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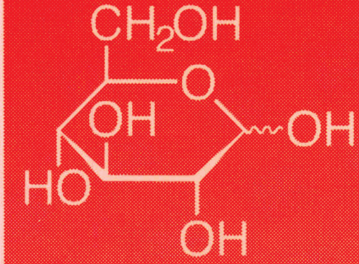

Carbohydrate Chemistry

Monosaccharides, Disaccharides and Specific Oligosaccharides

Volume 31

senior reporter R.J. FERRIER

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Volume 31

A Specialist Periodical Report

Carbohydrate Chemistry
Monosaccharides, Disaccharides and Specific Oligosaccharides
Volume 31

A Review of the Literature Published during 1997

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Preface

In the Preface to the preceding volume attention was drawn to the increase in the amount of research of relevance to these Reports that is appearing in the organic chemical literature. This year it is appropriate to highlight the point that very recent years have also seen major enhancement in the importance and scientific merit of much of the work described. In no area is this more evident than in the field of oligosaccharides – particularly their synthesis (Chapter 4) – the number of papers having doubled since 1990, but the quality and importance indices having increased by an appreciably larger factor.

It is, of course, the needs of scientists working in glycobiology that is driving activity in this area, the significance being notably exemplified by reports on the preparation of specific carbohydrate-based antigens – especially cancer-specific oligosaccharides and glycoconjugates. Glycomedicinal chemistry and its reliance on carbohydrate synthesis are now very well established.

Oligosaccharide synthetic methods are developing in line with demands, polymer-supported procedures now being common – several decades after analagous developments in the oligopeptide and oligonucleotide fields, and specific enzyme-dependent processes are at last in frequent use.

Concurrently, solution-phase methodology is progressing quickly with the overdue recognition that the differential reactivities of both glycosylating agents and carbohydrate acceptor alcohols can be harnessed for the opening of selective, multi-step, one-pot procedures. Startling consequences are beginning to appear, and surely herald major applications of this approach.

Other matters to catch the eye in the oligosaccharide field are the expanding use of intramolecular approaches and, inevitably, examples of the combinatorial strategy. With the sialic acids having such prominent significance in glycobiology their chemistry is being pursued with particular vigour.

I thank our unchanged team for shouldering the continuously more demanding task of surveying this field, and trust that the assistance that Prof. Rob Field and Dr Ravi Kartha, St Andrews University, will provide with future volumes will enable us to bring forward our completion dates.

R.J. Ferrier
September 1999

Contents

Carbohydrate Chemistry, Volume 31

Chapter 15 Aldosuloses and Other Dicarbonyl Compounds 200

Chapter 16 Sugar Acids and Lactones 202

Abbreviations

The following abbreviations have been used:

Ac	acetyl
Ade	adenin-9-yl
AIBN	2,2-azobisisobutyronitrile
All	allyl
Ar	aryl
Ara	arabinose
Asp	aspartic acid
BBN	9-borabicyclo[3.3.3]nonane
Bn	benzyl
Boc	*t*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CD	circular dichorism
Cer	ceramide
CI	chemical ionization
Cp	cyclopentadienyl
Cyt	cytosin-1-yl
Dahp	3-deoxy-D-*arabino*-2-heptulosonic acid 7-phosphate
DAST	diethylaminosulfur trifluoride
DBU	1,8-diazabicyclo[5.5.0]undec-5-ene
DCC	dicyclohexylcarbodi-imide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBALH	di-isobutylaluminium hydride
DMAD	dimethylacetylene dicarboxylate
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
Dmtr	dimethoxytrityl
e.e.	enantiomeric excess
Ee	1-ethoxyethyl
ESR	electron spin resonance
Et	ethyl
FAB	fast-atom bombardment

Fmoc	9-fluorenylmethylcarbonyl
Fru	fructose
FTIR	Fourier transform infrared
Fuc	fucose
Gal	galactose
GalNAc	2-acetamido-2-deoxy-D-galactose
GLC	gas–liquid chromatography
Glc	glucose
GlcNAc	2-acetamido-2-deoxy-D-glucose
Gly	glycine
Gua	guanin-9-yl
Hep	L-*glycero*-D-*amanno*-heptose
HMPA	hexamethylphosphoric triamide
HMPT	hexamethylphosphorous triamide
HPLC	high performance liquid chromatography
IDCP	iodonium dicollidine perchlorate
Ido	idose
Im	imidazolyl
IR	infrared
Kdo	3-deoxy-D-*manno*-2-octulosonic acid
LAH	lithium aluminium hydride
LDA	lithium di-isopropylamide
Leu	leucine
LTBH	lithium triethylborohydride
Lyx	lyxose
Man	mannose
*m*CPBA	*m*-chloroperbenzoic acid
Me	methyl
Mem	(2-methoxyethoxy)methyl
Mmtr	monomethoxytrityl
Mom	methoxymethyl
Ms	methanesulfonyl (mesyl)
MS	mass spectrometry
NAD	nicotinamide adenine dinucleotide
NBS	*N*-bromosuccinimide
NeuNAc	*N*-acetylneuraminic acid
NIS	*N*-iodosuccinimide
NMNO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
ORD	optical rotatory dispersion
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
Phe	phenylalanine
Piv	pivaloyl

Pmb	*p*-methoxybenzyl
Pr	propyl
Pro	proline
p.t.c.	phase transfer catalysis
Py	pyridine
Rha	rhamnose
Rib	ribose
Ser	serine
SIMS	secondary-ion mass spectrometry
TASF	tris(dimethylamino)sulfonium(trimethylsilyl)difluoride
Tbdms	*t*-butyldimethylsilyl
Tbdps	*t*-butyldiphenylsilyl
Tipds	tetraisopropyldisilox-1,3-diyl
Tips	triisopropylsilyl
Tf	triflluoromethanesulfonyl (triflyl)
Tfa	trifluoroacetyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Thp	tetrahydropyranyl
Thr	threonine
Thy	thymin-1-yl
Tips	1,1,3,3-tetraisopropyldisilox-1,3-diyl
TLC	thin layer chromatography
Tms	trimethylsilyl
TPP	triphenylphosphine
Tps	tri-isopropylbenzenesulfonyl
Tr	triphenylmethyl (trityl)
Ts	toluene-*p*-sulfonyl (tosyl)
Ura	uracil-1-yl
UDP	uridine diphosphate
UDPG	uridine diphosphate glucose
UV	ultraviolet
Xyl	xylose

1

Introduction and General Aspects

The long awaited comprehensive IUPAC/IUBMB paper on Nomenclature of Carbohydrates which covers all aspects of the subject has received wide dissemination.[1] Although the contents have the formal status of 'Recommendations', they are effectively the 'rules' to be followed. The subject has been revisited, particularly from the Hungarian perspective.[2] Hanessian's multi-authored book 'Preparative Carbohydrate Chemistry' deals with a wide range of practical aspects of modern synthesis. Examples, which include experimental details, cover such topics as oligosaccharide synthesis, the conversion of carbohydrates into carbocyclic compounds, free radical reactions, the use of organotin reagents in the field, selective *O*-substitution and oxidation reactions applied to carbohydrates. A further book on synthesis consists of 21 chapters written by experts on various aspects of the field including methodology and the synthesis of different carbohydrate-based natural products.[4]

A method for the representation of oligosaccharide structures by graphic theoretical methods has been developed for the purpose of storing and searching relevant information.[5]

Attention is drawn to the plethora of reviews that have appeared on specific features of the subject and which are noted in relevant chapters. An extreme example is Chapter 4 which begins with a catalogue of 39 references to review material relevant to oligosaccharide chemistry and biochemistry.

Reviews of wider interest have appeared on the following topics: protecting groups of value in carbohydrate chemistry;[6] protecting groups revealed in the 1997 literature;[7] the use of phase transfer catalyses in anomeric transformations and glycosylations; the use of sugar derivatives as phase transfer catalysts[8] and combinational synthesis in the field.[9,10]

Biologically inclined treatments have dealt with preparative biotransformations of carbohydrate derivatives (survey of the 1997 literature);[11] structure–biological activity relationships of natural products;[12] the role of 1-deoxy-D-*threo*-pentulose as a precursor in thiamine biosynthesis;[13] chemo-enzymic synthesis of oligosaccharides of importance in molecular glycobiology.[14] A brief discussion of molecular recognition events involving carbohydrates and their biological consequences has been written for non-specialists.[15]

A very interesting proposal by A.I. Scott regarding the prebiotic biosynthesis of polyketides, fatty acids and polyprenoids uses ribonucleosides 5′-linked to

Carbohydrate Chemistry, Volume 31

RNA as templates, the C-C bonding reactions involving monomeric units linked to O-3′.[16]

A survey has been presented on the carbohydrate transformations that can be induced by hypervalent iodine reagents. Such topics as the direct oxidation of tri-*O*-acetyl-D-glucal to the corresponding 1-en-3-one, C-1, C-2 bond oxidation of derivatives protected at all the hydroxyl groups except the anomeric and H-1 abstraction from *C*-glycosidic compounds were covered.[17]

A significant development has been made in use of sodium periodate for oxidizing carbohydrate α-diols with the reagent adsorbed on silica; oxidations are carried out in dichloromethane and can be followed by TLC; product isolation requires decanting of the solution and removal of the solvent; yields are very high.[18]

Carbohydrate-containing dendrimers are attracting considerable attention (see Chapter 3) and an overview of the topic by Stoddart and colleagues has appeared.[19]

The subject of dihexulose dianhydrides has been the subject of a thorough review.[20]

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2

Free Sugars

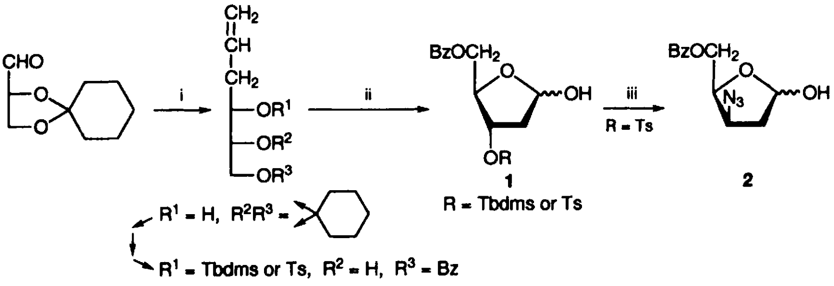
1 Theoretical Aspects

An improved method for partitioning the overall molecular charge distribution into atom-centred monopole charges has been applied to D-glucose and D-fructose.[1] The influence of the *exo*-anomeric effect on the conformations of D-glucose, as well as simpler tetrahydropyran derivatives, in the gas phase and in aqueous solution has been investigated by use of *ab initio* calculations.[2]

2 Synthesis

The synthesis and reactions of sugars and nucleosides under conditions pertinent to early evolution have been incorporated in a review on 'prebiotic chemistry'.[3]

2.1 Pentoses – *C*-3- Modified D-*erythro*- and D-*threo*-2-deoxypentofuranose derivatives, such as compounds **1** and **2**, useful as precursors of nucleoside analogues, have been synthesized from 2,3-*O*-cyclohexylidene-D-glyceraldehyde as outlined in Scheme 1; a zinc-mediated allylation was used for extending the carbon-chain.[4] 1-*O*-Acetyl-2,3,5-tri-*O*-benzyl-β-L-ribofuranose was obtained from 3,5-*O*-Tips-protected methyl L-arabinofuranoside *via* a 2-*O*-trifluoromethanesulfonyl-intermediate.[5]

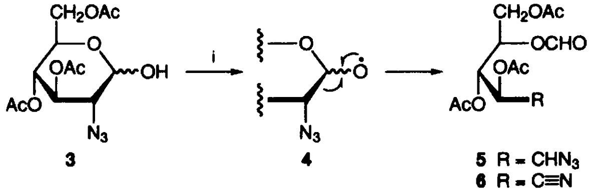


Reagents: i, AllBr, Zn; ii, O_3, PPh_3; iii, NaN_3, DMF

Scheme 1

Carbohydrate Chemistry, Volume 31

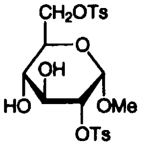
2.2 Hexoses – Trapping of dihydroxyacetone phosphate (prepared from α-L-glycerol phosphate by use of co-immobilized α-L-glycerolphosphate oxidase and catalase under anaerobic conditions) by DL-glyceraldehyde in the presence of an aldolase gave, after enzymic dephosphorylation, a mixture of D-fructose and D-sorbose.[6] 3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-D-glucopyranose (**3**) (or its *manno*-analogue) underwent fragmentation on exposure to (diacetoxyiodo)-benzene and iodine to give nitrile **6**, by way of alkoxyl radical **4** and α-azido-carbinyl radical **5**, as shown in Scheme 2.[7]



Reagent: i, PhI(OAc)$_2$, I$_2$

Scheme 2

In a novel isomerization reaction ditosylate **7** was converted to methyl α-D-altropyranoside (**8**) by treatment with sodium acetate in DMF, followed by aqueous-KOH; a *manno*-configured epoxide-intermediate has been postulated.[8]



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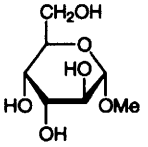

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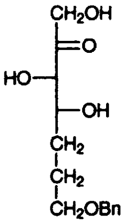
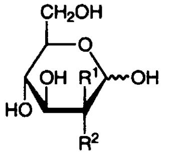


9

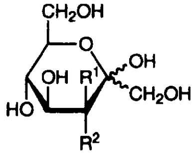
2,3,4,6-Tetra-*O*-allyl- and -benzyl-D-glucose have been obtained in 77% yield by thiolysis (EtSH/BF$_3$.OEt$_2$) of per-*O*-allyl- and per-*O*-benzylsucrose, respectively,[9] and hydrolysis of sucrose, maltose, cellobiose or starch by use of commercial, acidic zeolites at 80–150 °C in aqueous media gave D-glucose in >90% yield.[10] D-Fructose was available similarly by hydrolysis of inulin.[10]

2.3 Chain-extended Sugars – Fructose 1,6-diphosphate aldolase-catalysed condensation of 4-benzyloxybutanal with dihydroxyacetone phosphate furnished, after enzymic dephosphorylation, the 5,6-dideoxy-D-*threo*-hept-2-ulose derivative **9**; its use in the synthesis of the natural macrolactone (+)-aspicilin is referred to in Chapter 24.[11] Molybdic acid has been found to catalyse the carbon-skeleton rearrangement of 2-*C*-hydroxymethyl-D-aldohexoses to D-hept-2-uloses. In agreement with the known mechanism of the molybdate-catalysed epimerization of aldoses, 2-*C*-hydroxymethyl-D-glucose (**10**) gave D-

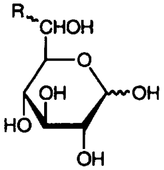
manno-heptulose (**12**), and 2-*C*-hydroxymethyl-D-mannose (**11**) gave D-*gluco*-heptulose (**13**) preferentially.[12]



10 $R^1 = CH_2OH$, $R^2 = OH$
11 $R^1 = OH$, $R^2 = CH_2OH$

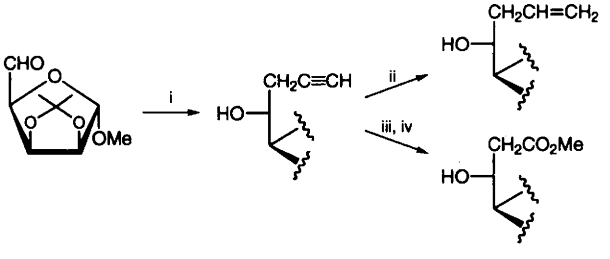


12 $R^1 = OH$, $R^2 = H$
13 $R^1 = H$, $R^2 = OH$



14 R = Me
15 R = Bn

2.3.1 Chain-extension at the 'Non-reducing End' – The epimeric 6-*C*-methyl-D-glucoses **14**[13] and their 6-*C*-butyl analogues **15**[14] have been synthesized by action of methyllithium and butyllithium, respectively, on 1,2-*O*-isopropylidene-5-*O*-Tbdms-α-D-glucurono-3,6-lactone and subsequent reduction and deprotection (see Vol. 30, Chapter 2, ref. 32). Addition of propargyl groups ($HC{\equiv}CCH_2Br/Zn$) to various 5-aldehydo-pentofuranose derivatives proceeded with good *erythro*-selectivity; the addition products were either partially hydrogenated to alkenes, as precursors of 6-deoxyheptoses, or ozonolysed to afford 6-deoxyhepturonates; an example is given in Scheme 3.[15]

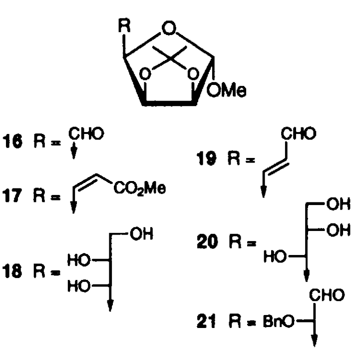


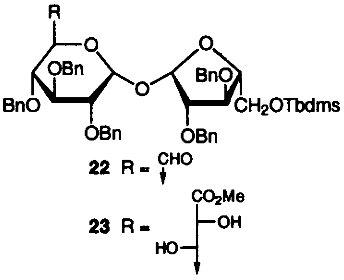
Reagents: i, $CH{\equiv}CCH_2Br$, Zn; ii, $Pd/BaSO_4$, H_2; iii, Ac_2O, Py; iv, O_3, MeOH–Py, $SOCl_2$

Scheme 3

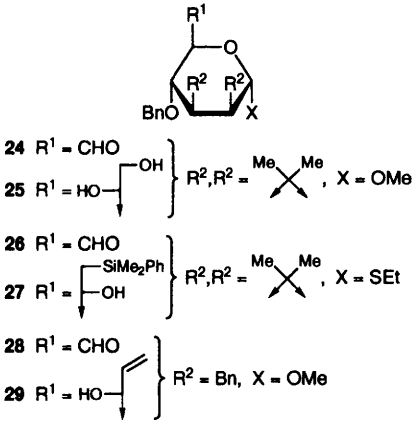
An improved procedure for the synthesis of D-*glycero*-D-*manno*-heptofuranoside derivative **18** from 5-aldehydopentofuranose derivative **16** by Wittig addition/*cis*-hydroxylation *via* *Z*-alkene **17** has been reported (see Vol. 20, Chapter 2, refs. 25–27); use of formylmethylenetriphenylphosphorane in place of (methoxycarbonylmethylene)triphenylphosphorane furnished mainly the *E*-alkene **19**, which on *cis*-hydroxylation gave the L-*glycero*-isomer **20** selectively. The D-*glycero* isomer **18** was also available by one-carbon elongation of the mannose-derived aldehyde **21** with benzyloxymethylmagnesium chloride.[16]

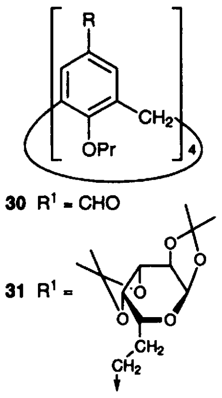
Several protected 1,6-dialdohexopyranoses have been extended by the Wittig reaction/*cis*-hydroxylation method (**22**→**23**,[17] **24**→**25**[18]) or by use of Grignard reagents (**26**→**27**,[18] **28**→**29**[19]). Reaction of carbohydrate-derived Wittig reagents with calixarene tetra-aldehyde **30**, followed by reduction of the double bonds, produced '*C*-calixsugars', for example compound **31**.[20]

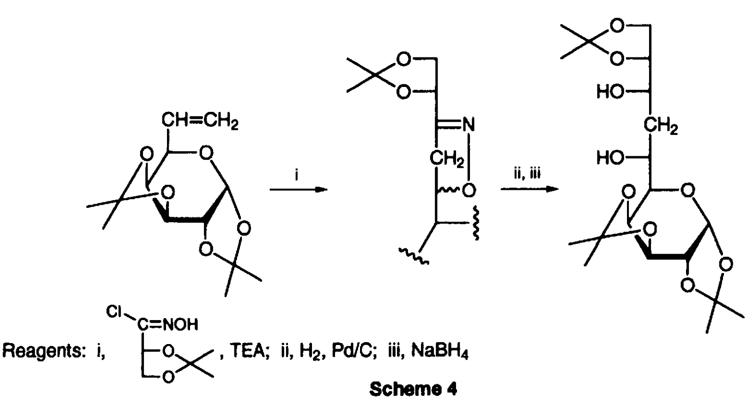




The nitrile oxide/oxazoline approach to higher sugars (see Vol. 27, Chapter 2, ref. 39) has now been applied to the syntheses of 7-deoxy-nonose and -decose derivatives, as illustrated in Scheme 4.[21]



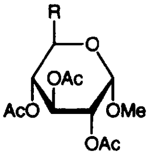




Reagents: i, ClC(=NOH)-acetonide, TEA; ii, H_2, Pd/C; iii, $NaBH_4$

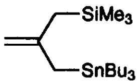
Scheme 4

Radical alkylation of 6-iodide **32** with trimethyl[(2-tributylstannylmethyl)-2-propenyl]silane (**34**) furnished the branched, unsaturated tetradeoxynonopyranose derivative **33** in 45% yield.[22]



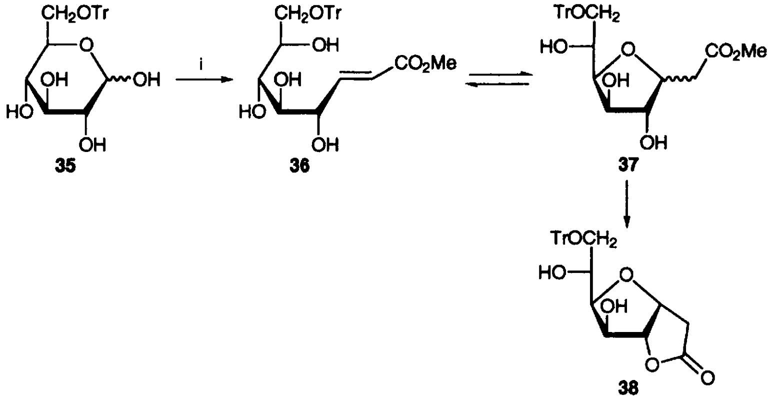
32 R = CH_2I

33 R = $CH_2CH_2C(=CH_2){-}CH_2Tms$



34

2.3.2 Chain-extension at the 'Reducing End' – A review on transition metal-catalysed functionalization at the anomeric centre of carbohydrates covered Heck-type and Pd-catalysed vinylic coupling reactions of glycals, as well as reactions of glycal-derived π-allyl complexes.[23]

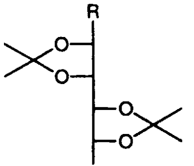


Reagents: i, $[Ph_3AsCH_2CO_2Et]^+Br^-$, Zn or $Ph_3As{=}CHCO_2Et$, BuLi (see text)

Scheme 5

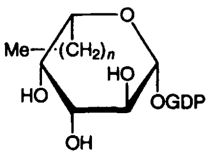
Partially protected free sugars reacted with arsonium ylids in toluene under neutral conditions ($[Ph_3AsCH_2CO_2Et]^+Br^-/Zn$) to give mainly *E*-alkenes (*e.g.*, **35**→**36** in Scheme 5); under basic conditions ($Ph_3As{=}CHCO_2Et/BuLi$) fused lactones were formed *via* *C*-glycofuranosides (*e.g.*, **36**→**37**→**38**).[24] D-Mannose has been extended by 4, 6, 8 or 10 carbon atoms by reaction of the protected aldehydo-sugar **39** with the appropriate Wittig reagents, followed by hydrogenation. Two of the products **40** were then elaborated into carbon-backbone-elongated GDP-L-fucose derivatives **41**.[25]

It has been demonstrated that Reformatzki alkylations of protected hexosuloses furnish 2-deoxy-4-octulosuronic acid derivatives with considerable diastereoselectivity; the methodology has been applied to the synthesis of oct-

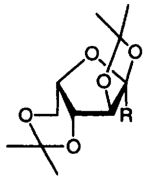


39 R = CHO

40 R = $(CH_2)_nMe$, n = 4, 6, 8, 10



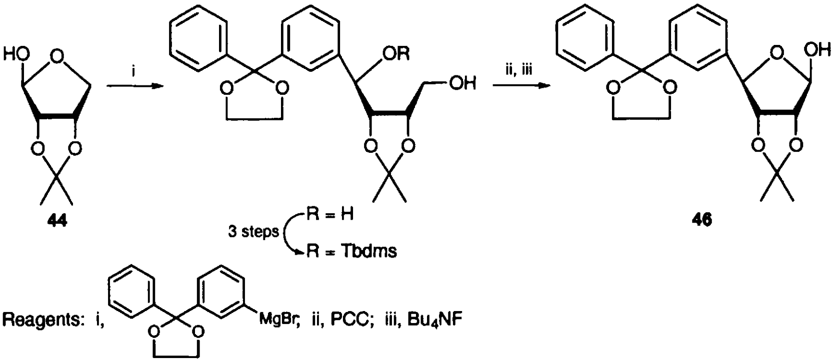
41 n = 4 or 6



42 R = CHO

43 R = $CH(OH)CH_2CO_2Me$

4-ulo-4,7-furanonate **43** from hexos-2-ulofuranose derivative **42**.[26] 4-Benzophenone-substituted ribofuranose derivative **46** has been prepared as a precursor of novel nucleoside analogues. The key step involved treatment of 2,3-*O*-isopropylidene-L-erythrose **44** with Grignard reagent **45**, as shown in Scheme 6.[27]

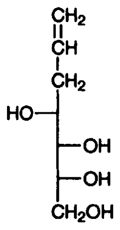


Reagents: i, **45** MgBr; ii, PCC; iii, Bu_4NF

Scheme 6

Indium-mediated allylation of D-erythrose in aqueous media generated the trideoxyhept-1-enitol **47** which offered convenient access to 3-deoxy-D-*arabino*-2-heptulose and 3-deoxy-D-*arabino*-2-heptulosonic acid.[28] 3-Carbon elongation of 2-acetamido-2-deoxy-D-mannose by similar indium-promoted allylation and subsequent ozonolysis of the terminal double bond furnished 4-acetamido-2,4-dideoxy-D-*glycero*-D-*galacto*-octose, isolated as the α-peracetate **48**.[29] Allylation at the reducing end of sugars has also been effected with tetraallyltin in micellar systems, although with only moderate stereoselectivity; alkenes **49** were obtained from D-arabinose in 82% yield as a 3:7 mixture of the D-*gluco*- and D-*manno*-compounds, for example.[30]

Commercial D-*glycero*-D-*gulo*-heptono-1,4-lactone (**50**) served as the starting material in a novel multi-step synthesis of *N*-acetylneuraminic acid (shown as the protected derivative **54**, Scheme 7). The chain-elongation was achieved by alkylation of a 2-alkoxy-2-cyanoacetate anion with the allylic bromide **51**. In a further key-step, opening of an epoxide by a neighbouring trichloroacetimidate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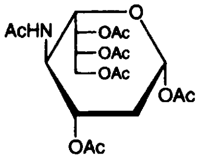
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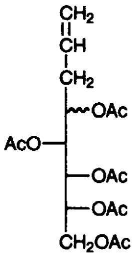
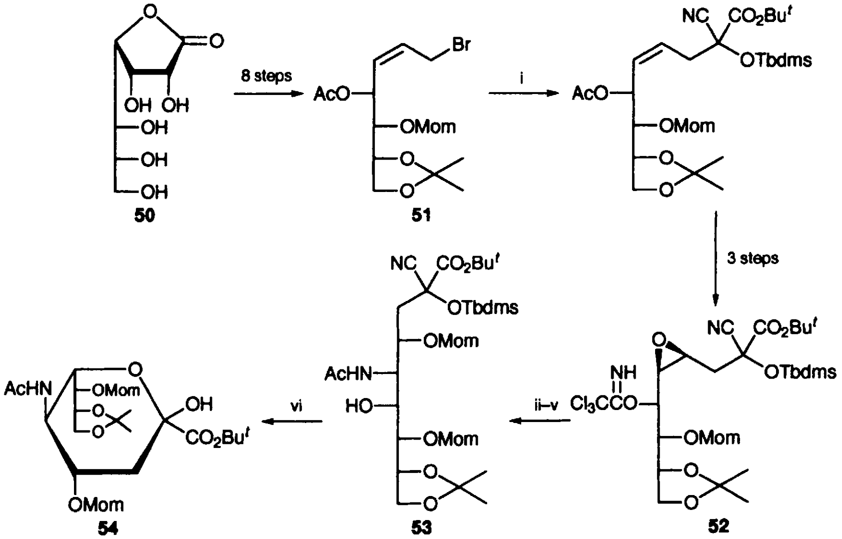
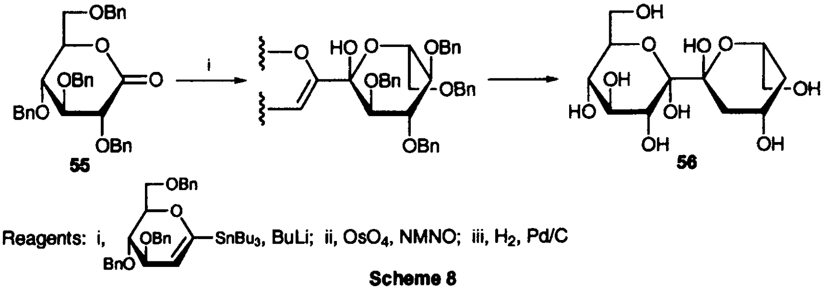

49

group was used to introduce the amino function (**52**→**53**).[31] A stereospecific addition reaction of lithiated tri-*O*-benzyl-D-glucal to tetra-*O*-benzyl-D-glucono-1,5-lactone (**55**) has been used in the synthesis of the C-C-linked analogue **56** of α,α-trehalose (Scheme 8).[32]



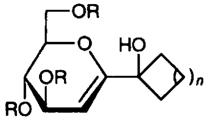
Reagents: i, $\mathrm{NC{-}\underset{\substack{|\\ OTbdms}}{C}HCO_2Bu^{t}}$, NaH; ii, $BF_3{\cdot}OEt_2$; iii, MomCl, $Pr^{i}Et_2N$; iv, TsOH, Py, H_2O; v, Bu_3SnH, AIBN; vi, Bu_4NF

Scheme 7



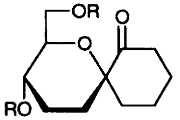
Reagents: i, [structure]–$SnBu_3$, BuLi; ii, OsO_4, NMNO; iii, H_2, Pd/C

Scheme 8

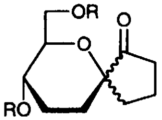


57 R = SiPr$^i_3$ or Tbdms, n = 2

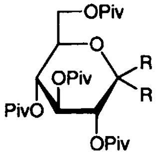
58 R = SiPr$^i_3$ or Tbdms, n = 1



59 R = SiPr$^i_3$ or Tbdms

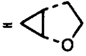


60 R = SiPr$^i_3$ or Tbdms



61 RR =

62 RR =



Full details on the acid-catalysed Wagner-Meerwein type rearrangements of glycal-derived carbinols (**57**→**59**, **58**→**60**; see Vol. 27, Chapter 3, Scheme 23) have been published.[33] Reaction of the pivaloylated diazirine **61** with dihydrofuran gave the sugar-spirocyclopropane derivative **62** in 70% yield. The benzylated analogue of **61** and alternative enol ethers (dihydropyran, glycals, 1-methoxyoct-1-ene) reacted poorly, however.[34]

3 Physical Measurements

A cost efficient method for determining the free energies of the anomers of free α- (axial) and β- (equatorial) anomers of D-mannose has been calculated by three different standard methods [i, free energy perturbation (FEP), ii, potential of mean free force (PMF) and iii, the recently described MC(JBW)/SD simulation technique], the last of which performed best.[36]

The solubilities of sucrose in aqueous MeOH, aqueous EtOH and in MeOH/EtOH mixtures have been measured at 25, 40 and 60 °C, and three UNIQUAC-based activity coefficient models were evaluated for their ability to describe these new data, as well as older ones taken from the literature.[37] Glass transition temperatures of aqueous glucose solutions calculated by molecular dynamics simulation were in good agreement with experimental data, in contrast to similarly calculated melting temperatures.[38]

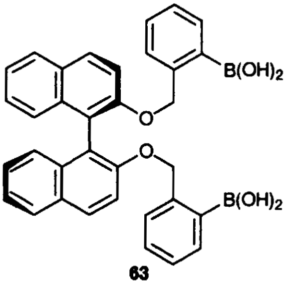
The diffusion constants of water in glassy systems of glucose and maltose syrups at various temperatures, water contents and molecular weights have been determined from the rates of desorption under reduced pressure.[39]

The activation energy for CAN-catalysed sucrose hydrolysis is referred to in Section 6 (ref. 45).

4 Isomerization

A study on the catalysis of mutarotation of tetramethylglucose by ribonucleosides found cytidine the most efficient, achieving a 20 fold rate increase which suggests a bifunctional mechanism.[40]

It has been postulated that the calcium ion-catalysed epimerization of glucose in alkaline solution proceeds *via* a complex of the cation with O-1,



63

O-2, O-3 and O-4 of the acyclic form of the sugar, and that the reaction, like the Bilik reaction, involves a rearrangement of the carbon skeleton.[41] The glucose-mannose epimerization reaction has been carried out with the chiral nickel complexes (*R*,*R*)- and (*S*,*S*)-1,2-bis(dimethylamino)-1,2-diphenylethane.[42]

5 Oxidation

Two major products, D-*arabino*-hex-2-ulosonic acid and D-*threo*-hexo-2,5-diulose, were formed on oxidation of D-fructose with molecular oxygen over Pt/C catalysts. Promotion of the catalyst with bismuth improved the selectivity for the former product, which, however, deactivated the catalyst.[43]

A kinetic and mechanistic study of the Pd(II)-catalysed oxidation of maltose and lactose by acidic NBS to give gluconic acid from maltose and both, gluconic and galactonic acid from lactose, has been published.[44]

6 Other Aspects

The activation energy for sucrose hydrolysis by ceric ammonium nitrate at pH 7 was found to be 5.88 kJ/mol, which is much less than that for hydrolysis by 0.18 N HCl (126 kJ/mol) The hydrolysis of various other disaccharides, such as lactose, maltose and cellobiose, with the former reagent was equally efficient.[45]

The degradation of D-ribose in the presence of propylamine in phosphate buffer at pH 7.4 and 70 °C furnished *N*-propylglycine propylamide, *N*-propylalanine propylamide, glycolic acid propylamide and lactic acid propylamide. Under similar conditions, D-glucose reacted more slowly giving the same products.[46]

The diboronic acid-appended (*R*)-binaphthyl **63** showed enantiomer discrimination in the complexation of some saccharides; L-xylose, in particular, was favoured 8.7-fold over D-xylose.[47]

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3

Glycosides and Disaccharides

1 O-Glycosides

1.1 Synthesis of Monosaccharide Glycosides – Sinaÿ and Mallet have presented a review on the preparation and use of glycosyl xanthates and enol ethers and related derivatives as glycosyl donors,[1] and Voelter and colleagues have written one on the use of sugar epoxides and unsaturated sugars as intermediates in carbohydrate synthesis which contains work relevant to glycosides synthesis.[2] A general review (in Chinese) on glycosylation methods has appeared.[3]

1.1.1 Methods of synthesis of glycosides – A new approach to the synthesis of furanosides adopts pentenyl glycofuranosides as donors, these being made from 4-pentenol and glucose, mannose and galactose using $FeCl_3$ as catalyst. The acetylated furanosyl products were used in the synthesis of furanosyl disaccharides, successful 1,2-*trans*-linking being achieved to the 4-position and, separately, to the 6-position of glucose.[4] A novel specific synthesis of furanosides of ADP-ribose uses the corresponding glycofuranosyl nicotinimide as donor with NAD-ase as the catalyst. Reasonable yields were obtained by transfer to simple primary alcohols.[5] A study of the effect of ultrasound on the glucosylation of butanol and octanol using the free sugar as glycosyl source and montmorillonite as catalyst has been reported.[6]

As usual peracetylated sugars have been used commonly as glycosyl donors, and in the cases of the peracetates of glucose, mannose, galactose and an *N*-protected glucosamine compound, the decyl glycosides have been made in good yield in a solvent-free system with $ZnCl_2$ as catalyst and with the aid of microwave activation.[7] Less commonly, *O*-benzylated α-D-mannopyranosyl trichloroacetate, activated with a hindered pyridine base, has been used, and it gave good yields of α-glycosides including those of a secondary monosaccharide alcohol and of phenols.[8]

The glycosyl trichloroacetimidate method remains highly favoured, and a further review article on the subject and on the O-1 alkylation approach to glycosides has been prepared by Schmidt.[9] (See also ref. 25 et seq.). Lithium triflate has been recommended as a new promoter for glycosylation using trichloroacetimidates as donors, but the results presented suggest that yields and α,β-ratios are similar to those obtained with other Lewis acid promoters.[10]

Carbohydrate Chemistry, Volume 31

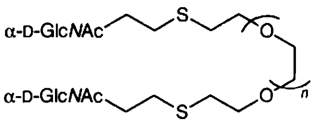
The versatility of glycosyl trichloracetimidates is illustrated by the use of the *O*-benzylated furanosyl glucose, mannose and galactose compounds in the synthesis of α-glycosides in good yields.[11] The method has also been used to prepare 4-carboxy-2,6-dimethoxyphenyl 2,3,4-tri-*O*-benzyl-6-*O*-mesyl-β-D-glucopyranoside,[12] and the syntheses of 2,6-dideoxy-β-glucosides have best been achieved using the α-trichloroacetimidate of 4-*O*-acetyl-6-bromo-6-deoxy-2-phenylthio-3-*O*-Tbdms-D-glucose. The anomeric selectivity of the coupling, however, decreases as the steric availability of the acceptor hydroxy group decreases.[13]

The *N*-*p*-nitrobenzyloxycarbonyl protecting group has been used in conjuction with 3,4,6-*O*-acetyl protection of glucosamine α-trichloroacetimidate, the compound being a donor which results in high β-selectivity when coupled to primary or secondary sugar alcohol groups. The *N*-protecting group can be selectively removed hydrogenolytically in the presence of *N*-acetyl- or *O*-benzyl-groups.[14] Nicolaou and colleagues utilized a selectively *O*-protected trichloroacetimidate derived from D-arabinose to introduce the sugar component of eleutherobin, a newly discovered antitumour agent with a mechanism of action similar to that of taxol.[15]

A review has appeared on the dihalogenomethyl methyl ether / Lewis acid method for generating glycosyl halides from various mono- and oligosaccharide derivates.[16] Further work has been reported on the use of glycosyl iodides, in particular tetra-*O*-benzyl-β-D-glucopyranosyl iodide which can be made using lithium iodide and lithium perchlorate from a variety of glycosyl esters. Treated with alcohols it gives rise mainly to α-glucosides with yields just above 50% with primary sugar alcohols, and less than that figure with secondary alcohols.[17] 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucosyl chloride activated with HgI_2 has been used to make β-D-*N*-acetylglucosaminides of different lipophilicities.[18] Tetra-*O*-acetyl-α-D-galactosyl bromide has given access to the β-glycoside of 4-methylumbelliferone for use in an enzyme assay,[19] and acetobromo- and benzobromo-glucose have been used to glycosylate hydroxycalix[4]arenes,[20] and model lignins having 3-aryl-2,3-dihydroxypropyl aglycons.[21] β-Xylosides were also made in the course of this latter work which was based on biosynthesis studies.

