_6 have been recorded; detailed consideration was given to the assignment of the C-6 methylene protons.[94] Double-tailed fluoroalkyl phosphosugars (see Chapter 7) have been characterized by ^{1}H-, ^{13}C-, ^{19}F-, and ^{31}P-n.m.r. methods.[95] Interunit through-space ^{13}C-^{19}F and ^{1}H-^{19}F couplings for fluorinated aminoglycosides have been observed by ^{1}H-detected shift correlated spectroscopy, a new n.m.r. technique.[96] The ^{1}H-, ^{13}C-, and ^{31}P-n.m.r. spectra of the four methyl α-D-mannose monophosphates have been fully assigned.[97] Low temperature ^{31}P-n.m.r. studies on cyclic AMP showed that hydrogen bonding has a significant effect on ^{31}P chemical shifts.[98] ^{29}Si chemical shifts have been assigned to different Tms groups in poly-trimethylsilylated methyl glycopyranosides by use of a 2D INEPT spin-flip J-resolved technique.[99] Attempts to elucidate the mechanism of the regioselective benzylation of methyl glycosides *via* stannylene acetals by use of ^{119}Sn n.m.r. spectroscopy were essentially unsuccessful but showed that a large number of different tin intermediates are involved.[100]



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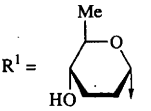

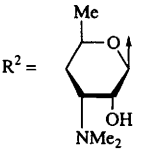

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22
Other Physical Methods

1 I.r. Spectroscopy

Vibrational Raman optical activity (ROA) fingerprint regions have been used to define relative orientations about the C-O bonds and anomeric configurations in D-glucose, some deuterated glucose-derivatives, D-glucosamine hydrochloride and 5-thio-D-glucose.[1] Similar ROA methods have also been applied to D-galactose, D-mannose and laminarin.[2] Furthermore, peaks at 427±10cm^{-1} in disaccharides and polysaccharides have been shown to reflect glycosidic configuration. ROA spectra of D-maltose, D-cellobiose, D-isomaltose, D-gentiobiose, D-trehalose and α-cyclodextrin provide a useful tool for measuring disaccharide stereochemistry in solution.[3] Raman spectra of oligosaccharides containing different glycosidic linkages (α-1,1, β-1,2 and β-1,3) have been reported and compared with calculated values, showing good agreement, including bands for heavy atoms involved in the glycosidic linkage.[4,5] A theoretical study of the vibrational spectrum of β-D-glucose has been reported.[6] The Raman spectrum of uniformly ^{13}C-labelled crystalline thymidine has allowed assignment of some deoxyribose vibrations.[7] A vibrational molecular force field of *N*-acetyl-α-D-glucosamine in the crystalline state has been described, with IR and Raman data being used to refine the force field. I.r. and Raman spectral lines can be assigned to vibrational modes in the molecule.[8]

A number of IR studies this year have concerned intramolecular H-bonding. The inaccuracies of earlier H-bond length determinations in β-D-glucose and cellulose II have been discussed, and a method proposed for more accurate determination from i.r. and Raman frequencies.[9] A variable temperature FTIR study of crystals of α-D-mannose, β-D-galactose and α-D-glucose has been reported, allowing assignment of peaks to different O-H···O systems.[10] Deuterium exchange was used to check the vibrational coupling. I.r. study of intramolecular H-bonds of methyl mono- and di-*O*-substituted β-D-xylopyranosides showed evidence for a substituent-dependent conformational equilibrium between $^4C_1$ and $^1C_4$ forms.[11]

The regiochemistry of glycosylations of allopyranose-derived 1,2-vicinal diols with glycosylidene carbenes has been studied by Vasella and co-workers, and rationalized on the basis of relative OH acidity-nucleophilicity, determined by means of FTIR study of intramolecular H-bonding.[12,13] This was extended to a study of glycosylation of monosaccharide triols,[14] and of 2-amino-N-phthalimido sugar diols.[15] These workers have also reported an extensive study of intramolecular H-bonding in the D-*manno*-, D-*galacto*- and D-*allo*- series for 4,6-*O*-benzylidene acetal methyl glycosides, leading to definition of the main H-bonding patterns involved.[16,17]

2 Mass Spectrometry

Electron impact and c.i. mass spectrometry have been used to determine the position of fluorination of methyl 1-deoxy-1-fluoro-, 2-deoxy-2-fluoro-, 3-deoxy-3-fluoro- and 4-deoxy-4-fluoro-per-*O*-methyl-

β-D-galactopyranosides.[18] The intensity of f.a.b. m.s. fragment ions from *N*- and *S*-glycosides of acetylated hexose isomers allows identification of the monosaccharide as mannose, galactose or glucose-derived.[19] A series of 3,4,6-tri-*O*-benzyl-β-*C*-glycopyranosides containing X-C_6H_4S (X=Me, Cl) at C2 have been characterized by mass spectrometry.[20] Secondary ion mass spectrometry (SIMS) has been used to characterise positional and anomeric isomers of methyl 2-*O*- and 3-*O*-sulfo-D-glucopyranosiduronic acids and methyl 2-*O*- and 3-*O*-sulfo-D-glucopyranosides.[21] Negative ion collisionally activated decomposition of isopropylidenated carbohydrates has been used to differentiate stereoisomers.[22]

Tandem mass spectrometry has been used to investigate the stereochemistry/structure of a series of monosaccharides and their boronate diesters.[23] 2-Deoxy-D-*ribo*-furanosides have been employed to investigate ionization processes occurring in liquid-assisted SIMS (LSIMS).[24] Several reports of metal-cationization in collision-induced decomposition in mass spectrometry of monosaccharide derivatives have been reported this year. A study of collision-induced decomposition of methyl 6-bromo-6-deoxy-α-D-glucopyranoside metal-cationized by alkali metals or Ag^+,[25] and of per-*O*-acetyl- and per-*O*-benzyl-α-D-thioglycosides cationized by Li^+ and Ag^+, have been described.[26] Studies on alkyl per-*O*-acetyl-2-deoxy-2-halo-α- -mannopyransides have also been reported.[27]

The electron impact m.s. fragmentation pattern of 1-[(2'-carbonyl)-pyrrolidinyl]-1-deoxy-D-fructose shows two main fragmentation pathways initiated by ring O and amino N, giving stabilized oxonium and imminium ions.[28]

It has been reported that m.s. of permethylated disaccharide hexopyranosyl-hexitols (19 examples) generates diagnostic ions from which the position of linkage to the alditol residue can be assigned.[29] The metastable kinetic energy and collision-induced dissociation of per-*O*-acetylated-D-trehalose under electron impact and c.i. m.s. were reported.[30] Determination of anomeric configuration of disaccharides (trehalose, sucrose and cellobiose) can be achieved by inspection of f.a.b.m.s. spectra run in dry glycerol.[31] A series of deoxynojirimycin (DNJ) containing di- and tri-saccharides, αNeu5Ac(2→6)-DNJ, αNeu5Ac(2→3)-β-D-Gal(1→4)DNJ, and αNeu5Ac(2→6)[α-L-Fuc(2→3)]DNJ have been characterized by ion-spray and tandem mass spectrometry.[32]

This year has seen continuing reports of applications of mass spectrometry towards structural analysis of oligosaccharides, including anomeric assignments. Atmospheric pressure m.s. has been used to analyse saccharides. Low temperature spectra only gave cationized undecomposed saccharides, but at high temperature, fragment ions from glycosidic cleavage were observed providing information about saccharide structure.[33]

Unsaturated C-aryl glycosides have been studied using f.a.b.-MIKE and f.a.b.-CAD-MIKE (Mass analysed Ion Kinetic Energy. Collision-Activated Dissociation) and tandem m.s. techniques, allowing anomers to be distinguished from $[M+H]^+$ and $[M+metal]^+$ ions (metal=Li or Na).[34] Two reports of glycoflavanoid analysis by mass spectrometry have appeared in 1994. Desorption c.i.m.s. of C-glycosylflavones (NH_3 carrier gas) allowed sequence and the pentosyl or pyranosyl nature of the sugar to be determined.[35] Reverse phase HPLC-thermospray mass spectrometry was utilized for identification of flavonoid glycosides from plant extracts, through determination of sequence and glycosylation site.[36]

F.a.b.m.s. on multisulfated oligosaccharides from human respiratory mucous glycoprotein, combined with monosaccharide composition, allowed for determination of carbohydrate sequence, and the number and position of sulfate esters.[37]

Electrospray mass spectrometry has provided valuable information regarding Ca^{2+} binding to Lewis acid derivatives. Sialyl Lewis X (SLe^x), 2-deoxyfucoseSLe^x, 3-deoxy-fucoseSLe^x and 4-deoxy-fucoseSLe^x were investigated, and results indicate the Ca^{2+} is mainly coordinated to the GalGlcNAc component.[38]

Electron spray ionization m.s. (ESIMS) has been utilised for structural analysis of large oligosaccharides and related glycoconjugates up to molecular weight of 9400, while collision-induced dissociation provided sugar sequence information.[39] ESIMS has also been applied to sequencing a tetrasaccharide monopeptide.[40] Matrix-assisted laser desorption ionization-time-of-flight (MALDI-TOF) m.s. has been used in the complete structural characterisation of oligosaccharides from RNAse B (with assistance from NMR).[41]

Matrix isolation has been applied to ^{252}Cf plasma-desorption m.s. (PDMS) of underivatized oligosaccharides, an examination of different matrices indicating certain heteroaromatic amines lead to enhanced ion intensities.[42]

3 X-ray and Neutron Diffraction Crystallography

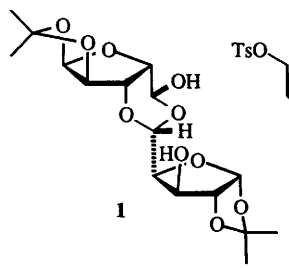
Specific X-ray crystal structures have been reported as follows (solvent molecules of crystallization are frequently not reported).

3.1 Free Sugars and Simple Derivatives Thereof. - A low temperature (140K) structure of α-D-glucose with no water of crystallization has been determined in which the often-reported C1-O5, C5-O5 bond length difference was not seen.[43] [The crystal was obtained from a drop of clear liquid hanging from a cactus on the windowsill of the authors' lab.] A method for predicting crystal structures of β-D-allose, α-D-glucose, α-D-galactose, β-D-galactose and α-D-talose was reported, and in four cases the prediction matched, or nearly matched, experimentally determined structures.[44] The dimeric sugar 1,2-*O*-isopropylidene-α-D-*xylo*-pento-dialdo-1,4-furanose **1** (which forms dimers in the crystalline state containing O3H···O2 and O5'H···O1' *inter*molecular H-bonds).[45]

3.2 Glycosides, Disaccharides and Derivatives Thereof. - Methyl α-D-galactopyranoside-3-(sodium sulfate),[46] methyl α-L-rhamnopyranoside[47] and *o*-iodophenyl β-D-galactopyranoside,[48] methyl-β-L-*threo*-D-*galacto*-8-nonulosopyranoside.[49]

Two polymorphs of α,α-trehalose octacetate monohydrate,[50] 4,4'-dideoxy-α,α-*xylo*-trehalose,[51] methyl 2,3,4,6,2',4',6'-hepta-*O*-acetyl-α-laminaribinoside,[52] 3,3'-dideoxy-α,α-*arabino*-trehalose.[53] Methyl 2,3-*O*-isopropylidene-5-*O*-tosyl-β-D-ribofuranoside **2**,[54] the 7-carbon glycoside **3** (see Chapter 17),[55] C-glycosidic furanoside **4** (see Chapter 14)[56] the oxazoline derivative **5**[57] and methyl 1,6-di-*O*-(4-bromobenzoyl)-3,4-di-*O*-(4-methoxycinnamoyl)-β-D-fructofuranoside.[58] Di-(3-deoxy-D-*glycero*-pentulose)-1,2':2,1'-dianhydride,[59] methyl 4,6-benzylidene-α-D-allopyranoside,[60] methyl-2,3,4-tri-*O*-acetyl-α-L-rhamnopyranoside,[61] 2-(indol-3-yl)ethyl 2,3,4-tri-*O*-acetyl-α-L-

arabinopyranoside,[62] the mixed propargylic acetal glycoside **6**,[63] the glycosides **7** and **8**, intermediates in an approach to the herbicidin skeleton (see Chapter 24 for synthesis),[64] methyl 6-*O*-(*N*-heptylcarbamoyl)-α-D-glucopyranoside.[65] The structure of flavocommelin octaacetate **9** was reported.[66]



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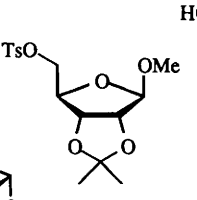

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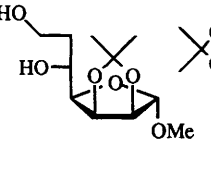

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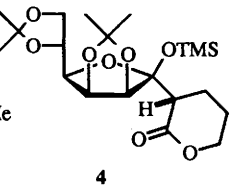

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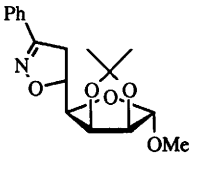

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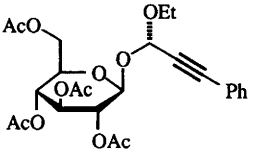

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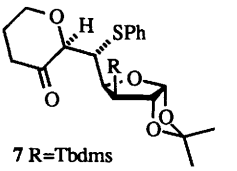

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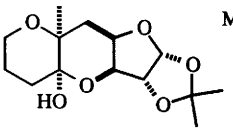

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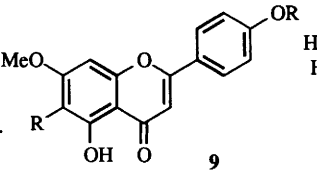

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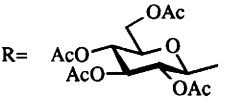

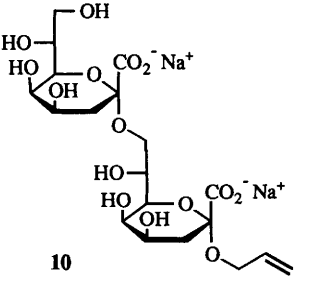

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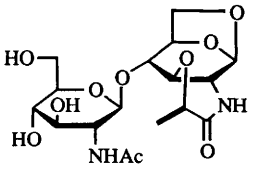

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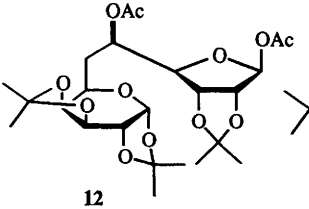

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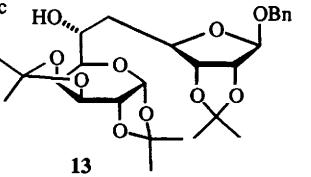


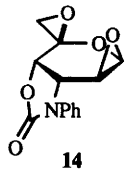
13

Disaccharides: 4,4',6,6'-tetrachloro-4,4',6,6'-tetradeoxy-α,α-*galacto*-trehalose,[67] allyl *O*-(sodium 3-deoxy-α-D-*manno*-2-octulopyranosylonate)-(2→8)-*O*-(sodium 3-deoxy-α-D-*manno*-2-

octulopyranosidonate)-monohydrate, the Kdo dimer **10**,[68] muramic acid lactam **11**,[69] 2,2',3,3'-tetra-*O*-acetyl-6,6'-dichloro-4,4',6,6'-tetradeoxy-α,α-trehalose,[70] 2,2'-di-*O*-acetyl-3,6,3',6'-dianhydro-4,4'-dideoxy-α,α-trehalose,[71] 2,2',3,3'-tetra-*O*-acetyl-4,4',6,6'-tetradeoxytrehalose,[72] benzyl 5-*C*-(2-amino-1-*O*-t-butyl-2,6-dideoxy-3,4-*O*-isopropylidene-2-*N*-phthaloyl-β-D-*galacto*-pyranosy-6-yl)-5-*O*-acetyl-2,3-*O*-isopropylidene-β-D-*allo*-pentofuranoside,[73] methyl-2,3,4,7-tetra-*O*-benzyl-6-deoxy-9-*C*-(6'-*O*-benzyl-1',2':3',4'-di-*O*-isopropylidene-D-*glycero*-α-D-galactopyranos-6-yl)-L-*ribo*-β-D-*galacto*-nonopyranoside,[74] and the two *C*-linked disaccharides **12** and **13**.[75]

3.3 Higher Oligosaccharides and *C*-Glycosides. - The trisaccharide erlose trihydrate, β-D-fructofuranosyl *O*-α-D-glucopyranosyl-(1→4)-D-glucopyranoside.$3H_2O$.[76] One tetrasaccharide structure has been reported: 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-(1→3)-[2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-(1→6)]-(2,4-di-*O*-acetyl-β-D-glucopyranosyl)-(1→3)-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose.[77] The crystal structure of α-cyclodextrin-(benzyl alcohol)$_2$.$6H_2O$ shows one benzyl alcohol included within the CD cavity, and one in contact with the outside of the cavity.[78] The structure of per-6-bromo-per-6-deoxy-2,3-di-*O*-methyl-β-cyclodextrin reported by Stoddart and co-workers shows that the conformation deviates significantly from C_7 symmetry.[79] A discussion has been presented on the reliability of assigning O-H···O hydrogen bonds to short intermolecular O···O separations in cyclodextrin and oligosaccharide crystal structures.[80]

3.4 Anhydro-sugars. - 2,7-Anhydro-4,5-*O*-isopropylidene-β-D-*altro*-2-heptulopyranose,[81] the bis epoxide **14**,[82] 1,6:3,4-dianhydro-2-*O*-(*p*-tolylsulfonyl)-β-D-galactopyranose **15**,[83] and 1,6-anhydro-3,4-dideoxy-3,4-epithio-2-*O*-(*p*-tolylsulfonyl)-β-D-allopyranose **16**.



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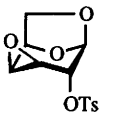

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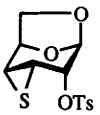
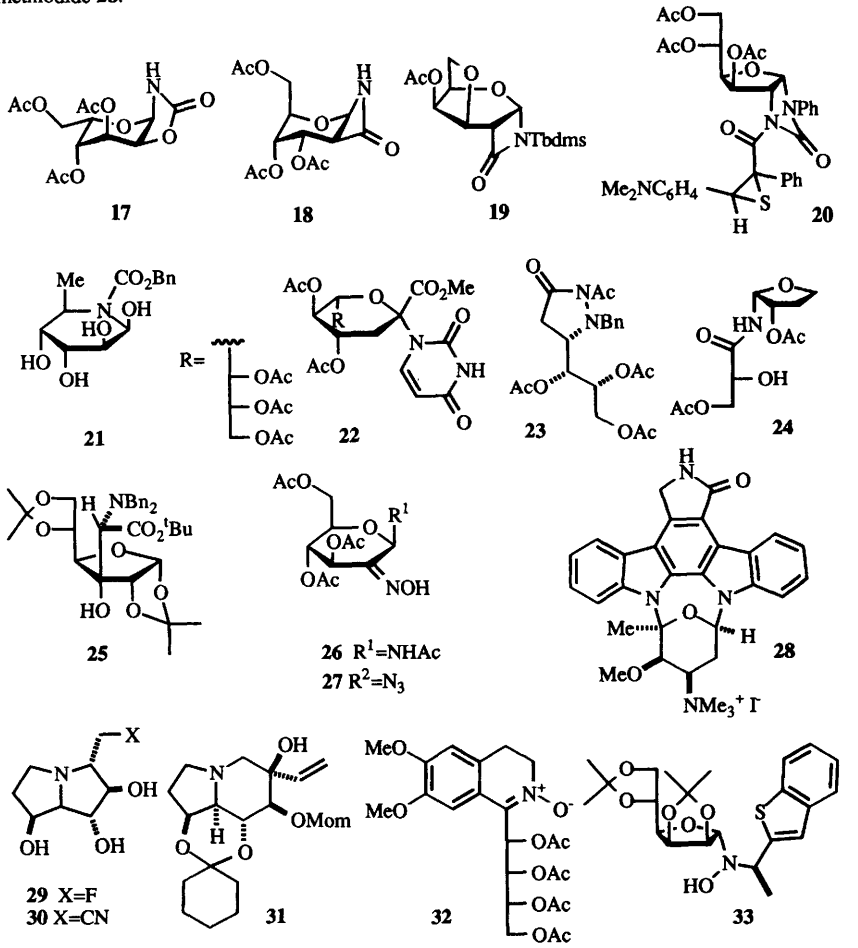


16

3.5 Nitrogen, Sulfur and Selenium-containing Compounds. - (1*S*, 2*S*)-1,2-bis-(D-gluconamido)cyclohexane,[84] 1-deoxy-1-nitro-D-altritol, providing information about 1,3-parallel C//O interactions in acyclic carbohydrates[85] (conformational similarities to D-altritol and its hexaacetate, with a sickle conformation in which parallel C//O C6, C3 interactions are tolerated in avoiding 1,3-parallel O//O interaction between O3 and O5). The isoxazolidinone **17**,[86] β-lactams **18** and **19**,[87] imidazolinone **20**,[88] 5,6-dideoxy-5-*N*-benzyloxycarbonyl-5-amino-β-DL-altropyranose **21**,[89] α-*N*-glycoside **22**, a derivative of Kdn,[90] and heterocycle **23** derived by conjugate addition of *N*-benzylhydrazine to a D-*erythro* unsaturated sugar lactone.[91]

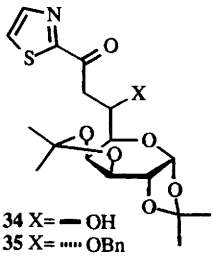
The amide **24**, an intermediate in synthesis of methyl 4,6-dideoxy-4-(3-deoxy-L-*glycero*-tetronamido)-α-D-mannopyranoside,[92] t-butyl-*N*,*N*-dibenzyl-2-(1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose-3-yl)-L-glycinate **25**,[93] 2-deoxy-2-hydroxyimino derivatives **26** and **27** of β-D-*arabino*-hexopyranose,[94] and 2,3,4,5-tetra-*O*-acetyl-6-amino-6-deoxy-D-galactonolactam.[95] The *N*-glycosidic

natural product, staurosporine has been characterized by X-ray crystallographic analysis of its methiodide **28**.[96]

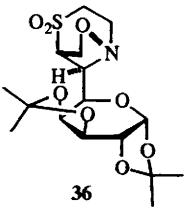


Several sugar-derived N-heterocycles have been reported: castanospermine analogues **29-31**,[97] 1-deoxynojirimycin.HCl,[98] the carbohydrate-derived dihydroisoquinoline-*N*-oxide **32**,[99] and *N*-trideca-5,7-diyne-D-glucosamine (a super-structure forming synthetic glycolipid) at 295, 100 and 20K.[100]

Sulfur-containing compounds reported were the (*R*)-zileuton precursor **33**,[101] aldol derivatives **34** and **35**,[102] the nitrone cycloaddition product **36**,[103] spiro-oxathiazole sugar-derivative **37**,[104] thioglycosides **38** and **39**,[105] and dihydrothiophene **40**.[106]



34 X= — OH
35 X= ····· OBn



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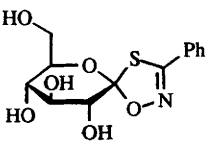

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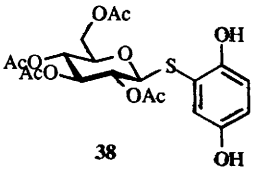

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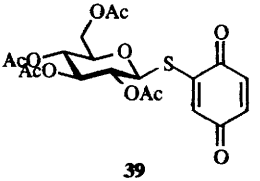

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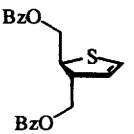
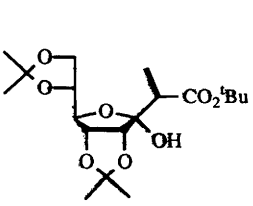


40

3.6 Branched-chain Sugars. - A ulosonic acid derivative **41**,[107] the squalastatin 1 analogue **42** (see Chapter 24),[108] and the spiroannelated α-methylene-γ-butyrolactone **43**.[109]



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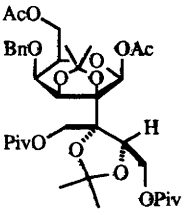

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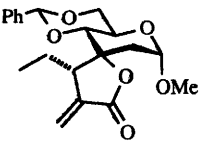
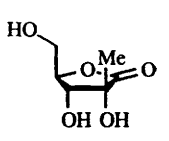


43

3.7 Sugar Acids and their Derivatives. - Methyl methyl α-D-galactopyranosiduronate,[110] 5-*O*-acetyl-2,3-*O*-(*R*)-benzylidene-D-ribono-1,4-lactone, 3,5-*O*-(*S*)-2-*O*-*p*-nitrobenzoyl-D-*xylono*-1,4-lactone and 3,5-*O*-(*S*)-benzylidene-D-lyxono-1,4-lactone,[111] 7-deoxy-3,4-*O*-isopropylidene-L-*glycero*-L-*galacto*-heptono-1,5-lactone,[112] D-*glycero*-D-*gulo*-heptono-γ-lactone and its 2,7-ditosylate,[113] 2,6-di-*O*-mesyl-D-mannono-γ-lactone, 2,6-di-*O*-mesyl-D-allono-γ-lactone and 2,6-di-*O*-mesyl-D-gulono-1,4-lactone.[114] 2-*C*-Methyl-D-ribono-1,4-lactone (**44**),[115] L-rhamnono-1,4-lactone **45**, and L-mannono-1,4-lactone **46** (**45** adopts an E_3 envelope conformation, slightly distorted towards $^2T_3$ and **46** adopts a perfect envelope).[116] The X-ray structures of the disodium and dipotassium salts of D-galactaric acid,[117] and of the D-galactonic acid-derived α,β-unsaturated ester **47** have also been described.[118]

3.8 Inorganic derivatives. - The amino boronate **48**,[119] the cyclic phosphonates **49** and **50** and derived disaccharide mimetics **51a** and **51b**,[120] 1,2:5,6-di-*O*-Isopropylidene-α-D-glucofuranosyl-

N,N-bis(2-chloroethyl)phosphordiamidate (*R* at phosphorus),[121] 1,4-anhydro-4-deoxy-2,3-*O*-isopropylidene-4-[(*R*)-methoxyphosphinyl)-L-ribitol **52**,[122] and glycosyl phosphonate **53**.[123] The phosphonamidate **54**[124] has been characterized by X-ray analysis.



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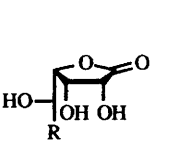
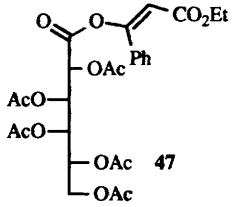


45 R=Me
46 R=CH_2OH



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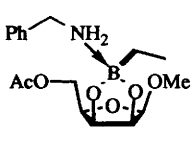
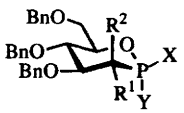
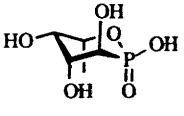


48



49a R^1=OH R^2=H X=OBn Y= =O
49b R^1=H R^2=OH X= =O Y=OBn
49c R^1=OAc R^2=H X= =O Y=OMe



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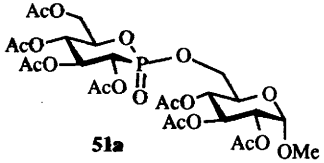
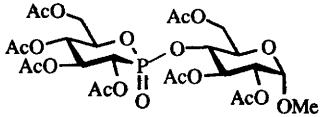


51a



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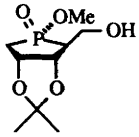

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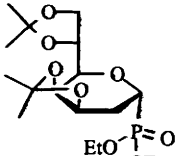

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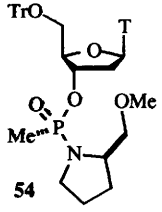
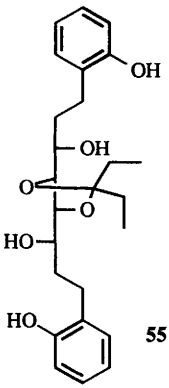


54

Tetraol **55** forms a linear trinuclear titanium complex,[125] and sugar-derived ferrocene **56**[126] (analogous mannopyranoside complex: Vol. 26, Chapter 22, ref. 96) and dilithium-*bis*-[methyl α-L-rhamnopyranoside-(2,3)-ato(2⁻)]cuprate(II) **57**[127] have been described This year has seen a series of reports of interesting complexes of multiply deprotonated sugars with various metals. Erythritol and galactitol (dulcitol) react with basic solutions containing excess copper to form linear coordination Cu(II) polymers of empirical formula $Na_2[Cu(ErytH)_{-4}].Eryt.12H_2O$, and $Li_2[Cu(DulcH)_{-4}].10H_2O$, respectively, represented by **58** and **59**.[128]

In related work, sixteen-fold deprotonated γ-cyclodextrin forms toroidal complexes with hexanuclear lead(II) of empirical formula $[Pb_{16}(\gamma\text{-}CDH_{-16})_2].ca.20H_2O$, and with a structure consisting of a ring of "inside" and a ring of "outside" lead atoms, **60**.[129] The structure of a 3,4-mannitolate bis(phosphine)platinum(II) carbamate complex[130] and the mannosyl stannane **61** have been reported.[131] The iron-dienyl complex **62**[132] has been described.



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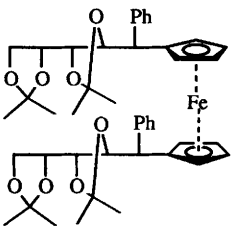

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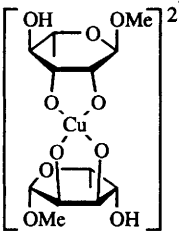

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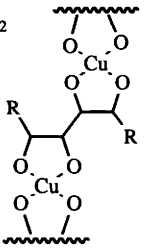
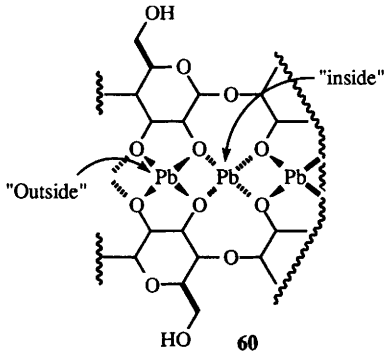


58 R=H
59 R=CH_2OH



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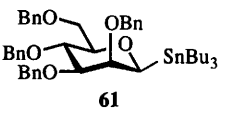

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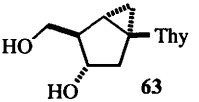

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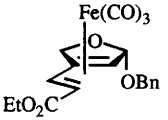

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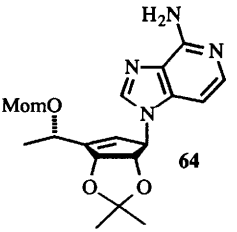

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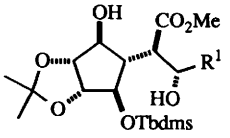
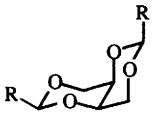
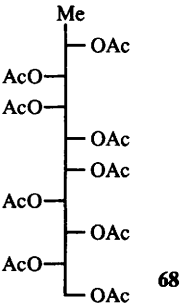


65 R^1=cychex



66 R=H
67 R=*trans*-CH=CHPh

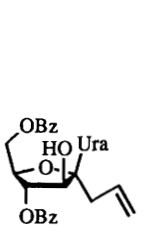


68

3.9 Alditols, Cyclitols and Derivatives Thereof.- Meso-D-*glycero*-L-*altro*-heptitol and its monohydrate and heptaacetate, meso-D-*glycero*-L-*ido*-heptitol and its heptaacetate,[133] 1,3,4,5-tetra-*O*-benzyl-β-D-fructopyranosyl cyanide,[134] the cyclopropane fused carbocyclic nucleoside analogue **63**,[135] neplanocin intermediate **64**,[136] the cyclopentane **65**,[137] 1,3,5,7-tetraoxadecalins **66** and **67**

(notably MM2 and MM3 calculations did not predict the unusually short C-C bond lengths observed),[138] and nona-*O*-acetyl-1-deoxy-L-*ido*-D-*galacto*-decitol **68**.[139] Structures of inositols and derivatives continue to be reported: *neo*-Inositol,[140] (±)-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol and (±)-1,2:5,6-di-*O*-isopropylidene-*myo*-inositol,[141,142] and L-quebrachitol.[143]

3.10 Nucleosides and their Analogues and Derivatives Thereof.- 1-(3',5'-Di-*O*-benzoyl-1'-*C*-allyl-β-D-arabino-furanosyl)uracil **69**,[144] 3-β-D-ribofuranosyl-6,7-dihydro-9H-thiazolo[3,2-*a*]purin-9-one **70**,[145] and sodium 5-bromo-cytidine-5'-phosphate.[146] The X-ray structure of 3-methyl-7-deazainosine (**71**) showed a conformation fixed *anti* about the glycosidic bond.[147] 2'3'-Dideoxy-3'-methylamino-ribosylthymine (ddT(3'NHMe)),[148] β-5-isopropyl-2'-deoxyuridine,[149] 5-hydroxymethyl-2'-deoxycytidine,[150] 3'-*O*-acetyl-2'-deoxy-5-(methoxymethyl)uridine,[151] 4-*O*-(4-acetylamino-2,6-dimethylphenyl)uridine **72**,[152] 3'-azido-2',3'-dideoxy-5-hydroxymethyluridine,[153] and 2',3'-didehydro-2',3'-dideoxy-5-hydroxymethyluridine.[154] The cyclobutyl-fused analogue of 2'-deoxythymidine **73** was obtained by photochemical [2+2] cycloaddition to the nucleobase with 2,3-dimethylbut-2-ene.[155] The structure of the potent anti-HIV agent, 4'-azidothymidine **74** showed a C3'-*endo*-conformation with axial azide group, an unusual conformation for an antiretroviral nucleoside analogue.[156] The unsaturated enamino nucleoside analogue **75**,[157] 3'-fluoro-3'-methyl-2',3'-dideoxythymidine **76**, prepared by asymmetric synthesis (see Chapter 20),[158] and the 2,2'-anhydro-1-(3'-bromo-3'-deoxy-5'-*O*-trityl-β-D-arabinofuranosyl)thymine derivative **77**.[159]



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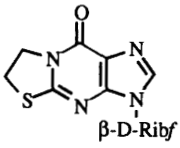

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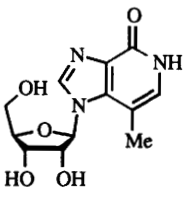

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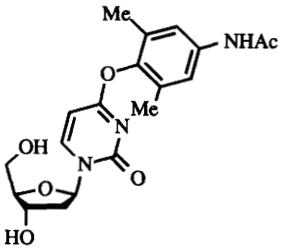

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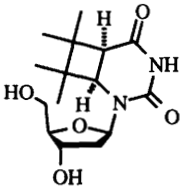

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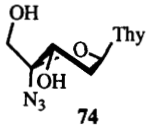

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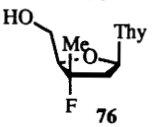

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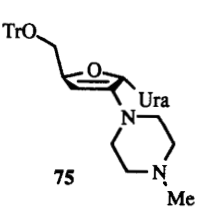

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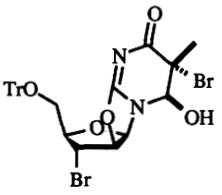
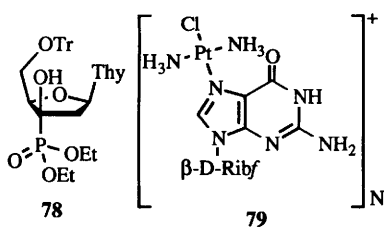


77

An X-ray structure of a phosphonate ester has been reported: 2'-deoxy-3'-diethylphosphono-5'-*O*-trityl-β-D-*threo*-pentofuranosylthymine **78**.[160] One metal complex has been reported: *cis*-diamminechloro(guanosine-N^7)-platinum (II) nitrate dihydrate **79**.[161]



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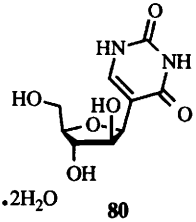

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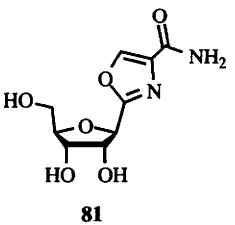

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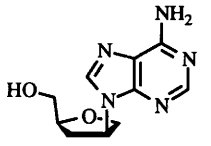

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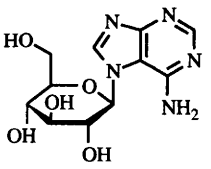

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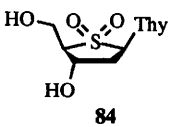
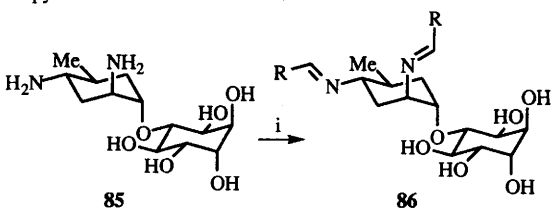


84

Several C-nucleoside, isonucleoside, thionucleoside and hexose nucleoside crystal structures have been reported this year: β-D-arabinosylcarbouridine **80**[162] and oxazofurin **81**,[163] isodideoxyadenosine **82**,[164] 7-β-D-glucopyranosyladenine **83**,[165] and the 4-thionucleoside derivative **84** (structural details and relationship to activity are discussed in Chapter 20).[166]

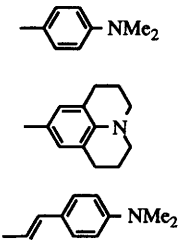
4 Polarimetry, Circular Dichroism, Calorimetry and Related Studies

The absolute sense of twist between the two amino groups of the diaminocyclohexane of kasugamin **85** can be determined from the signs of exciton-split c.d. curves of derivatives **86** bearing two chromophoric imino groups. The protonated forms lead to strong bathochromic and hypochromic shifts. Similar derivatizations were applied to methyl α-L-acosaminide and daunosamine.[167] The effects of stereochemistry and solvent on o.r.d., c.d. and u.v. spectra of 1-nitrophenyl D-galactopyranosides has been described.[168]



85 **86**

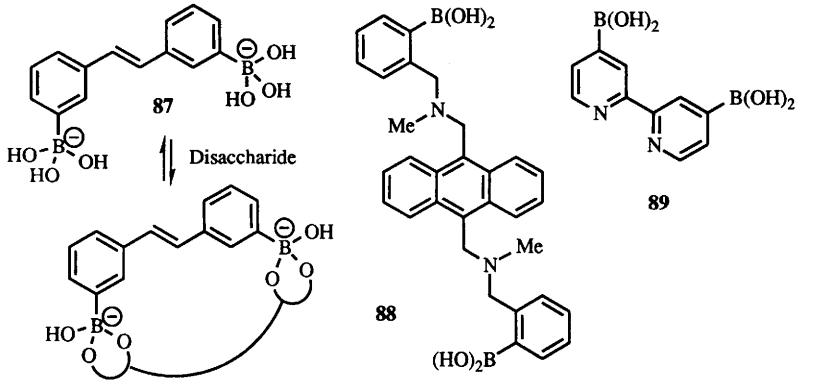
Reagents: i, RCHO.



Scheme 1

A short report describes applying the exciton chirality method to the study of carbohydrate conformations.[169]

Lehn and co-workers have described the antenna effect in multichromophoric cyclodextrins, where excitation energy is transferred from chromophores (attached to the c.d.) to complexed merocyanine, with an efficiency close to 1.[170]



Trans-3,3'-stilbenediboronic acid **87** has been shown to exhibit selective disaccharide recognition, determined by changes in fluorescence. D-(+)-Melibiose led to the largest enhancement in fluorescence.[171] The same group have developed **88** as a glucose-selective fluorescence sensor, which a 1:1 complex with glucose with maximum fluorescence changes in concentration ranges suitable for physiological determination of glucose levels (see Chapter 23).[172] This group also described the synthesis of 2,2'-bipyridine-4,4'-diboronic acid **89** which forms 1:1 c.d.-active complexes with diasaccharides (D-maltose, D-cellobiose and D-lactose). When Fe^{2+} (as $FeCl_2$) is added to these complexes, the resulting Fe^{2+}(**89**•disaccharide)$_3$ complexes are shown by c.d. spectra to be optically enriched.[173] The optical purity is estimated at *ca.* 20% in the maltose system.