Thioglycosides are now used commonly in di- and oligo-saccharides syntheses (see below). Uchiro and Mukaiyama, using tetra-*O*-benzyl-*S*-methyl-1-thio-β-D-glucopyranoside with trityl tetrakis(pentafluorophenyl)borate and periodate as activators, have developed a highly selective β-glucoside synthesis. With methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside as acceptor 85% yield of disaccharide was obtained with 10:1 β-selectivity.[22] Coupling of 3-(trifluoroacetamido)propanol with *O*-protected ethylthio glycosides of *N*-acetyl- and *N*-glycolyl-neuraminic acid with NIS/TmsOTf activation occurred with moderate selectivity.[22a] By use of an *O*-benzyl-protected xylofuranosyl xanthate, furanosides have been produced with the α,β-ratios dependent upon the polarity of the systems employed.[23]

Schmidt and co-workers have used quite a different approach starting with 2,3:5,6-di-*O*-isopropylidene-D-mannose and tetritol derivatives containing triflate ester leaving groups; a series of 2-*O*-mannofuranosyl-D-erythritol derivatives having surfactant properties were prepared.[24] Mukaiyama has also used O-1 unprotected compounds to make glycosides, treating tetra-*O*-benzylgalactose with alcohols in the presence of tin triflate, TmsCl and lithium perchlorate, and in this way producing good yields of glycosides with α,β-ratios in the region 10:1. α-1,6-Linked disaccharides were reported in the course of this work.[25] In related studies 2,3,4,6-tetra-*O*-benzylglucose has been used as a glycosyl donor with triflic anhydride as activator in diphenyl sulfoxide. Low temperatures were used and efficient coupling to alcohols, phenols, thiols and activated benzene rings were described. Yields were high but the α,β-ratios were very variable, favouring the β-glycosides with simple alcohols but the α-compounds with thiols and phenols. In the case of 1,3,5-trimethoxybenzene only the β-*C*-linked compound was reported. The method was found to be applicable also to *N*-Tms-amides and to carbohydrate alcohols, 88% of 1,6-linked glucobiosides being produced with α,β-ratio 1:3. When 2,3,4,6-tetrabenzoylglucose was used as alternative donor only β-products were obtained, demonstrating the expected neighbouring group effect.[26] A striking stereochemical factor was discovered when tetra-*O*-acetyl-D-glucopyranose was coupled with allyl bromide in the presence of sodium hydride in dichloromethane. Under these conditions the β-glycoside was produced; however, when tetrabutylammonium iodide was added the α,β-ratio swung dramatically to 98:2. In the course of this work the α-allyl glycoside of *N*-acetylglucosamine was treated with the appropriate thiol in water under light and the symmetrical glycoconjugates **1** were prepared.[27] It has now been shown that *O*-protection of the donor is not required for the generation of glycosyl donors and that free sugars in DMF with sodium hydride present react directly with 4-substituted benzyl bromides, the glycosidic products being separated by column chromatography. The reactions were conducted with α-D-glucose, α-D-*N*-acetylglucosamine and *N*-trifluoroacetylglucosamine, D-xylose, D-ribose and a range of 4-substituted benzyl bromides. Yields varied from 14 to 75% and α,β-ratios were mainly about 1:4 but, on some occasions, poorer selectivity was observed.[28] In a variation of the reactions of free sugars which result in glycosides 2,3,4,6-tetra-*O*-acetyl-D-glucose has been applied in a Mannich reaction with formaldehyde and penta-*N*-methylmelamine and, following deacetylation, compound **2** was isolated in low yield from the products.[29]



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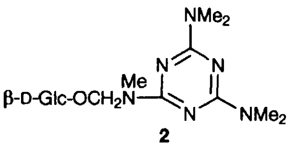


2

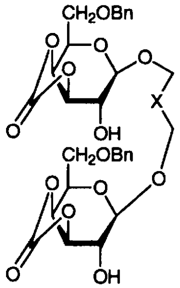
1,2-Anhydroaldopyranose chemistry has been exploited appreciably, mainly in the preparation of β-glucosides which are formed under basic conditions, whereas the Danishefsky method, involving the use of zinc chloride, normally leads to the production of α-products. The method applied with 3,4,6-tri-*O*-acetyl-1,2-anhydro-D-glucose and 4-substituted phenols gives modest α-selectivity when zinc chloride is used and β-selectivity up to 95% with potassium carbonate in the presence of a crown ether.[30] The related starting material was then used to prepare 2-naphthyl 3,4,6-tri-*O*-methyl-D-glucopyranoside from which was made the 2-crotyl ester and hence chiral acids by chiral-inductive addition processes involving Grignard reagents.[31] In related work allyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside was epoxidized, and the diastereomeric products were then ring opened with alcohols to give pure 1-glucosylglycerol derivatives.[32] This approach, but involving 1,2-anhydro-3,4,6-tri-*O*-pivaloyl-D-glucose, has been used to give β-glucosides using terpene alcohols as nucleophiles.[33] Closely related chemistry has been used to make compounds **3** which are spacer-linked 1,1′-bis-β-galactoside derivatives, and the paper also described the tris-β-glycoside having 6-*O*-benzyl-β-D-galactopyranosyloxy groups at positions 1, 3 and 5 on a benzene ring.[34]

Mukaiyama and colleagues have described transglycosylation from methyl glycosides to sugars derivatives, thus making disaccharides when monosaccharide derivatives were used as acceptors together with tin triflate and trimethylsilyl chloride as promoter. Good yields and moderate anomeric selectivities were reported.[35]

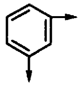
Enzymic methods have now become very important in glycoside synthesis and this year several relevant reviews have appeared. One deals with the use of glycosidases in preparing glycosidic bonds and also with the use of lipases in acylation and deacylation of carbohydrate derivatives,[36] another covers enzymic synthesis of glycosides and oligosaccharides,[37] while a further deals with glycosyl transferase acceptors, inhibitors and related compounds.[38] The syntheses of inhibitors of glycosidases and glycosyl transferases involved in the biosynthesis of glycoproteins have also been treated in a review.[39]

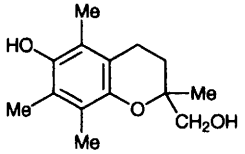
In the area of specific glucosides 4-hydroxybutyl-β-glucopyranoside was obtained in yields of up to 50% by use of a β-glucosidase on an inert support, the α-compound being prepared in reciprocal fashion using starch α-amylase, again held on a mineral support, as catalyst. Largely dry media were used to press the reaction in the direction of the product, and the effects of water and of the supports were particularly examined.[40] The α-glucosides derived from the aliphatic hydroxy group of diol **4**[41] and pyridoxine (4- and 5-isomers)[42] were made by use of α-glucosidases. β-D-Glucosidases, on the other hand, have been studied as synthesizing catalysts in dry media with microwave activation to make β-glucosides of various aliphatic diols,[43] 3-hydroxy-1-butene and related alcohols[44] and various cyclohexylethanoid acceptors. In the last work isorengyol (**5**) was glycosylated at the primary and secondary positions in the ratio 9:1, the overall yield being 44% when *p*-nitrophenyl β-D-glucopyranoside was used as donor.[45]

Some lipid-coated β-galactosidases have been found to be effective transglycosylation catalysts with lactose as donor and various alcohols, including carbohydrates, as acceptors. A two-phase system was used with the enzyme



3 X = $(CH_2)_4$, CH_2, C≡C,





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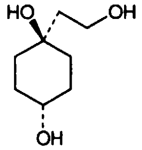


5

operating in the non-aqueous phase.[46] The reaction of galactose with various racemic secondary alcohols was catalysed selectively by a β-galactosidase from *E. coli*, and proceeded with enantioselectivity to give the *R*-products. The e.e. for the transfer to 1-phenylethanol was 98%.[47] A β-1,3-linked analogue of the T-antigen determinant was made on a preparative scale by use of a β-galactosidase,[48] and transglycosylation of α-galactose to various simple alcohols from the *p*-nitrophenyl α-glycoside has been described. Transfer also occurred to the substrate itself, in which case 1,6-linked di- and tri-saccharides resulted.[49]

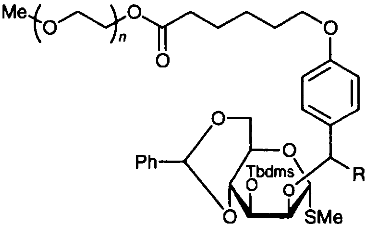
In a broader study, lipid-coated glycosidases were used in the transfer of α-D-Man, β-D-Glc*N*Ac, β-D-Glc and β-D-Gal to hydrophobic acceptors in dry isopropyl ether. Yields were in the range 23–71%.[50]

1.1.2 Classes of glycosides – In this section papers dealing with the synthesis of glycosides of particular categories of compounds are dealt with together.

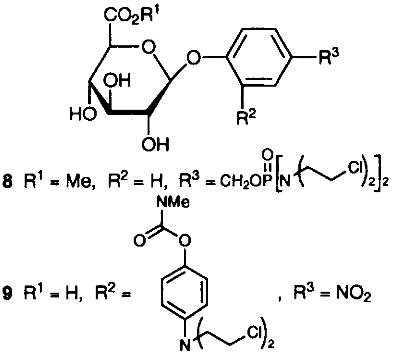
β-D-Mannopyranosides always present a special challenge, and a Japanese paper has described the preparation of such compounds and analogues with azido-, fluoro- and deoxy-groups at C-2, all formed by double nucleophilic displacements from alky 2,4-di-*O*-triflyl-galactosides. Initial inversion at C-4 with acetate gave the corresponding glucosides which were then subjected to nucleophilic displacement at C-2.[51] T. Ogawa has modified his intramolecular β-mannoside synthesis such that it can be applied on polymer supports. Compound **6**, on treatment with DDQ and an alcohol, gave the general type of acetal **7** which, with methyl triflate, collapsed to the corresponding R′-2-hydroxy-β-mannopyranosides. Various primary and secondary sugar alcohols were used as well as 2-azido long-chain alcohols. The products were easily separated from by-products, and the phrase 'gatekeeper monitored glycosylation' was coined to describe the overall process.[52] See Refs. 176-179 for other approaches to β-mannopyranosides.

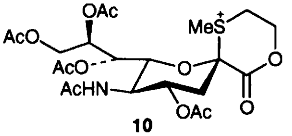
Glucuronides are of special interest because of their role in many natural products and as drug metabolites. Compounds **8**[53] and **9**[54] were synthesized by usual methods, the latter being found to be subject to hydrolysis by β-glucuronidase to release its toxic aglycon. The analogous glucuronide of raloxifene, an anti-osteoporosis drug, was tested for its affinity for the human estrogen receptor.[55] Standard glycosylations gave the β-glucuronides of tropolone and several of its substituted derivatives,[56] and the *p*-nitrophenyl β-furanosyl derivatives of D-glucuronic acid and D-xyluronic acid were made by standard procedures and found not to be better substrates for bovine β-D-glucuronidase than was the analogous pyranosyl glucuronoside.[57]

In the area of ulosonic acids the α- and β-glycosides of 3-deoxy-D-*lyxo*-hept-2-ulosonic acid were made by specific methods, the former by addition to the corresponding 2,3-unsaturated compound, and the latter by way of the αglycosyl chloride.[58] An ingenious way of making α-glycosides of sialic acid involves the use of long range participation which generates intermediate **10** from the corresponding 2-(methylthio)ethyl ester of the methylthio glycoside. The procedure was used to link sialic acid to O-6, and separately to O-3, of methyl β-D-galactopyranoside, and to make other glycosides, with α,β-ratios >5:1.[59] Sialylglycolipids **11** and **12** were made in stepwise fashion from the spacer group glycoside having a chloro-terminal unit.[60]



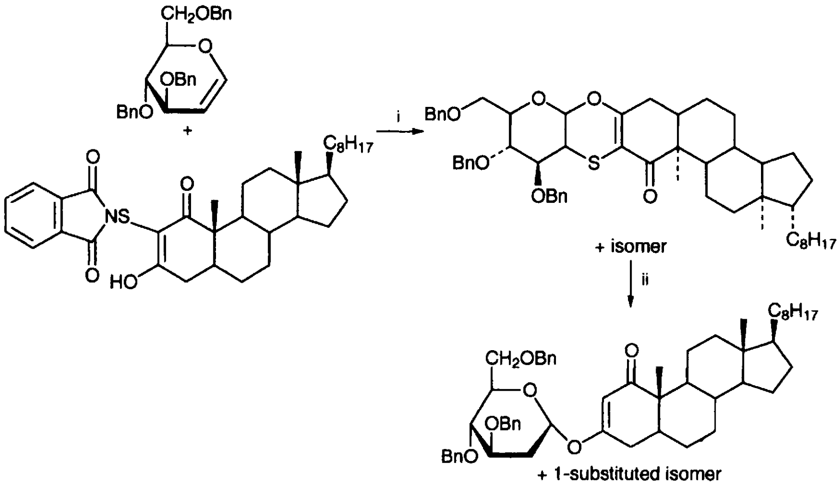
6 R = H
7 R = OR^1





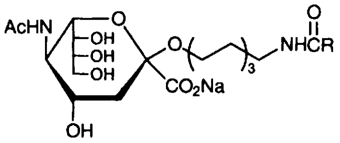
10

New work has been reported in the area of deoxy-glycosides. Compound **13**, activated with trimethylsilyl triflate, is a good donor yielding 80% of products with α,β-ratios approximately 20:1.[61] Glycosylation by use of peracetylated glycals together with IDCP and followed by reduction afforded 2-deoxy-α-glycosides of triterpene alcohols and deoxycholic acid.[62,63] Study of the influence of substituents at C-6 and C-4 on the stereoselectivity of the addition of PhSCl and PhSeCl to D-glucal derivatives has led to increased stereoselectivity in the synthesis of 2-deoxy-β-glycosides. Electronegative hetero atoms at C-6 favour the formation of 2-thio-D-*gluco*-products from *O*-substituted glucal derivatives.[64] Franck and Win have used ingeneous hetero-Diels-Alder addition reactions to confer selectivity on the production of 2-deoxy-α-glucosides in the steroid series as is exemplified in Scheme 1.[65]

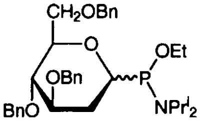


Reagents: i, 2,6-Lutidine; ii, Raney Ni

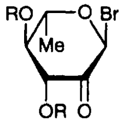
Scheme 1



11 R = $C_{15}H_{31}$
12 R = $CH(C_{16}H_{33})_2$



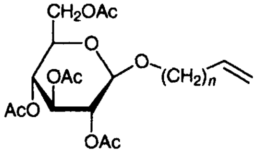
13



14

The ulosyl bromide compounds **14** can be applied satisfactorily to the synthesis of L-rhamnosides. Direct substitution leads to β-glycosides, and the final products are obtained by sodium borohydride reduction of the ketonic groups.[66] Wong and colleagues have used Selectofluor {1,4-diaza-1-chloromethy-4-fluoro-bicyclo[2.2.2]octane bis(tetrafluoroborate)} addition to pyranoid and furanoid glycals to produce 2-deoxy-2-fluoro-sugars which were then converted into glycosides under standard conditions.[67] 2-Deoxy-3,4,6-tri-*O*-methyl-2-(*N*-methylacetamido)-β-D-glucopyranoside, -β-D-galactopyranoside and -α-D-mannopyranoside were converted into the corresponding oxazolinium ions with Lewis acids. The reaction of these intermediates with (±)-2-butanol has been examined in the course of work which was aimed at the study of *R*- and *S*-2-butyl glycosides formed during polysaccharide analysis.[68]

Glycosides with unsaturated aglycons are useful for further functionalization purposes, and Stick has reviewed the preparation of epoxyallyl glycosides and aziridine and thiirane analogues as potential inhibitors of β-D-glucosidases and β-D-glucan hydrolases.[69] Stick's group has also reported the asymmetric dihydroxylation of the unsaturated glycosides **15**, compound **16** being the only product readily obtained pure by this procedure. It was converted into the episulfide with inverted stereochemistry as a potential inhibitor of β-D-glucan hydrolase.[70] In similar work the catalytic asymmetric hydroxylation of allyl 2-*O*-benzyl-3,4-di-*O*-substituted-α-D-xylopyranosides generally gave disappointing selectivity.[71] Several β-D-glycopyranosides of Glc, 3-*O*-Me-Glc and Glc*N*Ac have been reported with unsaturated and otherwise functionalized aglycons which permitted potential linking to peptides.[72] But-3-yne-2-yl and propargyl tetra-*O*-benzyl-β-D-glycopyranosides, on treatment with potassium t-butoxide and DMF, rearranged in good yield to give the corresponding allenyl glycosides **17**. These compounds, activated with trimethylsilyl triflate, proved to be potentially useful glycosyl donors, and with a sugar primary alcohol gave stereospecifically the β-1,6-linked disaccharide in 56% yield.[73] In very different studies involving additions to glycosides with unsaturated aglycons penta-*O*-allyl-D-glucose has been treated with cysteamine under light in the presence of HCl and the penta-substituted compound carrying $(CH_2)_3S(CH_2)_2NH_2$ groups resulted.[74]



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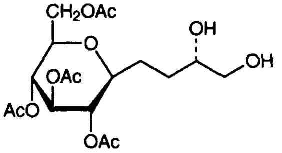

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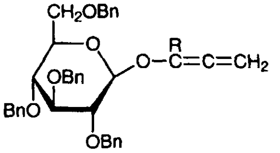
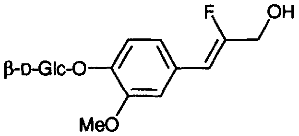
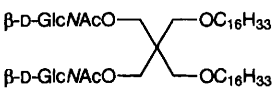


17 R = H, Me

The *p*-nitrophenyl glycosides of L-rhamnose or α-(1→3)-linked rhamnobiose or the related trisaccharide were converted into the corresponding glycosyl isothiocyanates for coupling to peptides and proteins,[75] and β-D-glucopyranosides have been made of a set of tetramethoxymono- and di-hydroxy-*cis*-and *trans*-stilbenes.[76] By use of the Mitsunobu reaction 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose has been linked to several hydroxylated calix[4]arenes. A range of related compounds including diglycosyl compounds and others with β-D-galactopyranose bonded to the upper rim of calix[4]arenes were reported.[77] The tetra-*O*-acetyl-β-D-glucopyranoside of 4-hydroxy-3-methoxybenzaldehyde has been elaborated by use of phosphonate technology to compound **18** which is an inhibitor of lignin polymerization.[78]

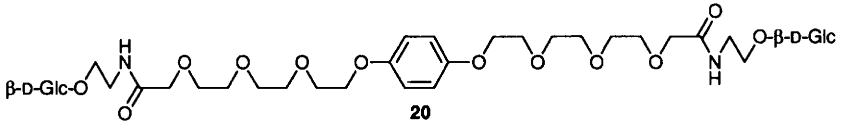


18



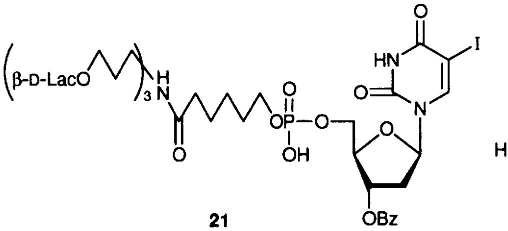
19

There is considerably increased interest in complex compounds which contain more than one sugar unit, most of these being produced for biological studies. The so-called gemini neoglycolipid **19** has been made for studies of its interfacial behaviour,[79] and a related report has described very similar compounds having β-D-galactopyranose or its 3-sulfate or 3,4-diphosphate esters as the sugars. The sulfate was the most potent competitive inhibitor of binding of HL-60 cells to immobilized selectins.[80] Stoddart and colleagues have now used monosaccharide derivatives as the terminal groups on dumbbell molecules and have described compound **20** and its characteristics as a precursor of rotaxanes carrying ring-like polar molecules added by either the slippage procedure or by clipping.[81]



20

The trilactosyl compound **21** was made as a potential means of delivery of 2′-deoxy-5-iodouridine to the liver,[82] and α-D-Gal*p*-(1→4)-D-Gal*p* has been attached to several di-, tri- and tetra-functional compounds to produce haemaglutination inhibitors. Generally the multivalent galactobiosides were more potent.[83]



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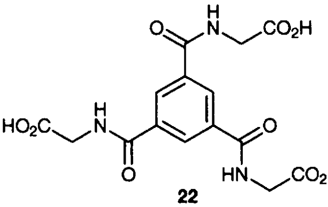
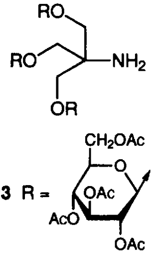
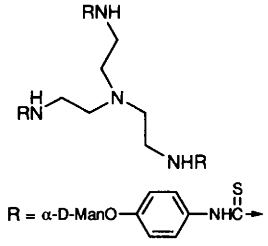


22

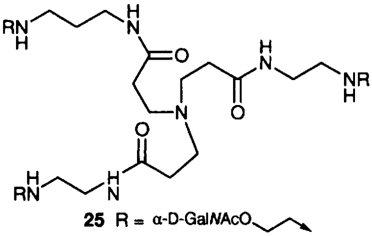
Considerable attention has been given to the preparation of dendrimeric compounds, particularly by Stoddart and his colleagues. Thus core compounds such as **22** condensed with triglycosides such as **23** offer means of obtaining products with multisugar components, and an extensive series of complex products of this sort have been reported this year.[84-86] Other workers in the



23 R =



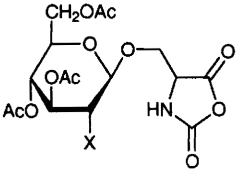
24 R = α-D-ManO



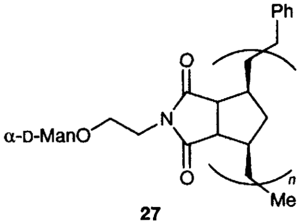
25 R = α-D-GalNAcO

same area have, for example, described complex compounds with structures **24**[87] and **25**.[88]

Compounds called 'sugar balls' have been made by polymerizing the glycosylated L-serine *N*-carboxyanhydrides **26** with dendrimeric polyamidoamines.[89] A somewhat different glycosylated polymeric compound **27** was made by polymerizing a diunsaturated cyclopentane derivative,[90] and an acrylamide homopolymer (**28**) having Sia Le^X as part of the repeating unit had increased activity relative to the corresponding monomer in inhibiting E-selectin-mediated cell adhesion.[91]



26 X = OAc, NHAc



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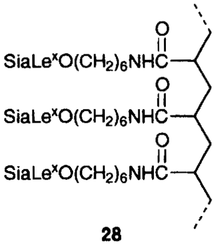
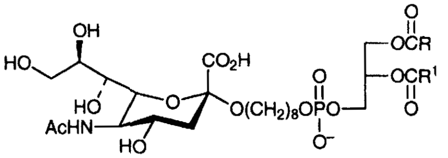


28

1.2 Synthesis of Glycosylated Natural Products and Their Analogues – In the area of glycosylated acyclic compounds the β-D-glucosides of ethyl and butyl 3-hydroxybutanoate have been made for comparison with compounds isolated from plants,[92] 2,3-di- and 2,3,4-tri-*O*-β-D-lactosyl-D-threitol have been reported[93] and the β-D-glucopyranoside of the primary alcohol of 2*S*,3*S*-3-*O*-acetyl-2-aminooctadecane-1,3-diol has been synthesized as a model for natural cerebrosides.[94] Sialylphospholipids of general structure **29** have been made as potential antirotaviral agents,[95] while two papers have described the synthesis of cerebrosides, for example **30**, with different degrees and positions of sulfation on 2-amino-2-deoxy-D-glucose and -galactose and glucose and galactose themselves.[96,97]



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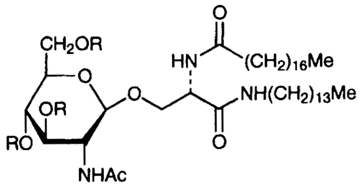
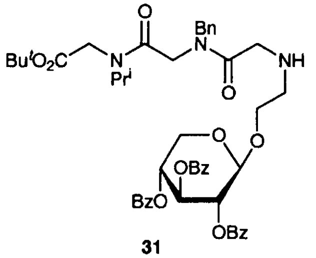


30 R = H, SO$_3$H

O-Protected 2-aminoethyl β-D-xylopyranoside has been coupled with a peptidomimetic to give compound **31**,[98] and in an extended piece of work along similar lines the 3-aminopropyl α-glycoside of D-*glycero*-D-*manno*-heptose has been linked to a solid-supported peptide and hence to a lipopeptide to produce a synthetic vaccine targeted at *Neisseria meningitidis*.[99] In parallel work glycosides carrying 4-carboxybutyl aglycons have been linked to solid-supported peptides to give complicated molecules such as **32**[100] and, likewise, artificial glycolipids based on β-D-galactose or β-D-Gal-(1→4)-β-D-Gal (compound **33**) have been made.[101]



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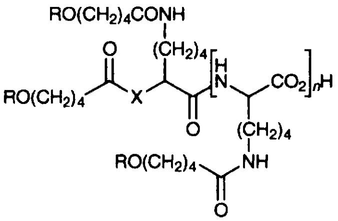
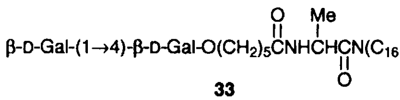


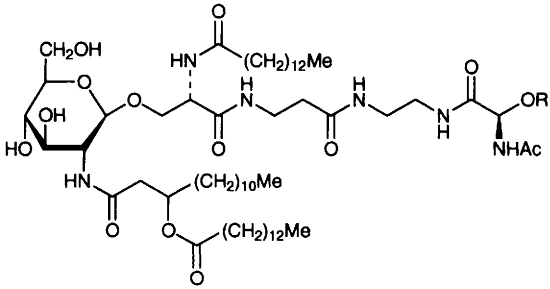
32 X = NH, HN(CH$_2$)$_y$CONH (y = 1,3)
R = β-D-Gal, β-D-GalNAc
n = 0, 1



$$\beta\text{-D-Gal-}(1\rightarrow4)\text{-}\beta\text{-D-Gal-O(CH}_2)_5\overset{\text{O}}{\overset{\|}{\text{C}}}\text{NH}\overset{\text{Me}}{\overset{|}{\text{C}}}\text{H}\underset{\text{O}}{\underset{\|}{\text{C}}}\text{N(C}_{16}\text{H}_{33})_2$$

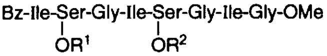
33

For the purposes of synthesizing glycosylated peptides *O*-glycosyl-substituted serine and threonine are very popular. Coupling of acetobromoglucose with the suitably protected amino- acids gave the β-D-glucosides and also some of the glycosides derived from β-D-Gluc-(1→2)-β-D-Glc, the conditions of coupling causing cleavage of the ester group at O-2 in the donor. Similar experiments were carried out with α-D-mannosyl and α-L-rhamnosyl bromides.[102] Related work gave protected derivatives of α-L-fucosyl-serine, -threonine and -tyrosine[103] and β-D-glucuronosylthreonine.[104] Schmidt and his group have compared variously *N*-substituted glucosamine-based glycosylating agents to produce a range of substituted compounds with the sugar β-bonded to serine and threonine.[105] These two amino-acids, *O*-substituted with α-D-*N*-acetylgalactosamine, have been used as acceptors for galactose transferred from its *p*-nitrophenyl β-glycoside with β-galactosidase which gave the β-(1→3)-linked T-antigenic determinants in 22 and 28% yield respectively.[106] A suitably protected threonine carrying *N*-protected 6-amino-6-deoxy-β-D-glucose as a glycosidic unit has been used in the synthesis of several α-helical peptides in order to study the effect of the *O*-glycosylation on the conformations of the peptides.[107] Compounds **34**, each of which contains a lipid A analogue section and a sugar antigen, have been made as potential vaccines against cancer.[108] Syntheses of α-D-Gal*N*Ac-*O*-Ser-Ser-Gly and β-D-Gal-(1→4)-α-D-Gal*N*Ac-*O*-Ser-Ser-Gly-Asp-Glu-Thr, which are microbial pro-



34 R = α-D-Gal*N*Ac, α-Neu5Ac-(2→6)-α-D-Gal*N*Ac

ducts that suppress the defence responses of plants, have been reported.[109] Compounds **35** are examples of several diglycosylated peptides to have been reported following their synthesis by solid phase technology.[110-]



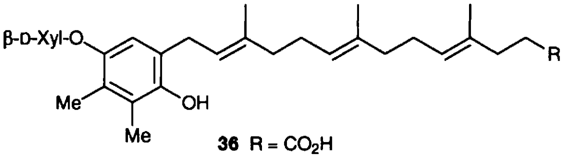
$$\text{Bz-Ile-}\underset{\text{OR}^1}{\text{Ser}}\text{-Gly-Ile-}\underset{\text{OR}^2}{\text{Ser}}\text{-Gly-Ile-Gly-OMe}$$

35 R¹ = R² = β-D-Gal
R¹ = R² = β-L-Fuc
R¹ = β-D-Gal, R² = β-L-Fuc
R¹ = β-L-Fuc, R² = β-D-Gal

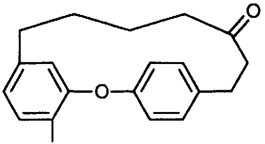
α-D-Gal-(1→1)-L-*myo*-inositol (galactinol), which is a natural donor of galactose in the biosynthesis of raffinose, has been made by standard procedures,[111] and 6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1-phosphate and its corresponding 1,2-cyclic phosphate have been prepared in connection with interests in insulin secondary messenger biochemistry.[112]

Interest continues in the glycosylation of steroidal compounds, cholesterol having been linked to β-D-Glc*N*Ac by way of ethyleneoxy bridges of length 1–4.[113] The unusual sugar 5-*C*-hydroxymethyl-D-galactose has been α-linked (it has the L-configuration) to cholesterol and diosgenin using the glycosyl fluoride coupling procedure,[114] and the glycosylphenyl sulfoxide method has been used to prepare a di-α-D-glucosyl derivative of a dihydroxy methyl cholate compound.[115] By application of the trichloroacetimidate method the β-D-glucosyl- and α-L-arabinofuranosyl-(1→6)-β-D-glucopyranosyl derivatives of the monoterpene (−)-myrtenol were made,[116] and in the same area diglycosides of neohancoside A, B and C were produced.[117]

In the triterpenoid field D-glucose, L-fucose and several fucosylglucoses were glycosidically bonded to diosgenin using the trichloroacetimidate procedure.[118] The 2-deoxy-α-D-glucosides and -α-galactoside of 18-β-glycyrrhetic acid and several analogues have been made by additions to glycals.[119,120] *O*-Acetylated cellobiosyl bromide[121] and fluoride[122] have been used in the preparation of several glycosides of tycogenin, and active inhibitors of cholesterol absorption were produced. The α-mannosides of stevioside and isosteviol were synthesized as Sia Le^X mimics, the latter compound having 100 times more affinity for P-selectin than does Sia



36 R = CO_2H
37 R = CH_2OH



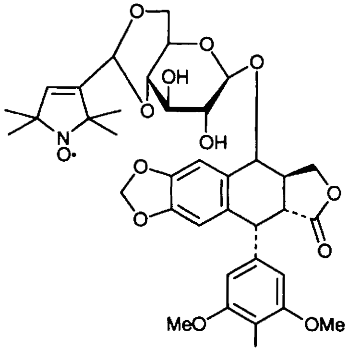
38

Le^X.[123] Vasella's group, using the glycosylidene diazirine procedure, have made the mono-, di- and tri-glucosides of ginkgolide A and B, these being highly oxidized triterpene trialactones.[124]

As usual, several aromatic natural products have been made by glycosylation, for example the sex pheromonal compounds of the *Chlamydomonas*, lurlenic acid (**36**)[125] and lurlenol (**37**),[126] and the diphenyl ether compound **38**, which is aceroside IV, a component of the bark of a Japanese tree.[127] An improved synthesis involving the use of the glucuronosyl trichloroacetimidate of the β-D-glucuronide of coumarin has been described,[128] the primary hydroxy group of the hepatoprotective flavolignan compound silybin (Flavobion™ and Legalon™) has been substituted to give the β-galactoside, -glucoside, -lactoside and -maltoside, some of which have increased hepatoprotective activity,[129] and the related α-tocopherol which is a potent natural antioxidant has been converted into the glycosides of the following di- and higher saccharides: β-maltose, α-cellobiose, β-lactose, β-malto-triose, -tetraose, -hexaose and -heptaose.[130] Grayanoside A, which belongs to the phenylpropanoid group of natural glycosides which have a range of biological activities, has been made. It is the 2-(4-hydroxyphenyl)ethyl β-glucoside having a substituted cinnamoyl ester group at O-6.[131] The configuration of the simple natural lactone β-D-glucoside of phyllanthurinolactone (4-hydroxy-7-oxa-8-oxo-bicyclo[4.3.0]nona-2,9-diene) has been established by synthesis.[132] Spin labelled derivatives *e.g.* **39** of podophyllotoxin glycoside exhibit anticancer activity.[133]

As always, some nitrogenous compounds have been glycosylated to give, for example, the enantiomer of compound **40** which is a natural acetal glycoside found in maize. It was made by the unusual use of L-glucose derivatives,[134] and L-biopterin has been converted to the 2′-*O*-(2-acetamido-2-deoxy-β-D-glucosyl) derivative limpterin.[135] Enzymic methods were used to make the β-glucosides **41** and **42** of calystegine B1 and B2 and other glycosides.[136]

1.3 O-Glycosides Isolated from Natural Products – As always, only a selection of papers published on this aspect of glycoside chemistry are dealt with: either



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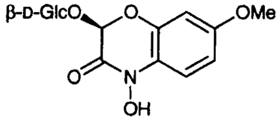

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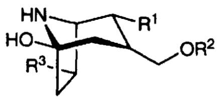
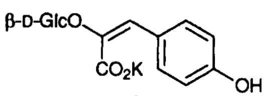


41 R^1 = H, R^2 = β-D-Glc, R^3 = OH
42 R^1 = O-β-D-Glc, R^2 = R^3 = H



43

those showing interesting structural features within the carbohydrate moieties or those describing notable biological properties.

A review has been presented on the benzoxazinoid acetal glucosides which occur in the *Gramineae*.[137] D-Ristosamine (3-amino-2,3,6-trideoxy-D-*ribo*-hexose) is the sugar component of a marine streptomyces aryl glycoside,[138] and α-L-Ara*f*-(1→5)-L-Ara*f* has been isolated as its 2-*trans*- feruloyl ester from sugar beet pulp.[139] 1-*O*-α-(1→3)-Mannobiosylglycerol has been isolated, as a derivative carrying two long-chain fatty acid ester groups at O-6 of the disaccharide and at O-3 of the glycerol moiety, from a sponge-associated *Micrococcus*.[140] β-D-Glc*p*-(1→4)-D-GalA occurs as the sugar component of a marine sponge tetramic acid glycoside,[141] and a group of saponins with hepatoprotective activity rely for that activity on the presence of β-D-Glc-(1→3)-D-Fuc.[142]

Amongst some biologically active glycosides to have been recorded is compound **43**, an α-keto acid glycoside, which causes leaf opening in plants in the daytime as opposed to potassium D-idarate, also present in the same plants, which has the opposite effect.[143] A 1-β-D-galactoside of glycerol bearing a long chain fatty acid ester group at O-3 and isolated from a marine sponge, is reported to have antileukemic activity.[144] A similar compound, (2*S*)-1-*O*-(hexadeca-4,7,10,13-tetraenoyl)-3-*O*-β-D-galactopyranosylglycerol, isolated from a marine micro-algae, inhibited platelet aggregation by a thromboxane analogue at 100 μg/mL and was cytotoxic *in vitro* at lower concentrations.[145] A galactose-based glycolipid from a further marine sponge was found to be immunosuppressive on activated T cells.[146]

1.4 Synthesis of Disaccharides and Their Derivatives – A review has been written on Dondoni's 1996 research into the preparation of α-linked ketodisaccharides using thiazolylketol acetates as glycosyl donors,[147] and one on chemoenzymatic methods used for the preparation of novel oligosaccharide mimetics designed for use in the study of cell adhesion includes material relevant to disaccharides.[148]

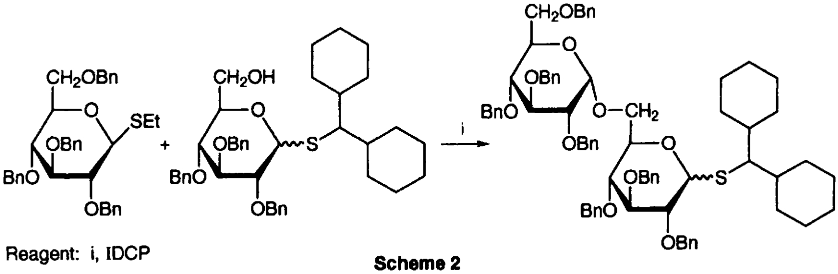
In the field of non-reducing disaccharides a review has appeared on the transformation of sucrose into potentially valuable chiral synthons,[149] and several sucrose analogues have been produced following the introduction of the triflate ester group at C-2 of the glucose residue which led to the α-mannopyranosyl, the α-*N*-acetylmannosaminyl and the altropyranosyl compounds.[150] Other analogues have been produced by chain extension from C-6 of the glucose moiety following selective Swern oxidation at that position,[151] and enzymic studies have led to the synthesis of 6-deoxy-α-L-sorbofuranosyl α-D-glucopyranoside.[152]

A review has appeared on the preparation of α,α-trehalose from dried yeast and on its production from starch by enzymic methods,[153] and the digalactose analogue has been made by stereochemical inversion at both C-4 positions.[154] New crystalline and amorphous forms of α,α-trehalose have been identified.[155]

In the field of reducing disaccharides, inulobiose and inulotriose have been isolated in nearly equal proportions following enzymic hydrolysis of inulin.[156]

Glucobiose chemistry has always attracted much attention and has been used to further exemplify elegant means of coupling sugars by intramolecular procedures. Maltose derivatives and analogues based on *N*-phthaloylmaltosamine have been made by intramolecular *S*-phenyl thioglycoside coupling to the 4-hydroxy group of a second glucose unit bound between O-2 of the former to O-3 of the latter by a succinic diester linkage. High yields and high selectivity were reported.[157] Japanese workers have carried out a related glycosidic 1,6-linking of two glucoses starting with a compound having O-1 and O-6 of two protected glucose derivatives linked by way of a four-carbon glycosidic/ester bridge having a phenylethynyl substituent which was activatible by cobalt octacarbonyl. The work was repeated in the galactose and mannose series, and on judicious choice of protecting groups good yields were produced with very high α-selectivities.[158]

The glycosylation reaction exhibited in Scheme 2 shows selectivity because

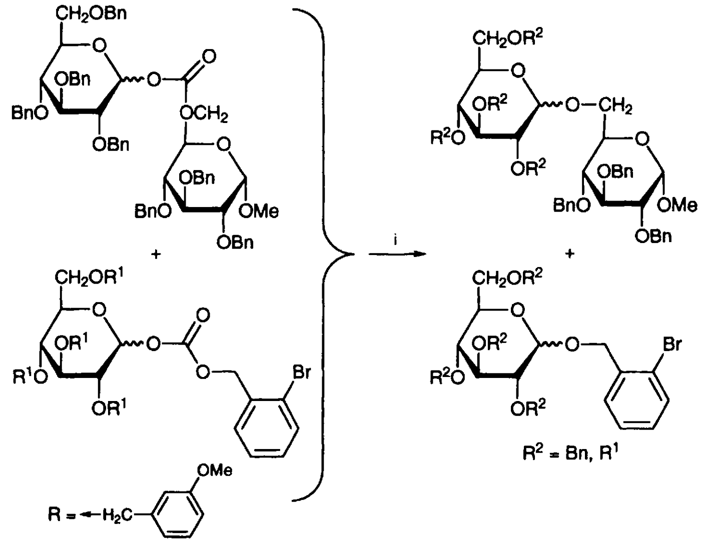


Reagent: i, IDCP

Scheme 2

the bulky *S*-protecting group inhibits activation at that centre. A 40% yield was reported, and then it was intriguingly shown that this bulk factor is less potent than is the disarming influence of benzoate substituents at O-2. This paper represents a very nice study of controlling factors in glycosylation which is leading to means of directing oligosaccharide synthesis much more precisely. To illustrate this the α-1,6-glucopentaose was made.[159]

By the finding that acid treatment of a mixture of the two carbonates shown in Scheme 3 gives the four illustrated products in similar proportions it is revealed that the reaction is intermolecular and not, as had been previously supposed, intramolacular.[160]

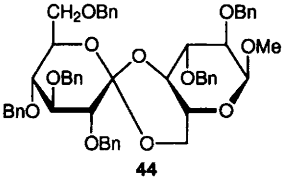


Reagent: i, TmsOTf

Scheme 3

β-D-Glc*p*-(1→2)-D-Glc (sophorose) has been made by standard methods,[161] and the α-trichloroacetimidate of the *O*-acetylated derivative of this compound having a benzyl group at O-2 of the non-reducing unit, on treatment with BF_3, formed a 1,2-internal glycoside, so the product is a 1,2′:1′,2-dianhydro compound.[162] The coupling of glycosyl thiocyanate to trityl ether glycosylation method has been adopted to make the 1,3-α-glucobiose as a methyl β-glucoside derivative.[163]

DIBALH reduction of tetra-*O*-benzyl-D-glucono-1,5-lactone ethylene acetal affords the 2-hydroxyethyl β-glycoside with high selectivity and good yield. The related acetal **44**, formed from the same lactone and the methyl glucoside 2,3-diether, on similar treatment, afforded the 6-hydroxycellobiose product in 92% yield, and galactose and mannose analogues likewise gave β-disaccharides in very high yields.[164] Cellobiose has been β-linked, using zinc fluoride catalysis and the acetylated glycosyl bromide, to the Pfizer ^{14}C-labelled cholesterol absorption inhibitor to give pamaqueside.[165] Cellobiose has also been linked



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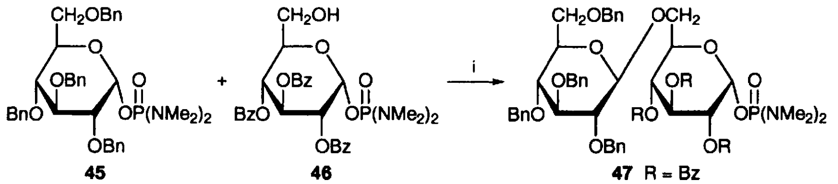
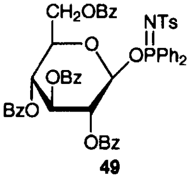
by way of glycosylamine bonding to a peptide,[166] and maltose by use of the 2-bromoethyl-*O*-acetylated glycoside has been bonded to the porphyrin benzochlorin.[167]

Tetra-*O*-benzyl-glucosyl *N*-phenyldiethylphosphorimidate is an efficient glycosyl donor which can give rise to either 1,2-*cis*- or 1,2-*trans*-glycosylated products, the anomeric ratios derived from a primary sugar alcohol being varied from 5.3:1 to 1:9 by alteration in the activation and condensation conditions.[168] In closely related work a very interesting experiment was done which tested *O*-benzyl compounds against *O*-benzoyl compounds in the tetramethyl phosphoroamidate series. Thus the armed donor **45** in the presence of the disarmed acceptor **46** gave an 86% yield of the directly coupled disaccharide derivative. The benzoyl groups in the product **47** were then exchanged for benzyl to give the glycosyl donor **48** (Scheme 4). Compound **49**, although nominally disarmed by virtue of the presence of the benzoyl groups, was a good enough glycosylating agent to couple with alcohol **46** and give 86% of the expected β-disaccharide.[169] Tetrabenzyl-*S*-ethyl β-thioglucoside condensed with 1,2:3,4-diisopropylidene-D-galactose afforded the (1→6)-linked products with 15:1 α,β-selectivity in toluene/dioxane which was much higher than the 0.7:1 observed in dichloromethane.[170]



Reagent: i, TmsOTf

Scheme 4



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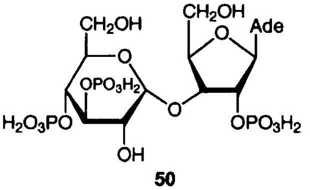

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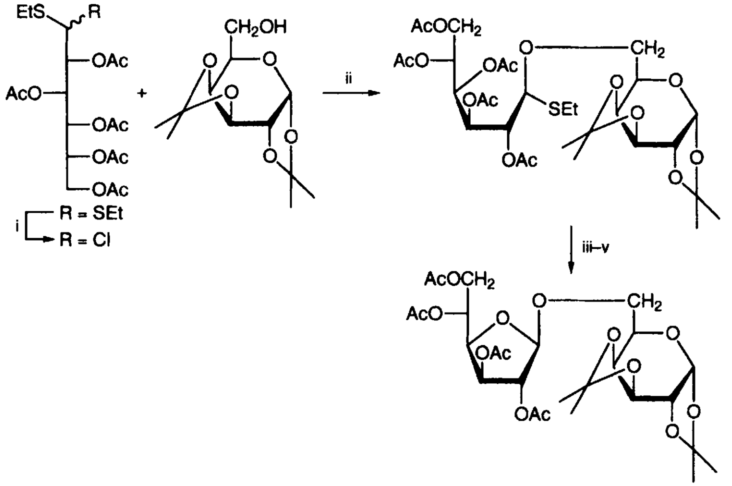
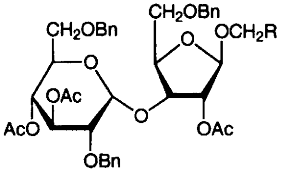
α-D-Glc*p*-(1→3)-L-Rha, the disaccharide unit of *Serratia marcescens* O4 antigen, has been made by the unusual use of the glycosyl trichloroacetate as donor.[171] The adenophostins, for example **50**, are full agonists of the IP_3 receptor, and this has led to the synthesis of compound **52** (by coupling of compound **51** with iodobenzene) and hence the 2,3′,4′-trisphosphate. When the coupling was repeated in the presence of 1,2,4,5-tetraiodobenzene cluster analogues of **52** were produced and hence the corresponding phosphorylated cluster analogue of **50**.[172] 1-β-D-Glucopyranosyl-D-ribitol has been prepared by the trichloroacetimidate method to provide a compound present in the hydrolysate of a novel triterpene glycoside. In the course of the work the corresponding 1-glucoside of L-ribitol was also made.[173] 6-*O*-β-D-Glucofuranosyl-D-galactose was obtained in high yield by the method outlined in Scheme 5. When the approach was applied to the corresponding α-mannofuranosyl compound, however, the yield was only 40%.[174] The disaccharide analogue **53** was made by enzymic glucosylation of the product of reduction of 5-azido-5-deoxyfructose.[175]