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23
Separatory and Analytical Methods

1 Chromatographic Methods

1.1 Gas-Liquid Chromatography. — All reports are concerned with the use of capillary columns. G.c.-(e.i.)m.s. analysis of partially methylated alditol acetate derivatives has been used in the study of water soluble pectins,[1] and the partially ethylated alditol and aldononitrile acetate derivatives of galactose and mono-*O*-methyl-galactoses have been similarly examined.[2]

A review on the chromatographic analysis of gibberellins included a section on g.c. analysis of permethylated glucosides.[3] Modified conditions have been reported for conducting the reductive cleavage of methylated polysaccharides so that *N*-acetylglucosamine residues can be detected together with other monosaccharides. *N*-Acetylglucosamine residues form oxazolinium ions by participation of their 2-NHAc groups, and are not further reduced under the conditions used, but can be converted into the corresponding glycosides by quenching the reaction mixture with alcohol. Thus in a model study, methyl 2-deoxy-3,4,6-tri-*O*-methyl-2-(*N*-methylacetamido)-β-D-glucopyranoside underwent transglycosidation *via* such an oxazolinium ion intermediate in the presence of trimethylsilyl triflate/triethylsilane followed by quenching with an alcohol. Use of methanol gave back the methyl glycoside, while use of (±)-2-butanol gave a pair of separable diastereomeric glycosides which establishes the potential of this method for determining the absolute configurations of 2-acetamido-sugars.[4] The absolute configurations of monosaccharide residues in plant glycosides, especially saponins, have been determined by β-glucuronidase hydrolysis, reaction with optically active 2-butanol, pertrimethylsilylation and g.c.-m.s. analysis.[5]

By use of *myo*-inositol and turanose as internal standards, mannitol and lactulose were determined in the present of glucose as their pertrimethylsilylated derivatives during an intestinal permeability test.[6] Purine and pyrimidine nucleosides and bases, and uric acid, all parts of the assembly pheromone of ticks, were detected by g.c.-m.s. analysis of pertrimethylsilylated derivatives using an ion-trap detector.[7]

The simultaneous g.c.-(e.i.)m.s. analysis of sugars (aldoses, ketoses, sugar acids, oligosaccharides and alditiols), carboxylic acids and phosphoric acid as their pertrimethylsiylated oxime derivatives has been optimized and applied to the analysis of over 40 such components in apple varieties.[8] G.c.-m.s. analysis of carbohydrates as their acetylated *O*-methyloxime derivatives was particularly useful for application to glycoconjugates of plant origin.[9]

1.2 Thin-Layer Chromatography. — Flavonoids and their glycosides were separated on silica and detected with a diphenyltin dichloride spray.[10] Digoxin, digoxigenin bis-digitoxoside and gitoxin in digoxin drug substances were determined on C_{18}-silica with densitometric assay.[11] High resolution separations of mono-, di- and poly-sialoganglioside fractions were achieved by automated three-fold development on silica.[12]

A device for micropreparative isolation of substances from t.l.c. plates was demonstrated with the separation and isolation of the *N*-(*p*-nitrophenyl)glycosylamines of glucose, galactose, *N*-acetylglucosamine and maltose.[13]

1.3 High-Pressure Liquid Chromatography. — References are grouped according to the class of sugar being analysed. H.p.l.c. on pellicular anion exchange packings with a strongly alkaline eluant and pulsed amperometric detection will be given the abbreviation h.p.a.e.c.

1.3.1. *General Reviews.* — Pre- and post-column fluorescence derivatization procedures used in the h.p.l.c. analysis of carbohydrates and nucleosides have been reviewed,[14] and a section on the reversed-phase h.p.l.c. analysis of glucosyl ester and glucoside derivatives has been included in a review on the chromatography of gibberellins.[3]

1.3.2. *Detection Methods.* — A nickel-titanium alloy electrode for stable and sensitive electrochemical detection of carbohydrates has been reported.[15] Similarly, several copper(II) oxide modified electrodes were highly sensitive for constant-potential amperometric detection of picomole levels of carbohydrates (Glc, Xyl, xylitol) in alkaline solution in flow through systems (anion-exchange h.p.l.c. and flow injection analysis), although problems with day-to-day reproducibility remained to be solved.[16]

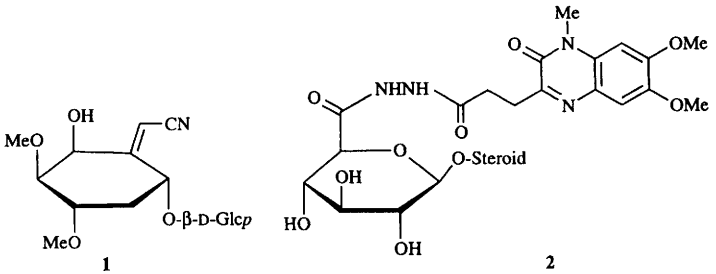
1.3.3 *Neutral Sugars, Amino-sugars, Alditols and Derivatives Thereof.* — H.p.a.e.c. has been applied to the analysis of monosaccharides in wood and pulp hydrolyzates and process liquors, the samples for analysis being prepurified by passage through a mixed-bed exchange resin. Results were in good agreement with those from g.c. analysis of alditol acetate derivatives.[17] H.p.a.e.c. was also used to determine the common mono-, di- and tri-saccharides in fermentation broths,[18,19] although problems with interfering phenolic substances were observed when lignocellulosic hydrolyzate was the sugar source. Otherwise Pb^{2+}-form cation exchange columns with refractive index detection could be used.[20]

Optimal conditions for analysis of synthetic glycopeptides containing *N*-acetyl-glucosamine and -galactosamine residues involved hydrolysis (6M HCl, 110°C), 4-(dimethylamino)azobenzene-4′-sulfonylation (i.e. dabsylation) and reversed-phase h.p.l.c. with visible detection. Dabsylated amino-sugar peaks were maximal after a 1 h hydrolysis treatment; the conventional amino-acid analysis protocol requires 4 h.[21] All the monosaccharides in the galactosaminoglycans from human aorta proteoglycans could be determined by reduction of uronic acid groups [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, $NaBH_4$ in H_2O], hydrolysis, perbenzoylation and reversed-phase h.p.l.c. analysis. Iduronic acid was detected as 1,6-anhydro-2,3,4-tri-*O*-benzoyl-β-L-idopyranose, *N*-acetyl-galactosamine as 2-amino-2-deoxy-α- and β-D-galactopyranose pentabenzoate.[22] A rapid if not entirely quantitative analysis of sugars and polyols in biological fluids involved benzoylation directly in aqueous solution (aq. NaOH, BzCl), neutralization and extraction (EtOAc). Separation of the extracts by reversed-phase h.p.l.c. and analysis by elecrospray m.s. indicated that glucose formed tetra- and penta-benzoyl derivatives, and mannitol formed penta- and hexa-benzoates.[23]

The methods of Honda *et al.* (Vol. 26, p.292, ref. 40), in which reducing-sugars are analysed as their 1-phenyl-3-methyl-5-pyrazolone derivatives by reversed-phase h.p.l.c., has been applied for the first time to acidic- and amino-sugars as well as neutral sugars, good separations being obtained. The method appears quite useful when applied to the analysis of glycoprotein hydrolyzates.[24] 3-Deoxyglucosone, an intermediate in non-enzymic glycosylation of proteins, has been determined by oxidation to 2-keto-3-deoxy-gluconic acid (by crude rabbit liver oxoaldehyde dehydrogenase), derivatization with 4,5-methylenedioxybenzene, and reversed-phase h.p.l.c. analysis with fluorescence detection, a borate buffer eluant being used to ensure separation from the corresponding N-acetylneuraminic acid derivative.[25]

1.3.4 *Glycosides and Glycosyl Ester Natural Products.* — Digoxin and three metabolites (digoxigenin mono- and di-digitoxosides) were determined in serum by reversed-phase h.p.l.c. analysis on a "restricted access support" (a C_{18}-alkyldiol phase, that has a hydrophilic outer layer with hydrophobic pores) with on-line immunochemical detection in which fluorescein-labelled antibodies to digoxigenin are added post-column. Excess unbound antibodies are removed from the eluant on a column of immobilized digitoxin prior to passage through the detector.[26]

Reversed-phase h.p.l.c. analyses have been reported for: simmondsin **1** in plasma (the glycoside is implicated in the inhibition of food uptake by animals fed jojoba meal in which it is the major glucoside);[27] the steroidal saponins of crude ginseng extracts, ginsenosides and malonylginsenosides;[28] glycoalkaloids in potato tubers;[29] the two toxic triterpenoid 2-*O*-



1 2

isopentanoyl-3,4-disulpho-β-D-galactopyranosides atractyloside and carboxyatractyloside (with evaporative light scattering detection);[30] the monoterpenoid β-glucoside paeoniflorin and the flavonoid β-glucuronoside baicalin in traditional chinese medicines (with an acidic eluant);[31] the immunostimulant flavonoid glycosides rholifolin and daidzin, in plasma;[32] the flavonoids and their *O*- and *C*-glycosides in *Cratageus* (hawthorn);[33] flavone *C*-glucosides in plant species of the family Curcurbitaceae;[34] and components of the food spice saffron such as crocins (β-glucosyl and β-gentiobiosyl esters of the carotenoid crocetin) and picrocrocin (a β-glucoside).[35]

Reversed-phase h.p.l.c.-thermospray m.s. was used for the identification of flavonol glycosides in plant extracts.[36]

Methylation (CH_2N_2 or Me_2SO_4) and acetylation were examined for derivatization of hydrolysable tannins (i.e. galloyl and hexahydroxydiphenoyl esters of glucose) prior to analysis by h.p.l.c. on silica or size exclusion chromatography. Both phenolic and sugar hydroxyl groups were effectively derivatized by acetylation, but methylation generally resulted in mixtures of products.[37]

1.3.5 *Oligosaccharides and Glycopeptides.* — A highly selective separation of isomeric disaccharides, and the separation of malto-oligosaccharides up to DP = 21, were achieved by h.p.a.e.c. on a relatively short column (75 x 4.6 mm i.d.) containing a highly cross-linked polystyrene-based resin with surface quaternary amine groups prepared by the researchers.[38] Linkage isomers within the four sets of mono- to tetra-sialogangliosides were separated and preparatively isolated by h.p.l.c. on a strong anion exchanger, trimethylammonioethyl-Fractogel, with gradient elution.[39] A new column, "poly-Glycoplex", a succinimide coated silica, has been investigated for the separation of the following oligosaccharides and their "PA-" and "PNB"-derivatives (c.f. Vol.24, p.199), made by reductive amination with 2-aminopyridine and 4-(*p*-nitrophenyl)butoxyamine, respectively: sialylated lactose and *N*-acetyl-lactosamine, biantennary *N*-linked oligosaccharides from glycoproteins, glycophosphoinositol glycans, and xyloglucan

oligosaccharides. Many useful separations were reported. The volatile eluant (MeCN-H_2O) was convenient for h.p.l.c.-m.s. applications.[40]

Synthetic glycoconjugates related to methionine- and leucine-enkephalins, with different sugar-peptide linkages (ester, amide, ether) and sugar position, type and substituents were examined by reversed-phase h.p.l.c. with CF_3CO_2H as an ion-pair reagent.[41]

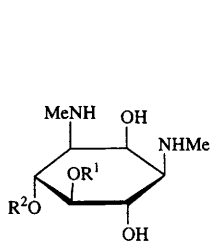
1.3.6 *Sugar Acids.* — The influence of alcohols in the eluant on the h.p.a.e.c. elution of a variety of anions, including gluconate, glucuronate and galacturonate has been investigated.[42] Acids present in honey, including gluconic, galacturonic and glucaric acids, were determined by solid-phase extraction onto a strong anion exchanger, and reversed-phase h.p.l.c. with an acidic eluant.[43] Lactose, lactobionic acid and lactobionolactone were separated on an aminopropyl-silica bonded phase (operated as a weak anion exchanger) or on β-cyclodextrin-silica bonded phase (in the normal mode). The latter column proved more stable, performing satisfactorily for two years. Lactose and lactobionic acid were readily separated on a Ca^{2+}-form cation exchange column (with 1.2 mM $CaSO_4$ as eluant).[44] An optimized separation of sialic acids (Neu5,9Ac_2, Neu5Ac, Neu5Gc, Neu2en5Ac, and CMP-Neu5Ac, where Gc is glycoloyl, i.e. $HOCH_2CO\rightarrow$) on a hydrophilic strong anion exchange resin has been applied to sialic acids (Neu5,9Ac_2, Neu5Ac, and Neu5Gc) released from bovine submandibular mucin.[45]

Urinary steroid glucuronides have been converted into fluorescent acylhydrazide derivatives **2** (by reaction with the corresponding hydrazine and a water soluble carbodiimide in aqueous pyridine) and determined by reversed-phase h.p.l.c.[46] H.p.l.c. analyses, generally reversed-phase with acidic eluant, of the following drugs and their metabolites including glucuronides have been reported: mycophenolic acid (cyanoalkyl bonded-phase),[47] salicylic acid,[48] sulfamethoxazole (forms an *N*-glucuronide),[49] and keptoprofen,[50] vitamin A[51] and furosemide[52] (all forming ester glucuronides).

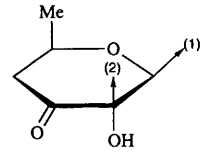
Ascorbic acid has been determined in biological samples by reversed-phase and ion-pair reversed-phase h.p.l.c. with u.v.- or electrochemical detection.[53-55]

1.3.7. *Antibiotics.* — The following antiobiotics have been determined in biological samples by reversed-phase h.p.l.c.: novobiocin, an anticancer coumarin 3-*O*-carbamoyl-4-*O*-,5-*C*-dimethyl-D-allopyranoside,[56] novel antitumor epipodophyllotoxins with *N*-methylated and *N,N*-dimethylated 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside residues,[57] the macrolide antibiotic mirosamine,[58] and the new anthracycline DA-125 and its metabolites which have 2,6-dideoxy-2-fluoro-α-L-talopyranosyl residues.[59] H.p.a.e.c. was used for analysis of the aminoglycoside

gentamicin C complex in an investigation of possible counterfeit suppliers.[60] Spectinomycin **3** and its degradation products actinamine **4** and actinospectinoic acid **5** were determined by h.p.l.c. on a cation-exchange column with post-column addition of sodium hydroxide and pulsed amperometric detection.[61]

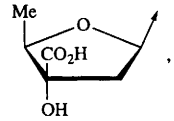


3 R^1, R^2 =



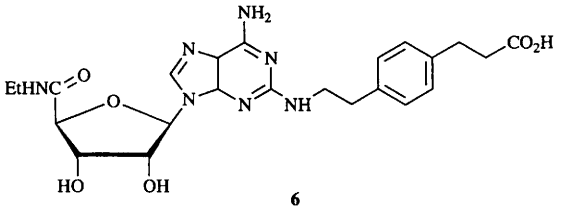
4 $R^1 = R^2 = H$

5 R^1 =



, $R^2 = H$

1.3.8 *Nucleosides.* — The following compounds (usually in biological samples) have been analysed by reversed-phase h.p.l.c.: purine and pyrimidine nucleosides and bases and uric acid (in tick pheromones) on both conventional and microbore (1 mm i.d.) columns,[7] twenty one purine and pyrimidine bases, (deoxy)nucleosides and (deoxy)nucleotides, in yeast autolysate flavour ingredients,[62] thymidine, its α-anomer and their pyranose isomers in a study of their isomerizations under acidic conditions,[63] 2-chloro-2′-deoxyadenosine, 2-chloroadenosine, 2-fluoroarabinosyladenosine, 5′-chloro-5′-deoxyadenosine and their non-halogenated analogues for determination of hydrophobicity parameters,[64] 5-fluorouridine, 5-fluoro-2′-deoxyuridine and their metabolites,[65] 1-(β-D-arabinofuranosyl)-5-(1-propynyl)uracil,[66] 8-chloroadenosine, its 3′,5′-cyclic phosphate and their metabolites,[67] 3′-azido-3′-deoxythymidine (AZT) and its 5′-glucuronide using 2,3-*O*-isopropylideneuridine as internal standard,[68] 2′-deoxy-3′-thiacytidine,[69,70] and the adenosine A_2 receptor antagonist **6** following solid-phase concentration on a silica-immobilized phenylboronic acid.[71]



6

3′-Amino-3′-deoxythymidine, a catabolite of AZT, was determined in plasma by derivatization with fluorescamine and reversed-phase h.p.l.c. with fluorescence detection.[72]

Ion-pair reversed-phase h.p.l.c. analyses have been reported for guanine and its nucleosides and nucleotides in human erythrocytes with post-column fluorescence derivatization with phenylglyoxal (a method that is selective for guanine-containing compounds),[73] and adenosine, its breakdown products inosine and hypoxanthine, and dopamine in rat tissue.[74]

Analytical and preparative separations of 5′-O-protected deoxynucleoside methylphosphonamidite diastereoisomers (chiral at phosphorus) on a silica column have been reported.[75]

1.4 Partition Chromatography. — A review on the use of counter-current chromatography (droplet, rotation locular and centrifugal) for the preparative isolation of natural products included many examples of glycosides.[76]

1.5 Column Chromatography — A model has been developed that closely predicts the elution of salt and sucrose during preparative chromatography on Na^+-form cation-exchange resin. It required minor adjustment for application to beet molasses due to an induced change in the resin from Na^+- to K^+-form, but was less accurate when the load of molasses containing 32% w/v dry matter was increased beyond 10% of bed volume.[77] The binding of nucleosides and nucleotides to boronate affinity columns at pH 7 was enhanced by fluoride ion (and to some extent chloride ion) in the eluant, due to the formation of tetravalent fluoroboronate species. As a consequence, an improved separation of adenosine from 2′-deoxyadenosine was achieved.[78]

2 Electrophoresis

All reports relate to capillary electroseparations (c.e.s.). Applications of c.e.s to carbohydrates including glycoproteins and glycolipids have been reviewed.[79] There are currently four distinct c.e.s. techniques, for which an improved nomenclature system has been recommended and will be used herein.[80]

Sugar acids and sugar sulfate and phosphate ester derivatives being charged, can be analysed directly by capillary electrophoresis (c.e.). L-Ascorbic, D-glucuronic and D-gluconic acids were included in a report on the separation of a large number of organic acids, with u.v. detection.[81] Sialyl-oligosaccharide alditols released from *O*-linked glycoproteins (with NaOH-$NaBH_4$) were best separated in a pH 9.6 buffer containing borate and sodium dodecyl sulphate (SDS), although it was

concluded that the separation relied neither on the formation of borate complexes (since phosphate was nearly as good) nor on micelle formation. They were detected by u.v. absorption at 185 nm.[82] Twelve nucleoside 2′-, 3′- and 5′-monophosphates were nicely separated in 15 min using borate and β-cyclodextrin-containing buffers.[83] Both c.e. and capillary isotachophoretic separations of *myo*-inositol mono- to hexa-phosphates have been used to monitor the enzymic hydrolysis of phytic acid (*myo*-inositol hexaphosphate). Indirect u.v. detection using 1-naphthol-3,6-disulfonic acid as the chromophore, or conductivity detection was employed, respectively.[84,85] For the c.e. analysis of sulfated synthetic heparin and dermatan oligosaccharides, and eight related unsaturated disaccharides at low pH, indirect u.v. detection proved better than direct detection because different structures had similar detectability, and an order of magnitude greater sensitivity (sub-picomole) was provided.[86] Complexation with 2-anilinonaphthalene-6-sulfonic acid (2,6-ANS) rendered α-, β- and γ-cyclodextrins and the various components of "2,6-di-*O*-methyl-β-cyclodextrin" both charged for c.e. separation and detectable by fluorescence. Complexation of 2,6-ANS with β-cyclodextrin enhances its fluorescence intensity 50-250 fold, whereas with α- and γ-cyclodextrins the enhancement is *ca.* 2 fold.[87]

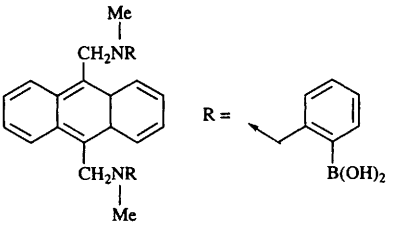
Natural sugars can be separated as their charged borate complexes, through use of borate-containing electrolytes at alkaline pH values, as in the following examples. The c.e. separation of sugars (Fuc, Gal, Glc, GalNAc, GlcNAc, Neu5Ac, GalA, GlcA, sucrose, Fru) with indirect u.v.-detection using potassium sorbate in the electrolyte as the chromophone, has been optimised and applied to fruit juices. In comparison to h.p.a.e.c., c.e. gave 10-20 fold greater separation of components but was 2-3 orders of magnitude less sensitive, although both methods gave comparable analytical results.[88] An impressive, simple c.e. separation of a wide range of carbohydrate compounds including simple sugars, sugar acids and alditols employing sensitive electrochemical detection at a copper electrode in a strongly alkaline medium has been reported and applied to apple juice and for monitoring the glucose oxidase-catalysed conversion of glucose to gluconic acid.[89] *O*- And *N*-linked oligosaccharides released from various IgG proteins by hydrazinoysis were separated in 6 min and could be detected directly by u.v. absorption without derivatization.[90] Components of bulk clindamycin phosphate (an aminoglycoside) and erthromycin stearate (a macrolide) antibiotic products were profiled to differentiate samples produced by different manufacturers,[91] and three separable peaks for the four components of gentamicin sulphate (an aminoglycoside) could be quantified.[92] The stability at various pHs of thymidine and its (dideoxy-D-*erythro*-hexopyranosyl)thymidine analogues has been monitored by c.e.[93] Seven neutral and two acetamido-sugars were separated as their 1-(1-naphthylamino)-1-deoxyalditol derivatives (formed by reductive amination).[94]

Capillary micellar electrochromatography (c.m.e.c.), in which surfactants are incorporated into the electrolyte, has been used for the determination of sugars as amino-alditol derivatives. Thus four 1-amino-1-deoxy-D-alditols (from Glc, Man, Gal and Fuc by $NaBH_4$ reduction of the corresponding *N*-benzylglycosylamines followed by hydrogenolytic *N*-debenzylation) and two 2-amino-2-deoxy-D-alditols (from reduction of $GlcNH_2$ and $GalNH_2$) were amide-linked to a fluorescent rhodamine dye, and separated by c.m.e.c. using a buffer containing SDS, phenylboronate and borate. A detection limit of ~10^{-22}mol, corresponding to about 100 molecules, was achieved using a laser-induced fluorescence detector in a sheath flow cuvette. A limitation of the method was the competitive hydrolysis of the labelling reagent during derivatization.[95] Mixtures containing a number of pentoses, hexoses, heptoses and a variety of oligosaccharides could be separated by c.m.e.c. of the fluorescent derivatives obtained by reductive amination with 2-aminoacridone. Racemic galactose, ribose and fucose could be resolved by adding β-cyclodextrin to the taurodeoxycholate and borate buffer system used.[96] Other separations reported were of ten flavonol 3-*O*-glycosides,[97] legume aromatic amino acid and heterocyclic *O*-glucosides,[98] and oxidized and normal deoxynucleosides released from DNA.[99]

3 Other Analytical Methods

The phenol-sulphuric acid colourimetric assay can be used for the quantitative determination (± 3-4%) of glycosides, oligosaccharides, glycopeptides and glycoproteins as long as the method has been appropriately calibrated for the compounds being assayed.[100]

Bis-boronate **7** forms a 1:1 complex with glucose selectively relative to other saccharides, and its enhanced fluorescence can be used as a glucose-selective molecular fluorescence sensor at physiological glucose concentrations.[101]



7

The polarographic behaviours of a variety of deoxy-sugars has been compared with those of their parent D-pentoses and -hexoses. The direct current polarographic determination of sugars as their aldimines proved suitable for kinetic measurements and the monitoring of syntheses.[102]

The development of a glucose oxidase-based solid-state electrochemical glucose sensor, applicable to flow through measurements,[103] and of an automated enzyme-based colourimetric system for detecting glucose, maltose and starch on microtiter plates,[104] have been reported.