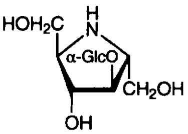
Reagents: i, AcCl, BF$_3$.Et$_2$O; ii, AgOTf, Ag$_2$CO$_3$; iii, NaOMe; iv, HgCl$_2$, H$_2$O; v, Ac$_2$O, Py

Scheme 5



51 R = C≡CH

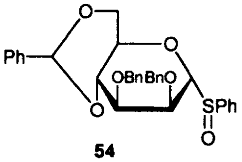
52 R = CH$_2$CH$_2$Ph



53

Two groups have looked at the use of 1,2-stannylene derivatives in the D-mannose series. In these *cis*-related β-compounds O-1 is activated as a nucleophile and therefore, on reaction with glycosylating electrophiles, gives rise to non-reducing disaccharides. For example 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl trichloroacetimidate generates a α,β-1,1′-linked mannobiose compound having potentially free C-2 hydroxyl groups, thereby making available routes to corresponding tri- and tetra-saccharides.[176] In similar fashion, O-1 of mannose may be used to displace other good leaving groups, and the consequent syntheses of β-D-mannopyranosyl 1,4- and 1,6-linked glucosides have been effected using a galactoside 4-triflate and a glucoside 6-triflate, respectively, this representing a novel approach to these types of compounds.[177] The glycosyl sulfoxide **54** is a further suitable β-mannosylating agent (*cf.* refs. 51, 52), and with an appropriately protected rhamnose compound has given rise to a β-D-Man*p*-(1→4)-L-Rha derivative in 90% yield with β,α-selectivity >25:1.[178] In parallel work β-mannosidase has been used to prepare β-D-Man-(1→4)-D-Man and higher related saccharides, and a transferase has been employed in similar fashion to produce alkyl β-D-mannopyranosides from the above mannobiose.[179]

L-Xylose was used as precursor of compound **55** which was converted into L-gulose and hence 2-*O*-(3-*O*-carbamoyl-α-D-mannopyranosyl)-L-gulose which is the sugar of bleomycin A2.[180,181] A further paper on the synthesis of the same compound gives a detailed account of work which has previously been reported (see Vol. 29, p. 33, ref. 169).[182] An α-D-mannofuranosyl disaccharide has been made from 2,3:5,6-di-*O*-isopropylidene-D-mannose and a 2,3-unsaturated glycoside bearing methoxycarbonyl ester groups at O-4 and O-6, the product (43%) being compound **56** and the coupling being effected by way of a π-allyl palladium complex.[183] A set of D-aza-mannopyranosyl disaccharides, made using a carbocyclic starting material for the aza sugar part, has been described in detail (*cf.* Vol. 28, p. 229, ref. 61).[184]



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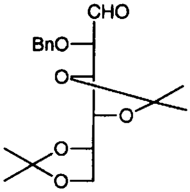

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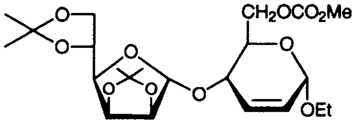

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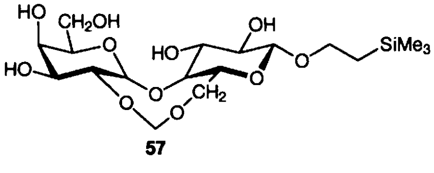
Considerable attention continues to be paid to galactosyl disaccharides. A review has appeared on the preparation of α-D-Gal*p*-(1→3)-D-Gal[185] and a transglycosylation reaction by use of α-galactosidase has given rise to the same disaccharide as its *p*-nitrophenyl α-glycoside. In the course of this work β-D-Gal-(1→3)-D-Gal*N*Ac was also produced,[186] and α- and β-D-Gal-(1→3)-D-Gal*N*Ac 3-(trifluoroacetylamino)propyl glycosides, and the corresponding di-Gal*N*Ac disaccharides, have been made by chemical synthesis.[187] The Koenigs Knorr reaction, adapted by use of IBr to make tetra-*O*-acetyl-α-galactosyl bromide from the corresponding *S*-methyl thioglycoside, has led to the 1,3- and 1,6-linked galactobioses.[188] β-D-Gal-(1→3)-D-Gal*N*Ac has been linked by way of a six-carbon spacer to biotin, both the α- and β-anomers having been obtained, and the amino-sugar having been developed from a disaccharide glycal.[189] The same disaccharide has been linked enzymically to serine to give the β-glycoside.[190] The α-(1→4)-linked **57** was prepared by formal synthesis involving the use of formaldehyde diphenyl dithioacetal as a means of locking the preferred conformation of the galactobiose. The neoglycolipid with the trimethylsilyl group replaced by $SC_{18}H_{37}$ was also made in attempts to obtain compounds which were resistant to enzymic hydrolysis.[191] Standard enzymic methods have been applied to the preparation of β-D-Gal-(1→6)-α-D-GalOMe and related compounds.[192]

Further enzymic work has led to β-D-Gal*p*-(1→3)-D-Glc*pN*Ac[193] and to its *p*-nitrophenyl β-glycoside.[194] When β-D-Gal*N*Ac was used as the acceptor, the 1→3- and 1→6-linked disaccharides were obtained in the ratio 7:3.[193]

New chemical methods have allowed access to a range of β-glycosides of the 1→4-linked *N*-acetyllactosamine series from the acetylated lactal. Iodoacetoxylation, followed by treatment with azide, gave the 2-deoxy-2-iodo-glycosyl azides which were then converted into the glycosides following treatment with alcohols and Ph_3P.[195] Ingenious work with lipid-coated β-D-galactosidase in a two phase system allowed the enzyme, in the aqueous phase for example, to hydrolyse lactose, whereas in the organic phase β-galactosides were produced from this sugar. In this way β-D-Gal*p*-(1→6)-D-Glc and the non-reducing glucosyl galactoside were made by galactosylation of the corresponding tetra-*O*-acetylglucoses.[196] Standard glycosidase-catalysed glycosylation of 3-*O*-methylglucose gave the β-(1→6)-galactosylated glucose 3-ether plus some of the β-(1→6)-linked galactobiose. Five enzymes and solvent systems were investigated and yields of up to 40% were recorded.[197] *Trans*-galactosylation from lactose has led to a set of lactosamine compounds and also to a set of β-(1→3)- and β-(1→6)-linked disaccharides,[198] and the ability of an enzyme from bovine colostrum to form β-(1→4)-linkages with glucose derivatives varying in substituents at C-1 has been examined. Notably, the compound with a β-hydroxymethyl substituent (2,6-anhydro-D-*glycero*-D-*gulo*-heptitol) is a substrate.[198a] Chemical syntheses using the glycosylating agents **58** and **59** were adopted in the preparation of D-Gal-(1→3)-Glc compounds, unusually high α-selectivities being recorded.[199] Polyglutamic acids carrying lactose and di-*N*-acetylchitobiose residues, made from the corresponding glycosylamines, have been described.[200]



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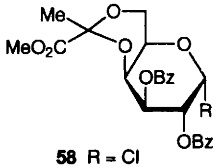
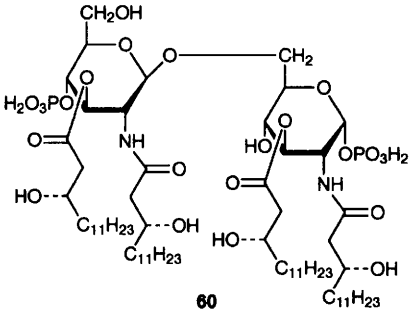


58 R = Cl

59 R = $\mathrm{O}\overset{\mathrm{NH}}{\overset{\|}{\mathrm{C}}}\mathrm{CCl_3}$

In the area of disaccharides based on 2-amino-2-deoxyhexoses *N,N'*-diacetylchitobiose has been made in 43% yield by chitinase coupling of *N*-acetylglucosamine and the 1,2-oxazoline derivable from it.[201] Structural characterization of lipid A from rough- and smooth-forms of the lipopolysaccharide of *Helicobacter pylori* has shown that they differ from lipid A of other bacteria.[202] Synthesis of the biosynthetic precursor of lipid A **60** has been reported,[203] and the analogue of lipid A with C_{14} and C_{12} acyl groups on the hydroxy functions of the ester and amide substituents of the non-reducing moiety has been described.[204] The differentially protected disaccharide derivative **61** of lipid A and several other glucosamine disaccharides with orthogonally protected amino groups have been made.[205]



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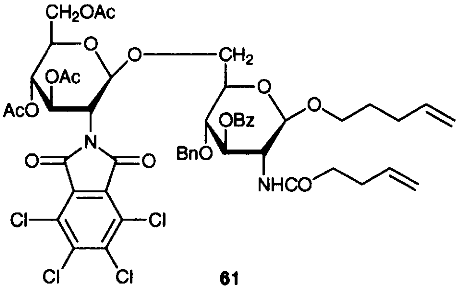
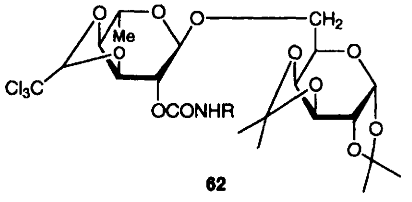


61

In the field of 2-deoxyglycosides Mukaiyama has reported the synthesis of α-linked 2-deoxyglucosides made by use of 3,4,6-tri-*O*-benzyl-2-deoxy-D-glucose coupled with alcohols, including carbohydrate alcohols, to give about 80% of products with α:β-ratios of the order of 9:1.[206] The L-altrosyl carbamoate **62** was made from the corresponding glycosyl fluoride, and following deesterification and radical reduction at C-2, gave the digitoxosyl galactose disaccharide. Using analogous compounds of the D-configuration the same authors reported the synthesis of an α-D-altrosyl-(1→6)-α-D-altrose derivative.[207]

6-Deoxy compounds continue to attract interest, particularly fucosyl disaccharides, and compound **63** has been made, as a blocker of L- and P-selectin binding, by way of the *S*-phenyl thiofucoside.[208] By use of 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannose thioglycosidically-linked to a polymer α-L-Fuc-(1→2)-α-D-ManOMe was made in 54% yield,[209] and methyl 3-*O*-β-D-fucopyranosyl-β-D-quinovopyranoside and its 3′- and 2,3′-dimethyl ethers were synthesized by Helferich glycosidation.[210] The S-in-the-ring compounds 5-thio-L-Fuc-(1→6)-, (1→3)- and (1→4)-linked to Glc*N*Ac and (1→2)-linked to β-D-Gal were all prepared as allyl β-glycosides which were all active in inhibiting bovine epididymis fucosidase. Only the last of them, however, inhibited bacterial fucosidase.[211]

2′-Deoxy-2′-fluorocellobiose has been made and found to be a mechan-



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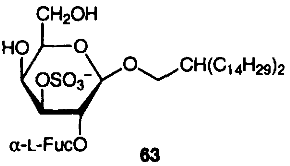

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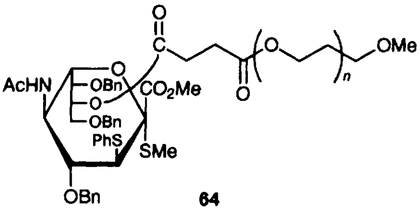
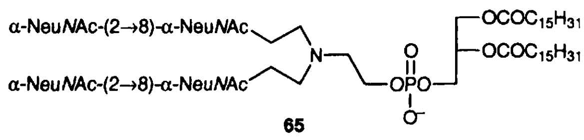


64

ism-based inhibitor of retaining glycosidases which exploit aglycon specificity.[212]

In the area of sugar acids sialic acids continue to attract major attention, and the glycosylating agents **64** on a polymer support have been used to link sialic acid to the 6-position of galactose. In the course of this work the α-(2→3)-sialyl galactose disaccharide was also made. Yields were in the 50-70% range.[213] Further solid support work has led to α-D-Neu*N*Ac-(2→6)-α-D-Gal*N*Ac linked to a decapeptide *via* a threonine unit.[214] Other workers have produced building blocks comprising the same disaccharide linked to threonine for the solid phase synthesis of analogous glycopeptides which are fragments of HIV gp120.[215] Schmidt and co-workers have studied the selective acceptor reactivity at positions 7 and 8 of 7,8-dihydroxy sialic acid derivatives on glycosylation with sialic acid glycosyl phosphites and halides. Yields of up to 55% of the β- and 66% of the α-(2→8)-linked dimers were recorded.[216] The artificial glycolipid **65**, containing the two (2→8)-linked dimers of sialic acid is a mimic of GQ_{1b} ganglioside. In the course of the work a compound containing one of the sialic acid dimers, which is a mimic of GD_3, was reported.[217] Tri-*O*-benzoyl-β-D-galactofuranosiduronic acid *S*-ethyl thioglycoside has been used to build disaccharides involving linkages to O-6 and O-3 of D-galactose and O-4 of L-fucose.[218]



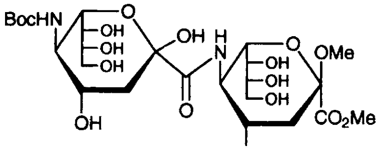
65

Several papers have focused on disaccharides having pentoses in the non-reducing position. A xylan has been degraded enzymically to give β-(1→4)-linked xylobiose which, by way of its hexaacetate, was converted into the *p*-

nitrophenyl β-glycoside.[219] β-D-Xyl*p*-(1→6)-D-Glc is a relatively common disaccharide of natural products several of which have been synthesized this year, the aglycons being *o*-hydroxyacetophenone,[220] 3*R*-linalool and 8-hydroxy-3*R*-linalool[221] and various triterpenoids.[222] In the last case the derived saponins were compared biologically with triterpenoid saponins synthesized previously. Nucleosides based on the disaccharide β-D-Rib*f*-(1→2)-β-D-Rib have been described[223] and 1,2-anhydro-3,5-di-*O*-benzyl-α-L-ribose has been used to make β-furanosides, β-linked nucleosides and a derivative of the disaccharide L-Rib*f*-(1→5)-D-Xyl.[224] The same workers have reported the preparation of the same type of products derived by use of 1,2-anhydro-3,5-di-*O*-benzyl-D-ribose.[225]

1.5 Disaccharides with Anomalous Linking or Containing Modified Rings – Reference to disaccharide analogues containing carba-sugars at the non-reducing end is made in Chapter 18.

Ester-linked disaccharide analogues involving cyclic 2-hydroxyketose derivatives and uronic acids were made by nucleophilic organometallic addition to aldonolactones followed by acylation of the derived tertiary alcohol with the acids in the presence of DCC as coupling agent.[226] Dehydrative condensation between a neuraminic acid derivative having a free carboxyl group and one with a 5-amino group led to the amide-linked **66**,[227] and a related compound with a longer bridge was made by the same researchers following condensation of a neuraminic acid carboxylic group with ethyl glycinate and then condensation between the ethyl ester group and the amino function of a second neuraminic acid. Similar work was done using serine and alanine as bridging units.[228] In Chapter 7 several references are made to the linking of two sugar units by diester bridges which do not involve the anomeric centre, and reference to the intramolecular syntheses of glycosides which involve related compounds is made earlier in this chapter. The methylene acetal analogue **67** is the first tri-component bisubstrate analogue for glycosyl transferase inhibition. It showed strong inhibition of UDP-Gal:Glc*N*Ac β-(1→4)-transferase.[229]



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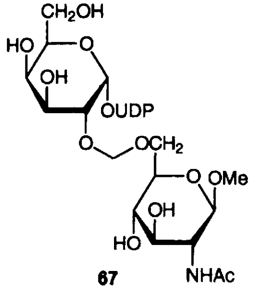
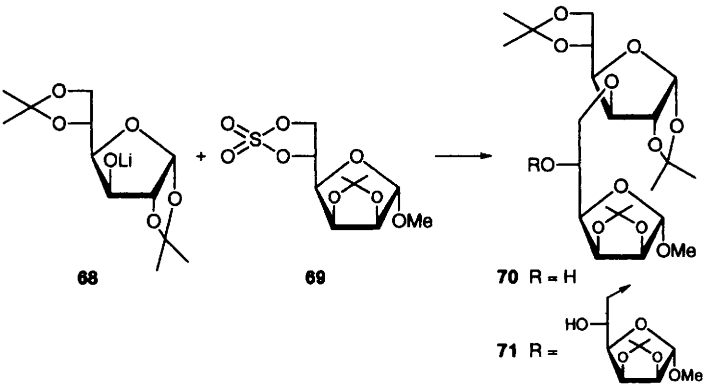


67

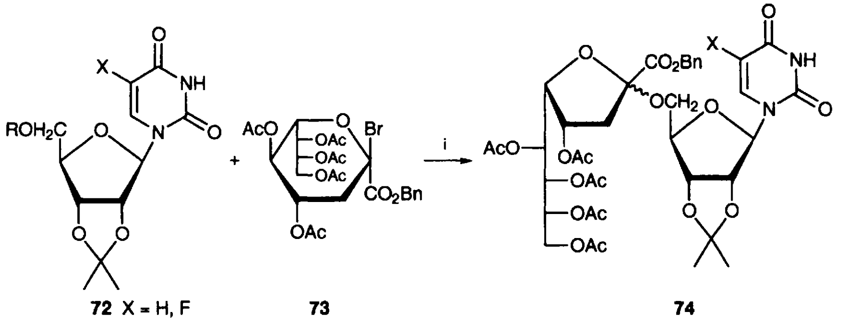
The ether-linked disaccharide 6-*O*-(5,6-anhydro-1,2-*O*-isopropylidene-D-glucos-3-yl)-3-*O*-dodecyl-1,2-*O*-isopropylidene-D-glucose, on treatment with KOH in toluene/DMSO, led to a disaccharide crown ether-like compound.[230] A related type of 3,6′-anhydrodisaccharide analogue was produced by nucleophilic attack by the lithio-derivative **68** on the cyclic sulfate **69** giving compound **70**. Reiteration of this procedure gave the trisaccharide analogue **71** (Scheme 6), and in the course of the work a further compound containing one mannofuranose unit and two glucofuranoses was also described.[231]



Scheme 6

1.6 Reactions, Complexation and Other Features of *O*-Glycosides – De-*O*-allylation of allyl glycosides under Wacker reaction conditions ($PdCl_2$, CuCl, O_2, DMF, H_2O) leads to the formation of the desired hydrolysis products but, in addition, ketones and π-palladium vinyl complexes are formed. A variety of sugar allyl glycosides and ethers were examined.[232] 2-Silylethyl glycosides with a substitutent on the silicon with linking potential may be cleaved by use of acetic anhydride and BF_3. This therefore affords means of releasing sugars as glycosyl acetates from silicon tethers by which they are bonded to resins.[233] Ceric ammonium nitrate effectively catalyses the hydrolysis of various disaccharides such as sucrose and maltose at pH 7. Some thermodynamic data on the processes were recorded.[234] In an interesting investigation involving the use of antibodies raised to a 2,5-dideoxy-2,5-iminohexitol derivative, *p*-nitrophenyl α-glucopyranoside and α-galactopyranoside were activated in glycosyl transfer reactions.[235] The examination of enzymic hydrolysis of monoglucuronides of vitamin D and 25-hydroxy-vitamin D has been described.[236]

Reactions of various alkyl and glycosyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosides with magnesium bromide and titanium tetrabromide etherate caused highly selective anomerization with resulting α:β ratios being 9:1 or larger.[237] An interesting study of the cleavage of per-*O*-allyl- or benzyl-sucrose with ethanethiol and other nucleophiles in the presence of BF_3 resulted in tetra-*O*-allyl- or benzyl-glucose and various fructofuranosyl derivatives. Ethanethiol gave the ethylthio furanosides, while Tms azide gave the corresponding glycosyl azido compounds and water resulted in degradation of the fructose moiety to a furanone derivative.[238]



Reagents: i, $Hg(CN)_2$, $HgBr_2$

Scheme 7

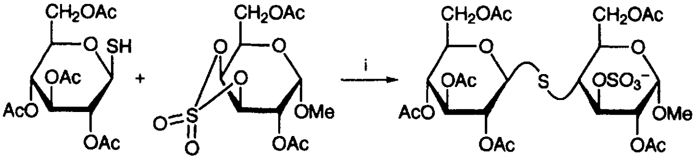
In the Koenigs-Knorr glycosidation of the acceptor **72** with the KDN glycosyl bromide **73**, ring contraction was observed and the products **74** were formed (Scheme 7). A mechanism was proposed for this reaction.[239]

Further observations (see Vol. 29, p. 37, ref. 216) on the use of zinc porphyrins containing both Lewis acid and Lewis base sites as molecular receptors for octyl glycosides have shown they have good affinity for *gluco*- and *manno*-compounds but poor affinity for *galacto*-analogues.[240]

2 *S*-, *Se* and *Te* Glycosides

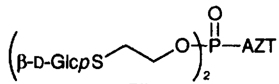
The use of thioglycosides as donors in oligosaccharide synthesis has been reviewed comprehensively by Garegg (see Chapter 1).

O-Protected 1-thiosugars retain their value as starting materials for thioglycosides and seven examples of 5-nitropyridine 2-thioglycosides have been produced from them.[241] Likewise ω-(aminoalkyl)thio-β-D-glycopyranosides have been obtained from the 1-thio- sugars by alkylation with ω-(phthalimido)alkyl bromides.[242] More complex compounds, however, can be made by this approach, and several *S*-linked disaccharides comprising glucose, galactose and 2-acetamido-2-deoxyglucose have been made using thio-nucleophilic opening of cyclic sulfates. (See for example Scheme 8). Interestingly, while the α-galactoside acceptor led to β-(1→4)-linked D-*gluco*-compounds, the corresponding β-glycoside sulfate gave predominantly β-(1→3)-linked D-*gulo*-analogues presumably because the aglycon no longer impedes attack at C-3 which is favoured according to the Furst-Plattner generalization. 4,6-Cyclic sulfate acceptors gave (1→6)-linked products.[243] This work highlights the use of cyclic sulfates in displacement reactions. Glycosyl thiols have also been used as the precursors of such compounds as **75** which is described as a 'pro-nucleotide' for use in anti-HIV work.[244] *N*-Chloroacetyl analogues have been used to obtain the thioglycosidic glycodendrimers **76**,[245] and in related work SiaLe^a-$O(CH_2)_3NHCO(CH_2)_3SH$ has been bonded to *N*-chloroacetyl-polylysine to give a thiolated derivative as a handle for ELISA.[246] Although the product is



Reagents: i, $CsCO_3$, DMF

Scheme 8



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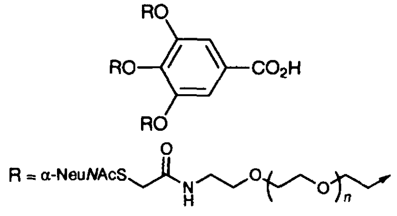


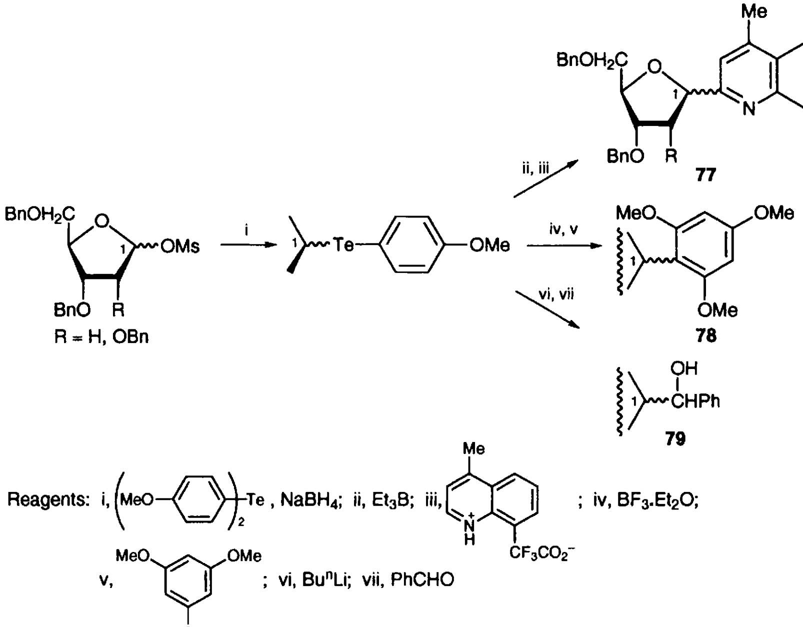
76

not a thioglycoside it suggests opportunities for thioglycosidic linkages to polypeptides.

A considerable range of *S*-alkyl 1-thioglycosides have been made in standard ways from the peracetates. In one study, while BF_3 etherate was a satisfactory catalyst for the glucosides and galactosides, in the mannose series ferric chloride had to be used.[247] The corresponding *O*-acetylated 2-deoxy-2-fluoro-α-D-glycosyl fluorides were used to obtain long chain alkyl 2-deoxy-2-fluoro-thioglycosides with the D-*gluco*- and D-*manno*-configurations. The effects of replacement of an hydroxyl group by fluorine and O-1 by S on liquid crystal properties were discussed.[248] The trichloroacetimidate method has been used to glycosylate cysteine at sulfur, the previously unknown α-anomer being made by this method.[249] 1,2-Anhydro-3,4,6-tris-*O*-Tbdms-α-D-glucose can be converted to β-thioglycosides by use of thio-nucleophiles in mild bases, the products being conveniently unprotected at O-2, but when lithium phenylthiolate was used as nucleophile, ether migration occurred from O-3 to O-2 so an O-3 unprotected product was isolated.[250]

Anomerization of methyl tetra-*O*-benzyl-1-thio-β-D-glucopyranoside with IDCP, somewhat surprisingly, has been shown to occur intermolecularly.[251] Selective sulfoxide formation from *S*-phenyl 6-*O*-acetyl-3,4-*O*-isopropylidine-1-thio-β-D-galactopyranoside has allowed a study of the diastereomeric sulfoxides of the thioglycoside, the *S*-isomer hydrolysing twice as fast as the *R*-compound under acid conditions. With β-galactosidase only the *S*-isomer reacted, thus a means of obtaining the *R*-isomer pure was developed.[252] *S*-Isopropyl 1-thio-β-D-glucopyranoside has been shown to be an inducer of the production of the β-D-glucosidase of *Aspergillus niger*, a process which is repressed by glucose itself.[253] In Chapter 22 the crystal structure of the 5-*S*-oxide of a 1,5-dithio-β-D-thiopyranoside is reported as well as those of other compounds with thioglycosidic nature.

A set of methyl-, benzyl- and phenyl-seleno- and telluro-β-D-glucopyranosides has been described,[254] and the work was interestingly extended to compare the reactivities of phenyltelluro-, phenylseleno- and phenylthio-glycosides activated with NIS/TfOH. Selective glycosylation of alcohols was possible with the tellurium compounds in the presence of the selenium analogues, and with selenium in the presence of sulfur-containing compounds.[255] Other workers have described the preparation of aryltelluryl glucosides, obtaining high selectivities for the β-compounds. However, these slowly epimerized on standing.[256] The preparation and use of aryltellurium furanosides in the production of *C*-ribofuranosides is illustrated in Scheme 9, the products **77–79** being formed by way of anomeric free radicals, carbocations and carbanions, respectively.[257]



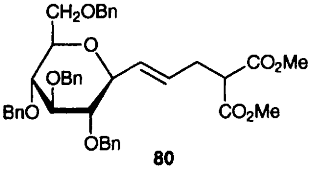
Scheme 9

3 *C*-Glycosides

3.1 Pyranoid Compounds – Several reviews have been published on *C*-glycosides one describing the synthesis of such compounds including *C*-disaccharides,[258] one on the synthesis of *C*-glycosidic analogues of biologicially significant *O*-glycosides,[259] one on the synthesis of *C*-glycosides using anionic and free radical donors,[260] another on the preparation of *C*-glycosides and their inhibition of *N*-linked glycoprotein biosynthesis,[261] while another has concentrated on the preparation of *C*-glycosides containing unsaturation within the glycosyl components. In this last case transition metal-catalysed functionalization was involved in each example and the material covered includes the conversion of glycals into phenyl 2,3-unsaturated *C*-glycosides and the replacement of various substituents on C-1 of glycals and on 2,3-unsaturated glycosyl compounds to give *C*-glycosidic glycals and 2,3-unsaturated compounds, respectively.[262] Successful enzymic β-(1→4)-galactosylation of hydroxymethyl β-*C*-glucopyranoside (2,6-anhydro-D-*glycero*-D-*gulo*-heptitol) has been reported.[198a]

A short synthesis of α-glycosyl cyanides of several sugars relies on the use of trimethylsilyl cyanide activated by methyl triflate and applied to *O*-benzylated-*S*-ethyl thioglycosides. The α-anomers derived from L-fucose, D-glucose, D-galactose and D-mannose predominated, and yields were close to 70%.[263] The β-glycosyl cyanide of *N*-acetylglucosamine, on reduction, gave the aminomethyl compound which was bonded to the aspartic acid unit of a pentapeptide. The corresponding pentapeptide derived from the analogous glycosylamine was made, and the products were tested as glycosidase inhibitors.[264]

The β-*C*-formyl glycosides of glucose, galactose, mannose and *N*-acetyl-glucosamine (2,6-anhydroheptoses) were derived by ozonolysis of the corresponding nitromethyl compounds and, following reaction with nitromethane, were converted into their corresponding 2-nitroethenyl and 2-nitroethyl *C*-glycosides.[265] Extended chain *C*-glycosides have been made from the corresponding *C*-formyl compounds following nucleophilic addition of the Grignard reagent of trimethylsilylacetylene, removal of the silyl group, partial reduction to give epimeric allylic alcohols which were converted to their 2,4-dichlorobenzoates. Palladium-promoted nucleophilic rearrangements involving such nucleophiles as dimethyl malonate gave a set of products, *e.g.* **80**.[266] Scheme 10 illustrates the preparation of a *C*-glycosylglycine which was made together with several related compounds.[267] Compounds **81**[268] and **82**[269] were made from analogues carrying a carboxymethyl C-1 substituent on the sugars, and were amide-bonded to give glycopeptide-like adducts. Conjugated dienes



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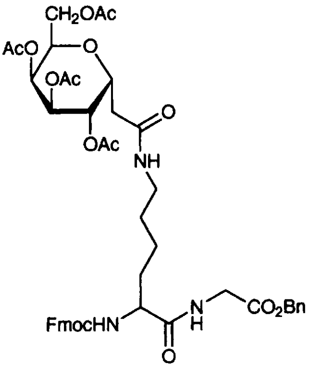

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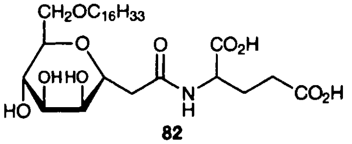

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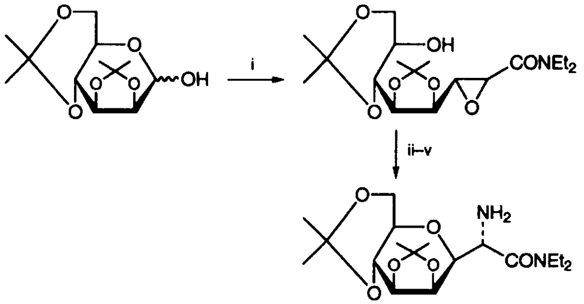
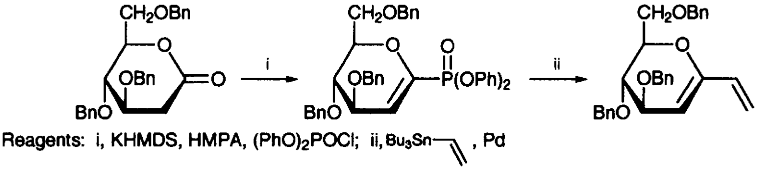


Reagents: i, $Me_2\overset{+}{S}\overset{-}{C}HCONEt_2$; ii, NaH, THF; iii, TsCl, Py; iv, NaN_3, DMF; v, Ph_3P, THF

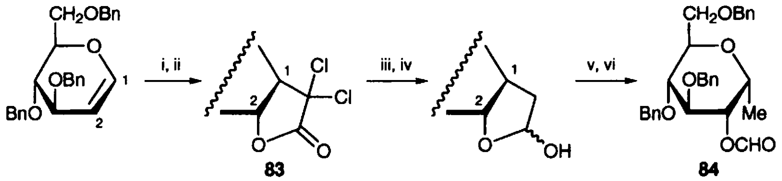
Scheme 10

can be made from aldonolactones as illustrated in Scheme 11.[270] Carbene addition to tribenzyl-D-glucal gave an adduct which was oxidatively ring expanded to **83** and taken through, as indicated in Scheme 12, to the 2-*O*-formyl-*C*-methyl compound **84**.[271] Related bicyclic compounds were made by Lewis acid-catalysed rearrangement of the phenyl sulfones indicated in Scheme 13. An α-D-galactopyranosyl analogue reacted similarily but gave epimers about the anomeric centre.[272]



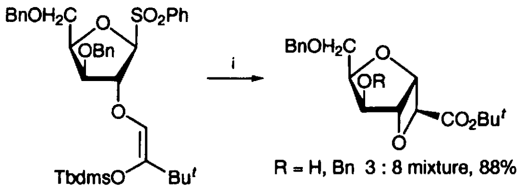
Reagents: i, KHMDS, HMPA, $(PhO)_2POCl$; ii, Bu_3Sn , Pd

Scheme 11



Reagents: i, Cl_3CCOCl, Zn–Cu, Et_2O; ii, MCPBA; iii, Zn, HOAc; iv, DIBALH; v, $PhI(OAc)_2$, I_2, *hν*; vi, Bu_3SnH, AIBN

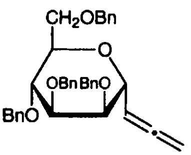
Scheme 12



Reagents: i, $SnCl_4$, –40 °C

Scheme 13

$BiBr_3$ has been used to catalyse the production of *C*-allyl glycosides from *O*-glycosides and allyltrimethylsilane, for example methyl tetra-*O*-benzyl-α-D-glucopyranoside gave the *C*-allyl analogues in 63% yield with an α:β-ratio of 8:1.[273] More commonly, such products are made by use of the same allyl source and TmsOTf as catalyst, and adaptation of this chemistry by use of 3-trimethylsilylpropyne led to the allenyl glycoside **85** in 72% yield.[274] Isomeric compounds, with 1,3-dienic functionality at C-1, for example **86**, were made from 1-*C*-allyl glycosyl chlorides by treatment with DBU. The starting materials were available from 1-bromo-1-chloro compounds which were converted by radical reduction to *C*-allyl chloro-analogues.[275] Treatment of tetra-*O*-benzyl-*C*-allyl glucosides with iodine gives good yields of compounds **87** which, with zinc and acetic acid were converted into the *C*-allyl compounds unprotected at O-2. From these, corresponding 2-deoxyamino derivatives were prepared by use of azide displacements, the work leading to *C*-glycosides in the glucosamine and mannosamine series.[276]



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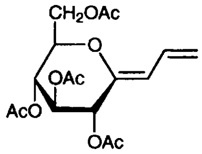

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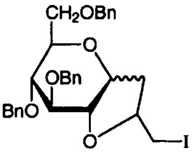
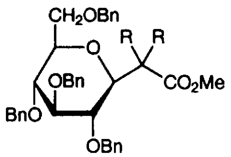
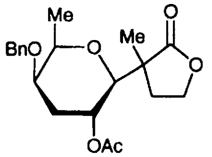


87

Silyl ketene acetals offer further means of obtaining *C*-glycosides, tetra-*O*-benzyl-D-glucosyl acetate affording compounds **88** on treatment with the Tbdms enol ether of the correspoding methyl ester. Compound **89** was made in analogous fashion by use of a dihydrofuran enolsilyl ether.[277] Glycal derivatives reacted as expected with trimethylsilyl ketene acetals under acidic conditions, triacetylglucal, for example, affording compound **90** with 1-methoxy-2-methyl-1-Tms-oxyprop-1-ene. Further use of trimethylsilyl ketene acetals in the preparation of branched-chain derivatives is referred in Chapter 13.[278]



88 R = H, Me



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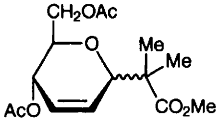
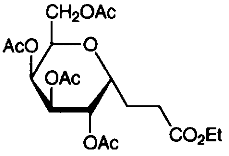


90

Two reports have been made on the well established addition of glycosyl radicals to alkyl acrylates and acrylonitrile,[279,280] compounds such as **91** and **92** being obtainable by this approach.