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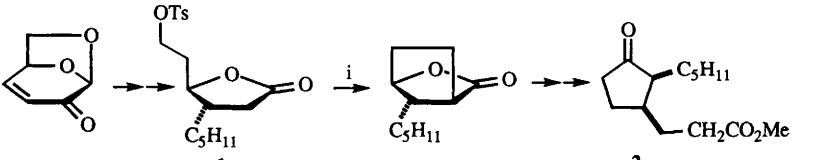
24
Synthesis of Enantiomerically Pure Non-carbohydrate Compounds

1 Carbocyclic Compounds

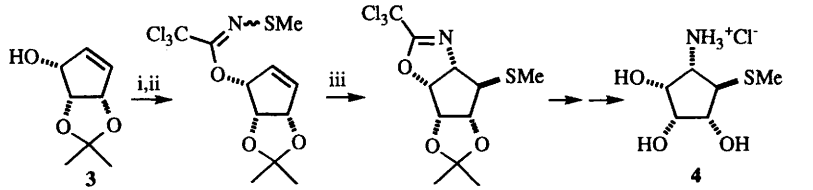
A comprehensive review has appeared this year on the conversion of carbohydrate derivatives to functionalized cyclopentanes and cyclohexanes,[1] and another review has described the synthesis of natural products from carbohydrates using the Ferrier rearrangement.[2] (+)-Methyldihydroepijasmonate **2** has been prepared from levoglucosenone (Scheme 1). The n-pentyl group was introduced by stereoselective cuprate addition, and the carbocyclic ring was formed *via* 5-*exo-trig* alkylation of the enolate derived from **1** (Scheme 1)[3]



Reagent: i, Tms_2NLi

Scheme 1

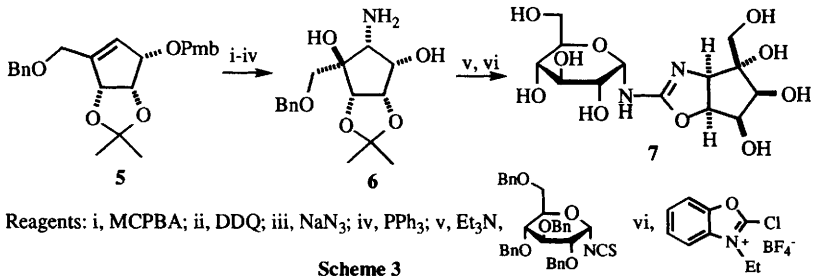
An improved route to (+)-mannostatin A **4** *via* the known intermediate **3** has been reported by Li and Fuchs starting from D-ribonolactone.[4] A key step is the intramolecular addition of the N-thiomethyl trichloroacetimidate functionality across the carbon-carbon double bond (Scheme 2).



Reagents: i, NaH, CCl_3CN; ii, MeSOTf, $^iPr_2NEt$, -78°C to 0°C;
iii, MeSOTf, $^iPr_2NEt$, -72°C to 20°C

Scheme 2

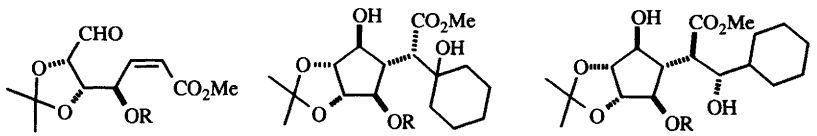
D-Ribonolactone has also been used as starting material for a synthesis of 6-epi-trehazolin, **7**, in which the key cyclopentanoid functionality and stereochemistry are introduced by diastereoselective epoxidation and regioselective epoxide ring opening by azide to convert **5** to **6** (Scheme 3).[5,6]



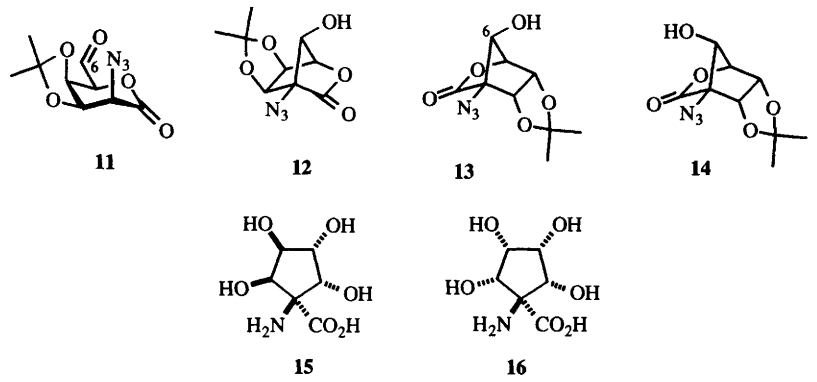
Reagents: i, MCPBA; ii, DDQ; iii, NaN_3; iv, PPh_3; v, Et_3N, vi,

Scheme 3

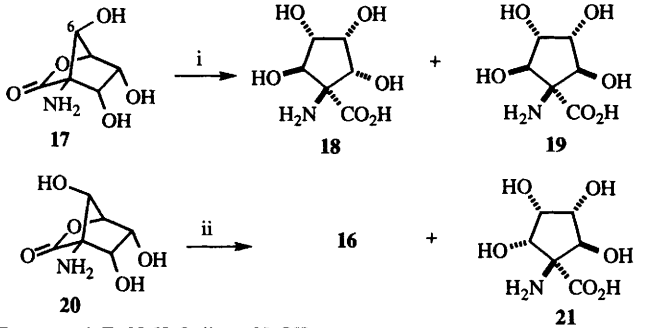
Cyclopentanoids have been prepared by samarium diiodide-catalysed reaction of **8** (R=Tbdms) with either aldehydes or ketones. The stereochemical outcome was dependent on the carbonyl compound used, with cyclohexanone giving **9** as a single product, while cyclohexane carboxaldehyde gave an isomeric mixture containing predominantly **10**.[7]



Fleet's group have examined the utility of carbohydrate-derived 2-azido- and 2-iodo-lactones for synthesis of novel, highly functionalized cyclopentanes and cyclohexanes.[8] The azido lactone **11** undergoes KF-catalysed intramolecular aldol reaction to give **12** (major) and **13** (minor). The minor isomer arises through epimerization at C5 *prior* to the aldol cyclization. Lactone hydrolysis of the major isomer leads to **15**. Similar hydrolysis of the minor isomer yields **16**, and thus epimerization *via* retro-aldol must *precede* lactone ring opening *via* the intermediacy of **14**.



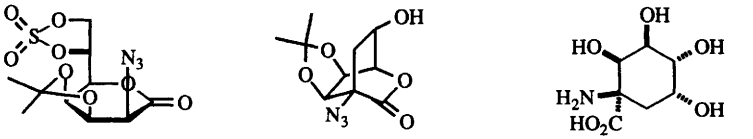
The versatile reactivity of the minor isomer **13** has been further explored by Fleet's group. When the azide is reduced and the acetal removed, the resulting amino compound **17** (presumed to be less susceptible to reversible aldol reaction) is opened to give the anticipated **18**, but a minor product **19** is obtained *via* reversible aldol cleavage of the C2-C3 bond.[9] The isomeric amino compound **20** undergoes lactone hydrolysis to **16** and **21**, with **21** as the major product derived from retroaldol-reclosure (Scheme 4).



Reagents: i, Et_3N, H_2O; ii, aq. NaOH.

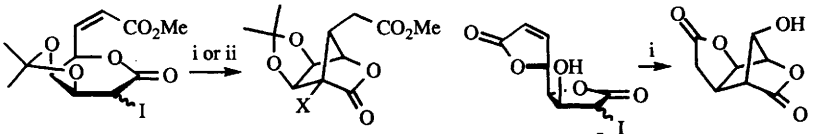
Scheme 4

The sodium enolate of the closely related cyclic sulfate **22** gives lactone **23**, lactone hydrolysis then providing the cyclohexane amino acid **24**, a precursor to a hydantocidin analogue.[8]



22 **23** **24**

Both radical and enolate cyclizations of the iodides **25** have been examined.[10] Both conditions generate the same ring system, **26**, which, in the ionic case bears a bridgehead iodine atom. The thermodynamic bisfuranolactone isomers of **25**, namely **27** both generate **28** under radical conditions (Scheme 5).

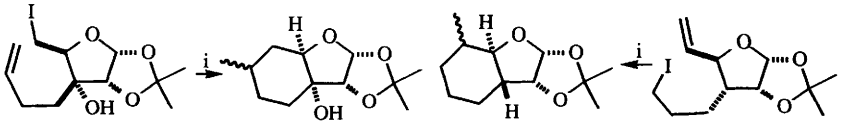


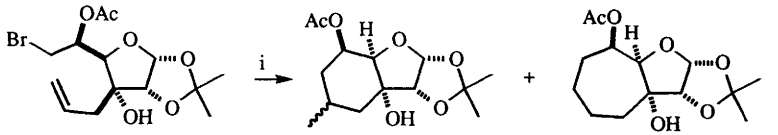
25 **a** α-I **b** β-I **26** **a** X=H **b** X=I **27** **a** α-I **b** β-I **28**

Reagents: i, AIBN, Bu_3SnH; ii, KO^tBu

Scheme 5

Further radical cyclizations of carbohydrates have attracted attention. A study on the ring size and diastereoisomeric outcomes on furanoside templates has been reported, with six membered rings preferred in all cases and modest diastereoselectivities observed (See examples in Scheme 6).[11]

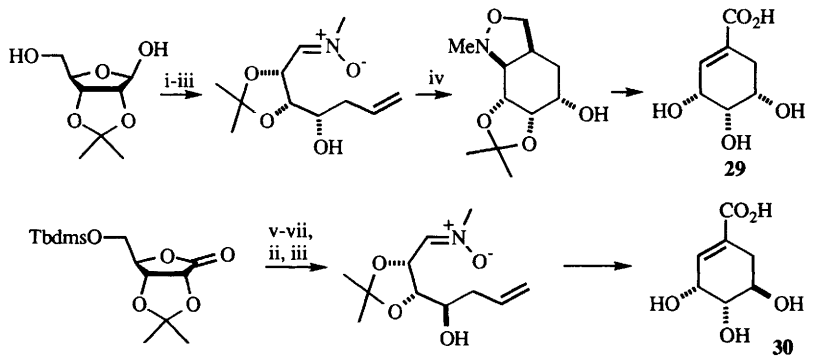




Reagents: i, AIBN, Bu_3SnH

Scheme 6

D-Ribose served as starting material in a synthesis of (-)-5-epi-shikimic acid **29** and (-)-shikimic acid **30**.[12] The key C5 stereochemistry is introduced by allylation of a ribonolactone intermediate, followed by DIBAL reduction in the case of (-)-shikimic acid, and by diallylzinc addition to 2,3-isopropylidene-D-ribose for the epi- analogue. The syntheses proceed through an intramolecular nitrone cycloaddition to construct the requisite cyclohexane rings (Scheme 7).

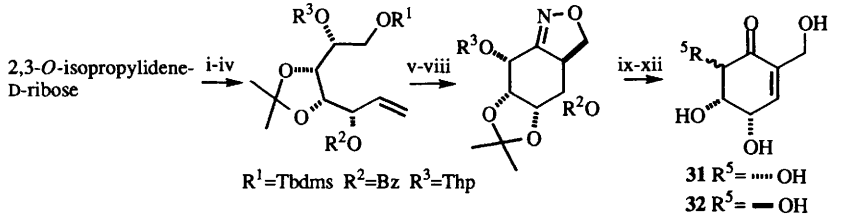


Reagents: i, Diallylzinc; ii, $NaIO_4$; iii, MeNHOH; iv, heat; v, allylmagnesium chloride; vi, DIBAL; vii, TBAF.

Scheme 7

The synthesis of the natural products Gabosine C **31** and Gabosine E **32** have also been achieved starting from 2,3-*O*-isopropylidene-D-ribose and proceeding *via* an intramolecular dipolar

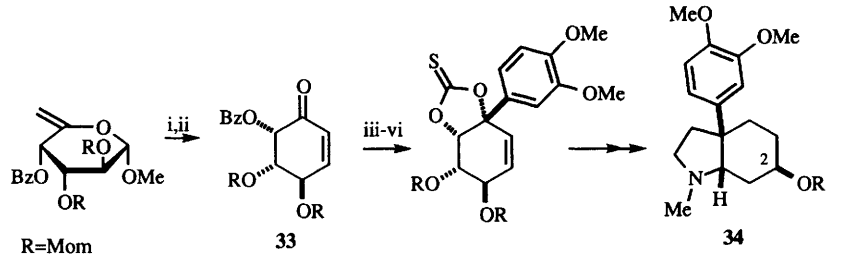
cycloaddition (Scheme 8).[13] Deprotection with Raney nickel and hydrogen, then allowed elimination of benzoic acid effected by DABCO, which occurred with concomitant epimerization at the tetrahdropyran ether bearing carbon. Deprotection of these epimers with TFA afforded Gabosine C **31** and Gabosine E **32**.

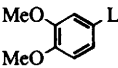


Reagents: i, CH_2=CHMgBr; ii, TbdmsCl, Pyr; iii, BzCl, Py; iv, DHP, H^+; v, Bu_4NF; vi, $(COCl)_2$, Et_3N, DMSO; vii, NH_2OH; viii, NaOCl; ix, Raney Ni, H_2; x, AcOH; xi, DABCO; xii, TFA, CH_2Cl_2.

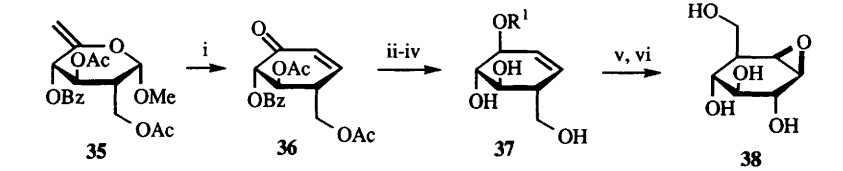
Scheme 8

D-Glucose is the starting material for a total synthesis of (-)-mesembranol **34** in which a key step is the Ferrier rearrangement to provide the cyclohexenone **33** (Scheme 9).[14] Although the natural product contains 3 chiral centres, only one of these is derived from those of D-glucose.



Reagents: i, $Hg(OCOCF_3)_2$, acetone, H_2O; ii, MsCl, Et_3N; iii,  ; iv, MeONa, MeOH; v, $Pd(OH)_2$, H_2; vi, 1,1-thiocarbonyldiimidazole.

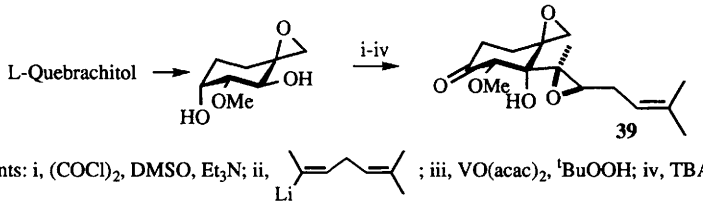
Scheme 9



Reagents: i, $HgCl_2$, acetone, H_2O; ii, $NaBH_4$; iii, TbdmsCl; iv, KOH, EtOH; v, MCPBA; vi, AcOH, H_2O

Scheme 10

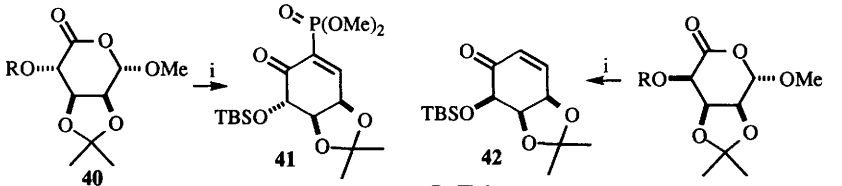
A total synthesis of the natural product cyclophellitol, **38**, a β-glucosidase inhibitor, has been described starting from D-glucose, in which the key transformations are Ferrier rearrangement of **35** and a stereoselective epoxidation of **37** (Scheme 10).[15] The natural product (-)-ovalicine **39**, another epoxy cyclohexane, has been prepared from the cyclitol L-quebrachitol (Scheme 11).[16]



Reagents: i, $(COCl)_2$, DMSO, Et_3N; ii, ; iii, $VO(acac)_2$, ^tBuOOH; iv, TBAF.

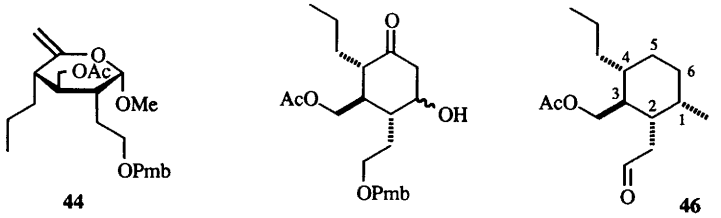
Scheme 11

The mannose-derived lactone **40**, produced by ozonolysis of the corresponding alkene, undergoes a modified Fujimoto-Belleau reaction yielding the vinyl phosphonate cyclohexenone **41**.[17] The epimeric lactone **43** however, yields the anticipated cyclcohexenone **42** (Scheme 12). Formation of **41** is rationalized by invoking hydroxide elimination from an enolate intermediate rather than the anticipated elimination of $(MeO)_2P(O)OH$.