Glycosyl pyridyl sulfoxides, treated with samarium diiodide, give glycosyl-samarium intermediates which may be used (effectively as glycosyl carbanions) to add to carbonyl compounds. Aldehydes and ketones may be employed, or otherwise more complex materials such as sugar derivatives carrying formyl *C*-branching groups (see below).[281]



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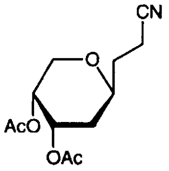

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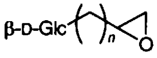
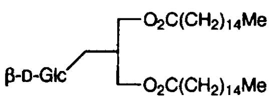


93 $n = 1\text{–}3$

Alkenylmagnesium bromides, added to tetrabenzylgluconolactone, have given intermediates from which the hydroxy groups may be cleaved reductively using triethylsilane/BF_3, to give specific products which were debenzylated and epoxidized to afford compounds **93**.[282] The same gluconolactone derivative, following methylenation, was used to make 1′- and 2′-linked *C*-glycosidic analogues of glycerolipids, for example **94**. Free radical addition of malonate was used to produce this compound, and butenyl Grignard reagent was utilized in the formation of the analogous 1-linked products.[283] In related work a novel *C*-glucosylsphingosine was made by oxidation of a C-1 allyl substituent followed by Wittig chemistry and elaboration of the derived alkene.[284] In the field of *C*-analogues of glycosylamino-acids the β-D-glucopyranosylserine analogue has been elaborated starting from the *O*-benzylated-δ-lactone which was treated with vinylmangesium halide to give a *C*-vinyl free sugar which was converted into the (methoxycarbonyl)methyl *O*-glycoside prior to sigmatropic rearrangement and elaboration of the C-1 substituents.[285] A glycosyltin reagent, added to an appropriate aldehyde, resulted in the β-D-Glc*N*Ac analogue of an *N*-glucosyl asparagine,[286] and a range of α-glucosyl, galactosyl and mannosyl *C*-analogues of glycosylserines have been built up using asymmetric additions on unsaturated aglycones.[287]



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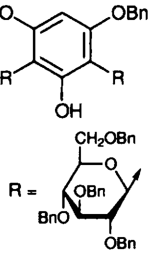
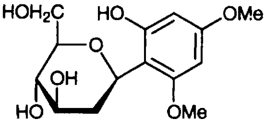


95

Interest continues in *C*-glycosyl aromatic compounds, tetrabenzylglucosyl fluoride with boron trifluoride catalysis having allowed the *C*-glycosylation of di-*O*-benzylphloroglucinol, and a second glycosylation proceeded efficiently to allow the production of compound **95**.[288] Unprotected 2-deoxy-sugars can be condensed with β-naphthol to give 1-*C*-glycosides in chloroform using montmorillonite as catalyst and, much more surprisingly, this type of chemistry can



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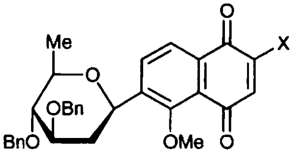
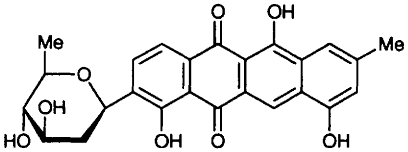
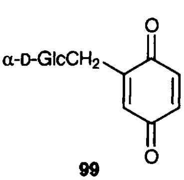


97 X = H, Cl



98

be effected in water. For example, 2-deoxyglucose and dimethylphloroglucinol gives compound **96** in 60% yield.[289] Full details of previous work (Vol. 29, p. 47, ref. 268 and *Synlett*, 1996, 433) on the synthesis of the *C*-glycosyljuglones **97** and their conversion into galtamycinone **98** have appeared, the chemistry involving an O→C glycosyl rearrangement.[290] An *O*-protected iodomethyl α-*C*-glucoside was used to obtain compound **99** and the naphthaquinone analogue, both of which inhibited an α-glucosidase, and continuation of the work led to the unnatural 6-*C*-linked diglycosyl compound **100**.[291] Free sugars were used to make several 2,6-dideoxy compounds, *e.g.* **101**, TmsOTf and $AgClO_4$ being the catalysts and MeCN the solvent. In closely related cases methyl glycosides were employed in CH_2Cl_2 with TmsOTf catalysis.[292]



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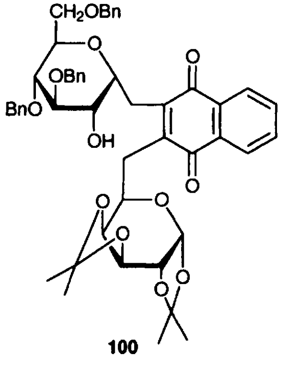

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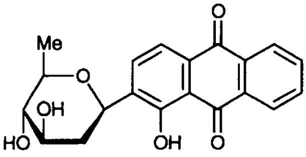

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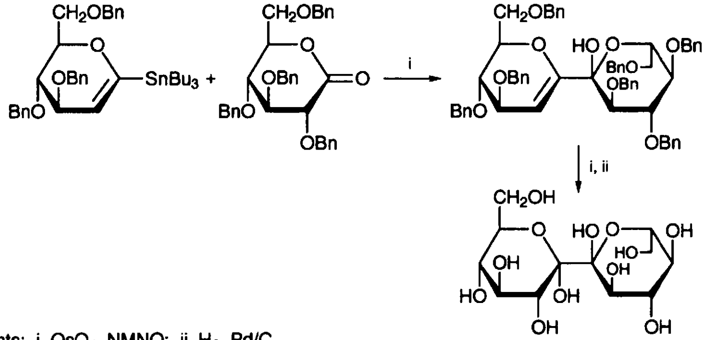
An interesting 2-*O*-acylation of a *C*-glycoside, involving migration of the acyl group from the aglycon, has led to compounds **102**.[293]

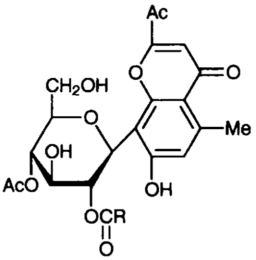
Considerable attention has been devoted to the preparation of *C*-linked disaccharides, and in this section the *C*-bonded group which replaces the oxygen atom linking the sugar units is indicated within the abbreviated names used. The following compounds were made by Wittig linking: β-D-Glc-(1-CH_2-6)-D-Gal, β-D-Gal-(1-CH_2-6)-D-Glc, β-D-Gal*N*Ac-(1-CH_2-6)-D-Glc, β-D-Glc-(1-CH_2-6)-D-Glc, α-D-Rib*f*-(1-CH_2-6)-D-Gal and α-D-Man*f*-(1-CH_2-6)-D-Gal.[294] A Michael addition applied to levoglucosenone has afforded an intermediate which was reduced to β-D-Glc-(1-CH_2-4)-3-deoxy-D-Glc.[295] The intramolecular condensation of tethered species is now commonplace for synthesizing disaccharides and their *C*-linked analogues, and α-D-Glc-(1-CH_2-6)-D-Glc has been made by this approach,[296] as has α-D-Gal*N*Ac-(1-CH_2-4)-β-D-GlcOMe. In the latter case the galactosamine and glucose (in the form of a 1-*exo*-methylene derivative) were initially bridged by way of a phosphate linkage between the amino group and O-6 of the latter.[297] Carbanion additions to formyl branched groups on monosaccharides leads to disaccharide analogues having a hydroxymethylene group between the sugar units, and by this approach α-D-Neu*N*Ac-(1-CHOH-3)-D-Gal has been made[298] as has α-D-Man-(1-CHOH-2)-D-Man.[281]



Reagents: i, OsO_4, NMNO; ii, H_2, Pd/C

Scheme 14

Several examples of disaccharide analogues derived by direct carbon-carbon coupling of monosaccharides have been reported. For example, electrochemical reduction of tetra-*O*-acetylglucosyl chloride has given the 1,1′-linked compound and 6-deoxy-6-halogeno-diisopropylidine-α-D-galactose, treated similarly, has given a dimer with direct C-6–C-6)-bonding.[299] Scheme 14 illustrates the production of a different type of trehalose analogue, the compound formally being a dodeca-6,7-diulose.[300] The unusual compound **103** was derived *via* **104** which in turn was made from the corresponding pentodialdose by treatment with furanyllithium.[301] Compound **105** is a further example of a *quasi*-disaccharide built on a monosaccharide template, on this occasion from **106** using ethyl vinyl ether in a hetero-Diels-Alder condensation to prepare the second pyranosyl ring.[302]



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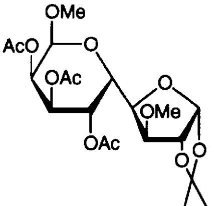

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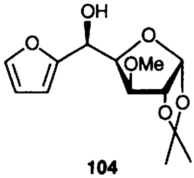

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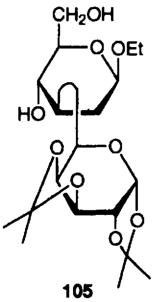
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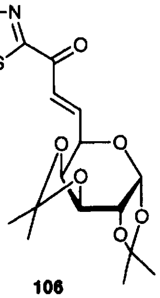
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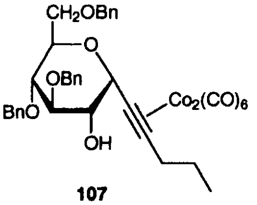
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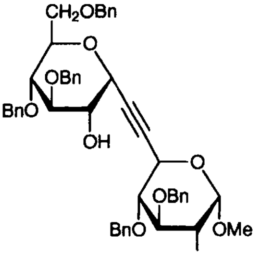
Interest in acetylenic *C*-glycosides continues and reaction of 1,2-anhydro-3,4,6-tri-*O*-benzyl-D-glucose with alkynes in the presence of n-butyllithium and zinc chloride gives α-acetylenic 2-hydroxy *C*-glycosidic compounds. Treated with cobalt octacarbonyl these give complexes, *e.g.* **107**, which, on treatment with triflic acid, give anomerized β-isomers. Extension of this work has given alkyne **108** which offers further access to α-D-Glcp-(1-CH_2-6)-D-Glc.[303] Vasella's team has continued its interest in macrocycles derived from carbohydrate diacetylenes, and palladium coupling of compound **109** has led to the cyclic trimer **110** and also an analogous tetramer.[304] Cyclic compounds with three and four diacetylenic dipyranoid ring units have also been described.[305] Palladium-catalysed addition of aryl halides to the double bonds of 2,6-anhydro-1-deoxyhept-1-enitols produced arylmethyl *C*-glycosides with the β-configuration in both the D-*gluco*- and D-*manno*-series. Extending this reaction, for example to *p*-dibromobenzene, has given rise to *C*-linked compounds involving two sugar units joined by way of a benzene ring, such as compound **111**.[306]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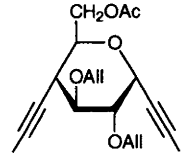
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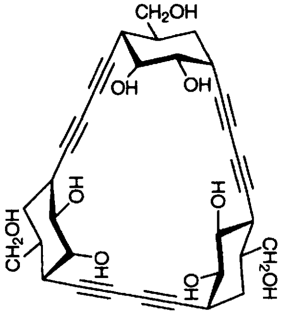
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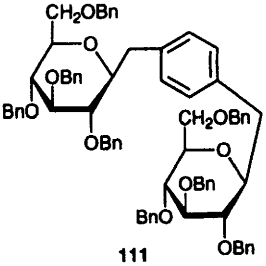
Several compounds having glucose *C*-linked to ring systems similar to pyranose rings have been described. Hetero-Diels-Alder chemistry conducted in water has allowed the formation of compound **112** from a glucosyl *C*-glycoside bearing a penta-1,3-dienyl group which was coupled with glyoxylic acid.[307] Otherwise the *C*-linked glycosylcarba-sugar **113** has been made by Diels-Alder chemistry applied to a *C*-glucoside having a dienophile in the aglycon.[308] In related studies a 2-deoxyglycosylstannyl compound was coupled



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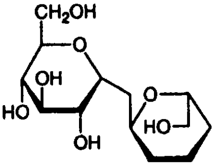

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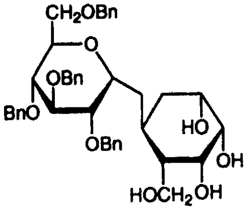

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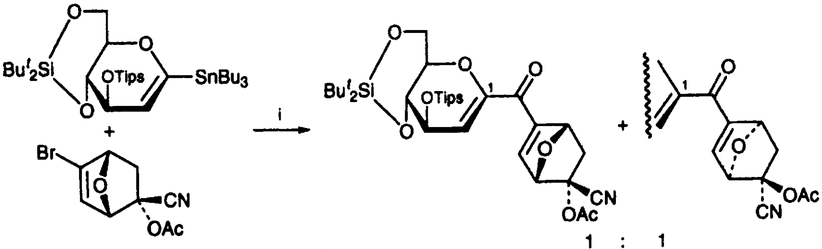
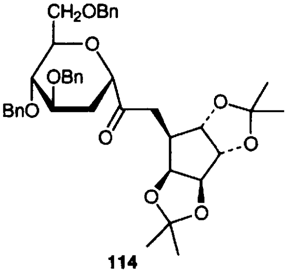


Reagents: i, CO(50 atm), $Pd_2(dba)_3$, Ph_3As

Scheme 15

in the presence of butyllithium with a cyclopentyl derivative bearing a formylmethyl group to give compound **114** and a diastereomer. In the course of the work an analogue was made having the sugar similarly linked to deoxyinositol derivative.[309] Scheme 15 illustrates chemistry which has given *C*-linked glycosylcarba-sugars analogous to compound **113**.[310] Extension of this work by Vogel and his team has led to the azasugar derivative **115** and hence



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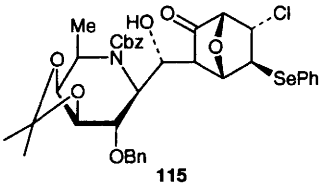

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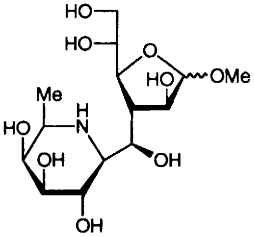
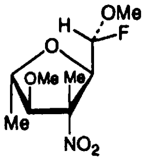


116

to the *C*-disaccharide analogue **116**. This chemistry was described in a long, complex paper with much detail.[311]

Enzymic galactosylation of *C*-glycosides is referred to earlier in this chapter and Paquette's work on the ring expansion of particular 1,2-unsaturated *C*-glycosides to give spirocyclic compounds is referred to in Chapter 2.

3.2 Furanoid Compounds – Palladium chloride-catalysed ring closure of 1,2-dideoxy-hex-1-enitols having a free hydroxyl group at C-5 leads to a new way of making methyl *C*-glycofuranosides. The reactions proceed by way of the 1-deoxyketofuranoses which, with triethylsilane and boron trifluoride, are dehydroxylated. The assigned configurations at the new anomeric centres in this work have to be viewed with care because they conflict with results presented in *J. Chem. Soc., Perkin 1*, 1995, 517, in which NOE evidence pertaining to configuration is provided.[312] The functionalized branched chain *C*-glycosidic compound **117** was the product of treatment of a corresponding methyl α-pyranosidic compound with DAST. The starting material with the alternative configuration at C-2 reacted quite differently affording a glycopyranosyl fluoride with methoxyl now attached to C-2. Clearly intermolecular rearrangements are proceeding in this chemistry, and the mechanisms of these are discussed.[313] From the corresponding *exo*-difluoromethylene glycosylidene compound the phosphonates **118** were produced by free radical addition processes.[314] Tri-*O*-benzyl-β-D-ribofuranosyl cyanide is, as expected, the product of reaction of the corresponding acetate with trimethylsilyl cyanide.[315] Also in the ribofuranosyl series α-*C*-glycosides having acetylmethyl-, benzoylmethyl- and cyanomethyl-α-substituents have been produced starting from the corresponding lactones which underwent nucleophilic additions to give free sugars which were reductively dehydroxylated in the normal way.[316] In the 2-deoxy-ribofuranosyl series an *O*-substituted glycosyl acetate, treated with the appropriate *O*-silylated ketene acetal in the presence of a Lewis acid, gave the α-furanosyl *C*-glycosidic compound having (benzyloxycarbonyl)methyl as the aglycon.[317]



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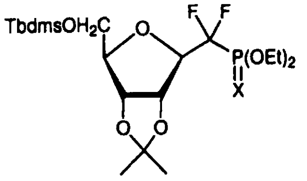
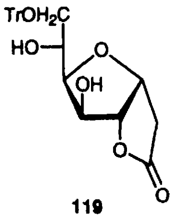


118 X = O, S

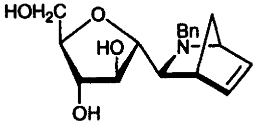


119

Reaction of partially protected free sugars with arsonium ylids under neutral conditions $[(Ph_3As\text{-}CH_2CO_2Et)^+Br^-/Zn]$ gave mainly *E*-alkenes, whereas under basic conditions $[(Ph_3As{=}CHCO_2Et/nBuLi)]$ the products were bicyclic compounds. For example, 6-*O*-tritylglucose afforded ultimately the bicyclic *C*-glycosidic **119**.[318] The same authors then described conditions for producing the analogous *O*-unprotected lactone in 70% yield directly from glucose.

Galactose afforded the analogous isomeric compound in 72% yield, but the pentoses mainly gave the unsaturated intermediates.[319] This represents a very much more convenient approach to compounds such as **119** than does an alternative route involving 2-*O*-bromoacetyl γ-lactones from which Wittig reagents were produced and hence the bicyclic lactones.[320]

Elaboration of the α-D-arabinofuranosyl *C*-formyl glycoside (2,5-anhydro-D-mannose), involving condensation with cyclopentadiene in the presence of benzylamine hydrochloride and $Nd(OTf)_3$ in water led to compound **120**. In the course of the work compound **121**, which can be considered to be a *C*-glycoside of an aza-sugar derivative, was made.[321]



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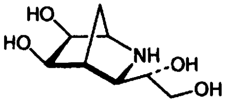

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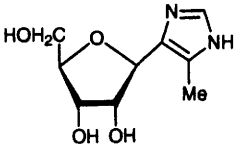

122

A review has been written on '*C*-nucleosides derived from simple aromatic hydrocarbons'. *i.e.* aryl *C*-glycosides of β-D-ribofuranose and its 2-deoxy derivative.[322] The heterocyclic compound **122** has been prepared starting from 2,3,5-tri-*O*-benzylribose to which was added a heterocyclic nucleophile. Several derivatives were made one of which was half as active as cimetidine as an anti-ulcer agent, and the paper refers to much other related medicinal chemistry.[323]

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4

Oligosaccharides

1 General

Following the major recent increase in activity in this field, this year has seen the production of a mass of relevant reviews. Paulsen has surveyed general developments in the chemical synthesis of oligosaccharides over the last 25 years,[1] and an assessment in Chinese has concentrated on the stereoselectivity of relevant reactions.[2]

Methods involving the use of polymer-supports are now used extensively, and Krepinsky has reviewed the production of oligosaccharides on poly(ethylene glycol)monomethyl ether (MPEG).[3] Solid-phase methods of synthesis of polylactosamine oligosaccharides involving orthogonal glycosylation have been surveyed,[4] as has the use of several new *p*-substituted benzyl or phenyl protecting/linking groups in solid-phase oligosaccharide synthesis. *p*-Acylaminobenzyl and *p*-azidobenzyl groups are, as expected, more acid-stable than *p*-methoxybenzyl analogues, but are readily cleaved by methods involving DDQ. The *p*-acylaminophenyl glycosidic linkage is easily broken with CAN.[5]

A further review has covered the synthesis of compounds, *e.g.* Sia Le^X mimetics, that interact with cell surface carbohydrates, and refers to the solid-phase approach and also combinatorial procedures,[6] while another[7] covers the latter technique applied to oligosaccharides and oligonucleotides.

Garegg has surveyed the use of thioglycosides as glycosylating agents,[8] and with colleagues, their use in the making of oligosaccharides found in fungal and bacterial polymers.[9] A related review has dealt with glycosylations based on thioglycosides, sulfoxides and other *S*-glycosidic donors,[10] and another has assessed phenylselenyl glycosides as donors and acceptors in reactions that lead to oligosaccharides.[11]

Glycals have particularly been exploited by Danishefsky who, with Bilodeau, has reviewed this impressive work,[12] while Fraser-Reid has dealt with his *n*-pentenyl glycoside approach[13] and other workers have covered Boons's latent-active glycosylation strategy (see ref. 42 below).[14]

Enzymic synthetic procedures are now of great use in specific oligosaccharide production, and several reviews have appeared. One dealt with the topic generally,[15] and another reported on the optimization of methods for application on the kg scale.[16] More selective surveys covered the use of glycosyl transferases in the synthesis of unnatural oligosaccharides,[17] and the applica-

Carbohydrate Chemistry, Volume 31

tion of α-(1→4)-galactosyltransferases for the same purpose.[18] The topic of inhibition of these enzymes has been dealt with; various mono-*O*-methyl UDP-Gal ethers and derivatives having acceptors bridged to UDP-Gal were discussed. Potent specific inhibitors have been discovered in this way.[19] A further survey of the use of enzymes emphasized the production of Sia Le^X antigen and dealt with the matter of inhibition of glycosidases and glycosyl transferases.[20]

The substrate specificity and synthetic applications of transferases have been discussed in a review that included treatment of the use of glycosyl phosphites in oligosaccharide synthesis and in the synthesis of glycopeptides,[21] and enzymic approaches to these latter compounds form part of a further review.[22] The variables involved in making glycoconjugate di- and tri-saccharides based on Gal, Glc*N*Ac, Fuc and Man by enzymic approaches have been assessed,[23] as have analogous procedures for making nucleotide deoxy-sugars and oligosaccharides.[24]

Reviews have appeared on the chemical synthesis of cello-oligosaccharides,[25] β-mannopyranoside-based compounds,[26] deoxy-sugar oligomers,[27] thio-oligosaccharides which are recognized by proteins,[28] heparan sulfate, heparin and heparinoid mimetics[29] and biologically active sulfated and phosphorylated oligomers.[30]

The important topic of the preparation of glycocongugates by chemical and enzymic procedures has been surveyed by Schmidt,[31] and several reviews have concentrated on such compounds – especially those which contain sialic acid components.[32-36]

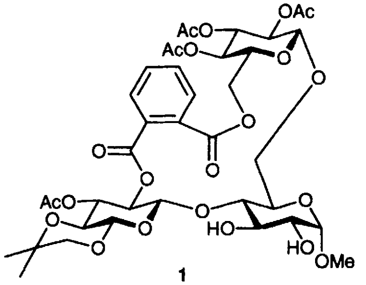
The specific topics of the synthesis of dimeric forms of the calicheamycin oligosaccharide and their docking in the minor groove of duplex DNA have been surveyed,[37] and reviews have appeared on the molecular recognition of oligosaccharides by proteins[38] and of oligosaccharide glycolipids in supramolecular self assemblies in aqueous media.[39]

Reports of new work of general importance are now dealt with. Powerful new methodologies continue to be developed to help overcome the limitations of traditional approaches to the synthesis of oligosaccharides. For example, the branched trisaccharide glycoside β-D-Glc-(1→4)-[β-D-Glc-(1(6)]-α-D-Glc-*O*Me has been made by linking O-6′ of the (1→6)-bonded dimer to O-2 of a suitably protected glucosyl fluoride by a phthalic diester bridge, and activating the fluoride with silver triflate and Cp_2HfCl, to give in 37% yield, the cyclic product **1** which was deprotected to give the trisaccharide.[40] Further evidence that the elegant intramolecular approach to disaccharide synthesis is being extended into oligosaccharide work comes from the synthesis of the streptococcal capsular polysaccharide unit β-D-GlcNAc-(1→3)-α-D-Gal-(1→4)-β-L-Rha-(1→4)-D-Glc for which the rhamnose moiety as an *S*-ethyl thioglycoside was succinic diester linked *via* O-2 to O-3 of the glucose unit in such a way that activation of the thioglycoside led to the required β-(1→4)-bond formation. The resulting disaccharide, still intramolecularly diester-linked, was then coupled with the Glc*N*Ac-Gal component.[41]

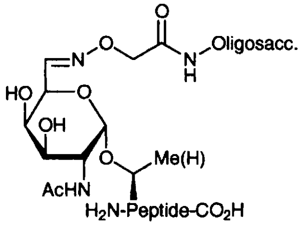
A most significant development is Boons's exploitation of the different reactivities towards glycosylation of different types of hydroxyl groups in acceptor molecules, equatorial groups being more reactive than axial, primary than secondary, and most importantly, hydroxyl groups neighboured by ether protecting groups being more reactive than those with neighbouring ester substituents. Using these differences and Fraser-Reid's armed and disarmed glycosylating agents he demonstrated high yields of selectively substituted disaccharides, and extended the principles into the preparation of the hetero-hexamer α-D-Glc-(1→6)-β-D-Gal-(1→4)-β-D-Glc-(1→6)-β-D-Gal-(1→4)-β-D-Glc-(1→6)-D-Man.[42]

A new approach to linking sugars and peptides involves galactose oxidase oxidation of galactosyl or *N*-acetylgalactosaminyl-*O*-peptides and coupling of the aldehydic products with glycosylamines (*e.g.* lactosylamine) elaborated to contain the -$NHCOCH_2ONH_2$ group. The products are therefore as indicated in **2**.[43]

A specific development involves the preparation of chito-oligosaccharides on a large scale using *E. coli* with genes encoding for relevant glycosidases and *N*-deacylases. The method led particularly to the pentaoses carrying four and five acetyl groups.[44]



1



2

2 Trisaccharides

2.1 General – Compounds in sections 2.1–2.4 are now characterized according to their non-reducing end sugars.

The combinatorial approach involving solid phase techniques on TentaGel resin has provided a library of 1200 di- and tri-saccharides which were screened against a *Bauhinia purpurea* lectin.[45]

In the area of non-reducing trisaccharides the enzymic syntheses of 6-*O*-α-D-mannopyranosyl-, 6-*O*-α-D-glucopyranosyl- and 6-*O*-α-D-galactopyranosyl-trehalose and 6-*O*-α-D-mannopyranosylsucrose have been optimized,[46] and Nicolaou and co-workers, using a 1,2-*O*-stannylidene derivative of β-D-mannopyranose coupled with a mannosyl trichloroacetimidate, have produced a 2-*O*-unprotected α,β-*manno*-trehalose analogue derivative and hence have made a 2-*O*-α-D-mannosylated-*manno*-trehalose. Several related compounds were prepared, and the methods were also used to make the F-G ring system of everninomicin 13,3841.[47]

2.2 Linear Homotrisaccharides – The use of *n*-pentenyl glycosides has been extended to the solid-support preparation of oligosaccharides with either the pentenyl donors or the acceptors bound to the resin, and the linkages to the polymers being photolabile. In the course of the work polymer-bound, fully deprotected oligomers were produced which points to the preparation of libraries of oligosaccharides. In this way α-D-Glc-(1→6)-α-D-Glc-(1→6)-D-Glc was made,[48] and the α-(1→6),β-(1→6)-linked analogue was produced as the glycosylamine for amide coupling to give the core structure of the nephritogenoside glycopeptide, the glycosyl phenyl sulfoxide method of glycosylation being used.[49] Thioglycosides were used in making the α-(1→4)-linked trimer of D-galacturonic acid.[50]

Hydrolysis of inulin with a bacterial endoinulase gave the β-Fru*f*-(2→1)-linked dimer and trimer in nearly equal proportions.[51]

2.3 Linear Heterotrisaccharides – β-D-Glc-(1→2)-β-D-Glc-(1→4)-β-D-Gal is the sugar component of a steroidal glycoside of the plant *Hosta plantaginea* which shows cytostatic activity against leukaemia cells.[52] Other glucosyl compounds of this set which have been synthesized are β-D-Hex-(1→4)-β-D-GlcNAc-(1→2)-α-D-Man (where Hex = D-Glc, 4-deoxy-D-Gal and 4-deoxy-4-fluoro-D-Gal),[53] and 3-*O*-Me-β-D-Glc-(1→3)-α-L-Rha-(1→3)-α-L-Rha which was prepared as the *p*-isothiocyanatophenyl glycoside for coupling to peptides.[54]

In the area of D-galactose-terminating compounds various trisaccharides were made from glucoside acceptors following the use of 4,6-*O*-pyruvylidine galactosyl chloride and trichloroacetimidate donors,[55] and the glycosyl phosphoroamidate method, coupled with the armed/disarmed concept, were employed in making a ceramide based on α-D-Gal-(1→4)-β-D-Gal-(1→4)-β-D-Glc.[56] The closely related α-D-Gal-(1→3)-β-D-Gal-(1→4)-β-D-Glc-$NHCO_2CH_2CCl_3$ was produced by enzymic methods as its *S*-ethyl thioglycoside,[57] and the galactobiosyl-Glc*N*Ac analogue was produced by chemico-enzymic procedures on an MPEG resin in the course of work on immunosuppression.[58] Solid-phase work led to β-D-Gal-(1→3)-β-D-Gal-(1→3)-α-D-Gal*N*Ac *O*-bonded to a peptide and to similar β-(1→3), β-(1→6) linked glycopeptides all of which are related to mucin core structures.[59] β-D-Gal-(1→2)-β-D-Glc-(1→6)-D-Glucal was reported in work designed to use complex glycals as glycosylating agents.[60] Modifications in the galactose unit of β-D-Gal-(1→4)-β-D-GlcNAc-(1→2)-α-D-Man gave a set of compounds required for the study of sialyl transferase specificity,[61] while a different group produced the unmodified trisaccharide and its β-D-Gal-(1→4)-β-D-Glc*N*Ac-(1→6)-α-D-Man isomer by use of a β-*N*-acetylglucosaminidase and a β-galactosidase.[62] Modification to the β-D-Gal-(1→4)-β-D-Glc*N*Ac-(1→2)-α-D-Man system gave several analogues terminating in moieties having modifications at C-3 of the galactose unit and with this sugar replaced by β-D-gulose, α-L-altrose and β-L-galactose.[63]

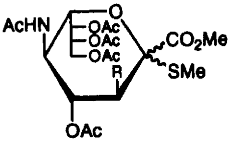
Solid-phase and *n*-pentenyl glycoside technologies were combined to afford β-D-Gal-(1→2)-α-D-Man-(1→6)-D-Glc*N*Ac.[48]

β-D-Man-(1→4)-β-D-Glc*N*Ac-(1→4)-D-Gal*N*Ac has been prepared by use of recombinant enzymes,[64] and an improved synthesis of α-L-Ara*f*-(1→3)-β-D-Gal-(1→6)-β-D-Gal has been described.[65]

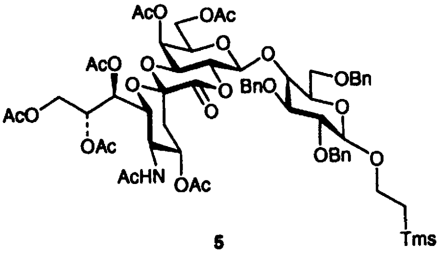
The following compounds terminating in 2-*N*-acetylaminohexoses have been synthesized: β-D-Glc*N*Ac-(1→3)-β-D-Gal-(1→4)-Glc*N*Ac and its β-(1→6), β-(1→4) linked isomer (enzymic procedure),[66] β-D-Glc*N*Ac-(1→2)-α-D-4-*N*HAc-Man-(1→6)-D-Glc (as well as seven analogues with other acyl groups on the 4-amino-4-deoxy-D-mannose moiety),[66] and β-D-Gal*N*Ac-(1→4)-3-*O*-SO_3H-β-D-Gal-(1→4)-β-D-Glc*N*Ac and its analogue with sulfate replaced by glycolyl.[67]

In the field of compounds containing L-*glycero*-D-*manno*-heptose the following trisaccharides have been made: α-D-GlcA-(1→2)-α-Hep-(1→3)-Hep[68] and Hep-(1→4)-Kdo-5-phosphate-(2→6)-Glc*N*Ac corresponding to the inner core region of a bacterial lipopolysaccharide.[69]

Because of their biological significance considerable activity has taken place on trisaccharides terminating in a sialic acid unit, the ganglioside GM_3 α-Neu*N*Ac-(2→3)-β-D-Gal-(1→4)-β-D-Glc-*O*-Cer and near analogues having been targets particularly favoured. Thioglycoside **3** has been used for the introduction of the sialic acid,[70] and in another chemical approach which led to the *N*-glycolyl analogue, compound **4** was employed.[71] Mainly, however, enzymic procedures have been used.[72-78] Lactone **5** of GM_3 has been made as a possible hapten for development of an anticancer vaccine.[79]



3 R = SPh
4 R = H



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Related work has resulted in the preparation of α-Neu*N*Ac-(2→3)-β-D-Gal-(1→3)-α-D-Gal*N*Ac linked to cysteine which is part of the B-chain of human α 2HS glycoprotein. Solid-phase procedures were used and, in the course of the work, compounds with the trisaccharide having lactone linking between the acid group and O-4′ are bonded to serine were involved.[80] Use of sialyl transferases has allowed the preparation of the closely related α-Neu*N*Ac-(2→3)-β-D-Gal-(1→4)-D-Glc*N*Ac and α-Neu*N*Ac-(2→3)-β-D-Gal-(1→3)-2-O-Ac-β-D-Gal.[81]

The xylose-containing trisaccharide α-Neu*N*Ac-(2→3)-β-D-Gal-(1→4)-β-D-Xyl has been made enzymically as its *p*-nitrophenyl glycoside as a potential inhibitor of human skin fibroblast glycosaminoglycan biosynthesis,[82] and derivatives of the same trimer glycosidically linked to a ceramide have been made in the form of a lactone involving the acid function and O-2 of Gal. The analogue with Gal replaced by $GalNH_2$, and with the amino group lactam-linked to the acid group, was also described.[83]

Trisaccharides terminating in 6-deoxyhexoses to have been synthesized are α-L-Rha-(1→4)-α-L-Rha-(1→2)-D-Fuc (the sugar of a resin glycoside),[84] and 6-deoxy-α-L-Tal-(1→2)-β-L-Rha*f*-(1→5)-DHA (a very unusual type of rhizobial compound; DHA being 3-deoxy-L-*lyxo*-heptulosaric acid). X-Ray structural analysis was carried out on a methyl glycoside, methyl ester peracetate.[85]

Glycal- and hence 1,2-anhydroglucofuranose-based methods were used in the preparation of α-L-Ara*f*-(1→2)-β-D-Glc*f*-(1→6)-D-Glc.[86]

2.4 Branched Homotrisaccharides – 4,6-Di-*O*-β-D-glucopyranosyl-D-glucose has been made by an intramolecular method,[40] while a solid support synthesis involving the use of a photolabile linkage was employed in the preparation of 3,6-di-*O*-mannopyranosyl-D-mannose.[87]

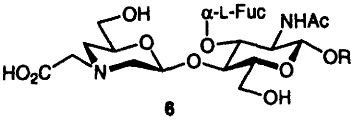
2.5 Branched Heterotrisaccharides – Compounds in this section are categorized according to their reducing end sugars.

Further attention has been given to the Le^X-related β-D-Gal-(1→4)-[α-L-Fuc-(1→3)]-D-Glc: its synthesis from lactose was described,[88] as were those of derivatives with sulfate groups at O-3[89,90] or O-4,[89] or O-3 and O-4,[89] or O-3 and/or O-6[91] of the galactose moiety. In the case of the 3′-sulfate dendrimers were made and their selectin-binding properties were measured.[90] An analogue with a 3-carboxymethyl-3-deoxy branch in the galactose unit was also reported,[92] and the Le^a antigen β-D-Gal-(1→3)-[α-L-Fuc-(1→4)]-D-Glc has been made with sulfate groups at O-3 and/or O-6.[91]

Le^X antigen, β-D-Gal-(1→4)-[α-L-Fuc-(1→3)]-D-Glc*N*Ac, has been made by use of two specific glycosidases,[93] and combined chemical and enzymic procedures were employed in making analogues with the fucose moiety modified by replacement of the C-6 methyl group by *n*-pentyl and *n*-heptyl groups.[94] The 3′-sulfate, esterified on O-3 of the galactose moiety, has been produced by chemical methods,[95] and several O-3′ ethers (*e.g.* the *S*- and *L*-lactyl ethers) were made following molecular modelling studies aimed at the rational design of E-selectin antagonists based on Sia Le^X as lead compound.[96] Solid-phase work involving enzymic fucosylation of the appropriate disaccharide disulfide-bonded to Sepharose led to β-D-Gal-(1→3)-[α-L-Fuc-(1→4)]-D-Glc*N*Ac.[97]

In work related to core glycopeptides of mucins the following branched trisaccharides have been made: β-D-Glc*N*Ac-(1→6)-[β-D-Gal-(1→3)]-Gal*N*Ac,[98-100] α-D-Neu*N*Ac-(2→6)-[β-D-Gal-(1→3)]-D-Gal*N*Ac,[101] and this compound with β-D-Gal replaced by α-D-Gal*N*Ac.[102]

2.6 Analogues of Trisaccharides and Compounds with Anomalous Linking – In studies of the Le^X antigen and its biological function mimic molecules to have been made are the morpholine-trisaccharide model **6**,[103] compounds **7** which contain mimics of two sugar units and the analogue with Fuc replaced by α-D-Man. Some of the products showed strong inhibition of leukocyte adhesion in rats.[104]



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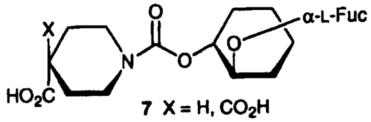
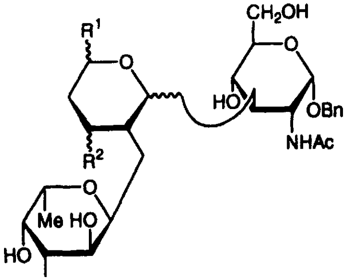


7 X = H, CO$_2$H

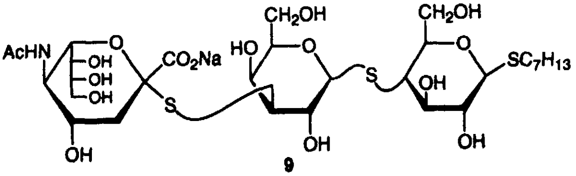
Compounds **8** (twelve were made) with methylene inter-unit linkages were prepared as potential inhibitors of the synthesis of the surface proteins of *Helicobacter pylori*. They allowed a study of the effects of systematic variation of the central moiety which was effected by Grignard-like coupling of a 2-bromoallyl 'aglycon' on the Fuc unit and a formylmethyl C-3 substituent on the 3-deoxyglucosamine.[105]

β-D-Glc*N*Ac-(1→2)-α-D-Man-(1→3)-α-D-Man-O-Me with a methylene acetal bridge between O-6 of Glc*N*Ac and O-2 of the terminal Man is locked in a suitable conformation for binding with a specific lectin.[106]

The trithio-ganglioside GM$_3$ epitope **9** has been specifically synthesized.[107]



8 R^1 = CH$_2$OH, Me; R^2 = OH



9

3 Tetrasaccharides

Compounds of this set and higher oligosaccharides 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 Homotetrasacharides – Pivaloylation of maltose gave 61% of a hepta-ester which led to the 3-deoxy-analogue which was coupled with a partially *O*-protected trehalose derivative to give α-D-Glc-(1→4)-3-deoxy-β-D-Glc-(1→4)-α-D-Glc-(1→1)-α-D-Glc.[108] A 6′-*O*-trityl maltoside was used in the preparation of α-D-Glc-(1→6)-β-D-Glc-(1→6)-α-D-Glc-(1→4)-D-Glc,[109] and α-D-Glc-(1→3)-α-D-Glc-(1→4)-α-D-Glc-(1→4)-D-Glc has been produced by use of a crude enzymic preparation from an *Acremonium* species.[110]

α-D-Man-(1→3)-α-D-Man-(1→2)-α-D-Man-(1→2)-D-Man, related to the antigen of an *E. coli*, has been synthesized[111] and the glycosyl trichloroacetimidate of *O*-benzylated α-D-Man-(1→4)-3-*O*-Me-α-D-Man-(1→4)-3-*O*-Me-α-D-Man-(1→4)-3-*O*-Me-α-D-Man has been made as a glycosylating agent together with a hexasaccharide analogue.[112]

3.2 Linear Heterotetrasaccharides – The non-reducing tetrasaccharide α-L-Fuc-(1→2)-β-D-Glc-(1→1)-β-D-Glc-(2←1)-α-L-Fuc (difucosyl-β,β-trehalose) has been made to mimic Le^b and Le^y antigens.[113] Incubation of cycloinulohexaose and methyl α-D-glucopyranoside in the presence of cycloinulo-oligosaccharide fructanotransferase gave, as the main product, β-D-Fru*f*-(2→1)-β-D-Fru*f*-(2→1)-β-D-Fru*f*-(2→6)-α-D-Glc-*O*-Me.[114] The hydroxylated derivative **10** of a diastereoisomer of acarbose was made by a 2+2 unit strategy involving a 'carba-disaccharide' having the amino group carbonyl linked to O-3 of the neighbouring sugar moiety.[115] Ganglioside GT4, containing α-Neu*N*Ac-(2→8)-α-Neu*N*Ac-(2→8)-α-Neu*N*Ac-(2→3)-β-D-Gal, was made as was the isomer with α-(2→6)-bonding to the Gal component.[116] The capsular polysaccharide of *Streptococcus pneumoniae*, β-D-Glc*N*Ac-(1→3)-α-D-Gal-(1→4)-β-L-Rha-(1→4)-D-Glc was made by an intramolecular reaction used to form the rhamnosyl glycosidic bond.[41]

α-Neu*N*Ac-(2→6)-β-D-Gal*N*Ac-(1→4)-β-D-Glc*N*Ac-(1→2)-α-D-Man, which is part of the *N*-linked chain of human lutropin,[117] and β-D-Gal-(1→4)-β-D-$GlcNH_2$-(1→3)-β-D-Gal-(1→4)-β-D-$GlcNH_2$, the tetrasaccharide of the glycoprotein of laminin,[118] have also been synthesized. β-D-$GlcNH_2$-(1→4)-β-D-Glc-(1→4)-β-D-Glc-(1→4)-β-D-Glc*N*Ac with a long chain acyl substituent on the amino group and as the *p*-methoxyphenyl glycoside has been made and subjected to conformational and molecular dynamics analysis,[119] and synthesis of the sulfated chondroitin sulfate tetrasaccharide terminating (reducing end) in glucuronic acid has been described.[120]

Two reports on the preparation of tricolorin A, a cytotoxin active against breast tumour cells and which is a derivative of α-L-Rha-(1→3)-α-L-Rha-(1→2)-β-D-Glc-(1→2)-β-D-Fuc have been published. The aglycon contains a branched C_{16} carboxylic acid chain which is lactonized with O-3 of the Glc moiety.[121,122]

Enzymic procedures were used in the preparation of the 4-methylumbelliferyl glycoside of β-D-GlcA-(1→3)-β-D-Gal-(1→3)-β-D-Gal-(1→4)-β-D-Xyl.[123] In the area of compounds containing L-*glycero*-D-*manno*-heptose (Hep), β-D-Gal-(1→2)-α-Hep-(1→2)-α-Hep-(1→3)-α-Hep and several related trisaccharides were made as their *p*-(trifluoroacetamido)phenyl glycosides.[123a]

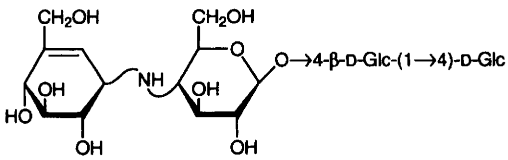
3.3 Branched Heterotetrasaccharides – Because of their biological importance much of the greatest interest in this category of branched compounds is found on sialylated members and syntheses have been reported of α-Neu*N*Ac-(2→3)-[β-D-Gal*N*Ac-(1→6)]-β-D-Gal-(1→4)-β-D-Glc which is the 6′-regioisomer of ganglioside GM$_2$,[124] and of the (2→3), (1→4), (1→4)-bonded isomer which is GM$_2$ itself.[125]

Compounds terminating in Man to have been made are α-D-Glc-(1→4)-β-D-Glc-(1→4)-[α-D-GlcA-(1→3)]-D-Man, which is related to the repeating unit of the antigen from *Klebsiella* type 2 polysaccharide,[126] and α-D-Man-(1→3)-[β-D-Xyl-(1→2)]-α-D-Man-(1→3)-α-D-Man, which is found in the capsular polysaccharide of a *Cryptococcus*.[127] In related work the *Mycobacterium* lipopolysaccharide component α-L-Rha-(1→2)-3-*O*-Me-α-L-Rha-(1→3)-[β-D-Xyl-(1→2)]-α-L-Rha has been produced synthetically.[128] Sialic acid also occurs in non-mammalian oligosaccharides, the repeating unit of a *Streptococcus* capsular polysaccharide β-L-Rha-(1→4)-β-D-Glc-(1→4)-[α-Neu*N*Ac-(2→3)]-D-Gal having been synthesized.[129]

Considerable attention has been paid to compounds terminating in Glc*N*Ac. Chemical methods which the authors describe as 'economical' have been used to make the Sia Le^X antigen α-Neu-(2→3)-β-D-Gal-(1→4)-[α-L-Fuc(1→3)]-D-Glc*N*Ac and in the course of the work the isomer with the galactose unit α-linked was produced.[130] Wong and colleagues using chemo-enzymic methods and solid-phase technology have produced Sia Le^X *O*-bonded through threonine to an octapeptide, the product representing the mucin domain of a specific cell adhesion compound,[131] and also a product of bonding this carbohydrate antigen to ribonuclease B by a glycosylamine-based linkage.[132] Enzymic methods have also been used to make analogues of Sia Le^X having D-arabinose and L-galactose in place of the fucose moiety.[133] De-*N*-acetylated modifications of the tetrasaccharide have been obtained by chemical procedures and a di-deacyl derivative showed enhanced binding to E- and P- selectins.[134]

α-L-Col-(1→2)-β-D-Gal-(1→3)-[α-L-Col-(1→4)]-β-D-Glc*N*Ac (Col = 3,6-dideoxy-α-L-*xylo*-hexopyranose), which was required for studies of *Salmonella* lipopolysaccharides,[135] and β-D-Glc*N*HR-(1→4)-β-D-Glc*N*Ac-(1→4)-[2-O-Me-β-L-Fuc-(1→6)]-D-Glc*N*Ac (R = long alkenoyl chain), which is the nodulation factor Rf-III,[136] have been reported.

Chemical procedures were also used to obtain the blood group Sd^a antigen α-Neu*N*Ac-(2→3)-[β-D-Gal*N*Ac-(1→4)]-β-D-Gal-(1→4)-β-D-Glc*N*Ac and analogues with β-D-Gal and β-D-Glc*N*Ac replacing the β-D-Gal*N*Ac unit.[137]



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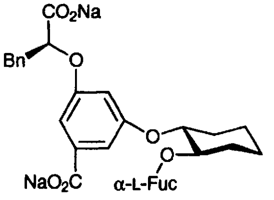


11

3.4 Analogues of Tetrasaccharides – An analogue (**10**) of acarbose which contains a carba-sugar is noted above (Ref. 115).

A plethora of Sia Le^X mimics have been described, such is the interest in their potential biological activity. These will be reported in rough order of their variation from Sia Le^X itself. A tetrasaccharide having the desialated Le^X trisaccharide glycosidically bonded to *O*-6 of D-Man and with a sulfate group at O-3 of the D-Gal moiety has been described,[138] as has an analogue of Sia Le^X having a 1,2,3,5-tetrahydroxy-5-(hydroxymethyl)cyclohexane in place of the terminal Glc*N*Ac group.[139]

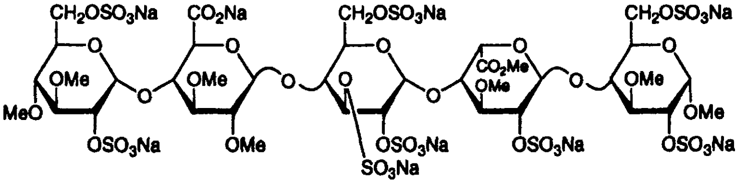
An analogue having α-L-Fuc and β-D-Gal appropriately linked to *trans*-cyclohexane-1,2-diol and with a cyclic non-carbohydrate substituent at O-3 of the D-Gal unit to mimic the Neu*N*Ac was made,[140] and the same laboratory made a derivative of this compound with the two sugars held rigid by a lactone bridge and found it to be recognized by E-selectin, but less well than is Sia Le^X.[141] A further mimic had the Fuc and Gal linked to *trans*-cyclohexane-1,2-diol, the latter sugar carrying a malonic acid group at the end of an ether tether bonded to O-2.[142] Other mimics have the Neu*N*Ac and Fuc units glycosidically linked together by way of alkyl or ether bridges or *via* *trans*-cyclohexane-1,2-diol,[143] and others have two sialic acid units bonded by way of alkyl spacer chains to catechol or cyclohexane 1,2-diol.[144]

A range of analogues have been reported which have only one sugar constituent of the Sia Le^X tetrasaccharide: α-L-Fucose *O*-bonded to D-Ser-L-Glu and L-Ser-D-Glu were potent blockers of E-selectin/Sia Le^X binding;[145] the same sugar glycosidically linked to one hydroxyl group of cyclohexane-1,2-diol also carrying a malonic acid tethered to the other hydroxyl group gave products which were equivalent to Sia Le^X in inhibiting selectin-mediated cell adhesion.[146] Compound **11** was made as a mimic with the aromatic spacer in place of the D-Gal moiety.[147]

4 Pentasaccharides

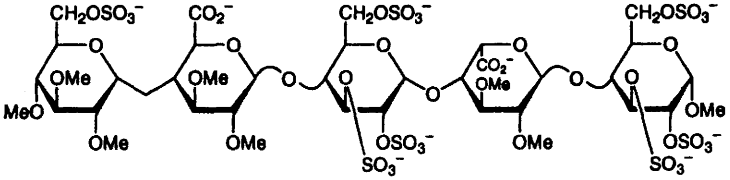
4.1 Linear Homopentasaccharides – The homologous series of α-(1→2)-linked glucoses up to the pentaose have been synthesized and bonded by way of a spacer group to human serum albumin to give neoglycoproteins with up to 28 oligosaccharides per albumin molecule.[148] *p*-Nitrophenyl α-D-maltopentaoside has been made by enzymic procedures.[149]

4.2 Linear Heteropentasaccharides – The structure of Acantha ganglioside has been shown to be β-D-Gal*f*-(1→3)-α-D-Gal*p*-(1→3)-α-Neu*N*Ac-(2→4)-β-D-Gal*p*-(1→4)-β-D-Glc-O-Cer rather than that proposed formerly which had both galactopyranosyl moieties (1→4)-linked.[150] The synthesis of ganglioside GT3, α-Neu-(2→8)-α-Neu-(2→8)-α-Neu-(2→3)-β-D-Gal-(1→4)-β-D-Glc-O-Cer, has been reported[116] and β-D-Gal-(1→4)-[α-D-Glc-(1→4)]$_3$-D-Glc has been made by enzymic methods.[149]



12

The synthetic partially sulfated pentamer **12**, which is an analogue of the antithrombin binding sequence of heparin with glucose units replacing glucosamine and the unsulfated hydroxyl groups methylated, has a better pharmacological profile than has the natural compound.[151] In the same research area the analogue **13**, with a methylene inter-sugar link, which was made by an intramolecular radical trapping process, has been shown to have similar biological activity to the corresponding *O*-linked compound.[152]



13

4.3 Branched Homopentasaccharides – In work focussing on novel protecting group srategies several D-mannose-based oligomers were made including α-D-Man-(1→6)-α-D-Man-(1→6)-[α-D-Man-(1→6)-α-D-Man-(1→2)]-D-Man.[153]

4.4 Branched Heteropentasaccharides – β-D-Gal*N*Ac-(1→3)-[β-D-(^{3}H)Glc*N*Ac-(1→6)]-α-D-Gal-(1→4)-β-D-Gal-(1→4)-Glc is a novel hybrid pentasaccharide of the lacto-globo type made by use of a transferase to introduce the labelled Glc*N*Ac moiety.[154] The pentamer α-Neu*N*Ac-(2→3)-β-D-Gal-(1→4)-[α-L-Fuc-(1→3)]-β-D-Glc*N*Ac-(1→6)-D-Man was made by chemical methods and is Sia Le^X-(1→6)-D-Man.[138]

Danishefsky's and Ogawa's groups have reported quite different syntheses of the high-mannose pentamer α-D-Man-(1→6)-[α-D-Man-(1→3)]-β-D-Man-(1→4)-β-D-Glc*N*Ac-(1→4)-D-Glc*N*Ac for incorporation by *N*-linking into glycopeptides.[155,156] A further Glc*N*Ac-terminating compound to have been made is β-D-Gal-(1→4)-β-D-Glc*N*Ac-(1→3)-[β-D-Glc*N*Ac-(1→6)]-β-D-Gal-(1→4)-D-Glc*N*Ac, the branching group having been introduced by enzymic means.[157]

Modelling studies using MM3(92) and CICADA protocols have been used in conformational analyses of α-L-Rha-(1→4)-α-D-GalA-(1→2)-[β-D-Gal-(1→4)]-α-L-Rha-(1→4)-D-GalA which is related to the plant rhamnogalacturonan I.[158]

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-Galp
4 D-Glc*p*NAc
5 D-Gal*p*NAc
6 Neu*p*NAc
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-glucopyranose)
13 L-*Glycero*-D-*manno*-heptose
14 L-Ara*f*
15 Kdn

5.1 Linear Hexasaccharides. – Amongst the products of enzymic hydrolysis of birch kraft pulp xylan the following were characterized:

4-*O*-Me-(β11) 1→4 (β4) 1→4 (β4) 1→4 (β4) 1→4 (β4) 1→4 (β4), the corresponding compound with a 4,5-double bond in the uronic acid moiety and the pentaose analogues having one fewer xylose unit.[159]

Treatment of the β-(1→3)-linked laminaribiosyl β-fluoride with a bacterial (1→3), (1→4)-glucan 4-hydrolase gave oligomeric products with alternate (1→3), (1→4)-linkages, the major product being the hexamer.[160]

A striking example of the application of synthetic methods to medical problems is the synthesis of hexamer **14** which, after coupling with a peptide, was used to raise anti-human cancer antibodies in mice.[161]

(α8) 1→2 (β3) 1→3 (β5) 1→3 (α3) 1→4 (β3) 1→4 (1)

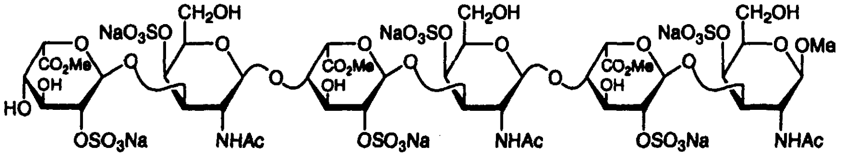
14

Boons's selective glycosylation methods have been used very impressively in the preparation of the hetero mannose-terminating compound **15**,[42] and the α-(1→4) linked D-mannohexaose having methyl groups at O-3 of all units except that at the non-reducing terminus, which is a fragment of a mycobacterial polysaccharide, has been synthesized.[162]

(α1) 1→6 (β3) 1→4 (β1) 1→6 (β3) 1→4 (β1) 1→6 (2)

15

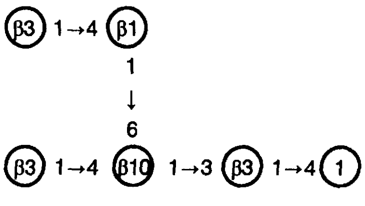
Hexasaccharides terminating in amino-sugars to have been prepared synthetically are **16**, which is representative of heparin cofactor II,[163] and oligomers up to the hexamer based on α-(1→2)-linked 4-acylamino-4,6-dideoxy-D-mannose (acyl = 2,4-dihydroxybutanoyl) which represent fragments of the O-antigen of *Vibria cholerae* have been described.[164]



16

5.2 Branched Hexasaccharides

5.2 Branched Hexasaccharides – Compounds of this set terminating in D-Glc are **17**[165] and **18**[166] which are, respectively, a component of group B type III streptococcus polysaccharide and a sulfated Sia Le^X-based compound which was made in attempts to find the structure of L-selectin.



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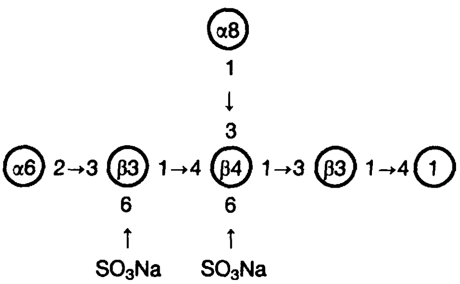
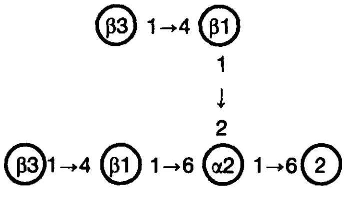


18

Synthesis of **19** was effected with 65% efficiency by lactosyl trichloroacetimidate coupling to O-2 of the branching mannosyl unit of the protected tetrasaccharide in the form of the α-methyl glycoside. Surprisingly, no hexamer was produced from the corresponding β-glycoside.[167]



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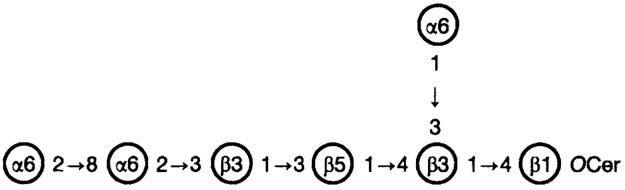
6 Heptasaccharides

6.1 Linear Heptasaccharides – By careful acid hydrolysis of peracetylated β-cyclodextrin maltoheptaose acetylated at all positions except O-1 and O-4 of the reducing and non-reducing terminal glucoses, respectively, has been produced,[168] and α-tocopheryl β-maltoheptaoside as well as the hexaoside, tetraoside and trioside have been prepared by chemical methods from the oligosaccharide peracetates.[169] In related work, a chitoheptaoside [a heptamer of β-(1→4)-linked Glc*N*Ac] with tetradecanoyl and tetradecyloxy at N-2 and O-1 of the reducing moiety was produced by successive additions of chitobiose units.[170]

6.2 Branched Heptasaccharides – Solid-phase methodology has been used to make the heptasaccharide phytoalexin elictor comprising the β-(1→6)-linked glucopentaose with β-(1→3)-branching glucose moieties on units 2 and 4.[171] An analogue was made of this compound with the (1→6)-glycosidic linkages replaced by amide bonds involving glycosylamino and uronic acid functions.[172] In the area of ganglioside chemistry Hasegawa and colleagues have reported the syntheses of the highly sialated GT1a (**20**)[173] and GT1aα (**21**).[174]



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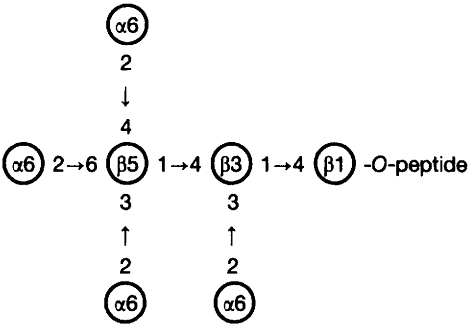

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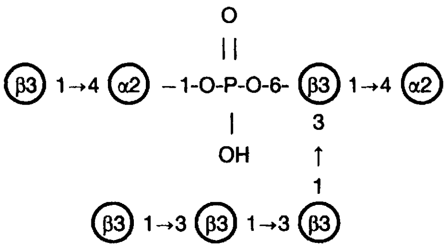
Mannose-containing heptamers to have been synthesized are the phosphoglycan portion **22** of a *Leishmania* lipophosphoglycan (trichloroacetimidate and *H*-phosphonate methodology),[175] and **23** which was made for the solid phase synthesis of glycopeptides.[176]



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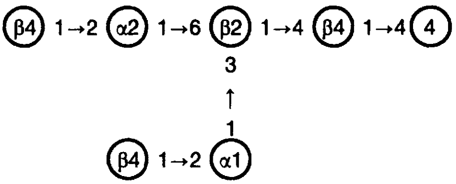

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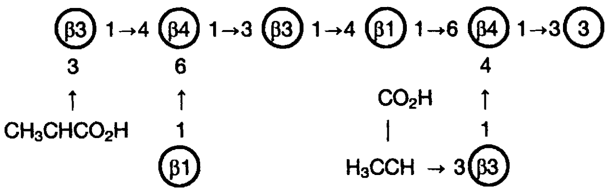
7 Octasaccharides

For studies associated with a mycobacterial 3-*O*-methyl-D-mannose-based polysaccharide an octamer of α-(1→4)-linked 2,6-di-*O*-benzyl-3-*O*-methyl-D-mannose was made by coupling of two tetramers.[177] Compound **24**, with the *S*-1-carboxyethyl group in place of sialic acid, has been made to mimic the repeating unit of type III, group B *Streptococcus* capsular polysaccharide.[178]



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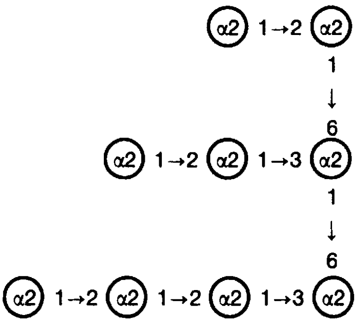
Dimers of the 'tetrasaccharide' of calicheamicin, which has four appreciably modified monosaccharides linked in very uncommon ways, have been made and studies of the DNA binding properties of oligomers of this type have been reviewed by Nicolaou and colleagues.[179]

8 Nonasaccharides

The synthesis of the highly branched mannose nonamer **25**, which is like portions of the high-mannose *N*-linked glycoproteins, was achieved in five steps by judicious tuning of the glycosyl donors used and employment of controlled selectivity in hydroxyl group protection, and represents the 'state of the art' in oligosaccharide work.[180]



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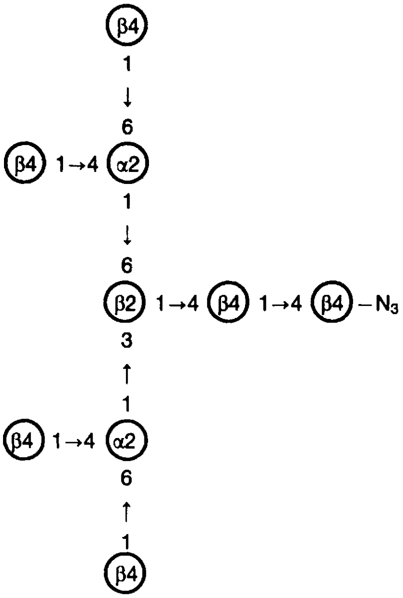
In related work which used a modular approach nonamer **26** was made as the glycosyl azide for incorporation into *N*-asparagine-linked glycoproteins.[181] Important work in the glycolipid area has yielded **27**, which is a sialated dimer of the Le^X antigen, and a closely related nonamer with α-(1→2)-linked fucose in place of the sialic acid, both compounds being tumour-associated antigens.[182] Two groups have synthesized the latter compound.[182,183]



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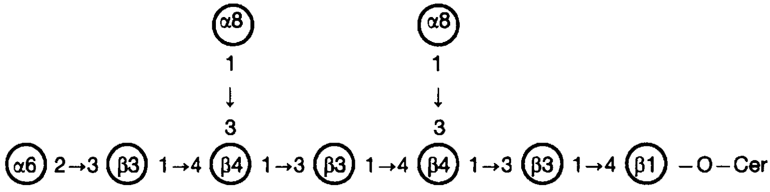

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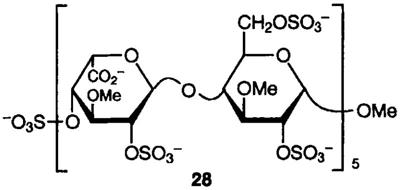
9 Higher Oligosaccharides

The decamer **28** has been prepared as a mimic of a similar decamer with glucosamine instead of the D-glucose unit, and shown to release lipase activity in rat tissue.[184] The decamer **29**, a biantennary *N*-glycan, has been made by enzymic galactosylation of an octamer,[185] and Unverzagt has also reported the undecamer analogue without the fucose unit, but carrying Neu*N*Ac-(2→6)-linked to both galactose units[186] and also the dodecamer with the fucose again present.[185] An isomer of the latter having the Neu*N*Ac-(1→3)-linked was also reported.[185] In this work the final steps were all enzymically controlled.



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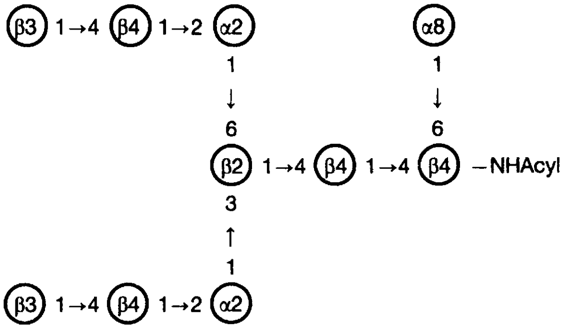

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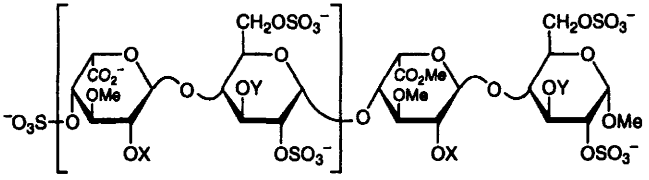
Solid-phase methods were used to make the set of oligomers **30** with $n = 2–5$ as heparan sulfate-like compounds,[187] and the dodecasaccharide **31**, a component of a *Vibrio cholerae* polysaccharide, was produced by use of trichloroacetimidate coupling.[188]

On a maltopentaose 'primer' bound to silica D-glucal additions occurred under the influence of glycogen phosphosylase to give a set of α-(1→4)-linked



30 X = Me, Y = SO_3^-
X = SO_3^-, Y = Me

2-deoxy-D-glucose oligomers bonded to maltotetraose.[189] Oligomers containing up to 20 β-(1→4) linked D-glucose units have been made by chemical methods starting from 3-*O*-benzyl-2,6-di-*O*-pivaloylglucose.[190]

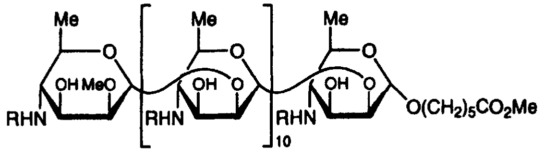
10 Cyclodextrins

Interest in these compounds continues to increase rapidly. As usual, this report concentrates almost exclusively on the chemistry of the cyclodextrins and their derivatives and disregards work related to their associating properties, the complexes they form and their effects as reaction catalysts.

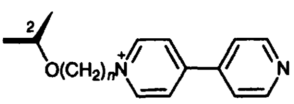
10.1 General Matters, and Synthesis of Cyclodextrins – A review has appeared on the production, characteristics and applications of the cyclodextrins,[191] another on their chemical modification,[192] and a third on the use of derivatives as artificial enzymes, in molecular recognition and in organic synthesis.[193]

A new type of cyclodextrin having alternating α-(1→4)-linked D- and L-rhamnose or D- and L-mannose and built from disaccharide repeating units has been made by $TrClO_4$-catalysed condensation. They have S_n-symmetry and are not optically active. Compounds containing 6, 8, 10, 12 and 14 sugar units were reported.[194,195]

Syntheses of the α-D-*altro*-analogues of α-, β- and γ-cyclodextrins were made by way of the corresponding *manno*-epoxides,[196] and the same workers have reported three regioisomeric β-cyclodextrins each containing two altrose units, these having been made by way of disulfonates and hence diepoxides.[197] Cyclic heptamers of α-L-rhamnose, and related compounds, have been made by acid-catalysed cycloglycosylation,[198] and cyclodextrins with 10, 11 and 13[199] and 14–17[200] glucose units have been isolated by chromatographic methods from commercial cyclodextrin powder made by the use of cyclodextrin glucanotransferase.



31 R = $\overset{O}{\overset{\|}{C}}-\overset{OH}{\overset{|}{C}}HCH_2CH_2OH$



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10.2 Branched Cyclodextrins – A symposium report on methods for making branched α-cyclodextrins has appeared. The enzymic attachment of maltose to the cyclic compound by use of pullulanase, and the subsequent cleavage of the intra-maltose bond with glucoamylase were particularly noted.[201] The same approach also gave rise to $6^A,6^N$-di-*O*-α-D-glucosylcyclodextrins.[202] Branched α-(1→6)-linked cycloisomaltooligosaccharides, having an α-glucosyl on an α-maltosyl unit bonded to O-4 of a glucose unit were also made by enzymic procedures,[203] and a different type of branched compound was made by condensing 6-monoamino-β-cyclodextrin with oligosaccharide aldonolactones.[204]

In the area of hetero-branched compounds one β-D-mannose unit has been linked enzymically to O-6 of α-, β- and γ-cyclodextrins,[205] and the six positional isomers of $6^A,2^N$-di-*O*-α-D-galactopyranosyl-α-cyclodextrin (N = A–F) were obtained by HPLC separtion of a mixture produced from the cyclodextrin treated with α-galactosidase in the presence of melibiose.[206]

10.3 Cyclodextrin Ethers – Several peralkylated (short chain alkyl groups) β-cyclodextrins have been made by a two-step procedure,[207] but the heptakis-2,6-di-*O*-methyl ether is the product of methylation in DMSO/NaOH.[208] Permethylation of mixed 6,6′-di-*O*-Tbdms derivatives of β-cyclodextrin allowed access to the $6^A,6^B$-, $6^A,6^C$- and $6^A,6^D$-dihydroxypermethyl ethers. Interestingly, the ditosylate derived from the A,B-diol has the aromatic ring of one of the ester groups within the molecule's cavity.[209]

2-*O*-Allyl-β-cyclodextrin, treated with $Hg(OAc)_2$/TFA and the product demercurated with $NaBH_4$, gave the $2^A,3^A$-*O*-(propane-1,2-diyl) product, and epoxidation of the same allyl compoound, followed by TFA treatment, led to the related 3-hydroxypropane-1,2-diyl derivative.[210] The hexakis- and heptakis-2,3-dimethyl ethers of α- and β-cyclodextrin were used as a source of the corresponding 6-carboxymethyl compounds.[211]

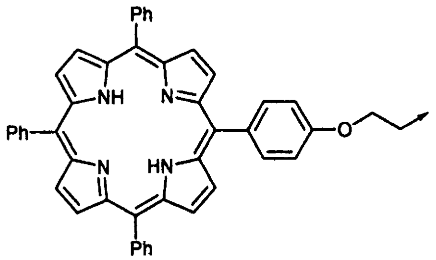
Mixtures of 4-sulfobutyl ethers of β-cyclodextrin were partially fractionated to give products for use as solubilizing and stabilizing compounds for drug delivery.[212] In the course of the work the 2-, 3- and 6-mono-substituted compounds were isolated and characterized.[213] Compounds with complex alkaryl ether substituents to have been reported are β-cyclodextrin having viologen (**32**)[214] and the porphyrin derivative (**33**)[215] linked as indicated to one of the O-2 positions of the dextrin.

In work aimed at making a photochemical microreactor, β-cyclodextrin carrying *n*-butyl groups at all O-2,3 positions and a naphthalenesulfonic acid ester linked at all O-6 positions, was made and studied.[216] *m*-Di(bromomethyl)benzene has been used to join two β-cyclodextrin molecules by way of an O-2,O-2′ diether linkage to give face-to-face dimeric products.[217]

10.4 Cyclodextrin Esters – The secondary ester groups of α-, β- and γ-cyclodextrin per-pivaloates are much more labile than the primary groups and can be removed selectively with hydrazine to give the per-6-pivaloates in high yield.[218] The anti-inflammatory (4-biphenyl)acetic acid has been ester-linked to

O-6 of α-, β- and γ-cyclodextrin and thus the latter was used to deliver the acid to the colon where the carbohydrate is metabolized microbiologically.[219] γ-Cyclodextrin has been reported with (*R*)-2-(1-naphthyl)propanoyl groups on sugars A and E,[220] and the product of coupling the cyanine dye **34** and β-cyclodextrin *via* O-6 is a photostable, fluorescent reagent.[221]

The 6^A6^B-, 6^A6^C-, 6^A6^D- and 6^A6^E-bis-(2-naphthylsulfoyl)-γ-cyclodextrins have been made as fluorescent sensors,[222] and β-cyclodextrin 6-diphenyl phosphate and monoethyl phosphate are enantioselective for amino acids.[223]



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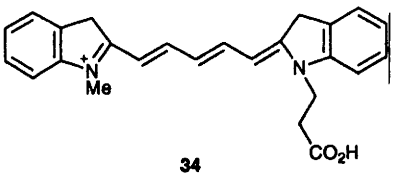

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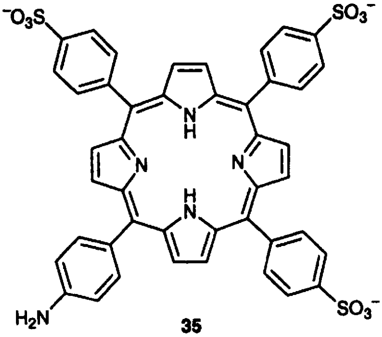
10.5 Amino Derivatives – Per-6-amino-6-deoxy-α-, β- and γ-cyclodextrins have been made from the corresponding bromo-derivatives *via* the azides, as well as the per-6-amino-6-deoxy-2,3-di-*O*-methyl- and per-*N*,*N*-(dimethylamino)ethylamino compounds. They were tested as peptidomimetics for the peptide binding site of antithrombin III.[224] Mono-2-amino-2-deoxy-β-cyclodextrin was made from the perbenzoylated derivative by selective debenzoylation at O-2 of one of the units, oxidation to the ketone and oxime formation. This amine and the 6-amino-isomer were then polysulfated.[225] 6-Amino compounds having additional amino groups at other centres have been produced by displacement of the leaving group of 6-*O*-tosyl-β-cyclodextrin with diamines such as 1,2-diaminoethane.[226] A related report described similar compounds derived from the 6-bromo-6-deoxy-derivatives of α-, β- and γ-cyclodextrin.[227]

Several derivatives having complex amino-substituents have been reported. Chemical coupling of mono-6-amino-6-deoxy-β-cyclodextrin with a suitably protected and activated Glc*N*Ac-asparagine derivative led to a starting material for specific enzymic glycosylation of the Glc*N*Ac moiety. Subsequent glycosylations led to several oligosaccharides bound to the dextrin, the most complex being the branched high-mannose *N*-linked nonasaccharide of glycoproteins.[228] Compounds having acyclic, variable length tethers to dansyl groups [*N*-(5-diethylaminonaphthalenesulfonamido)] have been made for study of the inclusion of the chromophore into the cavity.[229] Coupling of bis-[2-aminoethylamino]-bis-2-deoxy-β-cyclodextrin with *N*-2-(carboxyethyl)-thymine gave a product with two thymine-containing 6-substituents. Under light these thymine rings underwent 2+2 revisible dimerization.[230]

Attachment of the phenyl porphyrin sulfonate **35** by reductive amination to 6-monoformyl β-cyclodextrin gave a water-soluble product which, by NMR



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evidence, exists in solution as a dimer with a phenylsulfonate group of one molecule bound within the cavity of another.[231] A further communication has appeared (see Vol. 30, p. 82) on the product of reaction of 6^A6^C-(or 6^A6^D-) di-*O*-tosyl-β-cyclodextrin with *o*-phenylenediamine and the condensation of the diaryl product with *p*-cresol-2,6-dialdehyde which gave a bonded symmetrical bis-benzimidazolylphenyl system having the aromatic methyl group within the cavity.[232] The following *N*-substituted derivatives have also been described: β-cyclodextrin with a 6-deoxy-6-*N*-triazole dicarboxylic acid[233] or 6-deoxy-6-*N*-(2-methylamino) pyridinium group[234], and β-cyclodextrin having *N*-imidazole groups *N*-bonded at two or three C-3 positions, these compounds having been made from the di- or tri-2,3-anhydro-D-*allo*-derivatives.[235]

Several 6-mono-acylamino-6-monodeoxy derivatives of β-cyclodextrin have been reported: the (4-biphenyl)acetyl, 2-hydroxy-5-nitrobenzoyl and 2-(2′-hydroxy-4′-nitrophenyl)benzoyl,[236] and compounds having the following complex *N*-acyl substituents on N-6: β-D-Gal*N*HCO$(CH_2)_n$CO,[237] (n = 1–4, 7), peptide-CO$(CH_2)_2$CO[238] and *N*-dansyl-D and L-leucyl.[239] Sulfonamide derivatives, made with the *N*-dansyl group (5-dimethylaminonaphthalene-1-sulfonyl), and related compounds with ether spacer groups between the dextrin and the amino function have been made.[240]

10.6 Thio- and Halogeno-Derivatives – 6-Deoxy-6-iodo-β-cyclodextrin coupled with a cobalt porphyrin cobalamin disulfide gave a 6-thio-linked artificial enzyme which discriminates substrates and mimics mutase activity using coenzyme B-12.[241] Heptakis-6-thio-β-cyclodextrin has yielded a peptide-linked derivative made in studies of enzyme inhibition.[238]

The previously known per-6-chloro-6-deoxy-α-, β- and γ-cyclodextrins and the previously unknown bromo-analogues have been made in high yields by Vilsmeyer-Haack-like halogenations (using halomethylenemorpholium halides).[242]

10.7 Other Features of Cyclodextrins – Although the characteristics of cyclodextrins as complexing agents are not dealt with in this Report, other features of interest were noted as follows: vibrational Raman optical activity (ROA) studies of cylodextrins allowed the measurement of conformational flexibility as a function of methylation, solvent interaction and complex formation.[243] Cyclo-α-D-rhamno-(1 → 4)-decaose forms nanotubes in the crystalline form.[244]

Hexakis-(2,3-di-*O*-benzoyl)-and-(2,3,6-tri-*O*-benzoyl)-α-cyclodextrins are enantiomerically selective for chiral amines, aminoalcohols, carboxylic acids and amino-acids bearing a 3,5-dinitrophenyl group.[245] Laser flash photolysis of α-, β- and γ-cyclodextrins as complexes with ketones gives cyclodextrin free radicals.[246]

Both the hydrolysis and cyclizing formation of cyclodextrins have been subjected to thermodynamic examination. Equilibrium constants for the closure of long linear maltodextrins to give cyclodextrins and shortened linear compounds were determined.[247] α-Cyclodextrin together with trehalose, treated with cyclomaltodextrin glucanotransferase then β-amylase, gave α-D-maltotriosyl α-D-maltotrioside and four similar shorter-chain non-reducing oligosaccharides.[248]

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5

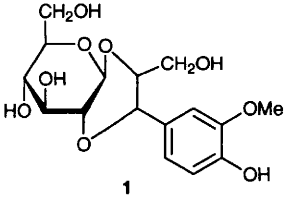
Ethers and Anhydro-Sugars

1 Ethers

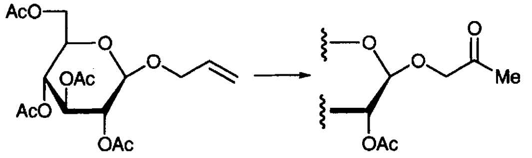
1.1 Methyl Ethers. – 6-Deoxy-2-*O*-methyl-β-D-glucopyranosyl residues have been identified in toxicariosides B and C isolated from the latex of *Antiaris toxicaria*[1] while toxicarioside A contains a 2-*O*-methyl-β-D-fucopyranoside residue.[2] Pentacyclic triterpenoid glycosyl esters isolated from aerial parts of *Rubus pileatus* contain esterified 6-*O*-methyl- and 3-*O*-methyl-β-D-glucopyranosyl moieties.[3] A hydroxyquinoline *O*-glycoside of 2,4-di-*O*-methyl-β-D-xylopyranose has been isolated from the marine cyanobacterium *Lyngbya majuscla*[4] and malyngamide J, isolated from the same cyanobacterium, also has a 2,4-di-*O*-methyl-xylopyranosyl residue.[5]

Partial methylation and then acylation has afforded all the positional isomers of *O*-methylated and benzoylated (or acetylated) 1,5-anhydro-D-xylitol[6] and the corresponding eight positional isomers of 1,5-anhydro-L-rhamnitol.[7]

1.2 Other Alkyl and Aryl Ethers – Junipetridoside A **1**, isolated from *Juniperus phoenica* leaves, has an unusual phenylglycolyl substituent as both a glycoside and *O*-2 ether.[8] A review on the protection of hydroxy groups as allyl ethers has included numerous carbohydrate examples.[9] The use of $PdCl_2$ under Wacker reaction conditions to effect de-*O*-allylation of a variety of sugar allyl glycosides and allyl ethers has been examined. Mixtures of the desired products and 'Wacker ketones' (such as **3** from **2**) were formed in unpredictable ratios.[10]



1

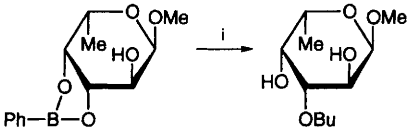


2 **3**

The use of phenylboronate ester derivatives with the boron complexed with a nitrogen base to selectively activate hydroxy groups in a manner analogous to organotin activation has been described. Thus the phenylboronate **4** was

Carbohydrate Chemistry, Volume 31

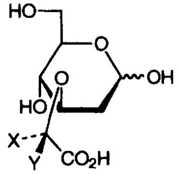
converted into the 3-butyl ether **5** in 80% yield (Scheme 1), whereas in the absence of Et_3N alkylation occurs, as expected, at the free OH group.[11]



4 **5**

Reagent: i, Bu^{n}I, Ag_2O, Et_3N, benzene

Scheme 1



6 X = H, Y = Me

7 X = Me, Y = H

O-Benzylations under acidic conditions using benzyl trichloroacetimidate can be performed with dioxane as solvent and perbenzylated aldonolactones were prepared in this way.[12] Freshly fused $ZnCl_2$ with Ac_2O/HOAc has been used to selectively debenzylate some hexopyranose glycosides at O-6. The 6-*O*-acetates were the products formed.[13]

Convenient syntheses of 2,3,4,6-tetra-*O*-allylated and benzylated D-glucopyranose and -D-galactopyranose have been developed by hydrolysis of per-*O*-alkylated sucrose and oxidative cleavage of ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-D-galactopyranoside with *N*-bromosuccinimide in the presence of water, respectively.[14]

The use of *O*-*p*-chlorobenzyl ethers as protecting groups on the three hydroxyls of a fucopyranoside moiety has been reported to stabilize the glycosidic bond to acid hydrolysis relative to the parent *O*-benzyl-protected glycoside.[15]

The Hanessian reagents (NBS, $CaCO_3$, CCl_4) applied to benzylidene acetals have been investigated in the presence of substituted benzyl ethers. Electron withdrawing substituents on the aromatic rings of the benzyl groups improved the selectivity of the acetal reactions by reducing the competing radical reactions of the benzyl ether groups.[16]

Quantitative detritylation of carbohydrate trityl ethers has been achieved by use of $FeCl_3.6H_2O$ in CH_2Cl_2.[17]

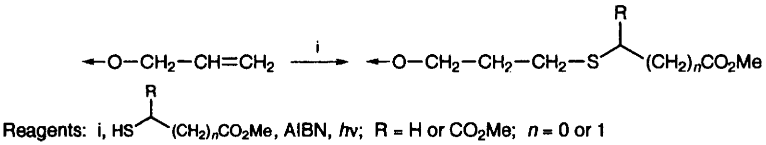
Improved conditions for separation of the *R*,*S* diastereomers of muramic acid **6** and isomuramic acid **7** has allowed a more convenient procedure for their synthesis.[18]

Some *O*-cyanomethyl ether derivatives of *N*-acetyllactosamine have been prepared and the nitrile groups were converted into carboxylic acid, amide, amidine and amino groups.[19]

2-Hydroxypropyl ethers of methyl α-D-glucopyranoside have been synthesized as standards for analysis of modified starch.[20]

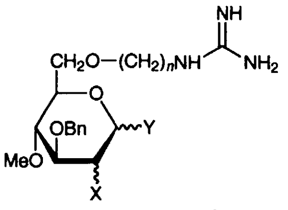
A number of carbohydrate per-allyl ethers have been functionalized into micelle-like anti-HIV polyanionic compounds by radical thiol addition to the olefin moieties (Scheme 2).[21]

The guanidine-functionalized carbohydrate ethers **8** and **9** have been synthesized as potential anti-angiogenesis agents.[22]

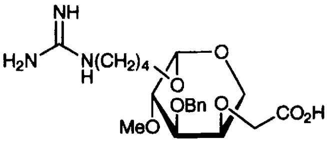


Reagents: i, HS(CHR)(CH$_2$)$_n$CO$_2$Me, AIBN, $h\nu$; R = H or CO$_2$Me; n = 0 or 1

Scheme 2

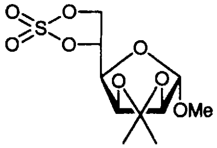


8 X = α-OMe, β-OCH$_2$CO$_2$H or H
Y = α or β-OCH$_2$CO$_2$H, OMe
n = 2 or 3

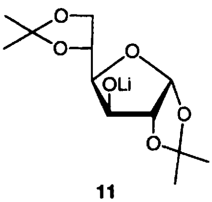


9

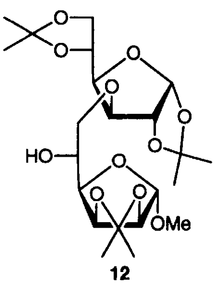
Carbohydrate alkoxides have been used to open 5,6-cyclic sulfate derivatives of protected manno- and gluco-furanoses. For example, treatment of cyclic sulfate **10** with alkoxide **11** afforded **12**, and the alkoxide of **12** was further treated with **10** to give **13**.[23]



10



11



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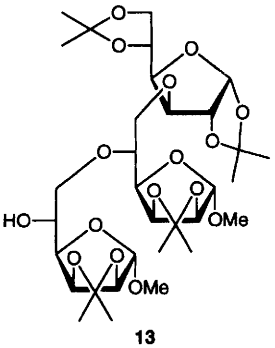
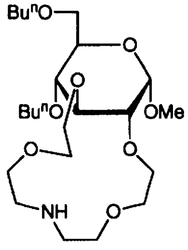


13

Chiral aza-crown ethers such as **14**, derived from D-glucose, have been prepared as catalysts for enantioselective Michael additions.[24]

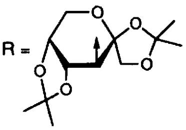
1.3 Silyl Ethers – Tri- and tetra-alkoxysilanes have been prepared with different alkoxy substituents by condensing MeSiCl$_3$ or SiCl$_4$ in pyridine with alcohols. Examples include **15–17**.[25]

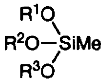


14

$(RO)_3SiMe$

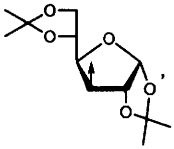
15

R =


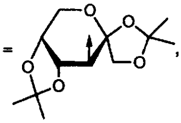


$(R^1O)(R^2O)(R^3O)SiMe$

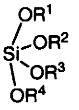
16

R^1,R^2 =


, R^3 = All

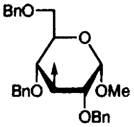
R^1 =


, R^2 = menthyl, $R^3 = PhCH_2CH_2$



$Si(OR^1)(OR^2)(OR^3)(OR^4)$

17

$R^1 = R^2 =$


$R^3 = R^4 =$ Bn

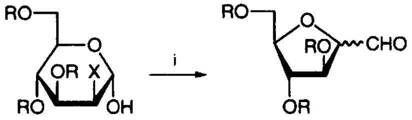
2 Intramolecular Ethers (Anhydro-Sugars)

2.1 Oxiranes. – The synthesis of 1,2-anhydro-gluco-pyranose and -furanose benzyl ethers has been reviewed. They were prepared by an intramolecular S_N2 reaction of *C*-2 alkoxides with *C*-1 chlorides, or *C*-1 alkoxides with *C*-2 tosylates.[26] 1,2-Anhydro-3,5-di-*O*-benzyl-α-D-and-L-ribofuranose have been prepared separately by the same procedure and opening of the anhydro-sugars by alcohols and *O*-silylated uracil has been investigated.[27,28] The glycosidation of phenols with 1,2-anhydro-3,4,6-tri-*O*-methyl-α-D-glucopyranose is mentioned in Chapter 3.

2.2 Other Anhydrides. – The synthesis of 1,3-anhydro-glucopyranose benzyl ethers has been reviewed,[26] and the preparation of 1,3-anhydro-2,6-dideoxy-4-*O*-methyl-α-D-glucopyranose as a thromboxane A_2 model has been described.[29]

The formation of 3,6-anhydro-D-glucofuranosides by acid catalysed alcoholysis of 6-*O*-tosyl glucose derivatives has been reported.[30]

The halohydrins **18** (X = Br, I) derived from the corresponding glycal undergo ring contraction to give the 2,5-anhydro aldose **19** (Scheme 3). When R = Me or Bn the same conditions afford predominantly methyl β-glucopyranosides *via* a 1,2-epoxide.[31]



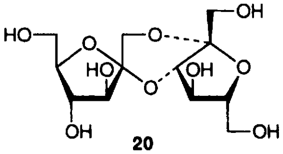
18 R = Tbdms **19** R = Tbdms

Reagent: i, Cs_2CO_3, MeOH

Scheme 3

The syntheses of 2,5-anhydro-L-mannitol derivatives with a nucleoside base attached at the 4- or 6- position as well as 3,5-anhydro-nucleosides are covered in Chapter 20.