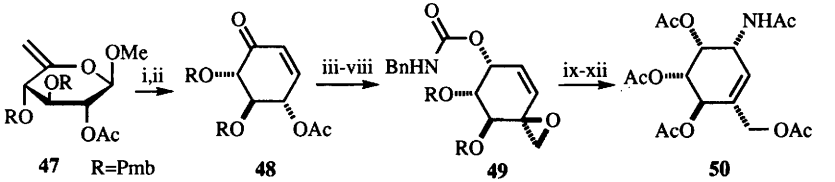
Reagents: i, n-BuLi, $(MeO)_2P(O)Me$

Scheme 12



Several other syntheses of cyclohexane-containing natural products reported also utilized Ferrier rearrangement as a key step. A synthesis of a compactin analogue involved conversion of the 1,6-anhydro-D-glucose-derived **44** to cyclohexanone **45**, which was further elaborated to **46** en route to the natural product, *via* elimination, stereoselective ketone reduction, cuprate methyl S_N2'

displacment, hydrogenation, and Pmb removal and PCC oxidation (sugar numbering indicated).[18] In their synthesis of valienamine **50**, a component of pseudo-oligosaccharides such as acarbose, Danishefsky's group utilized Ferrier rearrangement of D-glucal-derived **47** to **48**.[19] A key step was intramolecular carbamate anion S_N2' opening of an exocyclic epoxide **49** using potassium hexamethyldisilazide as base (Scheme 13).

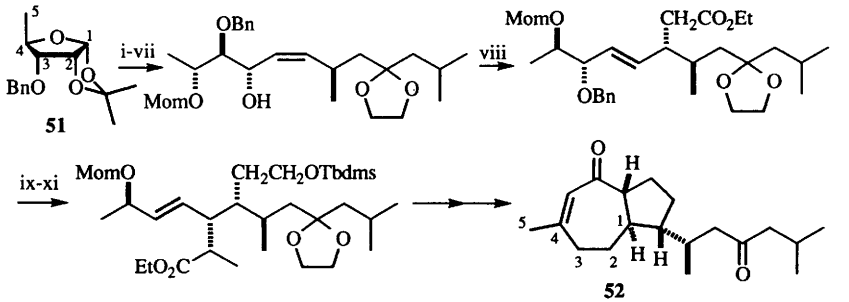


47 R=Pmb **48** **49** **50**

Reagents: i, $HgCl_2$, H_2O; ii, MsCl, DMAP; iii, $NaBH_4$, $CeCl_3$; iv, BuNCO; v, K_2CO_3, MeOH; vi, PDC; vii, CH_2I_2, Zn, $TiCl_4$; viii, m-CPBA; ix, KHMDS; x, Na, NH_3, THF; xi, LiOH, xii, Ac_2O, Pyr

Scheme 13

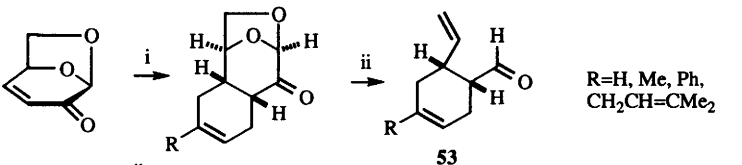
The marine natural product Reiswigin A **52** has been synthesized from the known compound **51**.[20] Two Claisen rearrangements serve as key transformations for chirality transpositions. The synthesis is notable in utilizing the sugar chiral centres to introduce four other chiral centres, while all the original stereocentres are lost (Scheme 14).



51 **52**

Reagents: i, I_2, MeOH; ii, Et_3N, BzCl; iii, H^+, EtSH; iv, MomCl, $^iPr_2NEt$; v, I_2, $NaHCO_3$; vi, Wittig; vii, K_2CO_3, MeOH; viii, $MeC(OEt)_3$, $EtCO_2H$; ix, Li, NH_3; x, TbdmsCl; xi, $EtC(OEt)_3$

Scheme 14



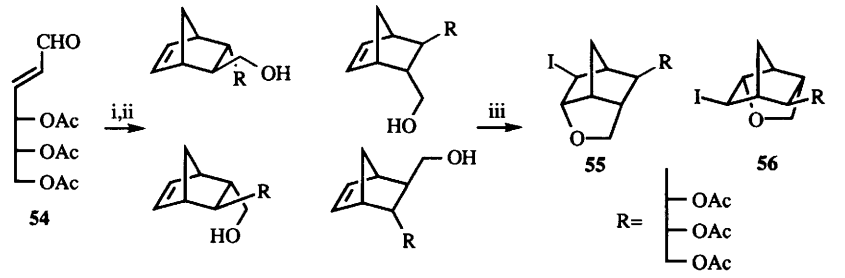
53

Reagents: i,  ; ii, hv, benzene

Scheme 15

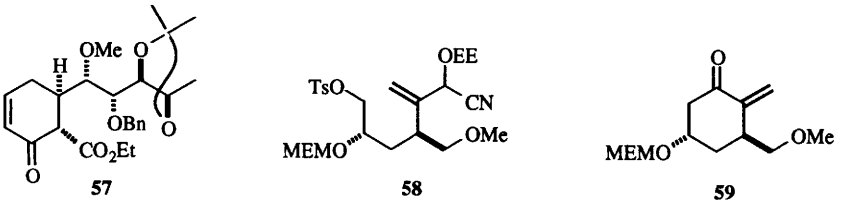
Diels-Alder reaction followed by photochemical carbon dioxide extrusion (*via* acetal diradical and acetal carbene) provided a versatile route to trisubstituted cyclohexenes **53** (Scheme 15).[21]

Cyclopentadiene cycloaddition to **54** provides an inseparable mixture of diastereoisomers, but reduction provides separable pairs of diastereoisomers, and only one isomer of each pair undergoes iodoetherification (Scheme 16). Thus, isomers **55** and **56** can be isolated.[22]



Reagents: i, cyclopentadiene; ii, $NaBH_4$; iii, I_2, K_2CO_3. **Scheme 16**

D-Glucose has been converted to the aureolic acid fragment **57**,[23] while D-mannitol has been converted to the 1α,25-dihydroxyvitamin D3 ring A synthon **59** *via* cyanohydrin **58**.[24] The abstract reported no synthetic details, but the cyclization is likely to proceed by displacement of the tosyloxy group by an α-cyano carbanion.

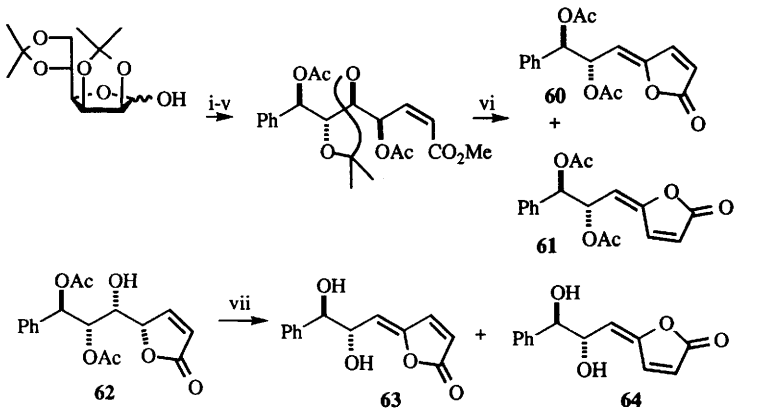


2 Lactones

A synthetic approach towards goniobutenolides A and B **63** and **64** from 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose was thwarted by decomposition accompanying attempted deacylation of **60** and **61**.[25] The synthesis was completed alternatively by dehydration of the known triol butenolide **62** which provided a mixture of the isomeric natural products (Scheme 16).

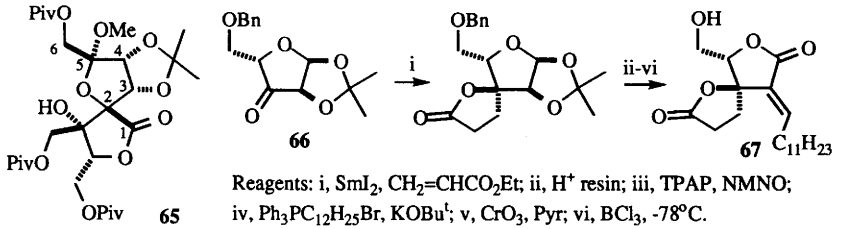
As part of a synthetic approach to squalestatin 1, 1,6-anhydrogalactose has been converted to intermediate isomeric butenolides and thence to the spirolactone **65**, an intermediate towards the natural product.[26] (For other synthetic approaches see Section 4). The 1,7-dioxaspiro[4.4]nonane bis-γ-butyrolactone **67** has been prepared as a rigid diacylglycerol analogue starting from L-xylose and

proceeding *via* **66** (Scheme 17). The product **67** is an inhibitor of phorbol-12,13-dibutyrate PKC-binding with K_i=13.6±7.1μM.[27] (The isomeric alkene was also obtained)



Reagents: i, PhMgBr; ii, Ac_2O, Py; iii, 50% aq. AcOH; iv, $NaIO_4$, MeOH;
v, $Ph_3P{=}CHCO_2Me$; vi, 80% aq. AcOH then Ac_2O, Py; vii, TFA, NEt_3 then MeOH.

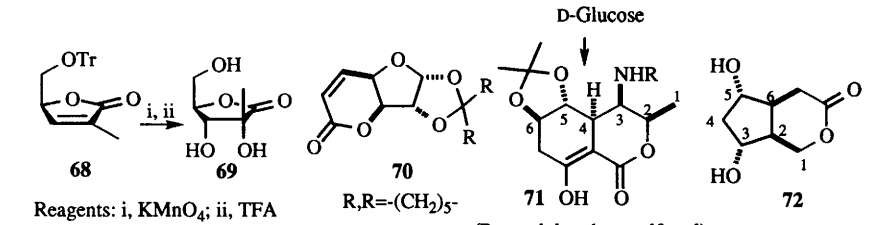
Scheme 16



Reagents: i, SmI_2, $CH_2{=}CHCO_2Et$; ii, H^+ resin; iii, TPAP, NMNO;
iv, $Ph_3PC_{12}H_{25}Br$, $KOBu^t$; v, CrO_3, Pyr; vi, BCl_3, -78°C.

Scheme 17

A new route to 2-*C*-methyl-D-ribonolactone **69** has been described utilizing stereoselective dihydroxylation of **68** (Scheme 18).[28] An efficient synthesis of the furanopyranone **70** in 94% overall yield from dicyclohexylidene-D-glucose has been described.[29]



Reagents: i, $KMnO_4$; ii, TFA

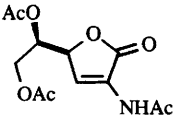
Scheme 18

(R=*p*-tolylmethanesulfonyl)

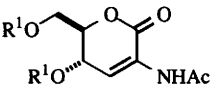
Scheme 19

D-Glucose has been converted to the bicyclic lactone **71**, in which a key 3-carbon chain homologation is effected *via* aldehyde allylation. This lactone is a known precursor of actinobolin, and this synthesis thus constitutes a formal total synthesis.[30] The cyclopentane-fused δ-lactone **72**, a potential prostaglandin synthetic intermediate, has been prepared from levoglucosan.[31]

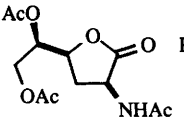
The highly stereoselective hydrogenation of the enamides **73** and **74** [R^1=Ac, Bz] (Vol. 23, p.139) is the key stereochemical step (facilitating inversion of C2 to introduce the amino acid α-configuration) in the synthesis of the lactone isomers **75** and **76** of (2*S*, 4*S*, 5*R*)-4,5,6-trihydroxynorleucine from D-glucosaminic acid.[32]



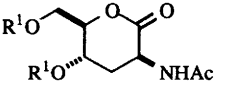
73



74

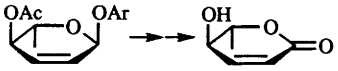


75

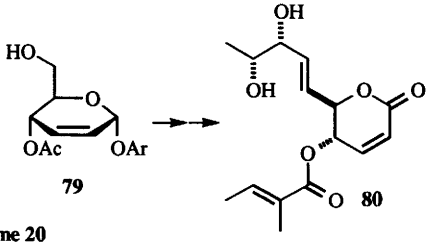


76

The use of low catalyst ratio and low temperature has been reported to direct reaction of phenols with glycals to the *O*-glycoside (rather than the *C*-glycoside) products *via* Ferrier reaction.[33] The aryl glycosides **77** and **79** obtained by such glycosylation of precursor glycals have been further elaborated to the natural products osmudalactone **78** and *ent*-phomopsolide B **80** respectively, utilizing an oxidative removal of the *p*-methoxyphenyl group (Scheme 20).



77 **78**

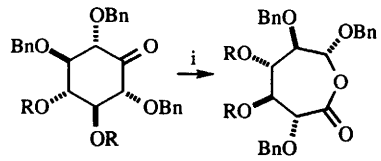


79 **80**

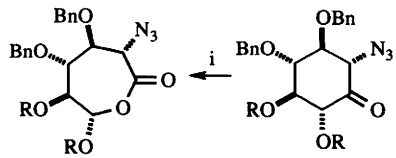
Ar=Ph, 4-OMePh

Scheme 20

Baeyer-Villiger oxidative ring expansion of myo-inositol derivatives **81** and **82** provides the ε-lactones **83** and **84** respectively, which are used as intermediates in a convergent synthesis of the antibiotic natural product polyoxin J (Scheme 21 - also see Chapter 19).[34]



81 **83**

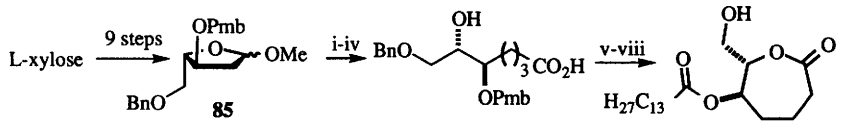


R=MPM **84** **82**

Reagents: i, MCPBA, $KHCO_3$

Scheme 21

A 17-step synthesis of the rigid ε-lactone diacylglycerol analogue, (5*R*, 6*S*)-5-*O*-tetradecanoyl-6-hydroxymethyl-6-heptanolide **86**, has been reported, starting from L-xylose and proceeding *via* L-2-deoxyribofuranoside **85** (Scheme 22).[35]

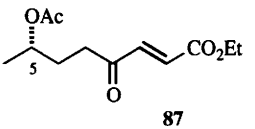


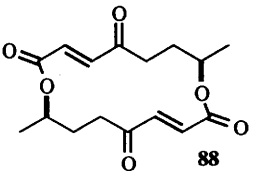
Reagents: i, HCl; ii, PPh_3CHCO_2Me; iii, $NaBH_4$, $NiCl_4$; iv, NaOH;
v, DCC, DMAP; vi, DDQ; vii, $C_{13}H_{27}COCl$, DMAP; viii, H_2, Pd-C, $C_{13}H_{27}CO_2H$

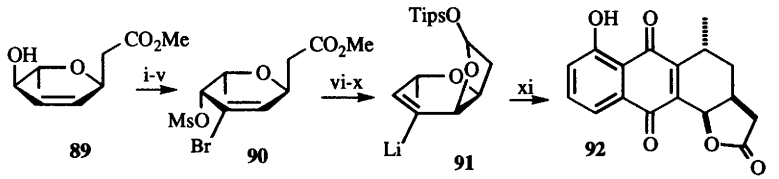
Scheme 22

3 Macrolides, Macrocyclic Lactams and their Constituent Segments

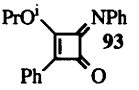
The antifungal macrolide soraphen $A_{1\alpha}$ has been prepared by a convergent synthesis, starting from D-glucose and from methyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucose.[36] The macrolide (-)-pyrenophorin **88** has been obtained starting from tri-*O*-acetyl-D-glucal, utilizing the C_2-symmetry of the target. The glucal is converted to the precursor **87** (containing one of the sugar chiral centres derived from C5) with an inversion of stereochemistry through Mitsunobu reaction. Dimerization of the ketal protected acid derived from **87** to the natural product is acheived through two 'head-to-tail' Mitsunobu reactions.[37]







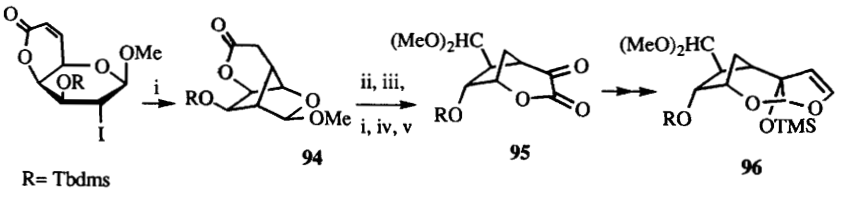
Reagents: i, $(COCl)_2$, DMSO; ii, Br_2; iii, Et_3N; iv, $NaBH_4$, $CeCl_3$; v, MsCl; vi, LiOH; vii, Et_3N;
viii, DIBAL; ix, TipsOTf; x, ^tBuLi, xi,



Scheme 23

L-Rhamnose derived **89** was the starting point for a synthesis of isochromanquinone natural product (-)-manaomycin D **92**.[38] An S_N2' intramolecular mesylate displacement followed by DIBAL reduction and hemiacetal silylation and lithiation gave **91**, and addition to cyclobutenone **93**, followed by rearrangement and oxidation, led to the product ring system (Scheme 23).

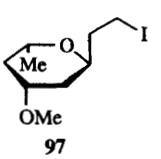
Fraser-Reid has reported the synthesis of **96**, corresponding to a component of the insect antifeedant azadirachtin, from galactose-derived starting material.[39] Radical conjugate addition gave the lactone intermediate **94**, and subsequent glycoside cleavage to form a dimethyl acetal, enolate hydroxylation and oxidation led to **95**, elaborated in six steps to **96** (Scheme 24).



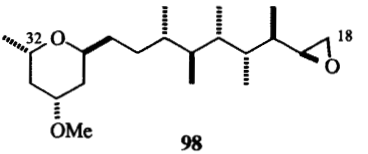
Reagents: i, Bu_3SnH, AIBN; ii, H^+, MeOH; iii, $ClC(S)OC_6H_4F$, Et_3N; iv, KHMDS,  v, PCC

Scheme 24

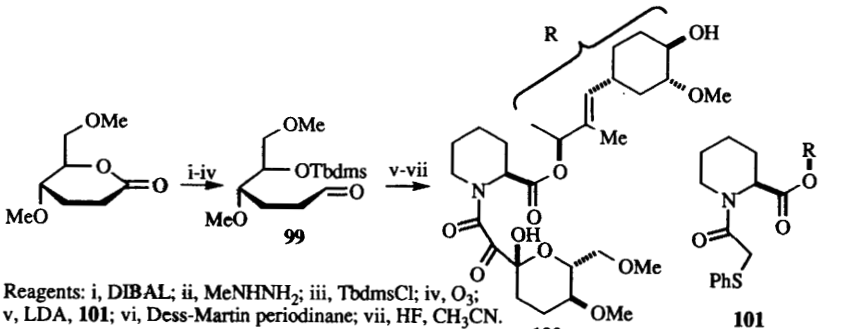
L-Rhamnose has been employed in an approach towards the C_{18}-C_{32} fragment **98** of swinholide A by Nicolaou's group, by conversion to the 2,4-dideoxy derivative **97**, followed by alkylation of the (*S*)-(-)-1-amino-2-(methoxymethyl)pyrrolidine-derived hydrazone of butan-2-one and further chain elaboration.[40]



97



98



99 **100** **101**

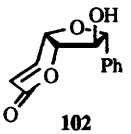
Reagents: i, DIBAL; ii, $MeNHNH_2$; iii, TbdmsCl; iv, O_3; v, LDA, **101**; vi, Dess-Martin periodinane; vii, HF, CH_3CN.