The low calorie sweetner di-D-fructofuranose 1,2′:2,3′-dianhydride **20** has been isolated from the supercritical CO_2 extracts of *Lycoris radiata*. This is the first time it has been isolated from natural sources.[32]



20

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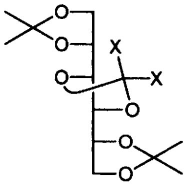
6

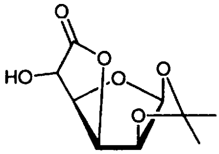
Acetals

1 Methylidene, Isopropylidene and Benzylidene Acetals

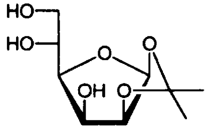
A new, high-yielding method for the synthesis of methylidene acetals from sugar diols employs DMSO as the source of methylene and $POCl_3$ or $SOCl_2$ as catalyst.[1] Preparation of a methylidene acetal by reduction of a thionocarbonate with Ph_3SnH/AIBN ($\mathbf{1} \rightarrow \mathbf{2}$) changed a base-sensitive protecting group to an acid-sensitive one.[2]



1 X,X = =S
2 X = H

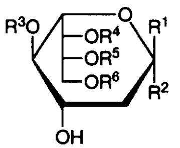


3

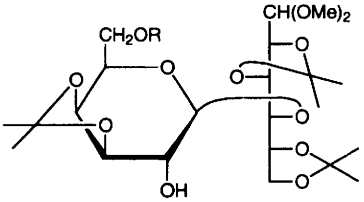


4

Acetonation of D-mannurono-6,3-lactone, the main product in the acid hydrolysis of alginic acid from kelp, gave the all-*cis*-furanoid derivative **3**, which on reduction with $LiBH_4$ furnished the new isopropylidene acetal **4** of α-D-mannofuranose.[3] Treatment of the methyl pyranoside of α-D-KDN methyl ester with excess of 2,2-dimethoxypropene in the presence of an acid catalyst gave the 5,7:8,9-di-*O*-acetal **5**, accompanied by smaller quantities of the 8,9-mono-acetal,[4] whereas the β-anomer afforded the 5,8:7.9-di-*O*-isopropylidene derivative **6** under the same conditions.[5]



5 R^1 = CO_2Me, R^2 = OMe, R^3, R^4 = R^5, R^6 = ${}^{Me}_{Me}$
6 R^1 = OMe, R^2 = CO_2Me, R^3, R^5 = R^4, R^6 = ${}^{Me}_{Me}$



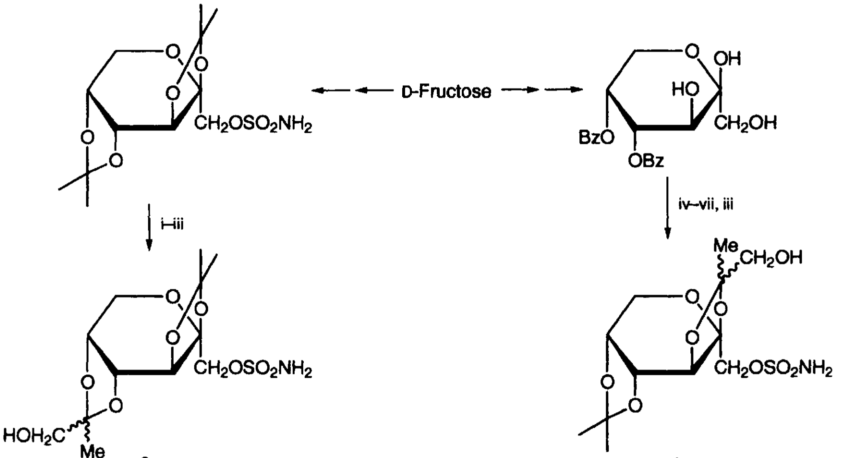
7 R = H
8 R = $C(Me)_2OMe$

Carbohydrate Chemistry, Volume 31

Improved procedures for the preparation of 2,3:5,6:3′,4′-tri- *O*-isopropylidenelactose dimethylacetal derivatives **7** and **8** have been reported.[6]

2 Other Acetals

Tantalum pentachloride absorbed on silica gel has been used as acid catalyst for the 3-*O*-tetrahydropyranylation of diacetoneglucose.[7]



9 **10**

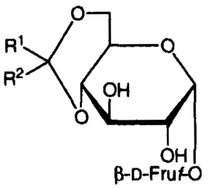
Reagents: i, H^+; ii, $BnOCH_2C(O)Me$, $(MeO)_3CH$, H^+; iii, H_2, Pd/C; iv, $BnOCH_2C(O)Me$, H_2SO_4, EtOAc; v, KOH, EtOH; vi, $Me_2C(OMe)_2$, H^+; vii, H_2NSO_2Cl, Et_3N

Scheme 1

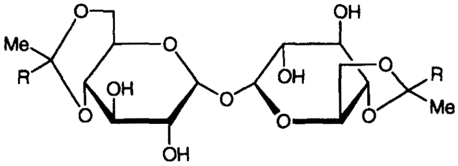
The mono- and di-(hydroxymethyl)ethylidene acetal derivatives **9** and **10**, respectively, of D-fructopyranose 1-sulfamate have been synthesized, as shown in Scheme 1. When making the latter compound it was necessary to introduce the sulfamate group as the last step, since no 2,3-*O*-acetalation took place when O-1 was substituted.[8] Long-chain acetals **11** and **12** of sucrose have been prepared as new surfactants. Compounds **11** were obtained by treatment of sucrose 1′,2,3,3′,4′,6′-hexaacetate with the appropriate aldehyde in pyridine in the presence of TsOH, followed by deacetylation, whereas compounds **12** were available from the free sugar by classical transacetalation with 2,2-dimethoxyalkanes.[9] Classical transacetalation has also been employed in the synthesis of 4,6:4′,6′-di-*O*-acetals **13** of α,α-trehalose.[10]

The syntheses of two iodinated acetals of D-glucose, compounds **14** and **15**, are outlined in Scheme 2.[11] Ethyl orthoacetate was used as promoter in the acid-catalysed condensation of the anticancer agent podophyllotoxin glucoside with the appropriate aldehydes to furnish the spin-labelled 4,6-acetal derivatives **16**.[12]

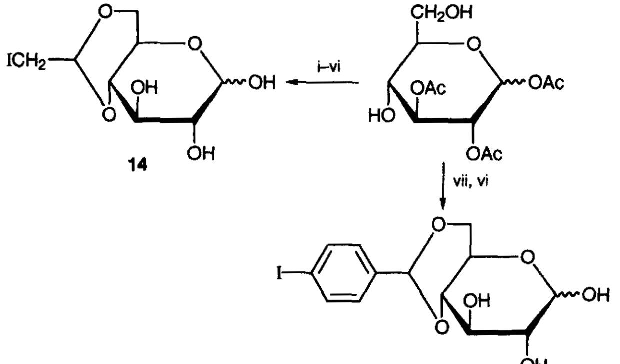
Full details on the preparation (by use of 1,1,2,2-tetramethoxycyclohexane in the presence of an acid catalyst), structure, derivatization and NMR analysis



11 $R^1 = H$, $R^2 = (CH_2)_nMe$
$n = 5, 8, 10, 12, 14, 16$
12 $R^1 = Me$, $R^2 = (CH_2)_nMe$
$n = 4, 7, 10, 12$

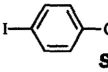


13 $R = (CH_2)_nMe$
$n = 3$ or 10

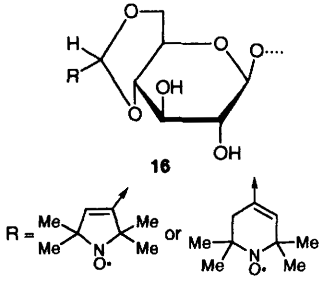


14

15

Reagents: i, CHO, $PhSO_3H$, $(PhO)_3P$; ii, O_2; iii, $NaBH_4$; iv, Tf_2O, Py; v, NaI, acetone; vi, MeO^-, MeOH; vii, $CHBr_2$, Py

Scheme 2



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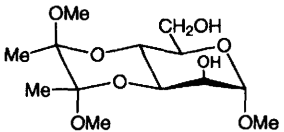
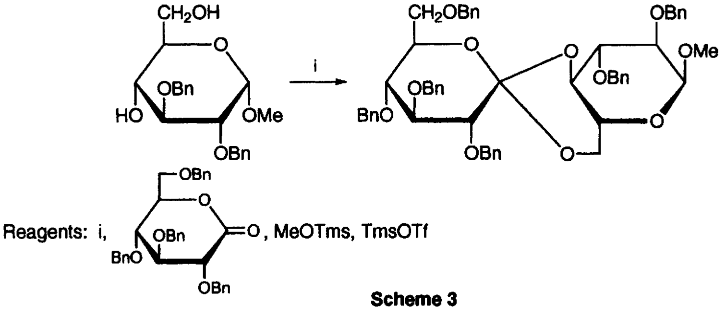


17

of cyclohexane-1,2-diacetal-protected sugars have been published (see Vol. 28, Chapter 6, refs. 22, 23).[13] Diacetal **17** has been obtained by direct reaction of methyl α-D-mannopyranoside with buta-2,3-dione in the presence of methyl orthoformate and camphorsulfonic acid in methanol, *i.e.*, there was no need to first convert the diketone to its tetramethoxydiacetal.[14] The use of butane-2,3-diacetal-protected intermediates in the synthesis of rare natural deoxysugars is covered in Chapter 12.

Glycosylidene acetals of sugars have been made, as exemplified in Scheme

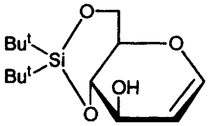
3.[15] The 4,6-OH groups of D-glucal have been efficiently protected by treatment with di-*tert*-butylsilyl ditriflate in DMF to give the 4,6-di-*O*-(*tert*-butyl)silanediyl derivative **18**.[16]



Scheme 3

3 Reactions of Acetals

Selective hydrolysis of isopropylidene acetals has been achieved by use of ozone in aqueous MeOH. As usual, acetals involving primary positions were hydrolysed selectively (*e.g.*, **19**→**20**, 80%).[17] One-pot oxidation of dioxolane acetals with $FeCl_3/NaIO_4$ in aqueous THF proceeded selectively to give aldehydes in high yield (*e.g.*, **19**→**21**, 72%).[18]



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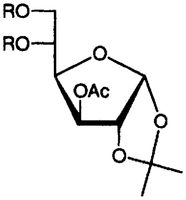
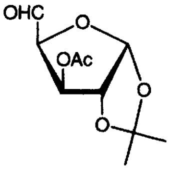


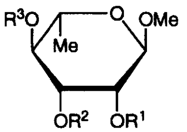
19 R,R = $>C<^{Me}_{Me}$
20 R = H



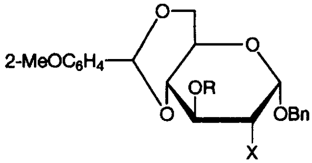
21

The reductive cleavage of dioxolane-type diphenylmethylene and fluorylidene acetals with $LAH/AlCl_3$ (see Vol. 27, Chapter 6, Ref. 17 and Vol. 25, Chapter 5, ref. 2, respectively) has been studied in some detail; fully protected methyl α-L-rhamnosides **22** furnished, as expected, mixtures of hydroxyethers **23** and **24**, with predominance of the equatorial 3-ethers **24**; when 4-OH was unprotected, however, the axial 2-ether **25** was formed exclusively, which is thought to be due to complexation of the free 4-hydroxyl group with aluminium.[19] Application of the same reagents to 2-methoxybenzylidene derivatives **26** with unprotected 3-OH gave the expected mixture of hydroxyethers; when 3-OH was protected as the methyl, benzyl, or allyl ether; however, little or no acetal cleavage was observed, and reaction took place at the amido group instead, affording products **28**–**30**, arising from a postulated isocyanate intermediate **27**.[20] Oxidative opening of benzylidene acetals with 2,2-bispyridinium chlorochromate/MCPBA is referred to in Chapter 7.

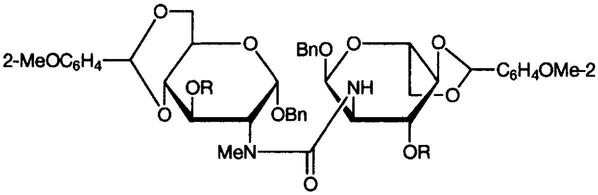
Cyclohexane diacetal protection has been used for tuning the reactivity in glycosylations. In glycosyl donor **31**, for example, 2-OH is deactivated by the *syn*-axial methoxyl group, thus avoiding homocoupling.[21]



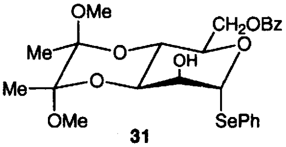
22 $R^1,R^2 =$ Ph Ph, R^3 = Me, Et, Bu, Bn, All *etc.*.
23 $R^1 = CHPh_2$, R^2 = H, R^3 = Me, Et, Bu, Bn, All *etc.*.
24 R^1 = H, $R^2 = CHPh_2$, R^3 = Me, Et, Bu, Bn, All *etc.*.
25 $R^1 = CHPh_2$, $R^2 = R^3$ = H



26 X = NHCbz, R = H
27 X = N=C=O, R = Me, All, Bn
28 X = NHMe, R = Me, All, Bn
29 X = NHCHO, R = Me, All, Bn



30 R = Me, Au, Bn



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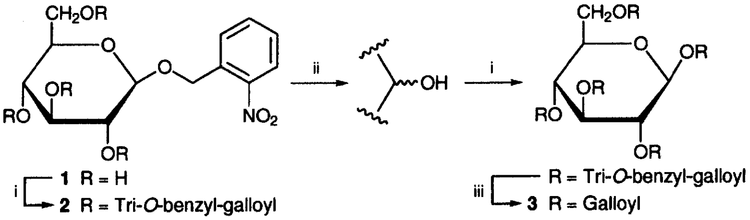
7

Esters

1 Carboxylic Esters

1.1 Synthesis – The relative reactivities of the carbohydrate hydroxyl groups have been reviewed with particular attention to the selective acylation of pentoses.[1] The high selectivity for D-ribose in the acylation of equimolar mixtures of all four D-aldopentoses under chemical or enzymic conditions is covered in Chapter 2.

1.1.1 Chemical Acylation and Deacylation – Highly efficient crotonoylation has been achieved with the acyl chloride in dichloromethane in the presence of 3Å molecular sieves instead of the traditional pyridine or triethylamine.[2] The efficiency of iodine as a Lewis acid to promote per-*O*-acylation, regioselective acylation and selective acetolysis of primary benzyl ether groups in carbohydrates has been explored.[3] All mono-, di-, and tri-pivaloates of methyl β-D-xylopyranoside have been obtained by use of varied amounts of pivaloyl chloride in pyridine.[4]



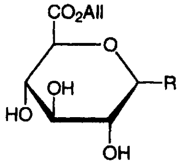
Reagents: i, Tri-*O*-benzylgallic acid, DCC, DMAP; ii, *hν*; iii, H_2, Pd/C

Scheme 1

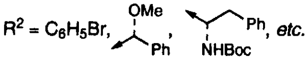
1,2-*cis*-Configured peracetylated hexopyranoses (*e.g.*, the β-peracetates of D-mannose, L-rhamnose, D-lyxose) have been prepared from unprotected sugars *via* 1,2-*cis*-stannylene acetals.[5] Anomerically pure 1,2,3,4,6-penta-*O*-galloyl-β-D-glucose **3** was synthesized by way of the tetraester **2**, using the photolabile 2-nitrobenzyl β-D-glucoside **1** as starting material (Scheme 1).[6] Various β-1-*O*-acyl derivatives of allyl glucuronate, such as compounds **5**, have been obtained in good yields from the free sugar, *e.g.* **4**, under Mitsunobu conditions.[7]

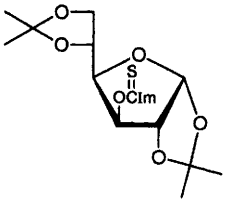
Carbohydrate Chemistry, Volume 31

The 3-*O*-(thiocarbonylimidazole) derivative **6** was prepared in 89% yield simply by grinding together diacetone glucose and thiocarbonyldiimidazole.[8] Benzyl L-rhamnopyranoside was selectively 3-*O*-acylated *via* tin-containing intermediates.[9] 3′-Aminoacylated 3′-deoxynucleosides are referred to in Chapter 20.



4 $R^1 = \alpha,\beta\text{-OH}$
5 $R^1 = \beta\text{-OCOR}^2$





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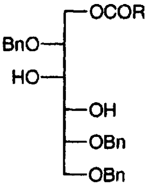
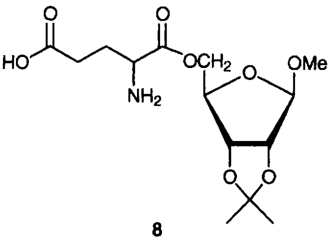


7 R = stearyl, palmityl *etc.*

DCC/DMAP-Promoted condensations were applied to the preparation of 1-*O*-fatty acid esters **7** of 2,5,6-tri-*O*-benzyl-D-mannitol[10] and glutamate **8** of methyl 2,3-*O*-isopropylidene-β-D-riboside.[11] Regioselective primary acylation with methyl orthoacetate and chlorides of rare earths on silica furnished primary esters of methyl pentofuranosides and methyl hexopyranosides selectively and in near 90% yields.[12]

Oxidative cleavage of benzylidene acetals with 2,2-dipyridinium chlorochromate/MCPBA gave mainly 4-hydroxy benzoates (*e.g.*, **9**→**10**, 70%).[13] Guanidine/guanidinium nitrate removed *O*-acetates without affecting other base-sensitive protecting groups such as, for example, the 2,2,2-trichloroethoxycarbonyl group in compound **11**.[14] Decarboxylation of the 6″-*O*-malonyl ester groups in isoflavone glucosides to give 6″-*O*-acetates occurred efficiently on heating in DMF at 60 °C, which may explain the increase in the latter components which occurs in soyabeans on toasting.[15]



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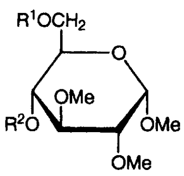
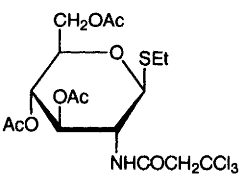


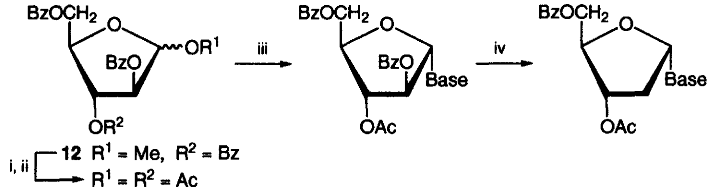
9 $R^1,R^2 = \text{CHPh}$
10 $R^1 = \text{Bz},\ R^2 = \text{H}$



11

A stereocontrolled synthesis of α-2′-deoxyribonucleosides, which is outlined in Scheme 2, involved selective hydrolysis of the 3-*O*-benzoate of arabinofuranose derivative **12** with hydrazine in pyridine, and then relied on the 2-*O*-

benzoate group acting as directing group before being removed by photo-induced electron transfer.[16] A further example of photosensitized selective deoxygenation of a secondary benzoate is given in Chapter 12.



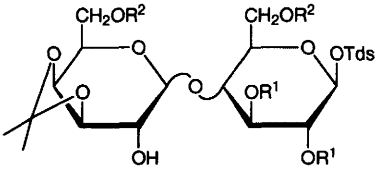
12 R^1 = Me, R^2 = Bz
R^1 = R^2 = Ac

Reagents: i, H_2NNH_2, Py; ii, Ac_2O, HOAc, H_2SO_4; iii, Vorbrüggen glycosylation; iv, 3,6-dimethyl-9-ethylcarbazole, $Mg(ClO_4)_2$, Pr^iOH, $h\nu$

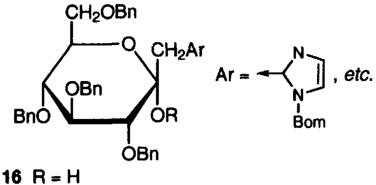
Scheme 2

In a study on the influence of the interaction between water and sucrose hydroxyl groups on the selectivity of esterification, sucrose was exposed to octanoyl chloride in aqueous base over a range of concentrations, which resulted in various degrees of substitution.[17] Sucrose 6-*O*-long-chain-fatty acid esters were obtained in yields of 50–70% *via* the 4,6-*O*-dibutylstannylene acetal, which was formed preferentially.[18] Benzoylation of lactose derivative **13** with benzoyl cyanide under a variety of conditions gave lactosides with 1, 2, or 3 free hydroxyl groups, *e.g.*, tetrabenzoate **14** and dibenzoate **15**.[19] Acetyl chloride in DMF in the presence of collidine at −70 °C caused selective acetylation of the primary hydroxyl groups of a tetrasaccharide.[20]

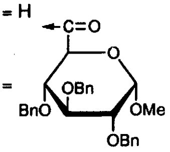
During the exploration of the reactivity of 1-deoxy-heteroaryl-substituted ketoses **16**, ester-linked disaccharide analogues **17** have been produced.[21] Diester-linked disaccharides, similar to that shown in Vol. 30, Chapter 7, structure 20, have been synthesized in the course of intramolecular glycosylation studies,[22,23] and as surfactants.[24] Positional isomers of glycolipid A-60 are referred to in Chapter 10.



Tds = thexyldimethylsilyl
13 R^1 = R^2 = H
14 R^1 = R^2 = Bz
15 R^1 = H, R^2 = Bz



16 R = H

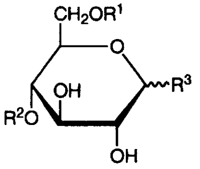


17 R =

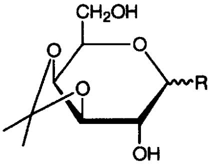
1.1.2 Enzymic Acylation and Deacylation – Reviews on ester synthesis by enzymic transesterification[25] and on the use of lipases in acylation/deacylation reactions of carbohydrates[26] have been published.

Mono-acrylates, -methacrylates and -crotonates were formed when sugars were exposed to activated esters of the respective carboxylic acids in the presence of an alkaline protease in anhydrous pyridine.[27] Various lipases have been tested for substrate-selectivity when added to a mixture of methyl α-D-galactopyranoside, β-D-glucopyranoside, β-D-mannopyranoside and octanoic acid in acetonitrile; the enzyme from *Pseudomonas cepacia* displayed high acylating specificity for the first-named sugar.[28]

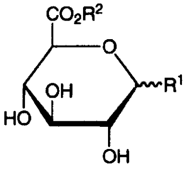
Methyl 6-*O*-tosyl-α-D-glucopyranoside (**18**) was acetylated at O-2 by *P. cepacia* lipase and vinyl acetate, whereas its β-anomer **19** reacted preferentially at O-3. The corresponding D-galactose and D-mannose derivatives behaved similarly.[29] Use of the same enzyme gave mixtures of the 2- and 3-*O*-acetates of phenyl 6-*O*-trityl-β-glucopyranoside (**20**), the ratio depending on the solvent,[30] but the 3-*O*-acetate was the sole product obtained from diol **21** with *P. fluorescens* lipase.[31]



18 R^1 = Ts, R^2 = H, R^3 = α-OMe
19 R^1 = Ts, R^2 = H, R^3 = β-OMe
20 R^1 = Tr, R^2 = H, R^3 = β-OPh
21 R^1,R^2 = >CHPh, R^3 = β-SEt



22 R = H, α-OMe, β-OMe, β-OBn, *etc.*

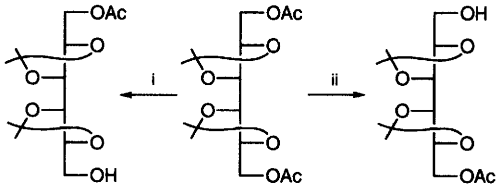


23 R^1 = α,β-OH, R^2 = $(CH_2)_4CO_2CH{=}CH_2$
24 R^1 = β-$O(CH_2)_7Me$, R^2 = CH(NHCbz)Ph

Good primary selectivity has been observed in the lipase-mediated acyl transfer from vinyl acetate to methyl 2,3-di-*O*-acetyl-D-glycopyranosides[32] and to 3,4-*O*-isopropylidene-D-galactose derivatives **22**.[33] Primary esters were also the main-products in the lipase-catalysed acylations of free sugars, especially D-glucose, with long-chain fatty acids in acetone or dioxane,[34] of D-glucono-1,5-lactone with fatty acid esters in *t*-butanol,[35] of alkyl glucosides with long-chain fatty acids at 75 °C/0.01 bar[36] or in microemulsions,[37] and of 1,2-*O*-isopropylidene-α-D-glucofuranose with fatty acid esters.[38] In the last three of these reports no added solvents were used.

The 6-vinyl adipate **23** was synthesized by exposure of D-glucose to divinyl adipate in the presence of an alkaline *Streptomyces* protease in DMF; this protease was chosen from 34 enzymes examined for their efficiency in the preparation of vinyl derivatives of sugar esters.[39,40] Use of cross-linked crystals of subtilisin, a versatile new catalyst with improved stability, gave the 6-(amino acid) ester **24** of octyl β-D-glucoside in 65% yield.[41]

The desymmetrization of D-galactitol has been achieved biocatalytically *via* its 1,6-di-*O*-acetyl-2,3:4,5-di-*O*-isopropylidene derivative **25**, as shown in Scheme 3.[42] Out of 28 enzymes tested, 9 displayed good activity and selectivity for deacetylation at O-2 of peracetylated derivatives of D-galacturonic acid in DMF.[43] Results obtained in a kinetic study on the pig liver esterase-catalysed hydrolysis of both anomers of methyl D-xyloside derivatives **26** have been

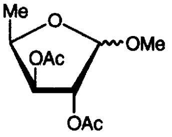


Reagents: i, *Pseudomonas fluorescens* lipase; ii, Lipase PS

Scheme 3

interpreted in terms of the active site model proposed by Jones (*J. Org. Chem.*, 1994, **59**, 2729).[44] Lipase-promoted acetylation/deacetylation reactions of conduritols are covered in Chapter 18.

Regioselective transesterifications between various disaccharides and an active ester of terephthalic acid have been undertaken, using Optimase M-440 in pyridine; in the case of sucrose, the 1′-mono- and 1′,6-di-terephthalate, **27** and **28**, respectively, were the main-products.[45] 6′-*O*-Monoesters of sucrose have been prepared *via* selectively acetal-protected intermediates (*e.g.*, **29**→**30**) by use of lipases in organic solvents or under solvent-free conditions.[46]



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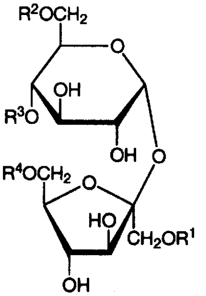


27 $R^1 = COC_6H_4CO_2CH_2CF_3$, $R^2 = R^3 = R^4 = H$

28 $R^1 = R^2 = COC_6H_4CO_2CH_2CF_3$, $R^3 = R^4 = H$

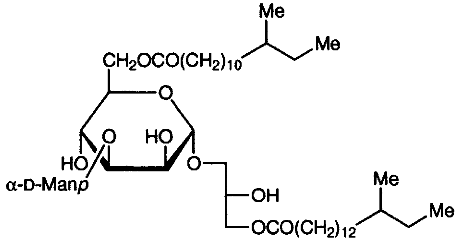
29 $R^1 = H$, $R^2,R^3 = {>}C{<}^{Me}_{Me}$, $R^4 = H$

30 $R^1 = H$, $R^2 = CO(CH_2)_nMe$, $R^3 = R^4 = H$
$n = 8, 10, 12, 14, 16$

1.2 Natural Products – The octanol-water partition coefficients of various hydrolysable gallotannins and ellagitannins have been determined; special attention was paid to the increased water solubility of tannins in hydrophobic association with the water-soluble, natural glycosides contained in crude medicinal herb extracts.[47]

The synthesis of 1,2,3,4,6-penta-*O*-galloyl-β-D-glucose is referred to in Section 1.1.1 above. The enantiomerically pure ellagitannins strictinin,[48] praecoxin B and pterocarinin C[49] have been synthesized by diastereoselective esterification of appropriately protected 2-nitrophenyl β-D-glucosides with racemic hexabenzyloxydiphenic acid as the key-step.

Carotenoid glucoside 6-*O*-mycolic acid esters were discovered for the first time in a red actinomycetes fungus.[50] The presence of 6-*O*-tigloyl-D-glucosyl moieties has been found responsible for the anti-sweet properties of certain oleanane-type triterpenoid glycosides (see Vol. 28, Chapter 4, ref. 51).[51]

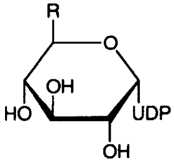


31

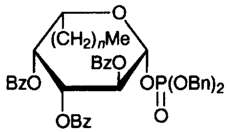
The resins of the Mexican plant *Ipomoea tricolor* are a complex mixture of glycolipids formed from tri- and tetra-saccharide cores and hydroxy-fatty acids; minor, dimeric constituents containing (11*S*)-hydroxyhexadecanoate moieties linking two tri-saccharide cores as well as two glycosyl residues within one trisaccharide unit have now been characterized.[52] Compound **31** and related esterified dimannosylglycerol derivatives have been found in *Arthrobacter atrocyaneus*.[53]

2 Phosphates and Related Esters

Uridine diphospho-α-D-*gluco*-dialdose **32** has been synthesized (see Chapter 13) to examine its intermediacy in the UDP-glucose dehydrogenase-promoted oxidation of UDP-glucose (**33**) to UDP-glucuronic acid (**34**).[54] The L-fucose 1-phosphate analogues **35** were intermediates in the synthesis of carbon-backbone-elongated GDP-L-fucose derivatives (see Chapter 2 for chain-elongation),[55] and 1-phosphate **36** was an intermediate in the synthesis of dTDP-6-deoxy-D-*ribo*-3-hexulose (see Chapter 15).[56] The glycogen phosphorylase-catalysed addition of inorganic phosphate to glucal with formation of 2-deoxy-α-D-*arabino*-hexopyranosyl phosphate is referred to in Chapter 12.



32 R = CHO
33 R = CH_2OH
34 R = CO_2H



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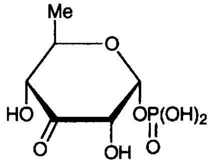
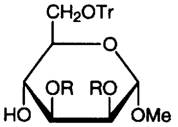
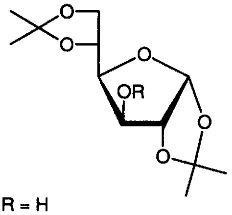


36

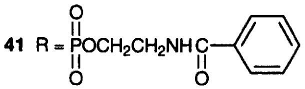
A new synthesis of D-galactopyranose-1,2,6-trisphosphate as an analogue of D-*myo*-inositol 1,4,5-trisphosphate has been reported.[57] The synthesis of further D-*myo*-inositol 1,4,5-trisphosphate analogues and of several D-*myo*-inositol pentakisphosphates are referred to in Chapter 18. The *O*-2-, *O*-3-, *O*-4-, *O*-6-and *O*-7-monophosphates of L-*glycero*-D-*manno*-heptose have been prepared from suitably protected precursors by standard methods (see Chapter 2 for a synthesis of L-*glycero*-D-*manno*-heptose).[58] The trisphosphinate **38**, obtained by phosphitylation of triol **37**, has been converted into tris(benzylpropanoyl)phosphonate **39** under Arbuzov conditions.[59]



37 R = H
38 R = $P(OBn)_2$
39 R = $\underset{\underset{O}{\|}}{P}(OBn)CH_2CH_2CO_2Bn$



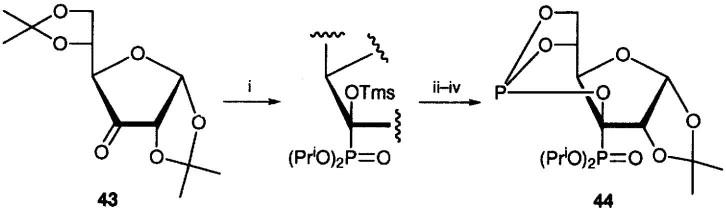
40 R = H



41 R = $\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{P}}OCH_2CH_2NH\underset{\underset{O}{\|}}{C}$

42 R = $\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{P}}OCH_2CH_2NH_2$

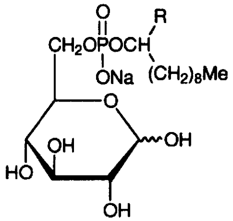
Ethanolamine phosphate moieties have been introduced by first preparing *N*-phenacetyl-protected intermediates by use of the phosphoramidite method, followed by cleavage of the protecting group with immobilized penicillin G acylase (*e.g.*, **40**→**41**→**42**).[60] Two further papers on the preparation and reactions of 6-deoxy-6-chloro-1,2-*O*-alkylidene-α-D-glucofuranose 3,5-cyclophosphorochloridate have appeared (see Vol. 30, Chapter 7, ref. 62),[61,62] and the synthesis of bicyclophosphito-phosphonates, such as **44**, from ketofuranose **43** has been described (Scheme 4).[63]



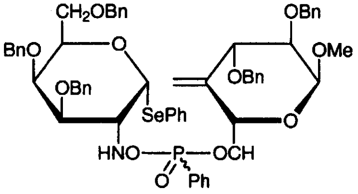
Reagents: i, $(Pr^iO)_2P(O)OTms$; ii, MeOH; iii, aq. HOAc; iv, $P(NEt_2)_3$

Scheme 4

Preparative primary phosphorylation with yeast hexokinase (EC 2.4.1.1) has been carried out on a wide range of furanose and pyranose derivatives; the enzyme was very tolerant of structural changes at C-2 and C-3, but less tolerant and intolerant, respectively of changes at C-1 and C-4.[64] D-Glucose 6-(sodium-secondary alkyl)phosphates **45** are a new family of amphiphilic tubule-forming anionic glycophospholipids.[65]



45 R = $(CH_2)_9Me$, $(CH_2)_2(CF_2)_7CF_3$, *etc.*



46

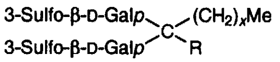
In a synthesis of *C*-disaccharides by radical coupling, the donor and acceptor were first connected through a phosphoramidite tether as, for example, in compound **46**.[66] Lactosyl phosphate- and thiophosphate-diesters of Ara-C and Ara-A have been prepared employing H-phosphonate and phosphoramidite methodology, respectively.[67] Novel phosphorylated galactolipids are mentioned in ref. 69 below.

Treatment of cyclodextrin with inorganic metaphosphate at pH 4 gave mixtures of 2-, 3-, and 6-monophosphates, which were separated by anion exchange chromatography.[68]

3 Sulfates and Related Esters

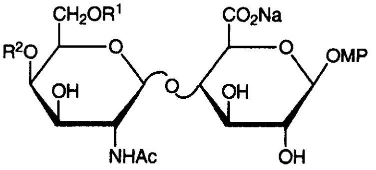
Novel sulfated galactolipids **47** have been prepared with introduction of the sulfate groups *via* stannylene-intermediates; the 3,4-bisphosphorylated analogues have also been made.[69] Synthetic approaches towards chondroitin sulfate oligomers have resulted in the systematic synthesis of sulfated disaccharides **48–50**.[70] During on-going efforts in the area of selectin ligands and blockers, a series of mono-and di-sulfated D-galactose derivatives, *e.g.*, sulfatide analogue **51**,[71] were prepared by conventional sulfation of protected precursors directly or *via* tin-intermediates.[71-75] Sulfate groups were similarly introduced at O-3 and/or O-6 of the D-galactosyl residues and of the adjacent D-glucosyl- or 2-acetamido-2-deoxy D-glucosyl residues, respectively, of 2-(tetradecyl)hexadecyl β-lactoside[73,74] and of sialyl Lewis X tri- and hexa-saccharide ceramides.[76-78] A trisaccharide glycoside sulfate, structurally related to these synthetic products, is the first sulfatide found in a starfish.[79]

The trifluoroethyl group has been used as a protecting group for sulfates that is stable under Zemplen conditions; conditions for its introduction and removal are indicated in Scheme 5.[80] The opening of carbohydrate cyclic sulfates by carbohydrate alkoxides is referred to in Chapter 3.

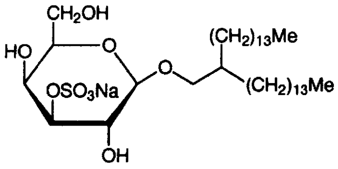


$$\begin{matrix}\text{3-Sulfo-}\beta\text{-D-Gal}p & & (CH_2)_xMe\\ & C & \\ \text{3-Sulfo-}\beta\text{-D-Gal}p & & R\end{matrix}$$

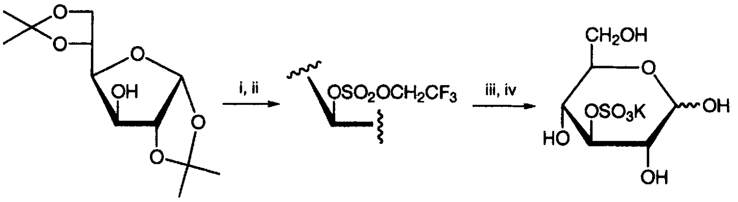
47 R = H or $(CH_2)_xMe$
x = 13 or 15



48 $R^1 = SO_3Na$, $R^2 = H$
49 $R^1 = H$, $R^2 = SO_3Na$
50 $R^1 = R^2 = SO_3Na$



51



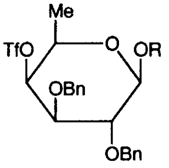
Reagents: i, SO_3, Py; ii, CF_3CHN_2; iii, TFA, EtOH; iv, Bu^{t}OK, Bu^{t}OH

Scheme 5

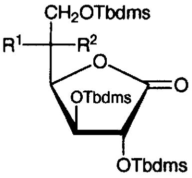
4 Sulfonate Esters

The mechanisms of the reactions undergone by certain triflates on treatment with *t*-BuOK (strong base) or pyridine (weak base) have been further elucidated by use of deuterated derivatives (see Vol. 30, Chapter 7, ref. 82).[81,82]

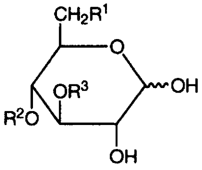
4-*O*-Triflated derivatives **52** of D-fucose have been synthesized from the corresponding 6-deoxy-D-glucose derivatives by conventional triflation following inversion at O-4 by oxidation/reduction.[83] Azide **56**, required for the preparation of-D-glucose- and D-galactose-related triazole derivatives (see Chapter 10), was obtained from D-glucuronolactone by double inversion *via* triflate **53**, trifluoroacetate **54**, and triflate **55**.[84] The monomesylates **57** and



52 R = Me, Bn, *etc.*



53 R^1 = TfO, R^2 = H
54 R^1 = H, R^2 = OC(O)CF_3
55 R^1 = H, R^2 = OTf
56 $R^1 = N_3$, R^2 = H



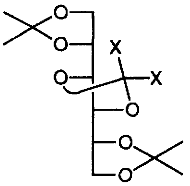
57 R^1 or R^2 or R^3 = Ms, others = H
58 R^2 or R^3 = H, others = Ms

dimesylates **58**, available by standard procedures, are hydrophilic analogues of the brain-tumour therapeutic 1,4-dimesyloxybutane.[85] The 6-*O*-dansyl derivative of 2-acetamido-2-deoxy-D-glucose has been prepared by conventional sulfonation for biological incorporation into chitin.[86]

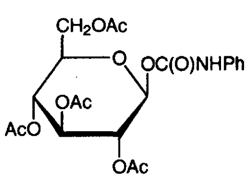
Removal of tosyl groups by sodium naphthalenide in THF is referred to in Chapter 20, and the preparation of sucrose analogues *via* the 2-*O*-triflate is covered in Chapter 3.

5 Other Esters

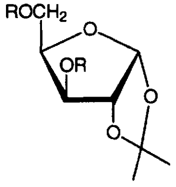
O-Benzyloxycarbonyl-protected derivatives of D-mannose (an alternative to benzyl ether protection) have been obtained in good yields by use of CbzCl and stochiometric quantities of DMAP.[87,88] Reduction of a thionocarbonate with Ph_3SnH/AIBN (**59**→**60**) changed a base-sensitive protecting group to an acid-sensitive one.[89] Glycosyl β-carbamates, such as **61**, formed on treatment of peracetylated free sugars with an aliphatic isocyanate in the presence of DABCO, are new glycosyl donors, as well as surfactants capable of solubilizing proteins.[90] Bis(carbamoyl ester) derivatives **63** of 1,2-*O*-isopropylidene-α-D-xylose and the thio-analogues **64** have been prepared as antifungals; the carbamoyl and thiocarbamoyl groups were introduced by reaction of **62** with either *N,N*-diethylcarbamoyl chloride or *N*-ethylisocyanate, or with the corresponding sulfur-containing reagents, respectively. The analogous dithiocarbamate derivatives are referred to in Chapter 11.[91] The per-(4-chloro- or -bromophenyl)carbamates of malto-penta-, -hexa- and -heptaose have been used as chiral recognizing HPLC stationary phases.[92]



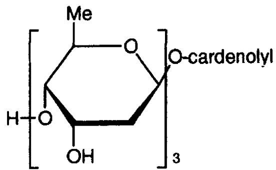
59 X,X = =S
60 X = H



61

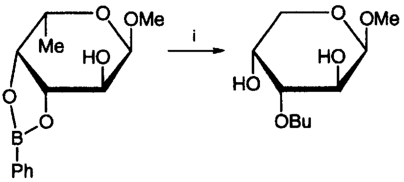


62 R = H
63 R = C(O)NXEt
64 R = C(S)NXEt
X = H or Et



65

The action of fuming HNO_3/Ac_2 on the 3‴,4‴-*O*-acetonide of the cardiac agent gitoxin (**65**) produced a mixture of mono-, di-, and tri-nitrate esters with nitrate groups in one or both of the internal 2,6-dideoxy-β-D-*ribo*-hexopyranosyl residues and/or in the aglycon.[93] Orthoesterification under kinetically controlled conditions [$CH_2=C(OMe)_2$/TsOH/DMF] gave the 4,6-derivative of sucrose and the 4′,6′-derivative of maltose; under similar conditions, α,α-trehalose formed the 4,6:4′,6′-di-orthoester in 47% yield (see Vol. 29, Chapter 7, refs. 94, 95).[94] An unusual side-reaction in the TmsOTf-promoted ortho-ester→glycoside rearrangement, which produced a disaccharide, has been reported.[95]



Reagent: i, Bu^{n}I, Ag$_2$O, Et$_3$N, benzene

Scheme 6

Cyclic sugar phenylboronates regioselectively activate hydroxyl groups, in parallel to stannylene acetals, provided the boron atom is *N*-coordinated. An example is given in Scheme 6. In the absence of triethylamine the unprotected hydroxyl group undergoes reaction.[96]

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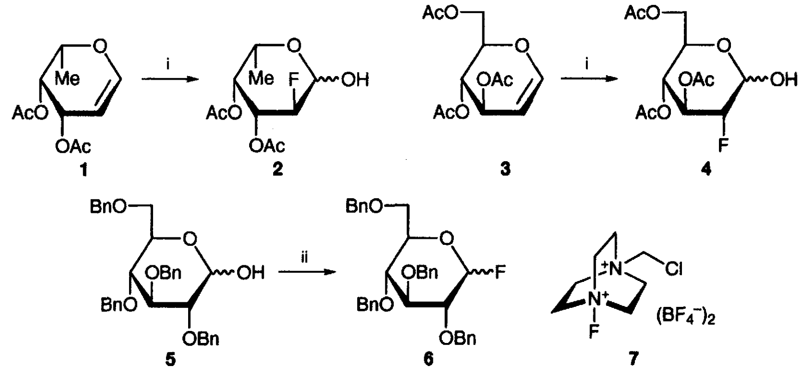
8

Halogeno-sugars

1 Fluoro-sugars

O-Acetylated glycosyl bromides when treated with trifluoromethylzinc bromide afforded the corresponding glycosyl fluorides and the same reagent with TiF_4 also converts anomerically unprotected derivatives to the glycosyl fluorides.[1] *O*-Acetylated or -benzylated glycals have been treated with an electrophilic fluorine source ('Selectfluor' **7**) in the presence of water to give 2-deoxy-2-fluoro-sugars. The fluorine was incorporated at C-2 from the opposite face of the ring to that of the C-3 substituent. Thus, for example, **1** gave **2** and **3** afforded **4**. Related conditions but with dimethyl sulfide replacing the water could be utilized to prepare the glycosyl fluoride **6** from **5** (Scheme 1).[2]



Reagents: i, **7**, DMF/H_2O; ii, **7**, Me_2S, DMF

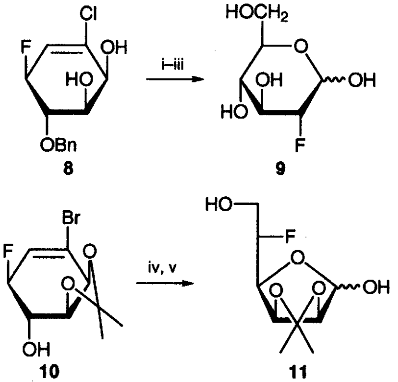
Scheme 1

2′-Deoxy-2′-fluorocellobiose has been prepared by standard methods as a mechanism-based inhibitor of 'retaining' glycosidases,[3] and homologous series of ampiphilic alkyl 2-deoxy-2-fluoro-1-thio-α-D-gluco- and -mannopyranosides have been made using standard methods.[4] 4-Deoxy-4-fluoro-D-arabinose has been synthesized starting from 2-deoxy-2-fluoro-D-glyceraldehyde, by way of a Wittig reaction and a Sharpless dihydroxylation.[5]

The fluorocyclitol derivatives **8** and **10**, obtained from halobenzene-derived microbial oxidation products, undergo oxidative cleavage by ozonolysis, the

Carbohydrate Chemistry, Volume 31

products being convertible to **9** and **11** respectively (Scheme 2).[6] Analogues of the terpenoid glycoside glycyrrhizin have been prepared which incorporated the 3′-, 4′-, 6′-, 3- and 4-monodeoxyfluoro derivatives of 2-*O*-β-D-glucopyranosyl-β-D-glucopyranoside as well as the 3- and 4-monodeoxyfluoro derivatives of 2-*O*-β-D-glucopyranuronosyl-β-D-glucopyranoside,[7] and a synthesis of methyl 3-deoxy-3-fluoro-β-D-allopyranoside has been described.[8]



Reagents: i, O_3, Me_2S; ii, $FeCl_3$, Ac_2O; iii, NaOMe; iv, O_3; v, $NaBH_4$

Scheme 2

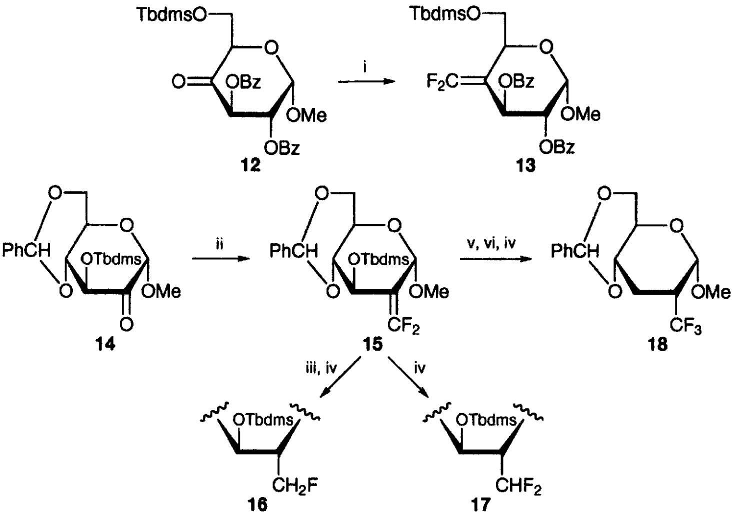
4-β-Glycosylation of a 6-deoxy-6-fluoroglucose derivative has given access to 6-deoxy-6-fluorocellobiose, whereas 6′-deoxy-6′-fluorocellobiose has been prepared from benzyl β-cellobioside.[9] Steroidal α-cellobiosides have been modified to the 6,6′-dideoxy-6,6′-difluoro analogues as potential cholesterol absorption inhibitors.[10]

The keto-sugar derivatives **12** and **14** have been converted into the difluoroalkenes **13** and **15** respectively (Scheme 3). Further processing of **15** gave rise to the mono-, di- or tri-fluoro compounds **16–18**.[11,12]

A Reformatsky reaction of ethyl bromodifluoracetate applied to 2,3-*O*-isopropylidene-L-glyceraldehyde, and further processing of the product followed by lactonization, has afforded the 2,2-difluorolactone **19** which was converted into some pyrimidine L-nucleosides.[13] Similarly, an aldol-like reaction of *tert*-butyl difluorothioacetate on 2,3-*O*-isopropylidene-D-glyceraldehyde has led, after further processing, to the 2,2-difluoro-D-lactone **20**.[14]

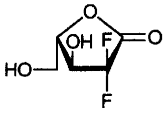
Full details have been published on the preparation of anomeric difluoromethylene phosphonates by phosphonyl radical addition to carbohydrate 1-difluoromethylene compounds (*cf.* Vol. 30, p. 119).[15] A synthesis has been reported of 6-deoxy-6,6-difluoro-α-D-glucopyranosyl fluoride as a potential inhibitor of sucrase phosphorylase.[16]

A synthesis of the enantiomerically pure 3-*C*-arylsulfonyl-4-fluoromethyl-5-phosphonate **21** from non-carbohydrate materials has been effected.[17] The syntheses of some 4′-*C*-fluoromethyl nucleosides as well as some 3′-deoxy-3′-difluoromethylene nucleosides are covered in Chapter 20.



Reagents: i, CF_2Br_2, $(Me_2N)_3P$; ii, CF_2Br_2, HMPT; iii, Red-Al; iv, H_2, Pd/C; v, Bu_4NF; vi, DAST

Scheme 3



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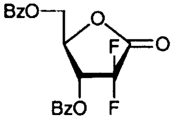

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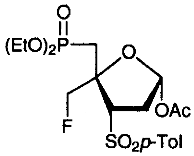


21

2 Chloro-, Bromo- and Iodo-sugars

A new mild procedure for the conversion of aldopyranose peracetates into acetylated glycopyranosyl halides uses BiX_3/TmsX in CH_2Cl_2 ($X = Cl$, Br or I).[18] A significant improvement has been claimed in the synthesis of the well known synthetic intermediate 2-deoxy-3,5-di-*O*-toluoyl-α-D-*erythro*-pentofuranosyl chloride.[19] Iodine bromide has been used to convert acetylated thioglycosides into the corresponding glycosyl bromides.[20]

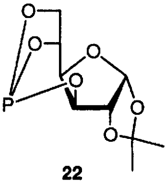
Treatment of aldopyranose peracetates with TmsI at low temperatures affords the β-glycosyl iodides which readily isomerize to the α-anomers when allowed to warm to RT. With a non-participating group at C-2 the glycosyl acetate is displaced with inversion at -100 °C, followed by equilibration to the α-iodide at higher temperatures.[21] 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl iodide prepared in this way has been treated with various nucleophiles (*e.g.* azide, carboxylate ions) to give predominantly β-products.[22] Another group has utilized an alternative synthesis of the unstable 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl iodide, and when treated with alcohols this β-iodide produced mainly α-glycosides.[23]

The influence of substituents at C-6 and C-4 on the stereoselectivity in the addition of PhSCl and PhSeCl to D-glucal derivatives has been investigated,[24] and the product ratios formed on addition of electrophilic halogen reagents (Br_2, NBS, ICl, Bu_4NBr_3, NBS-Et_3N.3HF) to tri-*O*-benzyl-D-glucal in aprotic and protic solvents have been determined by NMR spectroscopy.[25]

The synthesis and crystal structure of 6,6′-dichloro-6,6′-dideoxy-2,3,4,3′,4′-penta-*O*-benzylsucrose has been reported.[26]

The reaction of cyclic phosphite **22** with Cl_2 or *N*-chloroamines has given **23**.[27]

Treatment of carbohydrate epoxide derivatives with $Ti(OPr^i)_4/SmI_2$ has afforded the corresponding iodohydrins by *trans*-diaxial opening of the oxirane rings,[28] and reaction of epoxide **24** with LiBr, HOAc, NaOAc in CH_2Cl_2 has generated the expected bromohydrin **25** as the major product.[29] A study of the regioselectivity in the ring opening reactions of some aziridines with halide nucleophiles is mentioned in Chapter 9.



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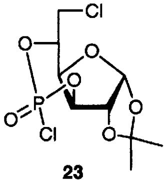

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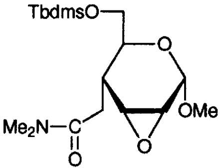

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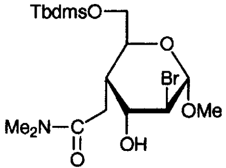

25

A synthesis of I-radiolabelled 4-deoxy-4-iodo-D-glucose from D-glucose has been reported.[30]

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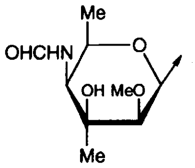
9

Amino-sugars

1 Natural Products

Acacic acid lactone 3-*O*-[2-acetamido-6-*O*-(α-L-arabinopyranosyl)-2-deoxy-β-D-glucopyranoside], a triterpenoid glycoside that is a rare example of a plant natural product containing an amino-sugar, has been isolated from *Acacia auriculiformis*.[1] The branched-chain amino sugars moieties **1** and **2** of undefined absolute stereochemistry are present in callipeltosides C, a 14-membered ring macrolide isolated from a *Callipelta* sp. marine sponge,[2] and nocardicyclins A and B, anthracycline antibiotics isolated from *Nocardia pseudobrasiliensis*, respectively.[3]



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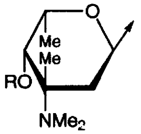


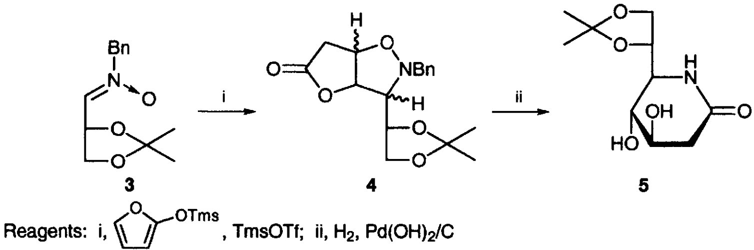
2 R = H or Ac

2 Syntheses

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

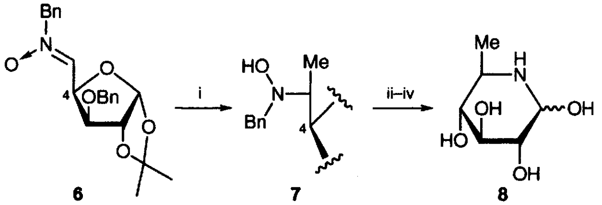
2.1 By Chain Extension – Dipolar cycloaddition of 2-trimethylsilyloxyfuran and the nitrone **3**, derived from D-glyceraldehyde, gave a mixture containing all four possible *cis*-fused isomers **4**, which could be separated and converted into the 5-amino-2,5-dideoxy-6,7-*O*-isopropylidene-D-*altro*-heptonolactam (**5**) and its D-*ido*-, D-*galacto*- and D-*gluco*-isomers (Scheme 1).[4] 6-Deoxynojirimycin (**8**), isolated as its bisulfite adduct, was prepared by a Lewis acid-catalysed addition of methyl Grignard reagent to the nitrone **6**, which led to a separable 7:1 mixture of D-*gluco*-**7** and its L-*ido*-isomer (Scheme 2). Addition of methyl Grignard reagent to the C-3 epimer of **6** was also investigated.[5]

Carbohydrate Chemistry, Volume 31



Reagents: i, OTms, TmsOTf; ii, H_2, $Pd(OH)_2/C$

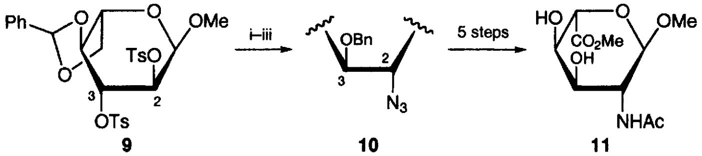
Scheme 1



Reagents: i,MeMgCl, TfOTms; ii, Zn/Cu, HOAc, H_2O; iii, HCO_2NH_4, Pd/C; iv, H_3O^+

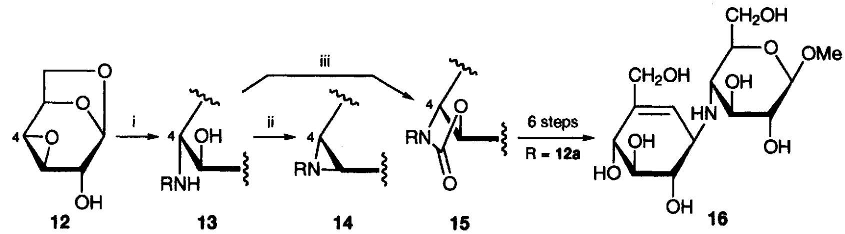
Scheme 2

2.2 By Epoxide Ring Opening – The 2-amino-2-deoxy-L-altruronic acid derivative **11** was synthesized from the ditosylate **9** by way of a L-*allo*-2,3-epoxide which was ring opened with azide ion to give **10**. This was followed by oxidation at C-6 using the TEMPO method (Scheme 3). This sugar acid and 2,4-diamino-2,4,6-trideoxy-D-galactose (the synthesis of which is covered in Section 4) are the constituent sugar residues of the O-specific lipopolysaccharide of the bacterium *Shigella sonnei.*[6] In studies directed towards the synthesis of a stereo-isomer of acarbose as a potential β-glucosidase inhibitor, reaction of the 1,6:3,4-dianhydride **12** with cyclohexylamine or the amino-cyclitol derivative from which the substituent **12a** is derived gave the 4-amino-sugar derivatives **13**, which could be converted into aziridine or cyclic carbamate derivatives, **14** and **15**, respectively, and thence into the methyl β-glycoside **16** (Scheme 4).[7,8] Synthesis of the C-6 branched-chain aminoheptose derivative **17**, by way of a reaction of a spiro-epoxide with azide, is covered in detail in Chapter 14.[9]

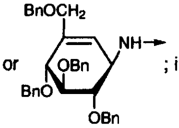


Reagents: i, NaOMe; ii, NaN_3, NH_4Cl; iii, BnBr, NaH

Scheme 3



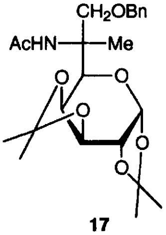
Reagents: i, RNH_2 where R = cyclohexyl or



12a

; ii, Im_2CO; iii, EtOCOCl or $COCl_2$

Scheme 4



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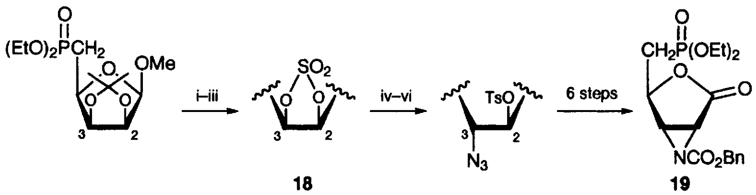
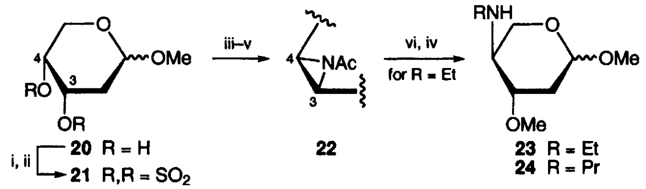
2.3 By Nucleophilic Displacement – Full details (*cf.* Vol. 29, p. 111, ref. 15) have been published of the synthesis of an L-daunosamine derivative and its 6-hydroxy-analogue from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, starting with sulfonate displacement by azide with inversion at C-3.[10] The 2,3-aziridino-D-lyxonolactone 5-phosphonate **19** has been synthesized by reaction of the D-ribfuranoside 2,3-cyclic sulfate **18** with azide with inversion at C-3 (Scheme 5).[11] Its D-*lyxo*-isomer was obtained in the same way starting from D-ribose.[12] Thiols opened aziridine **19** nucleophilically at C-2, while alcohols gave 2-amino-2-deoxy-D-ribonolactone 5-phosphonates following participation by the phosphonate in ring opening at C-3. The amino-sugar components of the E-ring of calicheamicin $\delta_1{}^1$ and esperamycin A_1 have been synthesized as the methyl α- or β-glycosides **23** and **24** from 2-deoxy-D-*erythro*-pentofuranosides **20**, the key step being the opening of the 3,4-cyclic sulfate **21** at both C-3 and C-4 with azide to give a mixture of azido-sulfates which are converted into



Reagents: i, I_2, MeOH; ii, $SOCl_2$, Et_3N; iii, $RuCl_3$, $NaIO_4$; iv, NaN_3; v, H_3O^+; vi, TsCl, py

Scheme 5

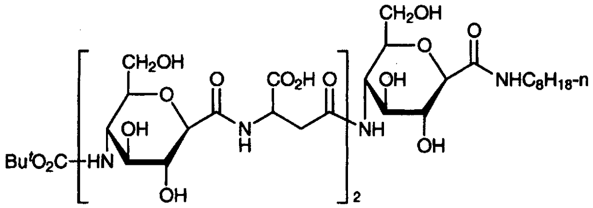
the single aziridine **22** on reaction with lithium aluminium hydride (Scheme 6).[13]



Reagents: i, $SOCl_2$, Et_3N; ii, $NaIO_4$, $RuCl_3$; iii, LiN_3; iv, $LiAlH_4$; v, K_2CO_3, Ac_2O; vi, MeOH, H^+

Scheme 6

Solution phase methods were used to prepare hybrid structures such as **25** incorporating alternating amino acid (D- or L-) and sugar moieties, with the key building block being **26**, which was available from a known galactose derivative by azide displacement of a 4-triflate group with inversion. Some showed anti-cancer activity.[14] Methyl 4-acetamido-4-deoxy-2,3,6-tri-*O*-methyl-α-D-galacto- and gluco-pyranoside (as well as the corresponding 4-*O*-acetyl derivatives) were prepared for studies on the impact of substituents on the rate of acetolysis at the glycosidic centre. The amino-functions were again introduced by sulfonate displacements reactions with azide.[15] Attempted displacement of secondary triflates with amines, as an alternative approach to the compounds exemplified in Scheme 4 above, led to low or no yield of the desired products, elimination being the main competing pathway. Surprisingly,



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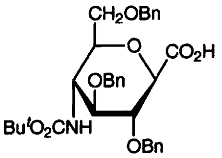

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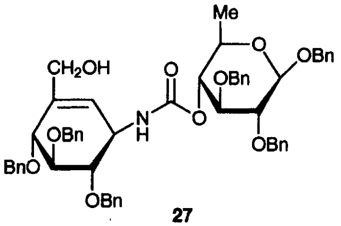

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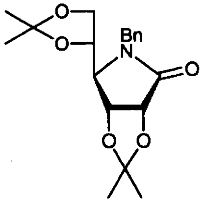

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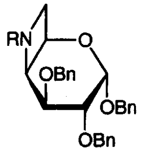
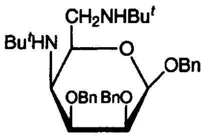


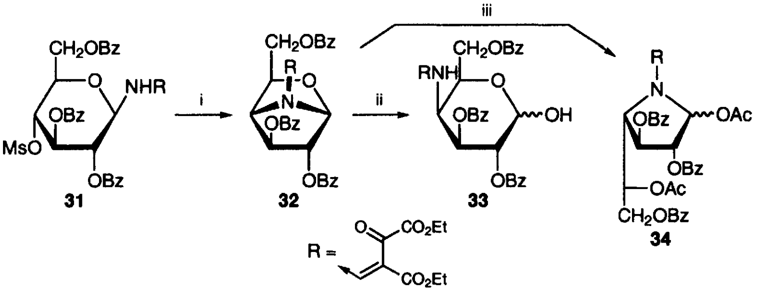
29 R = Me, Bn, Bu^t



30

when potassium carbonate was introduced into the reaction mixture, carbamates such as **27** were obtained in addition to the elimination products.[16]

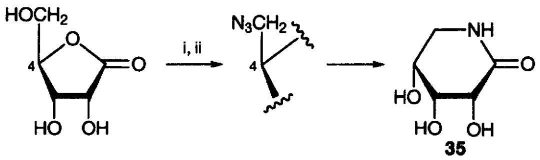
Intramolecular sulfonate displacement reactions were utilized for the preparation of a variety of lactams such as the D-*allo*-derivative **28** from an *N*-benzyl-D-gulonamide 4-mesylate derivative, the products being converted to lactim ethers and amidine analogues.[17] 4,6-Fused azetidines such as **29** were the major products on reaction of the corresponding D-glucopyranoside 4,6-ditosylate with primary amines in ethanol at 120 °C, whereas the 4,6-diamino-4,6-dideoxy-D-taloside **30** was obtained on reaction of the corresponding D-mannopyranoside 4,6-ditosylate with *tert*-butylamine.[18] The 1,4-epimino-derivative **32**, obtained from the β-D-glucosylamine 4-mesylate **31**, was converted either into the 4-amino-4-deoxy-D-galactopyranose derivative **33** on hydrolysis, or the five-membered ring derivative **34** on acetolysis (Scheme 7). In the same way, a D-xylosylamine 4-mesylate gave an 4-amino-4-deoxy-L-arabinose derivatives.[19]



Reagents: i, NaOMe, HMPT; ii, CF_3CO_2H, H_2O; iii, Ac_2O, TmsOTf

Scheme 7

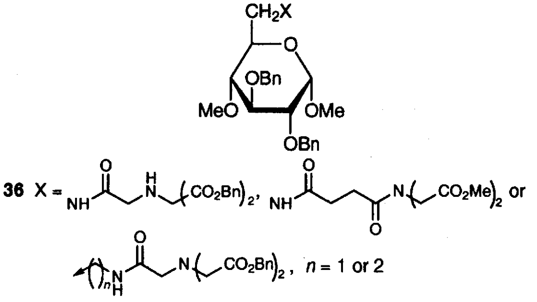
5-Amino-5-deoxy-D-ribo-, -arabino- and -xylonolactams were synthesized from unprotected D-pentonolactones in three steps and high yield as shown for the synthesis of D-*ribo*-isomer **35** (Scheme 8).[20] Methyl 6-amino-2,3-di-*O*-benzyl-6-deoxy-α-D-gluco- and galacto-pyranosides (and the *N*-benzyl derivative of the former) were made through ring opening reactions of the corresponding 4,6-cyclic sulfates with azide or benzylamine as analogues of the amino-alcohol components of neomycin B. Their ability to bind to RNA was studied by NMR methods with phosphodiester and nucleoside base compounds as models.[21] Various sugar-amino acid conjugates **36** were prepared by reaction of the corresponding 6-chloride or 6-tosylate with azide, succinimide

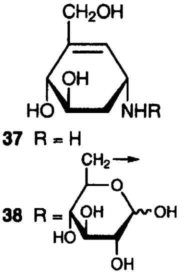


Reagents: i, $SOBr_2$, DMF; ii, LiN_3, DMF; iii, H_2, Pd/C

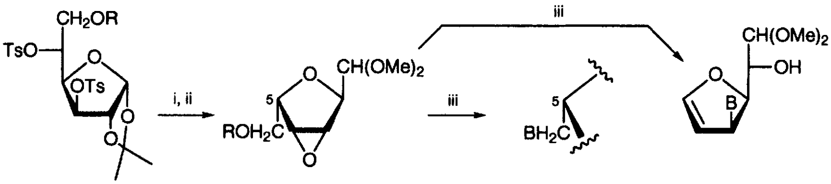
Scheme 8

or cyanide ions before further elaboration; several were then deprotected.[22] The modest α-glucosidase inhibitor **37** (see Chapter 18) was *N*-alkylated with a 2-azidoethyl α-D-glucopyranoside 6-triflate derivative to give, after deprotection, the 2-deoxy-isomaltose analogue **38** of acarbose, but it was not an α-glucosidase inhibitor.[23]





The 2,5:3,4-dianhydro-talitol 6-tosylate **40** (R = Ts), prepared from the tritosylate **39** (R = Ts), reacted preferentially at C-6 with uracil and thymidine to give **41**, but underwent elimination/rearrangement to **42** on reaction with adenine (Scheme 9). The epoxide ring of **40** (R = Bz) could be opened at C-4 to give 2,5-anhydro-4-deoxy-4-(nucleobase)-L-mannitols.[24]



39 R = Ts or Bz **40** R = Ts or Bz **41** B = uracil, thymine **42** B = adenine

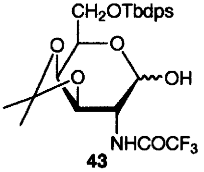
Reagents: i, HCl, MeOH; ii, K_2CO_3, MeOH; iii, BH, K_2CO_3, 18-crown-6

Scheme 9

2.4 By Amadori Reaction – 4,6-*O*-Benzylidene-1-deoxy-1-(2-hydroxyethylamino)-D-fructose was synthesized by reaction of 4,6-*O*-benzylidene-D-glucose with ethanolamine to form a β-glucopyranosylamine which underwent Amadori rearrangement in the presence of oxalic acid. It was converted into 4,6-unprotected *O*-methyloxime and chromogenic hydrazone derivatives as standards in GLC and HPLC analyses. 1-Deoxy-1-(2-hydroxyethylamino)-D-fructose could then be detected in a solution of glucose and a phosphatidylethanolamine kept at physiological pH and temperature for 4 weeks, after phospholipase D treatment and derivatization.[25]

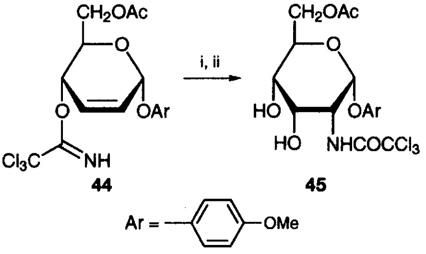
2.5 From Azido-sugars – Amphiphilic derivatives such as 6-deoxy-6-(*n*-octanoylamino)-D-glucose and its methyl α-glycoside have been prepared by Staudinger reaction (Ph_3P, *n*-$C_7H_{15}COCl$) of the corresponding 6-azido-sugar peracetates, followed by deacetylation.[26] A new method of converting azides to tert-butoxycarbonyl-protected amines, applied to 6-azido-6-deoxy-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose, involved reaction with Et_3SiH over $Pd(OH)_2/C$ in the presence of $(Bu^tO_2C)_2O$.[27] The synthesis of a 1,7-diamino-1,2,6,7-tetradeoxy-2,6-iminoheptitol from a 6-azido-glucoside is covered in Chapter 18.

2.6 From Unsaturated Sugars – A new direct, stereoselective route to 2-trifluoroacetamido-sugars by addition to pyranoid or furanoid glycals involves reaction with the complex nitrido [*N*,*N*′-(1,1,2,2-tetramethyl)ethylenebis(salicylideneaminato)]manganese(V) and trifluoroacetic anhydride, followed by silica gel. It was applied to a wide range of ether and acetal protected glycals. The substituents at C-2 of the main products were *trans* to those at C-3; thus the galactosamine derivative **43** was obtained in a 15:1 mixture with its C-2 epimer.[28] Azido-selenation of a glycal features in the synthesis of C-linked amino-sugars (detailed in Chapter 3).[29]



43

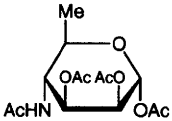
The 2-amino-2-deoxy-D-allopyranoside **45** was synthesized from a hex-3-enopyranoside by allylic rearrangement of the trichloroacetimidate **44**, the resulting 3,4-double bond being *cis*-dihydroxylated by a new procedure using a ruthenium oxidant which works well at low temperatures (Scheme 10).[30] A similar allylic rearrangement of an allyl cyanate (from a hex-4-enopyranoside) to an isocyanate (Vol. 28, p.124; Vol. 30, p. 127) featured in syntheses of the 4-amino-4,6-dideoxy-D-mannose (perosamine) and vicenisamine derivatives **46** and **47**.[31]



Reagents: i, Δ; ii, $NaIO_4$, RuCl

Scheme 10

The L-acosamine derivative **48** was synthesized in 12 steps from ethyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside utilizing the previously detailed conjugate addition of *N*-benzylhydroxylamine to an α,β-unsaturated lactone (Vol.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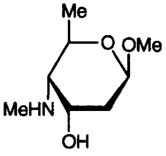
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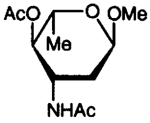
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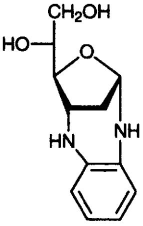
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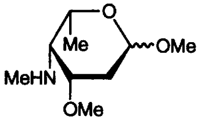
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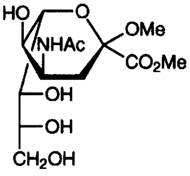
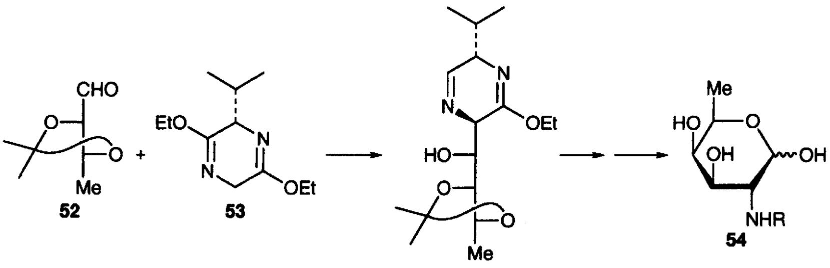

51

30, p. 151, ref. 50) and subsequent intramolecular sulfonate displacement to invert at C-5.[32] Reaction of 3,6-anhydo-2-deoxy-D-*arabino*-hexofuranose with 1,2-diaminobenzene gave the tricylcic 3-amino-sugar derivative **49**, the reaction being presumed to proceed by β-elimination of the anhydro-bridged substituent followed by Michael-type addition of the diamine at C-3 and then glycosylamine formation.[33]

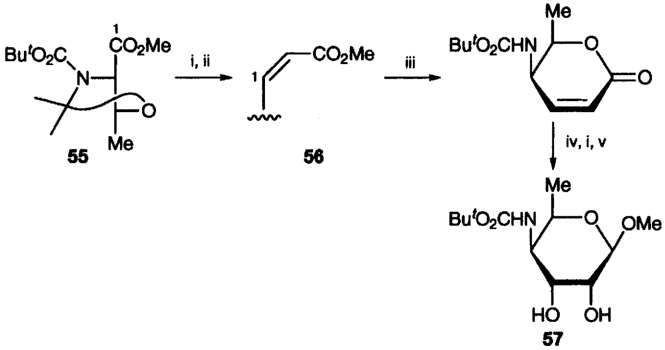
2.7 From Aldosuloses – The 4-methylamino-sugar **50** was obtained in 95% yield by electrochemical reductive amination ($MeNH_2$, CF_3SO_3H, MeCN in cathode cell; LiCl, MeCN in anode cell) of the corresponding 4-keto compound. This approach was also applied to a 4-oxo-derivative of avermectin B_1.[34] For the synthesis of the sialic acid analogue **51**, the free 4-OH in the 5,8:7,9-di-*O*-isopropylidene derivative of the methyl ester, methyl glycoside of KDN (a 3-deoxy-nonulosonic acid) was replaced with inversion by an NH_2-group by an oxidation-oximation-reduction sequence.[35]

2.8 From Aminoacids – D-Fucosamine and its *N*-methyl derivative **54** (R = Me) were synthesized by addition of the L-threonine-derived aldehyde **52** to the lithium salt of the glycine and L-valine-derived dihydropyrazine **53** (Scheme 11).[36] The 4-amino-4,6-dideoxy-D-gulopyranoside **57** was synthesized



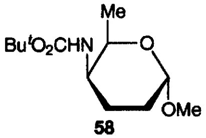
Scheme 11

from L-threonine in nine steps, 30% yield, *via* the known intermediate **55** (Scheme 12). The D-*epi*-tolyposamine derivative **58** was similarly obtained by reduction of the *trans*-isomer of intermediate **56**.[37]



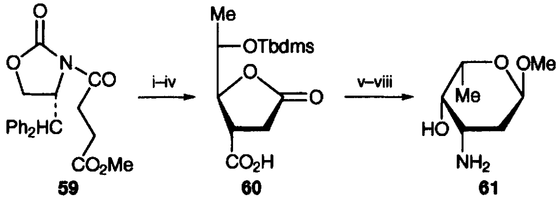
Reagents: i, Bu^i_2AlH; ii, $MeO_2CCH_2P(O)(OCH_2CF_3)_2$, K_2CO_3, 18-crown-6; iii, HOAc; iv, OsO_4, NMNO; v, MeOH, H^+

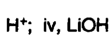
Scheme 12



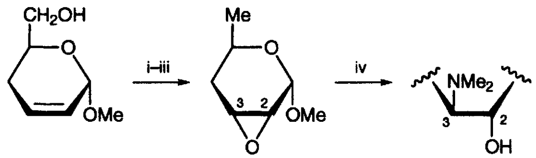
58

2.9 From Chiral Non-carbohydrates – Methyl α-L-daunosaminide **61** was synthesized by coupling an (*S*)-lactaldehyde derivative with **59**, lactonization of the resulting adduct to **60**, and introduction of the 3-amino-group by a Curtius reaction (Scheme 13). The C-5 epimer, methyl α-D-ristosamine, was obtained in the same way, starting from the corresponding (*R*)-lactaldehyde derivative.[38] 6-Deoxygenation, then epoxidation, of the enantiomerically pure dihydropyran **62**, available from a hetero-Diels-Alder reaction employing a chiral auxiliary, gave the D-*ribo*-epoxide **63** and its D-*lyxo*-isomer in a 1:2 ratio, the former giving mainly the 3,4,6-trideoxy-3-dimethylamino-D-*xylo*-hexoside **64** on reaction with dimethylamine (Scheme 14).[39]



Reagents: i, LiHMDS; ii,  $\mathrm{MeCH(OTbdms)CHO}$; iii, H^+; iv, LiOH, H_2O_2; v, Et_3N, $Ph_3P(O)N_3$, Bu^tOH; vi, Bu_4NF; vii, Bu^i_2AlH; viii, MeOH, HCl

Scheme 13

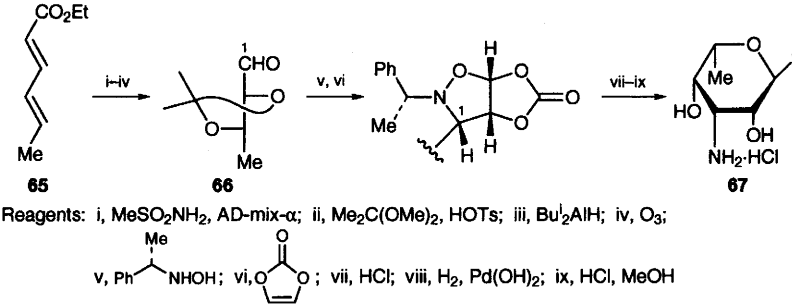


62 **63** **64**

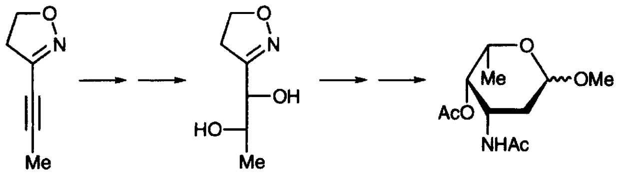
Reagents: i, TsCl, Py; ii, $LiAlH_4$; iii, MCPBA; iv, Me_2NH, H_2O

Scheme 14

2.10 From Achiral Non-carbohydrates – The 3-amino-3,6-dideoxy-L-taloside **67** was synthesized from ethyl sorbate **65** (Scheme 15), the chirality in aldehyde **66** arising from a Sharpless asymmetric *cis*-dihydroxylation reaction, and the amino-function being introduced by formation of a nitrone and subsequent dipolar cycloaddition with vinylene carbonate. Compound **67** was attached to a macrocycle to afford the antifungal agent fluvirucin B.[40] Sharpless asymmetric dihydroxylation was also used to introduce chirality (a) in the synthesis of the L-daunosamine derivative **70**, diol **69** being obtained from an alkene derived from acetylene **68** (Scheme 16),[41] and (b) in the synthesis of the branched-chain amino-sugar glycoside **73**, for the preparation of alkyne **71** from an alkenyne precursor. The subsequent conversion of **71** to the pyranoid glycal **72** was effected by tungsten- or molybdenum-mediated cyclizations (Scheme 17).[42] Full details (*cf.* Vol. 29, p.135, Scheme 22) of the syntheses of 6-deoxy-*allo*-nojirimycin (racemic and D-forms), 6-deoxy-*talo*-nojirimycin (racemic), and 2-acetamido-2,6-dideoxy-DL-allose using hetero-Diels-Alder chemistry have been published.[43]

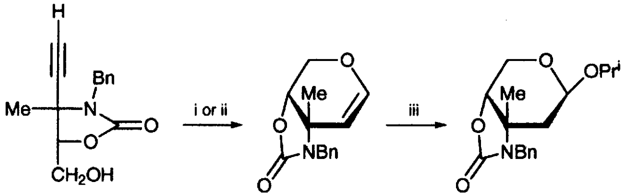


Scheme 15



68 **69** **70**

Scheme 16



71 **72** **73**

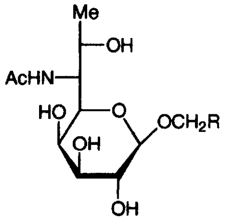
Reagents: i, $W(CO)_5{\cdot}THF$, then Et_3N; ii, $(Et_3N)Mo(CO)_5$, Et_3N; iii, Pr^iOH, $Ph_3P{\cdot}HBr$

Scheme 17

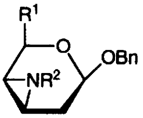
3 Properties and Reactions

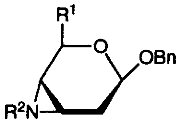
3.1 Interconversions – Two groups have reported detailed studies on the synthesis of sialic acids from 2-acetamido-2-deoxy-D-glucose (GlcNAc), and these are covered in detail in Chapter 16. In both cases, GlcNAc was epimerized to ManNAc (either with base resin or Ca^{2+}), *N*-deacetylated in strong acid, and re-*N*-acylated to the *N*-*tert*-butoxycarbonyl or *N*-glycolyl derivative, before chain extension using a sialic acid aldolase.[44,45] Another group has reported similarly on the preparation of a variety of sialic acid derivatives, *N*-acylated with amino-acids, aromatic acids or biotin, by acylation of 2-amino-2-deoxy-D-mannose and condensation of the products with pyruvic acid using sialic acid aldolase.[46]

The carboxylate and phosphonate derivatives **74**, made from lincomycin by hydrazinolysis, peracetylation, glycosidation [$HOCH_2CO_2Me$ or $HOCH_2PO(OBn)_2$, NIS, TfOH] and deprotection, were *Clostridium* sialidase inhibitors with K_i values in the mM range.[47] The extent of regiocontrol in the ring opening reactions of the racemic aziridines **75** and **76** with nucleophiles (Cl, OMe, N_3, NEt_2, SPh) under various conditions (alone, metal-assisted or acid catalysis) has been determined. Good stereoselectivity was attained with some combinations, attack occurring predominantly at C-2 or C-3 in each case.[48] Oxidation of the alcohol **77**, derived from Grignard reaction of a D-arabinopyranosylamine derivative, resulted primarily in the formation of lactam **78** following oxidative cleavage of the chain at C-6/C-7 and lactam formation (Scheme 18). Oxidation of related alcohols such as **79**, derived from D-gluco- or D-manno-pyranosylamine



74 R = CO_2Na or $PO(ONa)_2$

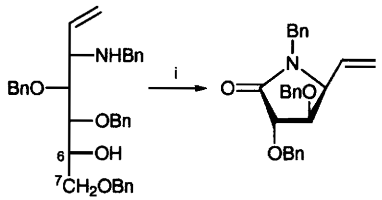




75 **76**

R^1 = H or Me, R^2 = Ts or CO_2Me

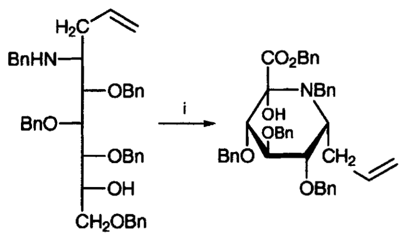
derivatives, however, stopped at the keto-ester stage to give hemiaminals such as **80** (Scheme 19).[49]