Scheme 25

Aldehyde **99** has been incorporated into the FK506 fragment **100** *via* an aldol addition, to provide a model to evaluate the contribution of the cyclohexane ring to FK506 binding (Scheme 25).[41]

4 Other Oxygen Heterocycles, including Polyether Ionophores

D-Gulonolactone was converted to (+)-altholactone **102** and three stereoisomers (preliminary report: Vol. 22, p.261, ref 24).[42] D-Glucose derivative **103** has been used as starting point for a synthesis of epiallomuscarine **104**.[43]



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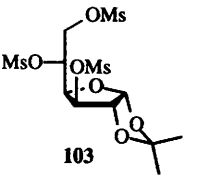
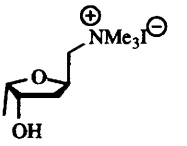
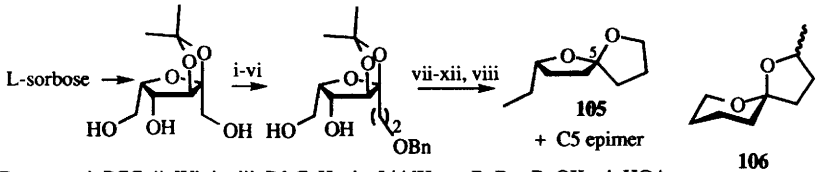


103



104

Chalcagran **105**, the aggregation pheromone of the spruce bark beetle, has been prepared from L-sorbose as an epimeric mixture at the spiro centre.[44] Key steps were a Wittig two-carbon homologation at C1, and an intramolecular glycosylation to establish the spiro centre (Scheme 26). D-Fructose has also been converted to (2*S*,5*R*)- and (2*R*,5*R*)-2-methyl-1,6-dioxaspiro[4.5]decane **106**, a minor component of the odour of *Paravespula vulgaris*.[45] The carbohydrate-derived vinyl sulfone **107** has been converted to the chiral tetrahydrofurans **108** and **109**.[46]

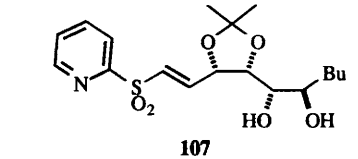


105
+ C5 epimer

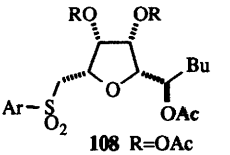
106

Reagents: i, PCC, ii, Wittig, iii, Pd-C, H_2; iv, $LiAlH_4$; v, BnBr, tBuOK; vi, HOAc; vii, TbdpsCl; viii, Barton deoxygenation; ix, TBAF; x, TsCl, Py; xi, MeLi, Me_2SCuBr, Me_2S; xii, TFA, Pd-C, H_2.

Scheme 26



107

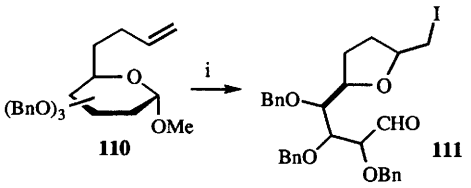


108 R=OAc
109 R,R= -CMe_2 -

Ar=2-pyridyl

An interesting route to chiral tetrahydrofurans with a highly oxygenated branch has been described. 6-Iodo-tribenzyl methyl glycosides (D-gluco, D-manno and D-galacto) were converted to

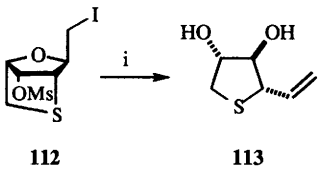
the alkenes **110** *via* Keck allylation, and under iodoetherification conditions these were directly converted to the tetrahydrofurans **111**, by nucleophilic ring oxygen participation in iodonium-promoted addition to the alkene (Scheme 27).[47] The bicyclic tetrahydrofuran derivative **112** has been prepared from idose as a precursor to the tetrahydrothiophene **113** (Scheme 28).[48]



110 **111**

Reagents: i, $I(Coll)_2ClO_4$, wet CH_2Cl_2.

Scheme 27

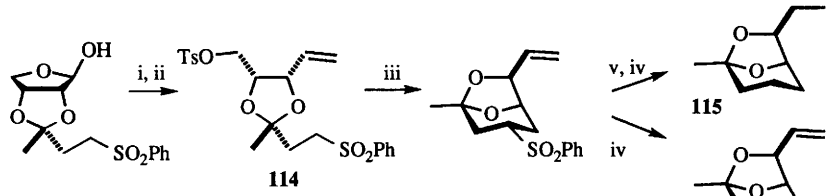


112 **113**

Reagents: i, Zn

Scheme 28

(+)-Endo-brevecomin **115** and an analogue **116**, have been prepared from D-erythronolactone, *via* the intermediate sulfone **114**, obtained by diastereoselective acetalation with 4-(phenylsulfonyl)-2-butanone (Scheme 29).[49] The key bicyclic framework forming step involved intramolecular alkylation of the α-sulfone anion from **114**. The enantiomers of both **115** and **116** were also prepared, starting from 2,3-*O*-isopropylidine-L-erythrose through the intermediacy of the enantiomer of **114**.



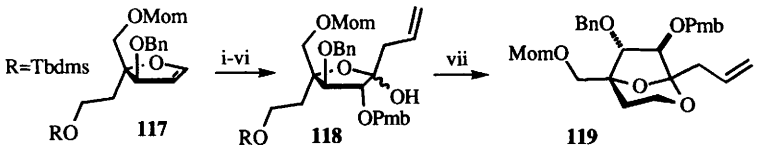
114 **115** **116**

Reagents: i. Wittig; ii, TsCl; iii, NaH, toluene; iv, Na-Hg, MeOH; v, Pd-C, H_2.

Scheme 29

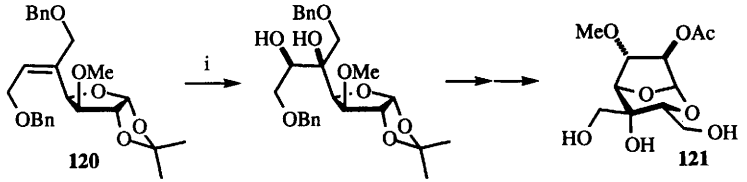
This year has seen several approaches to the core of the zaragozic acids/squalestatins from carbohydrate starting materials. D-Mannose was converted to the glycal **117**, elaborated to precursor **118** by α-selective dioxirane oxidation and C1 epoxide ring opening by allyl alcohol, deallylation, oxidation and Grignard addition. Desilylation of **118** with concomitant intramolecular acetalation afforded the core analogue **119** (Scheme 30).[50]

In another approach, diastereoselective osmylation of **120** introduced the two non-carbohydrate-derived stereocentres, and acid-catalysed trans-acetalation and further manipulations converted the major isomer to core analogue **121** (Scheme 31).[51] Monocyclic analogues of zaragozic acid are discussed in Chapter 16.



Reagents: i,  ; ii, $HOCH_2CH=CH_2$; iii, PmbCl; iv, $(PPh_3)_3RhCl$; v, $Hg(OAc)_2$, H_2O; vi, $CH_2=CHCH_2MgCl$; vii, 50% HF.

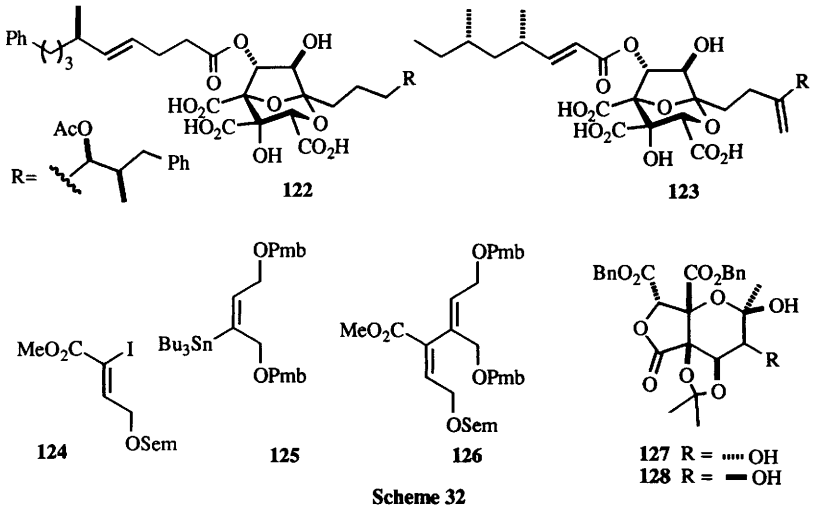
Scheme 30



Reagents: i, OsO_4

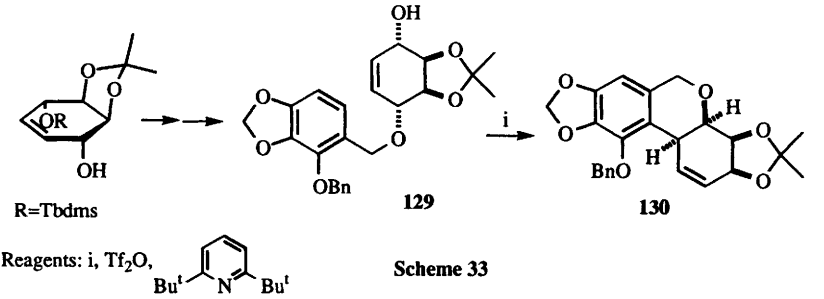
Scheme 31

The first two completed total syntheses of zaragozic acids have been reported this year. Carreira's synthesis of zaragozic acid C **122** commenced from D-erythronolactone.[52] The synthesis of zaragozic A/squalestatin S1 **123** by the Nicolaou group was based on sequential asymmetric dihydroxylations of the achiral diene **126**, prepared by Stille coupling of **124** and **125** (Scheme 32).[53,54] The dihydroxylation was not completely diastereoselective, and elaboration led to the two epimeric pyranose derivative intermediates **127** and **128** en route to the natural product.



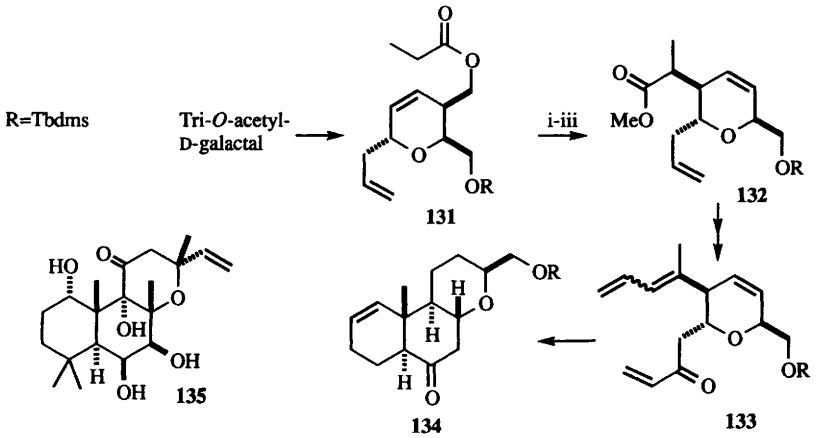
Scheme 32

An approach to an analogue of pancratistatin from conduritol-derived **129** led instead to the isomeric ring system **130**, presumably due to an alternative C-C bond migration during electrophilic cycloalkylation onto the aromatic nucleus (Scheme 33).[55]



Scheme 33

Tri-*O*-acetyl-D-galactal has been converted to the tricyclic ring system of forskolin **135** (Scheme 34).[56] Ireland-Claisen rearrangement of **131** to **132**, established the tetrahydropyran ring substitution, elaborated to the polyene **133**. Thermal intramolecular Diels-Alder reaction completed the construction of ring system **134**. Unfortunately, the Diels-Alder reaction was unsuccessful when applied to an analogous substrate containing the A-ring gem-dimethyl substituents of the natural product.

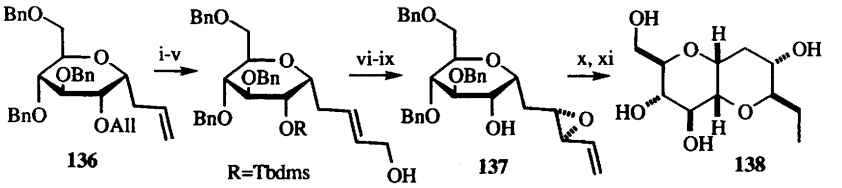


Reagents: i, HMDS, BuLi then TbdmsCl; ii, heat, toluene; iii, KF then MeI

Scheme 34

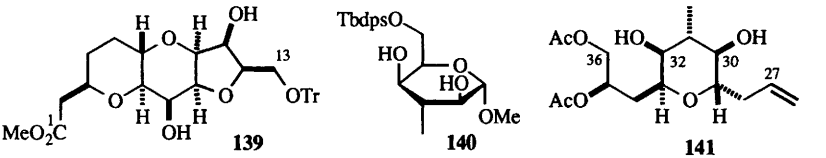
Maitotoxin is one of the most complex (32 ether rings) marine polyether natural product toxins so far discovered, and one of the most potent toxins known. D-Glucose has been converted to **138** confirming the stereochemistry of the L/M and N/O ring systems of maitotoxin.[57] The synthesis

involved homologation of the *C*-glycoside **136**, asymmetric epoxidation and one-carbon homologation to **137**, followed by acid catalysed cyclization *via* epoxide opening (Scheme 35).

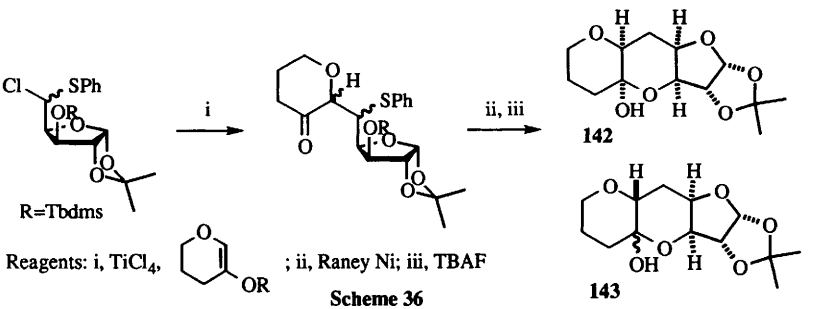


Reagents: i, $(Ph_3P)_4RhH$, TFA; ii, TbdmsCl; iii, O_3, Me_2S; iv, $Ph_3P{=}CHCO_2Me$; v, DIBAL; vi, ^tBuOOH, (+)-diethyl tartrate, $Ti(O^iPr)_4$; vii, SO_3.Py, DMSO; viii, $PPh_3{=}CH_2$; ix, TBAF; x, CSA; xi, H_2, Pd-C. **Scheme 35**

Diacetone-D-glucose was the starting material for synthesis of the C_1-C_{13} component **139** of halichondrin B, in which the right hand ring is derived from the carbohydrate and the central and left hand rings established through conjugate additions by oxygen nucleophiles.[58] The same group prepared the C_{27}-C_{36} subunit **141** of halichondrin B from dimethyl L-tartrate proceeding *via* the glycoside **140**.[59]

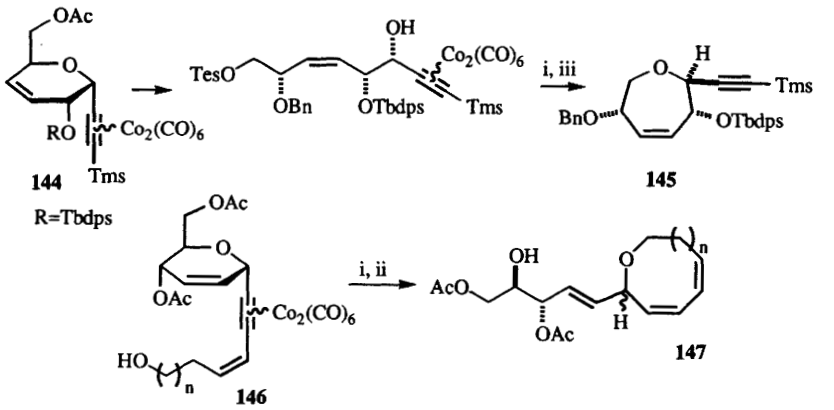


The herbicidins continue to prove a synthetic challenge, and this year Gallagher's group have reported the synthesis of **142** and **143** possessing the furano-pyrano-pyran skeleton of the herbicidins. Key synthetic steps are fluoride-mediated alkoxide cyclization onto a ketone functionality after desulfurization (Scheme 36).[60]

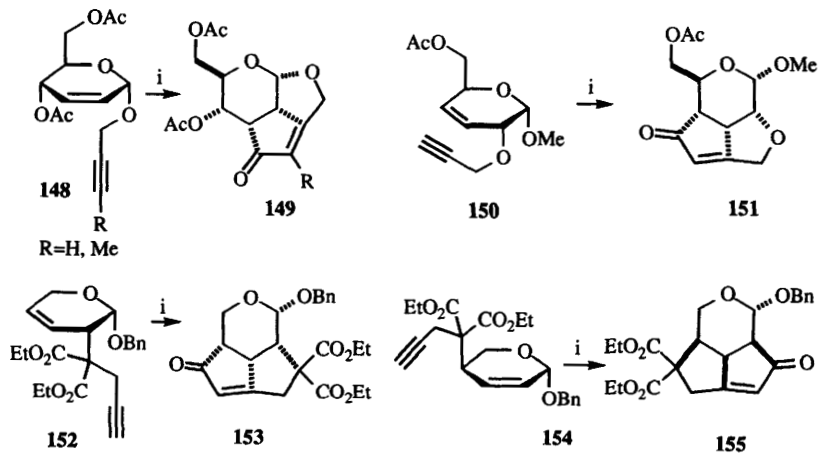


Scheme 36

Two applications of α-carbocation stabilization by dicobalthexacarbonyl alkyne complexes in *O*-heterocycle construction from carbohydrates have been reported this year, both providing medium ring ether components of polyether marine natural products. Ring opening of the *C*-glycoside **144** is favoured by stabilization by the alkyne complex, and after functional group elaborations, the α-carbocation stabilization now assists in acid catalysed cyclization during *in situ* desilylation, after deprotection, providing the oxepane **145**.[61] A similar strategy utilized *C*-glycoside opening and *in situ* cyclization from a free remote hydroxyl group, converting **146** (derived from tri-*O*-acetyl glucal) to **147**, a building block for the brevetoxins/ciguatoxins (Scheme 37).[62]



Reagents: i, TfOH; ii, H_2, Rh-C; iii, I_2. **Scheme 37**

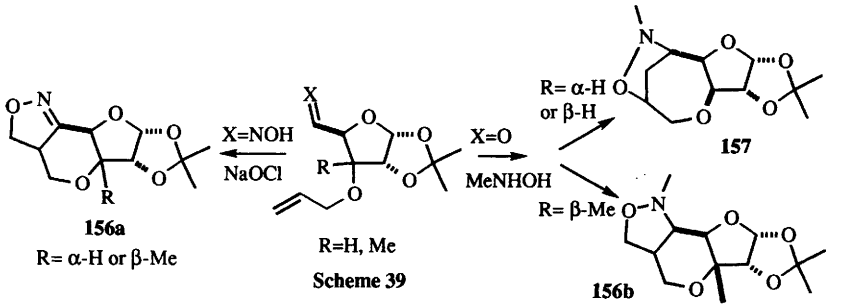


Reagents: i, $Co_2(CO)_8$, then NMNO

Scheme 38

Continuing the organocobalt theme, two groups have reported using the Pauson-Khand reaction with carbohydrate templates to construct bis-annulated pyranosides. Propargylic ether substrates such as **148** and **150** provided the isomeric tricyclic systems **149** and **151**,[63] while the propargyl malonate substrates **152** and **154**, cyclized to the isomeric tricyclic systems **153** and **155** (Scheme 38).[64]

Intramolecular nitrone or nitrile oxide cycloadditions have been used to construct tricylic ring systems **156** and **157** from furanoside templates (Scheme 39).[65]



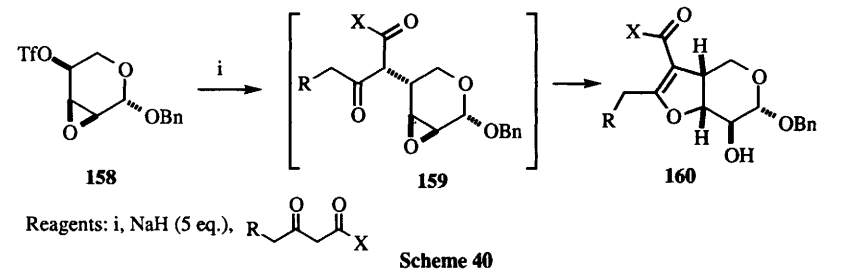
156a

157

156b

Scheme 39

An interesting one-pot route to fused pyranosides from anhydro sugars has been reported, in which initial triflate displacement on **158** by a 1,3-dicarbonyl carbanion generates an intermediate **159** which on further deprotonation generates a second enolate which undergoes 5-*exo-tet* epoxide ring opening to give **160** (Scheme 40).[66]



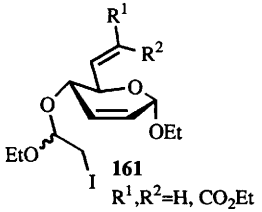
158 **159** **160**

Reagents: i, NaH (5 eq.),

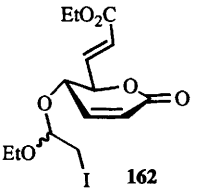
Scheme 40

Fraser-Reid has reported studies on factors controlling the outcome of intramolecular radical cyclizations on carbohydrate templates.[67] On templates bearing an acetal linked radical centre precursor, **161**, cyclizations gave mixtures of 5-*exo-trig*, **165** and **166**, and 6-*exo-trig* products **164**. The ratio in the case of the *E*-alkene acceptor geometry was 2.3:2.7, with the 6-*exo-trig* overall preferred but obtained as a 1.6:1 diastereoisomeric mixture. The lactone analogue of this system **162** however underwent 5-*exo-trig* cyclization predominantly (9:1). Use of an alternative centre bearing the radical, and changing the electronic nature of the radical acceptor, had significant effects. Silyl ether

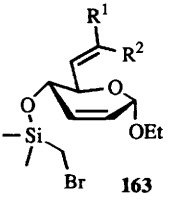
substrates with a non-conjugated alkene acceptor, **163**, cyclized to give only 5-*exo-trig* products, while the analogous α,β-unsaturated ester acceptor afforded only 6-*exo-trig* cyclization.



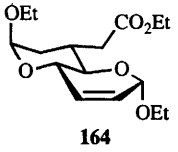
161
R^1,R^2=H, CO_2Et



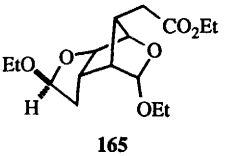
162



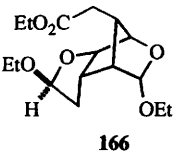
163



164

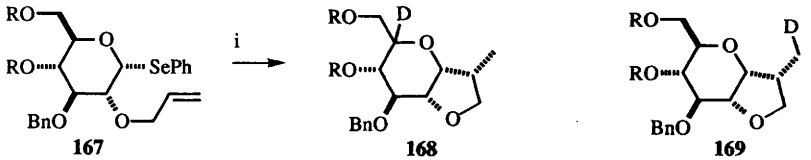


165



166

Effects of carbohydrate structure and functionality on radical translocation during cyclization onto C1 radicals have been probed using deuterium radical trapping. The radical generated from the tribenzylated selenoglucoside **167** gives a 78:22 mixture of the translocated product **168** and non-translocated product **169**, while the 4,6-*O*-benzylidene acetal analogue gives a 97:3 mixture in favour of translocation (Scheme 41). A similar effect was observed for the galacto series, the tribenzylated selenogalactoside giving a 57:43 mixture, but the 4,6-*O*-benzylidene acetal analogue giving exclusively the translocation product.[68] Routes to sesbanamide and it's enantiomer from D- and L-xylose have been reviewed in a lecture by Pandit.[69]



167 **168** **169**

R=R=Bn 78 22
R,R = -CHPh- 97 3

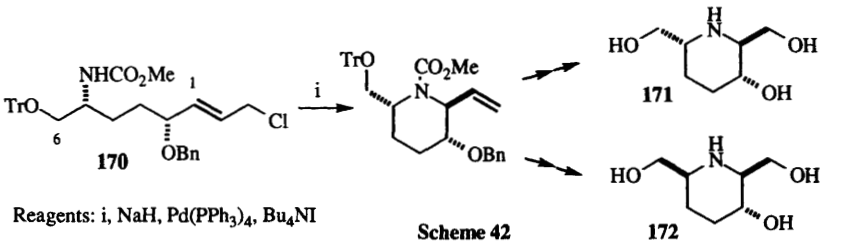
Reagents: i, Bu_3SnD

Scheme 41

5 N-Heterocycles

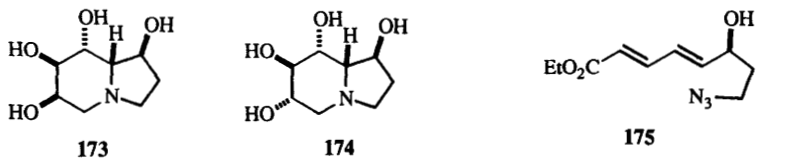
D-Glucose (*via* its known methyl 3,4-dideoxy derivative) has also been used as starting material for synthesis of (-)-desoxyprosopinine **171** and (-)-desoxoprosophylline **172**. The heterocycle is formed by amination of the π-allyl Pd° intermediate generated from **170** (Scheme 42).[70] A formal total

synthesis of the enantiomers was also achieved by converting glucose to an intermediate enantiomeric with one used in the synthesis of the natural (-)-enantiomer.

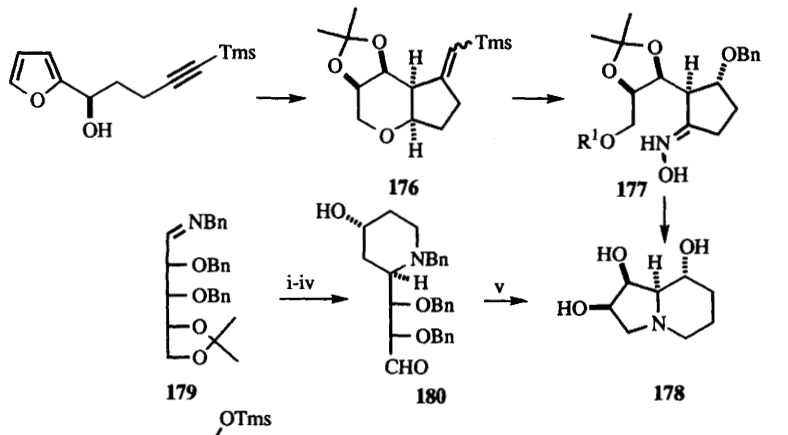


Reagents: i, NaH, $Pd(PPh_3)_4$, Bu_4NI

Scheme 42



A number of routes to polyhydroxy indolizidines from carbohydrates have been described this year. Syntheses of 6,8a-di-epicastanospermine **173** from D-arabinose and of 8a-epicastanospermine **174** from L-xylose has been reported,[71] utilizing allylation chemistry essentially analogous to that previously described by Burgess [Vol. 26, p. 196, ref. 65]. Cha and colleagues have reported improvement of his route to (+)-6,7-diepicastanospermine from **175**, which utilizes Sharpless AE and AD sequential processes to introduce four of the stereogenic centres.[72]

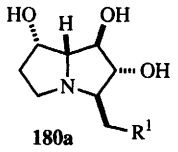


Reagents: i, MeO–⟨OTms⟩ $ZnCl_2$; ii, L-selectride; iii, HOAc, H_2O; iv, $Pb(OAc)_4$; v, H_2, Pd-C, HOAc

Scheme 43

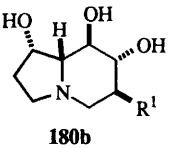
(-)-Swainsonine **178** has been synthesized from 1-(2'-furyl)-5-(trimethylsilyl)pent-4-yn-1-ol *via* the glycoside **176**. Beckmann ring expansion of intermediate **177** provides entry to the piperidine ring.[73] The synthesis of five isomers of swainsonine has been reported, the key transformation being diastereoselective hetero-Diels Alder reaction of sugar-derived imines and Danishefsky's diene or analogues.[74] For example, the D-ribose-derived imine **179** reacts to give **180** and is elaborated to **178** (Scheme 43). A preliminary report of this work has been reviewed [Vol. 26, p. 314, ref. 70 and p. 195, ref. 63].

Reactions of castanospermine derivatives have also been described, notable for the participation of the ring nitrogen in substitution reactions (presumably *via* aziridinium intermediates) leading to retention and ring contractions during introduction of fluoro, amino, azido and cyano groups to give pyrrolizidine and indolizidine systems **180a-c** [see Chapter 22].[75,76]

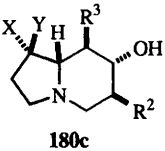


180a

R^1 = F, NH_2, OMe



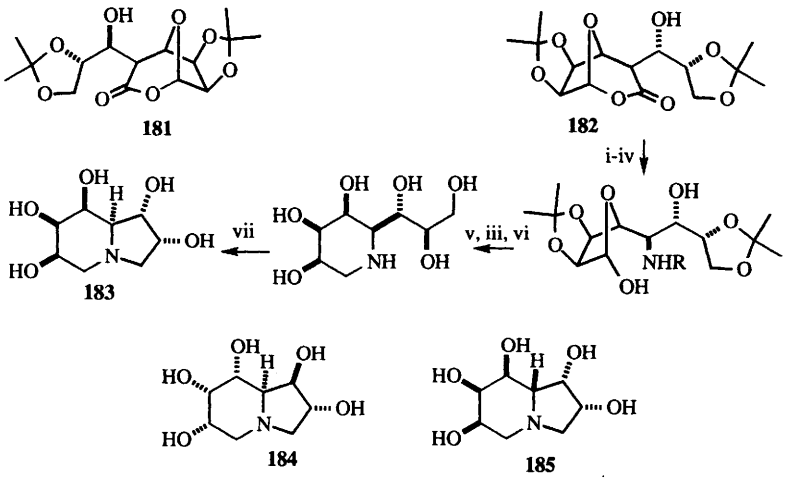
180b



180c

X=F, Y=H, R^2=R^3=OH
X=H, Y=F, R^2=R=OH
X=OH, Y=H, R^2=F, R^3=OH

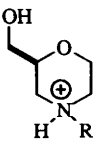
Chen and Vogel have described a versatile asymmetric route to 1,5-amino-1,5-dideoxy-octitols and 1,2,6,7,8-pentahydroxyindolizidines **183**, **184** and **185** proceeding *via* alcoholyses of the homochiral diastereoisomeric lactones **181** and **182** (Scheme 44).[77]



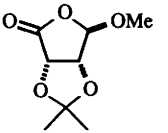
Reagents: i, BnOH, CsF; ii, TbdmsOTf; iii, H_2, Pd-C; iv, $N_3PO(OPh)_2$ then BnOH; v, TBAF; vi, Dowex 50WX8; viii, Ph_3P, DEAD, Py.

Scheme 44

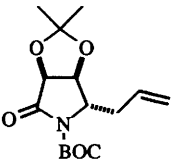
D-Ribono- and D-gulonolactones have been converted into homochiral 3-hydroxymethyl morpholinium derivatives **186**,[78] while the D-ribose-derived lactone **187** has been used to synthesize the pyrrolidinone **188**, a precursor to the hydroxyamino acid moiety of AI-77B.[79] L-Quebrachitol has been converted to the lactam **189**, a component of bengamide B.[80]



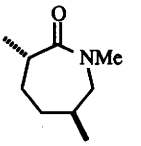
186 R=Bn, $CHMe_2$, CH_2Bn



187

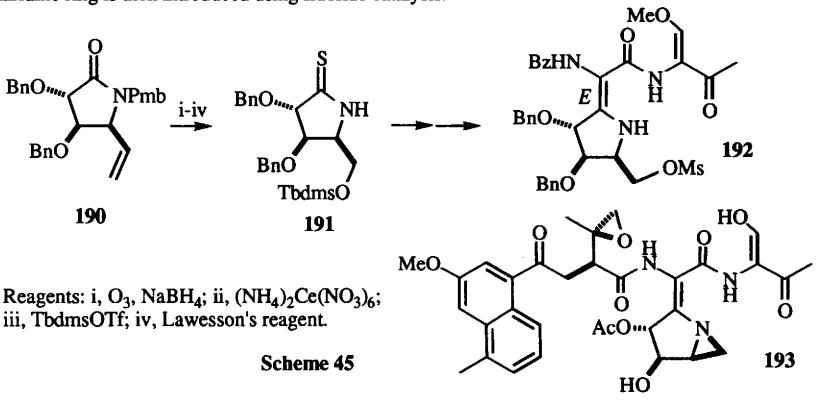


188



189

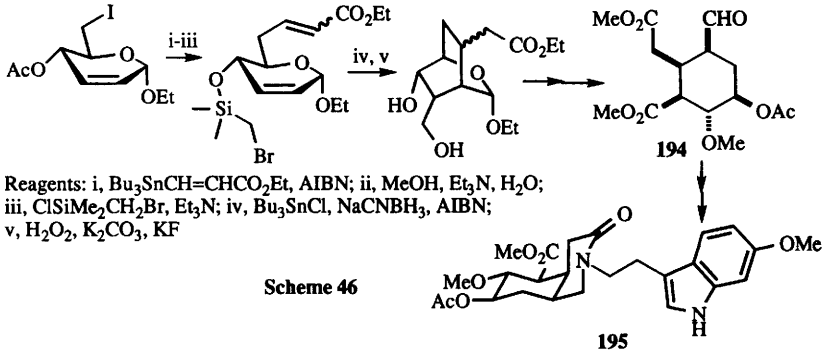
A synthesis of the C1-C17 fragment of the cytotoxic natural product carzinophilin (azinomycin B) **193** has been reported.[81,82] The synthesis proceeds *via* the known pyrrolidinone **190** converted to the thiolactam **191**,[81] then elaborated to intermediate **192** (Scheme 45). The key *E* alkene stereochemistry is obtained by isomerization of the *E*/*Z* mixture of **192** on standing, and the aziridine ring is then introduced using fluoride catalysis.



190 **191** **192** **193**

Reagents: i, O_3, $NaBH_4$; ii, $(NH_4)_2Ce(NO_3)_6$; iii, TbdmsOTf; iv, Lawesson's reagent.

Scheme 45



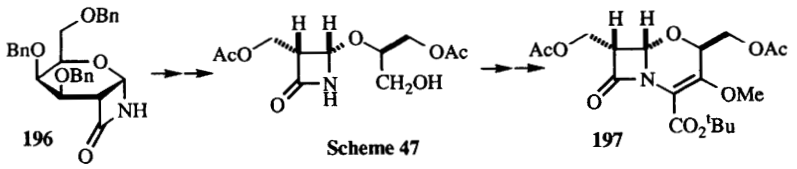
194 **195**

Reagents: i, $Bu_3SnCH{=}CHCO_2Et$, AIBN; ii, MeOH, Et_3N, H_2O; iii, $ClSiMe_2CH_2Br$, Et_3N; iv, Bu_3SnCl, $NaCNBH_3$, AIBN; v, H_2O_2, K_2CO_3, KF

Scheme 46

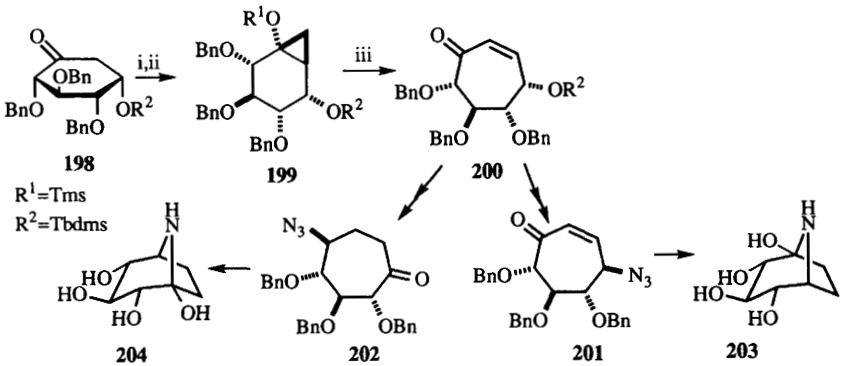
A route to Woodward's reserpine precursor **195** has been developed by Fraser-Reid, utilizing a tandem radical cyclization, and proceeding *via* the homochiral cyclohexane intermediate **194** (Scheme 46),[83] [see section 4 for other related radical cyclizations].

Tri-*O*-benzyl-D-galactal has been converted into 1-oxacephem skeleton **197** *via* the known (Vol. 26, p.313, ref. 60) [2+2] isocyanate cycloaddition product, **196** (Scheme 47).[84]



Scheme 47

The natural products (+)-calystegine and its enantiomer have been synthesized from D-glucose *via* the Ferrier rearrangement product **198**. Ring expansion of the cyclopropane derivative **199** gives **200**, converted to either **201** or **202**, precursors to the natural product **203** or its enantiomer **204** respectively (Scheme 48).[85] [preliminary report see: Vol. 26, p. 314-5, ref. 73].



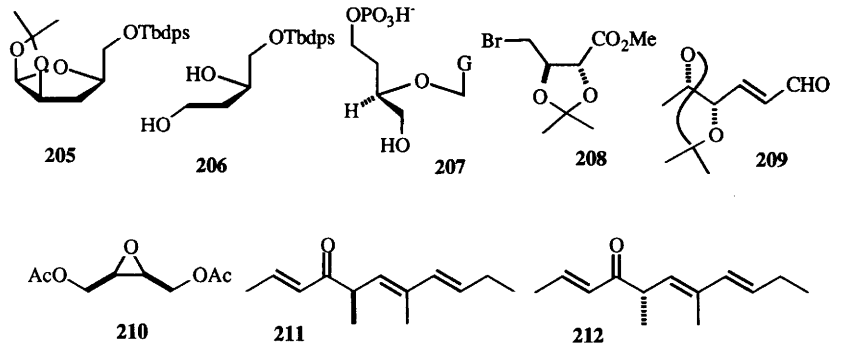
Reagents: i, LDA, TmsCl; ii, Et_2Zn, CH_2I_2; iii, $FeCl_3$, DMF.

Scheme 48

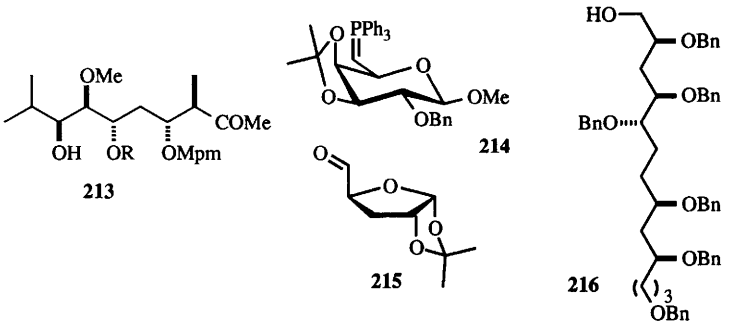
6 Acyclic Compounds

The L-arabinose derivative **205** provides the starting point for synthesis of the 2-deoxythreose derivative **206**, then converted to the acyclic nucleotide analogue **207** (which is twice as active against cytomegalovirus as its (*S*)-enantiomer).[86] The chiron **208** has been synthesized starting from L-ascorbic acid,[87] while diacetyl-D-rhamnal has been converted to **209** in six steps.[88] The carbohydrate-derived *meso* epoxide diacetate **210** has been efficiently desymmetrized (to the monoacetate) using

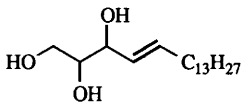
porcine pancreatic lipase, and this chiron then elaborated to either enantiomer **211** or **212** of the sex pheromone of the Israeli pine bast scale, *Matsucoccus josephi*.[89]



A number of syntheses of acyclic chain extended compounds have been reported this year. 2-Deoxy-D-glucose has been elaborated to **213** a precursor to the C_{14}-C_{24} section of tautomycin,[90] and a synthesis of the C_1-C_{12} fragment **216** of amphotericin B utilizes a Wittig coupling of two carbohydrate components, the 3-deoxy-D-ribofuranose derivative **215** and the galactose-derived **214**.[91]

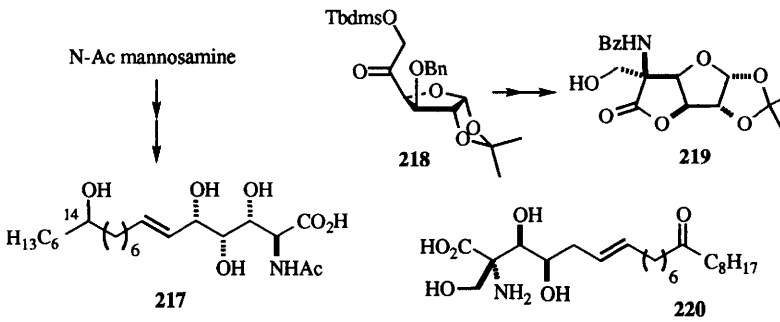


D-Xylose, D-glucose and D-mannose have been used as starting materials for synthesis of the four stereoisomers of 1,2,3-trihydroxy-4*E*-octadecene, intermediates for the synthesis of various sphingosines.[92]

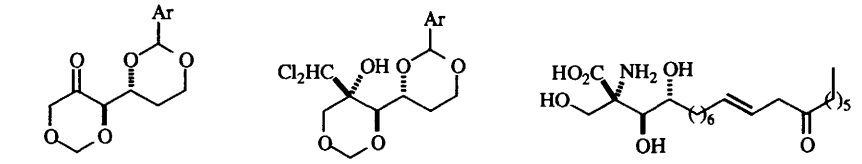


The synthesis of sphingosines, ceramides and other amino polyols has seen a number of reports this year. A synthesis of sphingofungin D **217**, the anifungal metabolite of *Aspergillus*

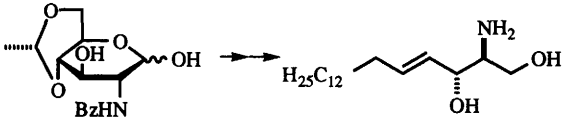
fumigatus ATCC 20857, and of its C14 epimer has been reported, starting from *N*-acetyl mannosamine, in which the enantiomeric C6-C20 chain is attached by $NiCl_2$-$CrCl_2$ catalysed vinyl iodide addition (Nozaki coupling). The absolute configuration at C14 of the natural product is uncertain, and the activity of the two epimers provided by this new synthesis were so similar that absolute assignment remains unresolved.[93] The bicyclic furanoside **219** has been prepared from D-glucose-derived **218**, and has previously been converted to myriocin **220**.[94]



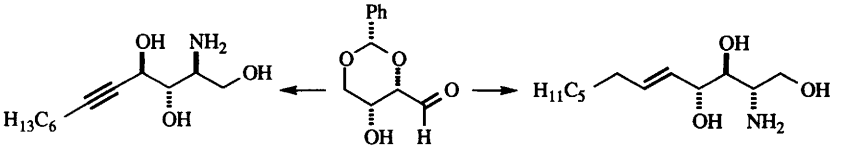
2-Deoxy-D-glucose also serves as starting material for a 19-step synthesis of the antifungal and immunosupressive agent myriocin A **223**. Key steps in this synthesis involved conversion of ketone **221** to **222** *via* modified Darzens reaction, and introduction of the amino functionality through azide opening of an intermediate chloroepoxide derived from **222**.[95]



N-Benzoyl-D-glucosamine has been used for synthesis of both D-*erythro*-sphingosine **224** and of phytosphingosine (Scheme 49),[96] while a synthesis of **226** has also been reported starting from 2,4-*O*-benzylidene-D-threose, **225** (Scheme 50).[97]



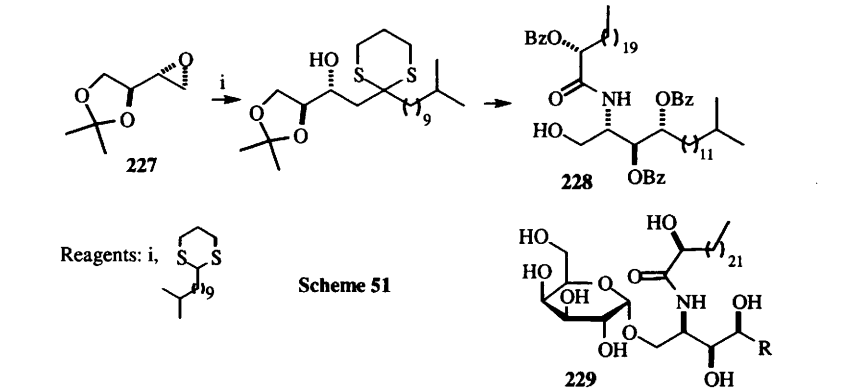
Scheme 49



226a **225** **226b**

Scheme 50

The protected ceramide **228**, part of the cerobroside from the marine sponge *Halichondrica japonica*, has been prepared starting from L-ascorbic acid and then **227** (Scheme 51).[98] D-Arabinose has been elaborated to the appropriate ceramide and coupled to tetrabenzylgalactosyl fluoride in a synthesis of the α-galactosyl ceramides **229**, the agelasphins, antitumour and immunostimulatory agents from the sponge *Agelas mauritianus*.[99]

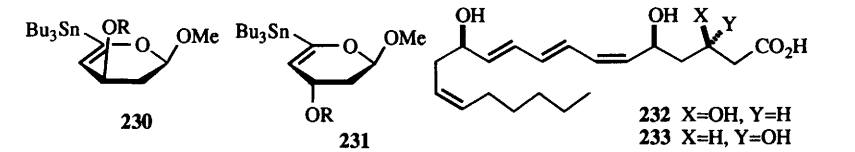


227 **228** **229**

Reagents: i,

Scheme 51

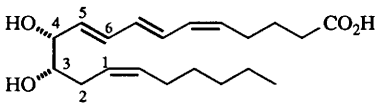
The synthesis of eicosanoids from carbohydrates has seen a number of reports this year. Methyl β-2-deoxy-D-ribofuranoside is the starting point for synthesis of 3-hydroxyleukotriene B4 **232** and its C3 epimer **233**.[100] A double Mitsunobu inversion on the starting material provides the divergence towards the epimeric target. The synthesis utilizes the derived epimeric vinyl stannanes **230** and **231** as a key step.



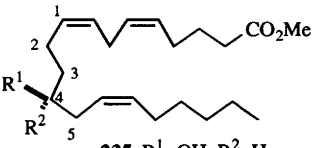
230 **231** **232** X=OH, Y=H **233** X=H, Y=OH

(11*R*,12*S*)-Dihydroxy-5,7,9,14-eicosatetraenoic acid **234** (carbohydrate numbering shown) has been synthesised from 1,2:5,6-di-*O*-isopropylidene-D-glucose.[101] Methyl 2-deoxy-D-ribofuranoside has been converted, *via* C3 deoxygenation and chain extension at C5, to the (12*R*) and (12*S*)-

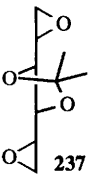
hydroxy-eicosan-5*Z*,8*Z*,14*Z*-trienoic acid methyl esters, **235** and **236**, and also to the 14,15-dehydro analogues.[102] Enal **238**, a precursor to the barnacle hatching factor **239**, has been prepared by double epoxide opening of the *bis*-epoxide **237** followed by diol cleavage of the symmetrical intermediate obtained.[103]



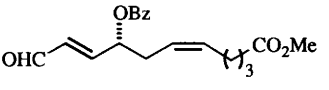
234



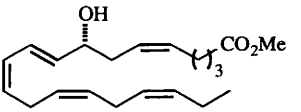
235 R^1=OH, R^2=H
236 R^1=H, R^2=OH



237

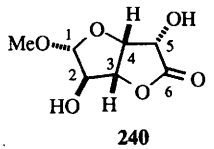


238

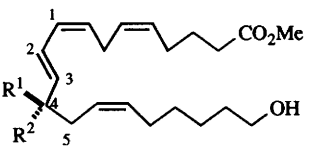


239

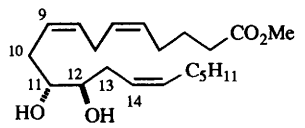
The D-glucurono-6,3-lactone derivative **240** provides the starting point for several syntheses reported this year, all involving elaboration of this material through double Barton deoxygenation, DIBAL reduction and then Wittig reactions of the intermediate lactol. Both enantiomeric (12*R*),20- and (12*S*),20-dihydroxyeicosatetraenoic acids **241** and **242** have been prepared (Mitsunobu inversion providing the enantiomer at the end of the synthesis) - sugar numbering shown.[104] The same group has also reported elaboration of **240** to (11*R*),(12*R*)-dihydroxyeicosatetraenoic acid **243** and to the three stereoisomers (*via* appropriate Mitsunobu inversions), and also to the regioisomeric product **244**.[105] (11*R*),(12*R*)-Dihydroxyeicosatetraenoic acid has also been synthesized from 2-deoxy-D-glucose in which the carbohydrate carbons provide C_9-C_{14} of the natural product.[106]



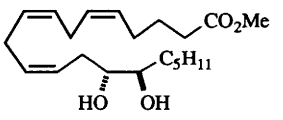
240



241 R^1=OH R^2=H
242 R^1=H R^2=OH

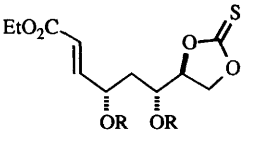


243

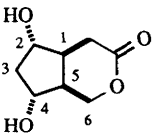


244

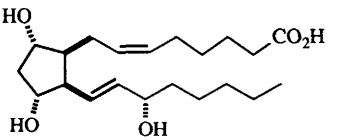
A synthesis of 8-epi-$PGF_{2\alpha}$ **246** has been achieved starting from L-glucose, in which the key functionalized cyclopentane is constructed *via* intramolecular radical conjugate addition of the intermediate **245** to give **72**, Wittig and Horner-Emmons chemistry being employed for chain assembly.[107]



R=Tbdms **245**



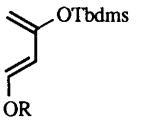
72



246

7 Carbohydrates as Chiral Auxiliaries, Reagents and Catalysts

A review has appeared on asymmetric synthesis of α-amino acids, in which uses of carbohydrates as auxiliaries - particularly pivaloylated glycosylamines - for asymmetric Strecker and Ugi reactions is described.[108]



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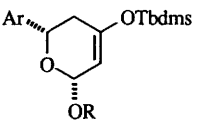

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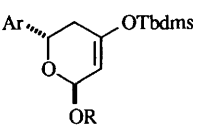

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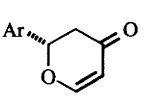

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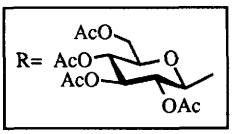

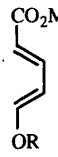

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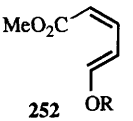

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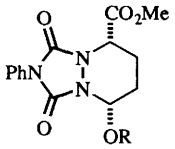

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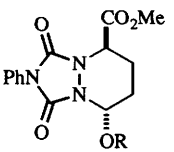

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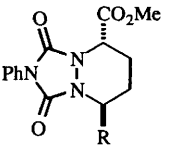
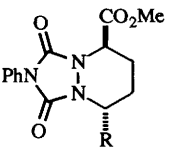


255

R=CN
R=OMe
$R=CH_2CH=CH_2$



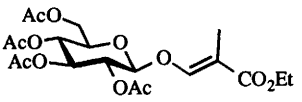
256

R=CN
R=OMe
$R=CH_2CH=CH_2$

This year has seen several further applications of carbohydrates as auxiliaries in hetero-Diels Alder reactions. The glucopyranosyl diene **247** undergoes Lewis acid catalysed cycloaddition with aromatic aldehydes to give primarily diastereoisomer **248**, with minor amounts of the other diastereoisomeric *trans* adduct **249**.[109] The adduct **248** isomerises to **249** with time in the presence of the catalyst, but both epimers are converted to the enone **250**.

The glucopyranosyl diene **251** undergoes hetero-Diels Alder addition to give **253**, which serves then as substrate for several diastereoselective reactions[110] to provide **255**. The geometrical isomer **252** provides the trans Diels Alder adduct **254** which can be converted to **256**, enantiomeric with **255**. The outcome of these transformations imply that the mechanism of the reaction in which the auxiliary is lost involves nucleophilic addition to an acyliminium intermediate.

The utility of the tetraacetyl glucopyranosyl auxiliary has been extended to diastereoselective functionalizations of glycosyl enol ether derivatives.[111] Hydrogenation of **257** affords an 84:16 epimeric mixture predominantly **258**, while the lactone **259** is hydrogenated with 50-65% d.e. to **260** as major product.



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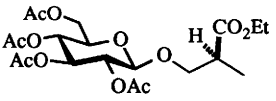

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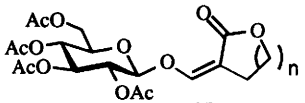

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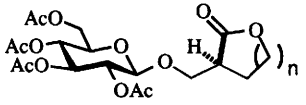
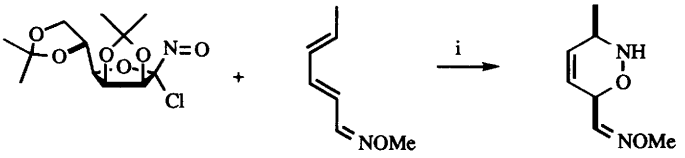


260

Carbohydrates have also been used as auxiliaries to control additions to nitroso dienophiles, as a *de novo* route to 5-amino-5,6-dideoxy-D-allose derivatives *via* **261** (Scheme 52) (see Chapter 16 and 18).[112]

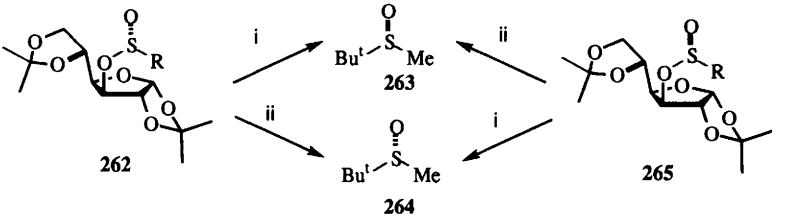


Reagents: i, EtOH

Scheme 52

A further report has appeared describing the stereochemistry of Grignard displacement reactions of the xylose-derived sulfinates **262** and **265**, correcting previous reports (Vol. 26, p. 321). Reaction of either *S* or *R* sulfinates proceeds with inversion on reaction with t-butylmagnesium chloride or methylmagnesium iodide, to give enantiomeric sulfides **263** and **264** (Scheme 53).[113]

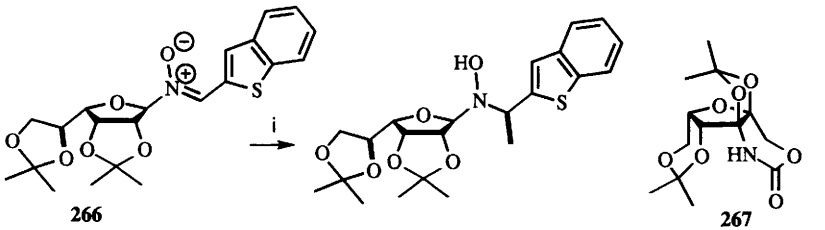
Similar reactions of thiomethylmethyllithium with the ethyl and methyl sulfinate analogues of **262** and **265** have also been reported by others to proceed with the same stereochemical outcome.[114]



Reagents: i, ^{t}BuMgCl (R=Me); ii, MeMgI (R=^{t}Bu).

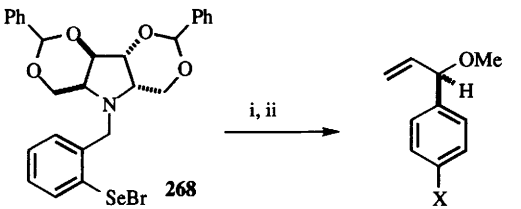
Scheme 53

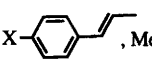
The nitrone **266** bearing a D-gulono-γ-lactone auxiliary directs addition of methylmagnesium bromide as a key step in synthesis of (*R*)-zilegton (Scheme 54).[115] The gulonic-acid derived auxiliary **267** has been described as an improvement on a previously reported carbohydrate oxazolidinone auxilary (see Chapter 10)



Reagents: i, MeMgBr **Scheme 54**

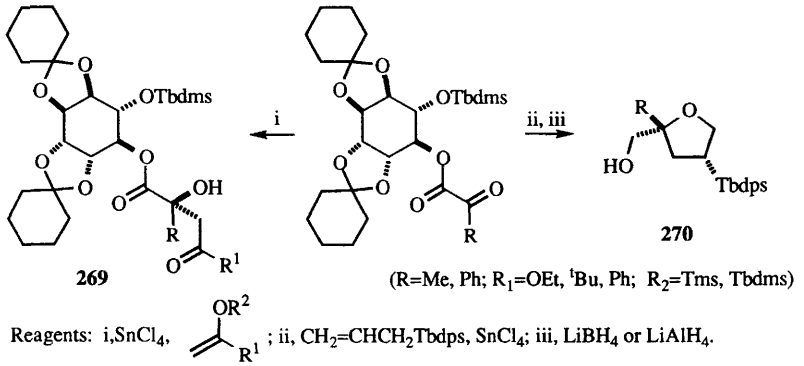
The C_2-symmetric pyrrolidine-containing selenyl bromide **268** has been described as a reagent for enantioselective methoxyselenation of styrene derivatives in 50-60% d.e., leading, after oxidative elimination, to 1-arylallyl methyl ethers of predominantly *R* configuration (Scheme 55).[116]



Reagents: i, X-  , MeOH; ii, H_2O_2.

Scheme 55

The use of the cyclitol, L-quebrachitol, as chiral auxiliary for ketone alkylation has been extended to additions of silyl enol ethers and silyl enol esters, providing α-hydroxyacid precursors, **269** with d.e. ≥ 98% in most cases (Scheme 56).[117] [Grignard, alkylithium and allylsilane additions to this substrate, Vol. 26, p. 319, ref. 93]. The same α-keto esters bearing this L-quebrachitol auxiliary undergo diastereoselective [3+2] cycloadditions with allylsilanes, providing a route to chiral functionalized tetrahydrofurans **270**.[118]



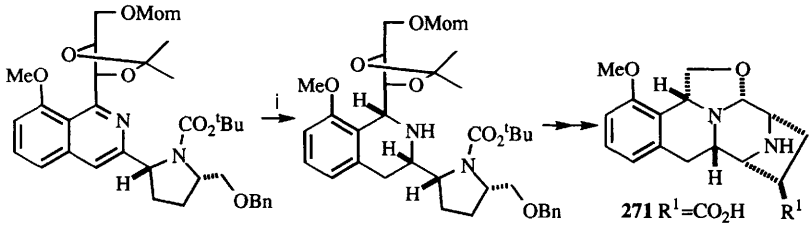
269 **270**

(R=Me, Ph; R_1=OEt, ^{t}Bu, Ph; R_2=Tms, Tbdms)

Reagents: i,$SnCl_4$, ; ii, CH_2=$CHCH_2$Tbdps, $SnCl_4$; iii, $LiBH_4$ or $LiAlH_4$.

Scheme 56

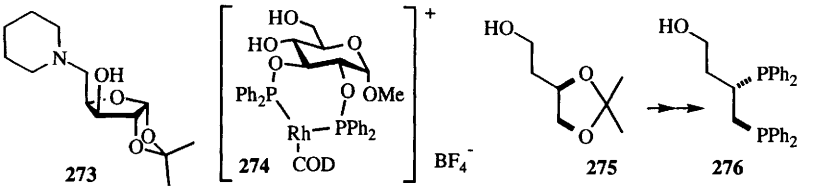
D- and L-Threose derivatives have been utilized as chiral auxiliaries for asymmetric imine reductions in the total synthesis of quinocarcin **271** and 1-decarboxyquinocarcin **272** (Scheme 57).[119] The methodology has also been applied to a range of model compounds.[120,121]



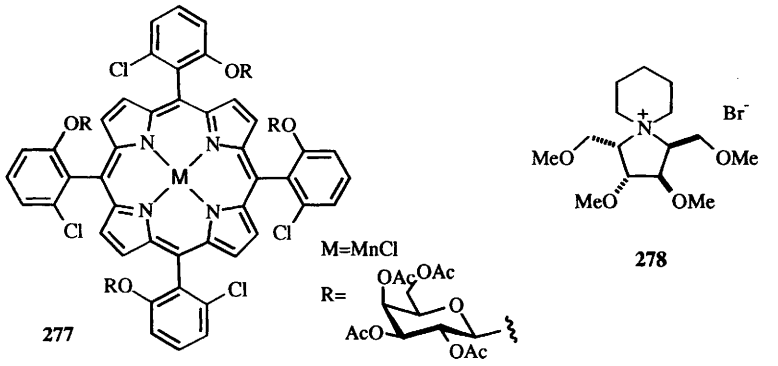
Reagents: i, $NaCNBH_3$, HCl

Scheme 57

This year has seen several new reports of carbohydrate derivatives as ligands for catalytic asymmetric processes. 5-Deoxy-1,2-*O*-isopropylidene-5-piperidinyl-α-D-xylose **273** is a reasonably effective amino alcohol catalyst for asymmetric diethylzinc addition to aldehydes, alkylation of benzaldehyde proceeding in 87% e.e.[122] The rhodium-cyclooctadiene bis-phosphinite methylglucoside derivative **274** (derivatized analogues have been previously employed for hydrogenations) has been shown to be a very efficient catalyst for asymmetric hydrogenations of 2-*N*-acetyl-aminocunnamates in water when sodium dodecylsulfate is employed as additive, affording amino acids in 96-98% e.e.[123] The triol acetonide **275**, derived from L-ascorbic acid (Vol. 24, p. 315, ref. 79) has been converted to the chiral bisphosphine **276**, a chiral ligand for catalytic enantioselective hydrogenation.[124]



Galactosylated Mn porphyrins **277** have been prepared as catalysts for asymmetric epoxidation, affording predominantly epoxides of (*R*) configuration from styrenes in up to 23% e.e.[125] The αβαβ, ααββ and αααβ atropisomers of **277** were isolated. Homochiral C_2-symmetric quaternary ammonium salts, e.g. **278**, have been prepared from chiral 2,5-imino-hexitols as chiral phase transfer catalysts. However, these were found to give only low asymmetric induction in asymmetric epoxidation and Darzens condensations.[126]



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