77 **78**

Reagent: i, PCC, CH_2Cl_2

Scheme 18



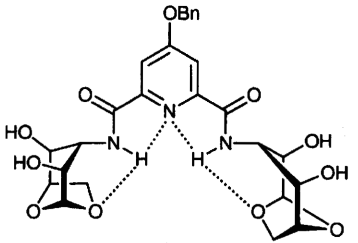
79 **80**

Reagent: i, PCC, CH_2Cl_2

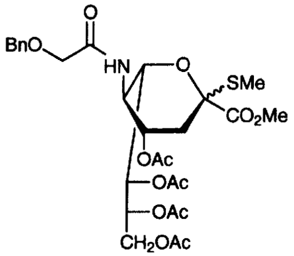
Scheme 19

3.2 *N*-Acyl and *N*-Carbamoyl Derivatives – Recent advances in the use of *N*-protecting groups, such as *N*-tetrachlorophthaloyl, *N*-4,5-dichlorophthaloyl, *N*-dithiasuccinoyl, *N*-pent-4-enoyl and *N*,*N*-diacetyl, and their advantages/disadvantages in the synthesis of amino-sugar-containing oligosaccharides have been reviewed,[50] while in another report the same authors have focused on the utility of the *N*-tetrachlorophthaloyl (TCP) group.[51]

2-Deoxy-2-[3-(1-pyrenyl)propanamido]-glucose has been prepared as a fluorescent amphiphilic derivative of glucosamine, and its fluorescence properties were reported briefly.[52] Compound **81**, which adopts the hydrogen-bonded structure shown (as determined by IR and variable temperature NMR studies), was obtained following condensation of 3-amino-1,6-anhydro-2,4-di-*O*-benzyl-β-D-glucopyranose with the pyridine-2,6-dicarboxylic acid in the presence of DCC.[53]

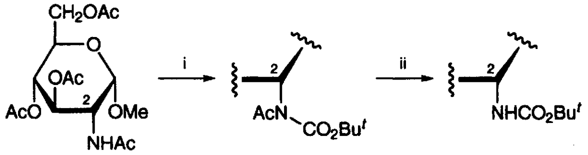


81



82

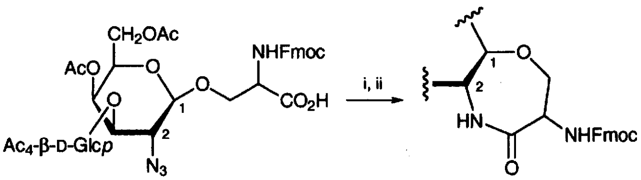
One approach to the synthesis of *N*-glycolyl-neuraminic acid derivatives is covered in Section 3.1, but in an alternative approach, resulting in the derivative **82** used subsequently as a glycosyl donor, sialic acid was converted into its peracetylated anomeric methyl thioglycosides, *O*,*N*-deacetylated ($MeSO_3H$, MeOH), *N*-acylated [with *N*-(benzyloxacetoxy)succinimide] and *O*-acetylated.[54] Chitosan oligosaccharides (DP 3 and 4) and β-GlcNH$_2$-(1→4)-GlcNHAc were obtained by *N*-deacetylation of the corresponding chitooligosaccharide using the purified chitin deacetylase from *Colletotrichum lindemuthianum*.[55] A mild, one-pot method to convert an acetamido-group to a carbamate is exemplified in Scheme 20.[56]



Reagents: i, $(Bu^tO_2C)_2O$, DMAP, THF; ii, NH_2NH_2 or LiOH, MeOH

Scheme 20

Reduction then attempted acylation of the 2-azido-sugar disaccharide β-glycoside **83** gave the cyclic amide **84** (Scheme 21). In contrast, the corresponding α-anomer was smoothly converted to the 2-acetamido-derivative and then into a biotinylated T-antigen by conjugation *via* the acid group in its aglycon to biotinaminocaproyl hydrazide and deprotection.[57] Circular dichroism and FTIR studies on peptides carrying an *N*-terminal 1-deoxy-D-fructos-1-yl moiety, *i.e.* Amadori compounds (see Vol. 30, p. 125 for their synthesis), have been reported.[58]



83

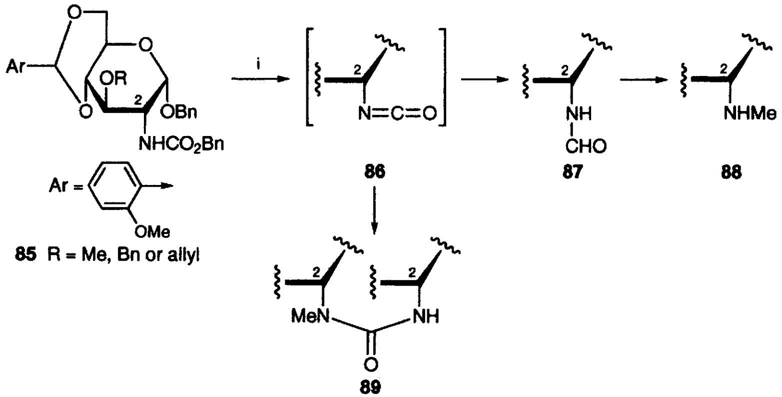
84

Reagents: i, $NaBH_4$, $NiCl_2$; ii, Ac_2O

Scheme 21

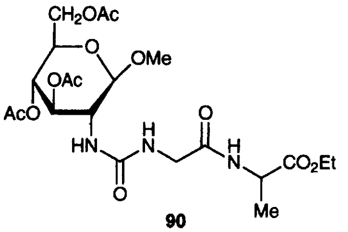
Attempted reductive cleavage of the 4,6-*O*-(2-methoxybenzylidene) acetal in **85** led instead to mixtures of compounds **87** and **88** as well as the dimer **89**, which can be explained as arising from a 2-isocyanate intermediate **86** (Scheme 22).[59] Ureido-sugar derivatives such as **90** have been synthesized by reaction of peptides with the corresponding *N*-(4-nitrophenyloxycarbonylated) amino-sugar derivative, and characterized by solution and solid-state NMR techniques.[60]

3.3 *N*-Sulfonates and *N*-Sulfates – *N*-Arylsulfonyl-groups (*e.g.* $PhSO_2$) can be reductively cleaved from amino-sugars using samarium(II) iodide, the method being compatible with *p*-methoxybenzyl acetals and *N*-acetyl but not *O*-acetyl groups.[61] Full details (*cf.* Vol. 30, p.160, ref. 11) have been published on the use of a 2-*N*,3-*O*-cyclic sulfated derivative of allosamine for the introduction of thio, azido and acetoxy nucleophiles at C-3 with inversion.[62]

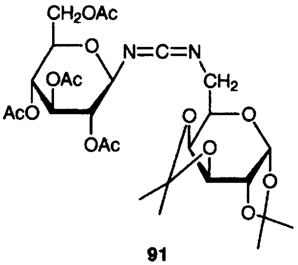


Reagent: i, $LiAlH_4$, $AlCl_3$

Scheme 22

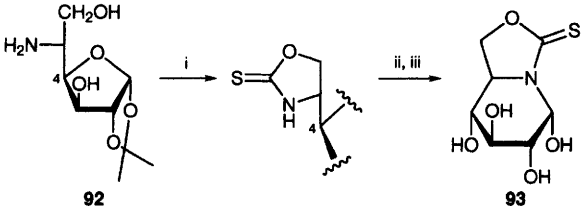


90



91

3.4 Imide, Isothiocyanate and Thiocarbonyl Derivatives – Unsymmetrical sugar carbodiimides such as **91** were obtained by aza-Wittig coupling between a glycosyl phosphimine and a sugar isothiocyanate, or between a glycosyl isothiocyanate and a sugar phosphimine (made *in situ* by reaction of Ph_3P with an azido-sugar derivative). These could be further converted to urea or thiourea linked dimers.[63, 64] *N*-Thioacetyl derivatives of amino-sugars and glycosylamines react with $Hg(OAc)_2$ or AgOBz to give the corresponding *N*,*N*-diacetyl- or *N*-acetyl-*N*-benzoyl derivatives, respectively.[65] The α-D-*gluco*-thiocarbonyl-azasugar **93** was obtained by DCC-induced condensation of the amine **92** with CS_2, acid hydrolysis then treatment with a base resin (Scheme 23). Its L-*ido*-isomer was prepared in the same way from the C-5 epimeric amine.[66]

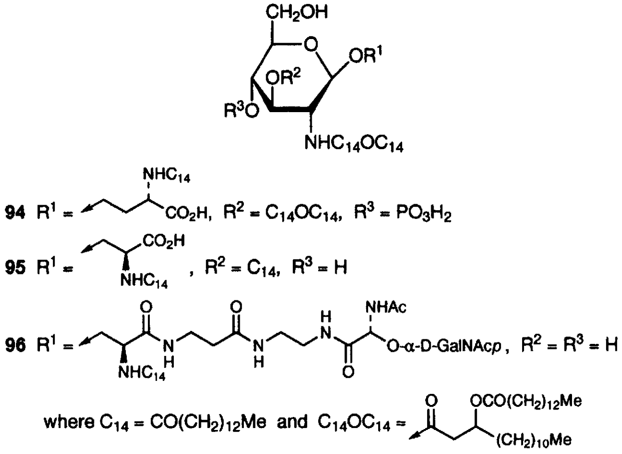


Reagents: i, CS_2, DCC; ii, CF_3CO_2H, H_2O; iii, Resin (OH^-)

Scheme 23

3.5 *N*-Alkyl Derivatives – *N*,*N*-Dialkylation of 2- and 6-amino- and 2,6-diamino-glucosides was achieved by *N*-benzylation, through borohydride reduction of an imine formed by condensation with benzaldehyde, then *N*-ethylation. This was surprisingly effected by treatment with excess of $NaBH_4$ in acetic acid solution.[67]

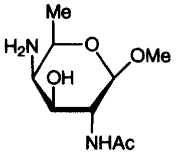
3.6 Lipid A Analogues – A variety of Lipid A analogues based upon acylated 2-amino-2-deoxy-D-glucosides of *N*-acyl-L-homoserine, -L-serine or -L-threonine derivatives, as exemplified by compounds **94** and **95**, have been prepared and their mitogenic activities studied in a mouse model.[68, 69] Related glycopeptides such as **96**, combining a Lipid A analogue with the Tn or sialyl-Tn antigen [α-D-GalNAc or α-D-Neu5Ac-(2→6)-α-D-GalNAc, respectively], were made as potential cancer vaccines.[70] Full details (*cf.* Vol. 30, p. 205, ref. 27) on the synthesis and anti-inflammatory properties of Lipid A analogues, based on 3-amino-2,6-anhydro-3-deoxyheptonic acid and its 7-deoxy-7-fluoro-analogue as the core, have been published.[71]



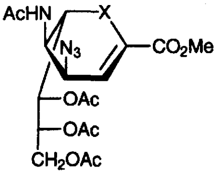
3.7 Other References to Amino-sugars – A mechanistic study on the oxidative degradation of 2-amino-2-deoxy-D-glucose and -D-galactose to D-arabinonic and D-lyxonic acids, respectively, by Chloramine T and *N*-chlorotoluenesulfonamide in alkaline solution has been reported.[72] The 6-*O*-dansyl derivative of 2-acetamido-2-deoxy-D-glucose is covered in Chapter 7, while the use of a 5-amino-5-deoxy-D-xyloside as a chiral auxiliary is covered in Chapter 20.

4 Diamino-sugars

The synthesis of 2,4-diamino-2,4,6-trideoxy-D-galactoside **97**, a constituent sugar of the O-specific lipopolysaccharide of *Shigella sonnei*, from a 2-deoxy-2-phthalimido-D-glucoside 4,6-ditosylate involved selective formation and reduc-

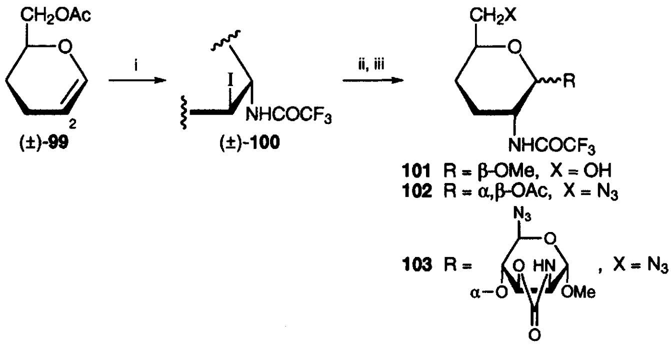


97



98 X = O or S

tion of a 6-iodide, then azide displacement at C-4 with inversion.[6] The 5-acetamido-4-azido-derivatives **98**, with either an O- or an S-atom in the ring, were obtained from the corresponding 4-acetoxy-derivatives of the same configuration on reaction with NaN_3 and catalytic $Pd(PPh_3)_4$, the reactions proceeding *via* π-Pd complexes.[73] Synthesis of the D-purpurosamine donor **102** from acrolein dimer involved reduction and acetylation to the racemic 3,4-dideoxyglycal **99**, iodo-amidation to racemic **100**, rearrangement *via* a 1,2-aziridine intermediate to introduce the 2-amino function, and enantioselective lipase-catalysed hydrolysis of the 6-acetate to provide the β-D-glycoside **101** (Scheme 24). A 6-azido-group was then introduced by sulfonate displacement, and acetolysis then gave **102**, which was used to glycosylate a cyclitolamine to give **103** under Lewis acid catalysis.[74]



Reagents: i, I(*sym*-collidine)$_2$ClO$_4$, CF_3CONH_2, MeCN; ii, Et_3N, MeOH; iii, lipase, H_2O

Scheme 24

Rhenium complexes of 2′,3′-diamino-2′,3′-dideoxy-uracil are covered in Chapter 17, while syntheses of 1-*N*-substituted 3-acetamido-1,3,5-trideoxy-1,5-imino-D-xylitols (by reduction of a 3,5-diacylamino-3,5-dideoxy-D-xylose) and of 1-amino-1,2,5-trideoxy-2,5-imino-D-mannitol (by reduction of a 5-azido-1,5-dideoxy-1-*N*,*N*-dibenzylamino-D-fructose) are covered in Chapter 18.

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10

Miscellaneous Nitrogen-containing Derivatives

1 Glycosylamines and Related Glycosyl-*N*-bonded Compounds

1.1 Glycosylamines – The 3,6-anhydro-2-deoxy-hexosylamine derivative **1** was obtained by direct condensation of the corresponding free sugar with 2-aminopyridine in methanol. Analogous reaction with 1,2-diaminobenzene led to a cyclized rearrangement product (see Chapter 9, Section 2.6).[1] The kinetics and mechanism for the acid-catalysed mutarotation of *N*-(4-chlorophenyl)-β-D-glucopyranosylamine in methanolic benzoate buffer solution have been reported.[2] Tijpanazole F1 (**2**) has been synthesized by direct condensation of D-xylose with a precursor with a tetrahydro-C-ring followed by dehydrogenation (with DDQ); no glycosylation occurred on the indole nitrogen atom.[3]

Lewis acid-catalysed glycosylation was used in the synthesis of three ergot alkaloid *N*-(2-deoxy-D-*erythro*-pentofuranosyl)-derivatives.[4] The new anticancer agents NB-506 (**3**), which has topoisomerase inhibitory properties from its indolocarbazole moiety and enhanced aqueous solubility due to its sugar moiety, has been synthesized by reaction of benzyl protected aglycon and glycosyl chloride moieties in the presence of KOH in MeCN.[5] A range of related unsymmetric indolocarbazole *N*-glycosides were synthesized by application of the Mitsunobu reaction to benzylated sugar derivatives with a free 1-hydroxy group.[6] *N*-β-D-Gluco- and galacto-pyranosylated condensed pyridine-2(1*H*)-thiones were synthesized using a glycosyl bromide and KOH, or by reaction of a silylated base derivative with a glycosyl acetate.[7] The aglycon moieties in various 2-glycosylamino-4,5-di(methoxycarbonyl)pyridines have been modified to yield 5-glycosylaminopyrrolo[3,4-*d*]pyridin-1,3(2*H*)-diones and 7-glycosylaminopyrido[3,4-*d*]pyridazin-1,4(2*H*,3*H*)-diones.[8]

The synthesis of 1-*C*-difluoromethyl-1,4-dideoxy-1,4-iminopentitols from pentofuranosylamine derivatives is covered in Chapter 18.

1.2 Glycosylamides Including *N*-Glycopeptides – *N*-Retinoyl β-D-glucopyranosyl- and glucuronosyl-amines were prepared by acylation of the corresponding glycosylamines with a retinoid acyl chloride and tested as antitumour agents.[9] (2*S*)-2-Hydroxy-3-phenyl-*N*-(β-D-glucopyranosyl)propanoamide was prepared, by DCC coupling of the corresponding acid and glycosylamine moieties, as a simple mimic of the C-7–C-10 fragment of the antitumour sponge metabolites, the mycalamides.[10] Glycosyl azides have been converted

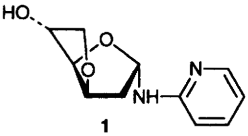
Carbohydrate Chemistry, Volume 31

into glycosylamides, *e.g.* *N*-heptanoyl-β-D-glucopyranosylamine, potential non-ionic surfactants, using the Staudinger reaction (Ph_3P and an acyl chloride in CH_2Cl_2, then H_2O).[11] A range of *N*-chloroacetyl-glycosylamines were synthesized by reaction of the corresponding glycosylamines with chloroacetic anhydride in DMF.[12] Galactosylated-cyclodextrins were created by amide linking the amino-groups of mono- or hepta-(6-aminodeoxy)-β-cyclodextrin with the carboxylic acid moiety of *N*-(ω)-carboxyalkanoyl)-β-D-galactopyranosylamine (made by reaction of tetra-*O*-acetyl-β-D-galactopyranosyl isothiocyanate with a 3, 4, 5, 6 or 8-carbon chain ω-methoxycarbonylalkanoic acid and Et_3N, and deprotection). Their abilities to bind to a galactose-specific lectin were determined.[13] 'Bolaamphiphiles' such a **4** have been synthesized by treating *O*-acetylated glycosylamines with bis-acid chlorides; their single crystal X-ray structures were determined.[14-16] The elaboration of the sugar chains of an oligosaccharide *N*-(6-aminohexanoyl)glycosylamine is covered in Chapter 4.

N-Nonanoyl-, lauroyl-, and stearoyl-di-α-D-mannofuranosylamines (*e.g.* **5**) were prepared as non-ionic surfactants by conversion of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosylamine into the *O*-protected di-β-D-mannofurano-sylamine by heating in methanol under reflux. This was then condensed with the corresponding acid chloride, and the protecting groups were removed by acid-catalysed ethanolysis.[17] *N*-Acetyl-di-β-D-gluco- and β-L-rhamnopyranosylamine were obtained by peracetylation then *O*-deacetylation of the corresponding per-*O*-acetyl-di-β-D-glycosylamines.[18]

'Peptidodisaccharides' such as **6** were synthesized by reduction of glycosyl azides and coupling the resulting glycosylamines with uronic acid derivatives.[19] The syntheses of positional isomers such as **7** of the Lipid A moiety GLA-60, a 2-*N*-,3-*O*-diacyl-2-amino-2-deoxy-D-glucose 4-phosphate, have been reported.[20]

The catalytic reaction mechanism of aspartylglucosaminidase, which converts N^4-(2-acetamido-2-deoxy-β-D-glucopyranosyl)asparagine into aspartic acid and the corresponding glycosylamine, has been studied by *ab initio* quantum mechanical and molecular dynamics calculations.[21] Chemical and enzymatic methods were employed for the synthesis of glycosylpeptides containing this N^4-(2-acetamido-2-deoxy-β-D-glucopyranosyl)asparagine core and of C-glycosyl analogues (see Chapter 4), the products being evaluated as inhibitors of the above enzyme.[22] A one-pot two-step synthesis of glutamic acid glycoconjugates, exemplified in Scheme 1 for lactose, involved direct condensation of an unprotected oligosaccharide with the amino acid derivative **8** in DMF with imidazole at 50 °C to give the β-glycosylamine **9**, which could be stabilized by intramolecular acylation on addition of a carboxylic acid group activator, leading to the pyroglutamate derivative **10**.[23] The solid-phase synthesis of the carbohydrate-modified enkephalins **13** with 5 or 6 amino acid peptide moieties, one of which proved to be a potent α-selective δ-opiod receptor agonist, involved preparing the glucuronosyl azide **11** from D-glucuronic acid (i, Ac_2O, I_2; ii, $TmsN_3$, $SnCl_4$), coupling this to a σ-chlorotrityl-resin to give **12**, reducing the azido-group, then using conventional solid-phase



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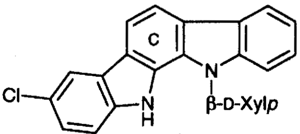

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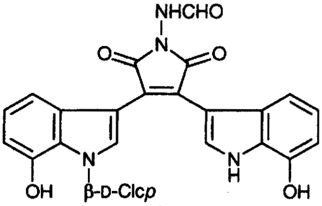

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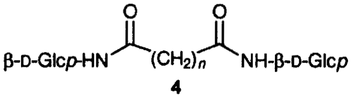

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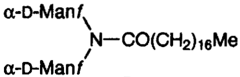

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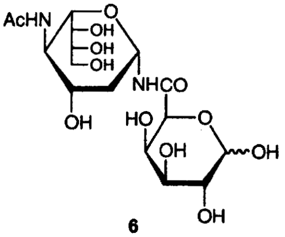

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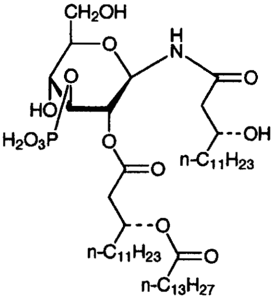

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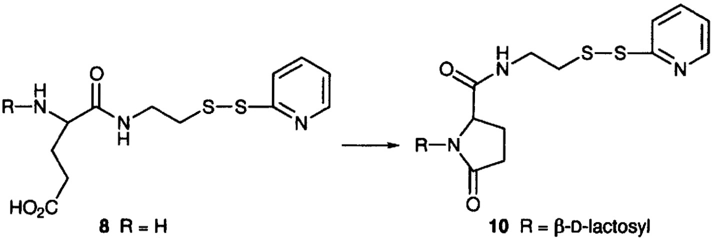
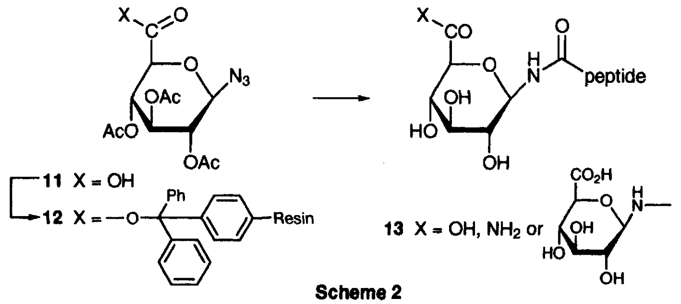


8 R = H
9 R = β-D-lactosyl
10 R = β-D-lactosyl

Scheme 1

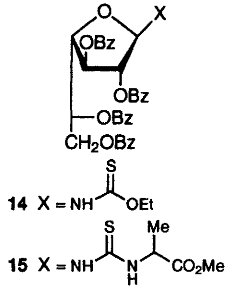
peptide coupling methods (Scheme 2).[24] A review on the enzymatic synthesis of peptide conjugates has included a section on glycopeptides.[25]

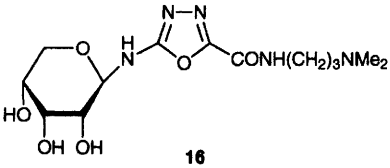
1.3 *N*-Glycosyl-carbamates, -isothiocyanates, -thioureas and Related Compounds – 2,3,5,6-Tetra-*O*-benzoyl-β-D-galactofuranosyl isothiocyanate has been prepared from the corresponding pentabenzoate *via* the glycosyl chloride or bromide. It reacts with alcohols to give thiourethanes, *e.g.* **14**, with amines



Scheme 2

or amino acid esters to give thioureas *e.g.* **15**. It was used in this way to resolve racemic 1-amino-2-propanol by chromatographic separation of the derived thiourea derivatives.[26,27] Per-*O*-acetyl-*N*-thioacetyl-β-glycosylamines are converted into the corresponding *N*,*N*-diacetyl-derivatives on reaction with mercury(II) or silver(I) acetate. An *N*-propyl-*N*-thioacetyl analogue was similarly converted into an *N*-acetyl-*N*-propyl derivative.[28] Syntheses of 5-substituted 2-pentosylamino-1,3,4-oxadiazoles such as **16** have been reported.[29,30]



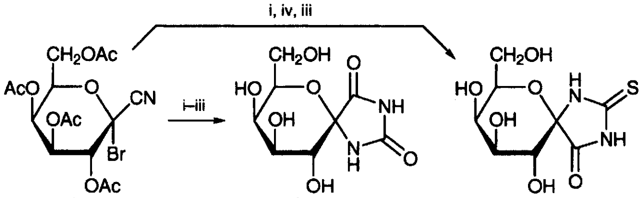


16

The 1-*epi*-hydantocidin and thiohydantocidin analogues **18** and **19**, respectively, were synthesized from the 1-bromo-β-D-galactopyranosyl cyanide **17** (Scheme 3). Addition of cyanate and cyclization occurred with retention of configuration at the anomeric centre, while addition of thiocyanate and cyclization occurred with inversion.[31] The D-*gluco*-analogue **22** was synthesized from the 2-azido-heptonolactone **20** or its C-2 epimer, by way of the bicyclic derivative **21** formed from an 2-imine intermediate (Scheme 4), and shown to be a potent inhibitor of glycogen phosphorylase (K_i 3 μM).[32] An alternative route starting with the 2-azido-heptonolactone **23**, and relying upon oxidative cyclization of **24** led to a mixture of anomers **25**, in a 2:1 ratio favouring the inactive α-anomer (Scheme 5).[33]

2 Azido-sugars

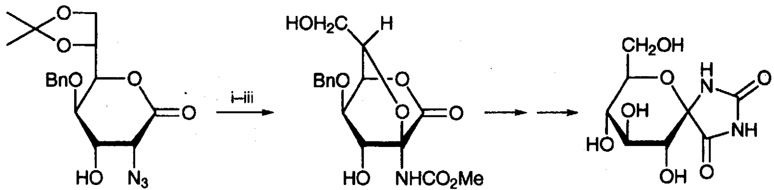
The combination of 2,4,4,6-tetrabromo-2,5-cyclohexadienone, Ph$_3$P and Zn(N$_3$)$_2$.2Py in acetonitrile–toluene is effective for converting primary and



17 **18** **19**

Reagents: i, $TiCl_4$, H_2O, HOAc; ii, AgOCN, $MeNO_2$; iii, NaOMe, MeOH; iv, KSCN

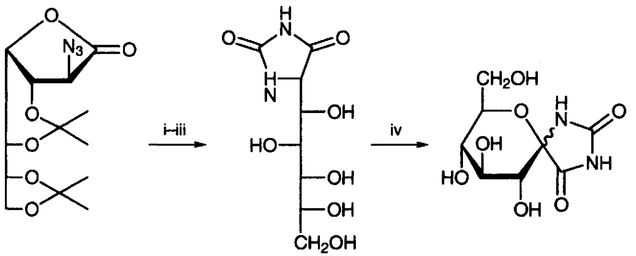
Scheme 3



20 **21** **22**

Reagents: i, H_2, Pd then Et_3N, $ClCO_2Me$; ii, AcOH, H_2O; iii, NBS, AcONa

Scheme 4



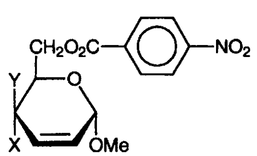
23 **24** **25**

Reagents: i, H_2, Pd/C; ii, KOCN, AcOH; iii, AcOH, H_2O; iv, Br_2, AcONa

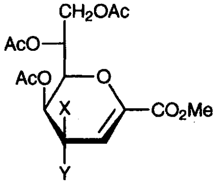
Scheme 5

secondary alcohols into azides. In this way, 2,3,4,6-tetra-*O*-benzyl-D-glucose was quantitatively converted into the β-glucosyl azide, and the unsaturated sugar **26** gave the azide **27** with inversion in 72% yield.[34] The ability of the $Ph_3P–CBr_4–NaN_3$ reagent system to effect azidation of primary alcohol groups in mono-, di- and oligo-saccharides (cyclodextrins) has been investigated. For optimal yields, the reactive species $[(Ph_3P\text{-}CBr_3)^+ N_3^-]$ must be preformed using a large excess of NaN_3. The reaction was found to be sensitive to substrate structure. Uridine gave 92% of the 5′-azide, whereas N^2-benzoylguanosine gave no product. The primary hydroxy group on glucose was more reactive than those on fructofuranose, so that 6-azido-6-deoxysucrose could be obtained directly in 45% yield.[35]

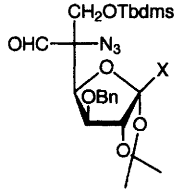
Reaction of per-*O*-benzyl-sucrose with $TmsN_3$ – $BF_3.OEt_2$ gave the anomeric tetra-*O*-benzyl-D-fructofuranosyl azides along with 2,3,4,6-tetra-*O*-benzyl-D-glucose.[36] Similar reaction of the unsaturated ulosonic acid derivatives such as **28** gave mixtures of C-3 epimeric azides such as **29**.[37] The proportions of isomeric 2-deoxy-2-iodo-glycosyl azides formed on reaction of tri-*O*-benzyl-D-glucal with ICl–NaN_3 were determined by NMR spectroscopy.[38]



26 X = OH, Y = H
27 X = H, Y = N_3

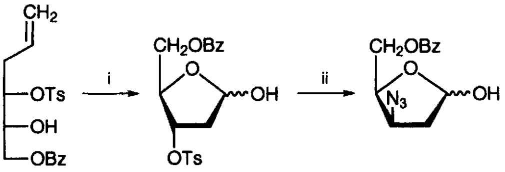


28 X = OAc, Y = H
29 X,Y = N_3, H



30

The α-azido-aldehyde **30** was obtained from the corresponding 5-keto-derivative by reaction with dichloromethyllithium followed by azide ion, the reaction proceeding by way of a *spiro*-epoxide intermediate.[39] 3-Azido-2,3-dideoxy-D-*threo*-pentose derivative **32** (Scheme 6) was synthesized from the tosylate **31**, derived in several steps from 2,3-*O*-cyclohexylidene-D-glyceraldehyde.[40] 5-Azido-5-deoxy-L-gulurono-6,3-lactone was obtained from D-mannurono-6,3-lactone by reaction of the 1,2-*O*-isopropylidene-5-triflyl derivative with NaN_3.[41]

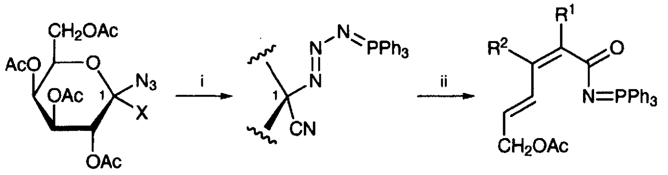


31 **32**

Reagents: i, O_3 then Ph_3P; ii, NaN_3, DMF

Scheme 6

Reaction of the 1-azido-1-cyano-galactoside **33** with Ph_3P gave the phosphazide **35** (which crystallized from the reaction mixture in ether) rather than the expected phosphinimine (Scheme 7). In toluene, **35** gave mainly the ring-opened elimination products **36** and **37**. In contrast the corresponding carboxamide **34** gave the expected phosphinimine as a mixture of relatively unreactive anomers.[42]



33 X = CN
34 X = $CONH_2$

35

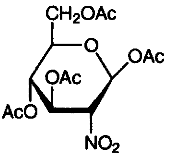
36 R^1 = H, R^2 = CN
37 R^1 = OAc, R^2 = H

Reagents: i, Ph_3P, Et_2O; ii, PhMe

Scheme 7

3 Nitro-sugars

O-Protected 2-amino-2-deoxy-sugar derivatives have been converted into the corresponding 2-nitro-sugars, *e.g.* **38**, on treatment with *m*-chloroperbenzoic acid, and some reactions of these nitro-sugar products were studied.[43] The potential rubranitrose precursor **39** was synthesized from the known C-4 epimeric branched-chain 3-aminosugar, by treatment with dimethydioxirane ($3\text{-}NH_2 \rightarrow 3\text{-}NO_2$) and inversion at C-4 by triflate displacement with CsOAc in the presence of a crown ether. An alternative approach to effect epimerization of the 3-nitrosugar intermediate at C-4 with NaOMe in MeOH led to a mixture from which **40** could be isolated in a 42% yield, along with 22% of its C-4 epimer, both of which have undergone epimerization at C-3.[44] Methyl 5-*O*-benzoyl-2,3-dideoxy-3-nitro-α- and β-D-*erythro*-pentofuranosides were synthesized in several steps from 5-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-3-nitro-D-ribofuranose.[45]



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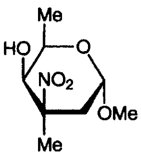

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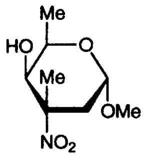
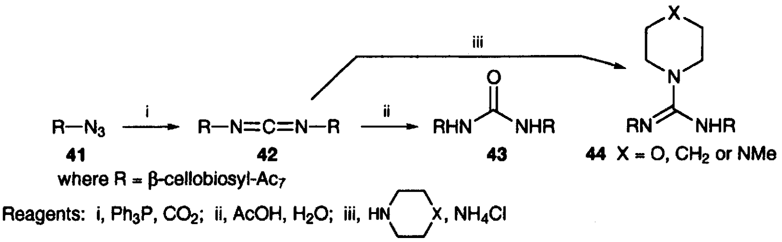


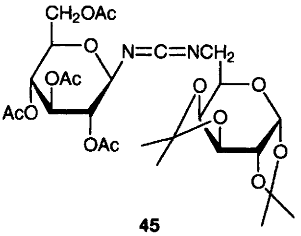
40

4 Carbodiimides

The 1,3-dicellobiosylcarbodiimide **42** was obtained by reaction of hepta-acetyl-β-cellobiosyl azide **41** with Ph_3P and CO_2 (Scheme 8), and converted into the urea or guanidine derivatives **43** and **44**, respectively.[46] Unsymmetrical carbodiimides such as **45** were obtained by condensation either of a 6-deoxy-6-isothiocyanato-sugar derivative with a phosphinimine derived from a glycosyl azide, or of a glycosyl isothiocyanate with a phosphinimine derived from a 6-azido-6-deoxy-sugar derivative. These could be converted to the corresponding urea and thiourea derivatives.[47,48]



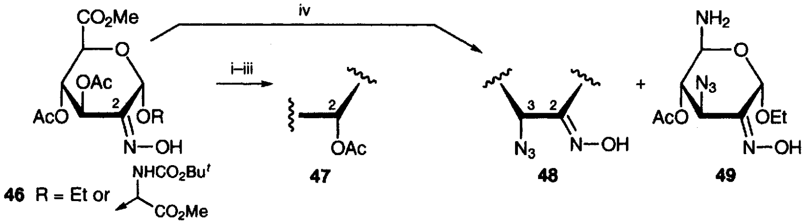
Scheme 8



45

5 Oximes, Hydroxylamines, Nitriles, Imines and Amidines

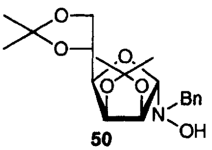
Oximes **46** were converted exclusively or largely into the corresponding glucuronide derivatives **47** on deoximation and reduction (Scheme 9). Reaction of **46** with sodium azide in ethanol heated under reflux gave the 3-azido sugar derivatives **48**, smaller amounts of their C-3 epimers and, in the case of R = Et, the product **49** proposed to have arisen by Curtius rearrangement of an intermediate hexosiduronoyl azide.[49] Syntheses of the 4- and 5-oximino-derivatives of sialic acid from KDN have been described.[50]



Reagents: i, MeCHO, HCl; ii, $NaBH_4$; iii, Ac_2O, Py; iv, NaN_3, EtOH

Scheme 9

N-Benzyl-*N*-glycosyl-hydroxylamines such as **50** were prepared by reaction of the corresponding free sugar derivatives with BnNHOH and $ZnCl_2$.[51,52] Addition of BnNHOH to the unsaturated lactone **51** gave the isoxazolidinone **52**, which was further cyclized to **53** (Scheme 10) by a rearrangement that is proposed to involve intramolecular displacement of a triflate group from C-6, β-elimination then intramolecular addition to the resulting α,β-unsaturated lactone.[53]



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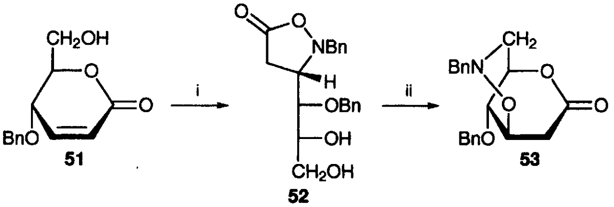
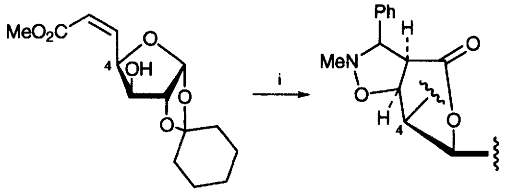
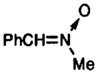


Reagents: i, BnNHOH; ii, Tf_2O, lutidine

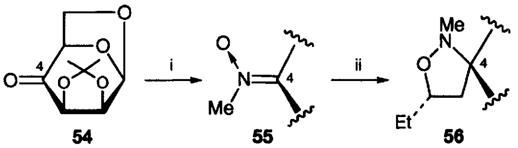
Scheme 10

A review on the synthesis of optically active isoxazolidines by dipolar cycloaddition of nitrones to alkenes, and the use of the products in organic synthesis, covered a number of carbohydrate examples involving sugar nitrones or unsaturated sugars as reactants.[54] The regioselectivity observed in addition reactions between nitrones and unsaturated sugars, *e.g.* Scheme 11, was shown to be consistent with predictions from frontier molecular orbital calculations. Additions involving two nitrones and seven unsaturated sugars were examined.[55] Eight examples of the addition to alkenes of sugar keto-nitrones such as **55**, obtained by reaction of the corresponding keto-sugar derivative (*e.g.* **54**) with MeNHOH, which gave isoxazolidines such as **56** (obtained in 62% yield along with 11% of its C-4 epimer) (Scheme 12), have been reported and included an intramolecular example in which the alkene component was in an *O*-allyl protecting group.[56] The synthesis of a 1,4-dideoxy-2-*C*-(D-glucos-2-yl)-1,4-imino-D-threitol from the cycloadduct obtained from tri-*O*-acetyl-D-glucal and a pyrroline *N*-oxide is detailed in Chapter 18.



Reagent: i, 
$PhCH{=}N(\rightarrow O)Me$

Scheme 11

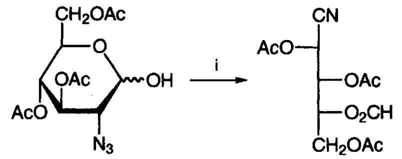


Reagents: i, MeNHOH, Py; ii, $EtOCH{=}CH_2$

Scheme 12

The nitrile **58** was obtained from cleavage of the C-1–C-2 bond of the 2-azido-2-deoxy-D-glucose derivative **57** (Scheme 13). Two similar examples were also reported.[57]

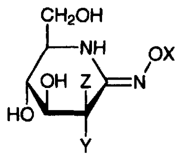
The oxyamidine glycosidase inhibitors **59** and **60** were synthesized from the corresponding *O*-acetylated lactams by conversion to the thiolactams (with Lawesson's reagent), reaction with (*O*-substituted)-hydroxylamine and deacetylation. Compound **60** had a K_i of 0.15 μM against jack bean α-mannosidase.[58]



57 **58**

Reagent: i, $PhI(OAc)_2$, I_2

Scheme 13

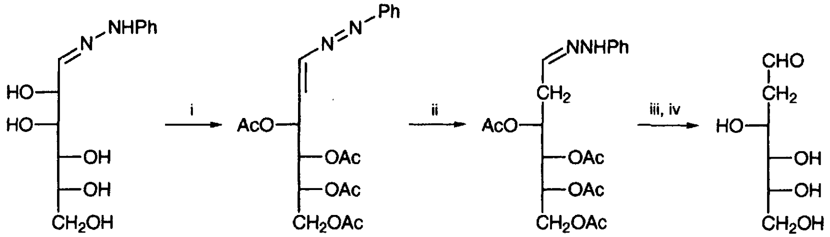


59 X = CH_2SMe, Y = OH, Z = H

60 X = Y = H, Z = OH

6 Hydrazones and Related Compounds

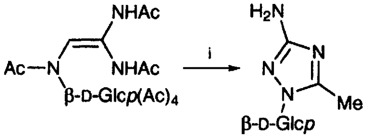
1-Glycosyl-2-acetylhydrazines have been prepared by condensation of *N*-acetylhydrazine with aldoses (15 examples) and characterized by ^{1}H-NMR spectroscopy.[59] Acetylation of the phenylhydrazone of D-mannose (**61**), D-galactose, D-arabinose or L-rhamnose gave acetylated 1-phenylazo-ald-1-enitols (*e.g.* **62**) which on reduction afforded the corresponding 2-deoxyaldose phenylhydrazones (*e.g.* **63**) (Scheme 14). Deacetylation and hydrolysis then provided the 2-deoxyaldose (*e.g.* 2-deoxy-D-*arabino*-hexose **64**).[60] The peracetylated derivatives of *N*-β-D-gluco- (**65**), *N*-β-D-galacto-, and *N*-β-L-arabinopyranosyl-aminoguanidine have been prepared (*cf.* Vol. 29, p. 146) and cyclized by deacetylation to the corresponding 3-amino-*N*-glycosyl-5-methyl-1*H*-1,2,4-triazoles (*e.g.* **66**) (Scheme 15).[61] A one pot synthesis of heterocyclic compounds such as **67** involved condensation of free sugar such as D-glucose with a pyrazinehydrazone such as **68** and subsequent treatment of the resulting hydrazone with bromine in methanol.[62] 1,3,4-Thiadiazole derivatives such as



61 **62** **63** **64**

Reagents: i, Ac_2O, Py; ii, $NaBH_4$, pH 8; iii, NaOMe, MeOH; iv, Resin(H^+), H_2O

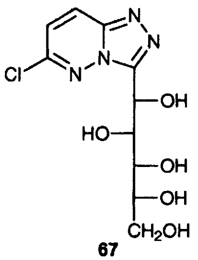
Scheme 14



65 **66**

Reagent: i, NaOMe, MeOH

Scheme 15



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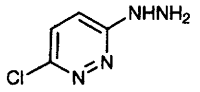
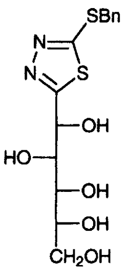


68

69 (*cf.* Vol. 29, p. 160) have been obtained by condensation of aldoses with *S*-methyl- or benzyl-hydrazonecarbodithioates followed by oxidative cyclization (Br_2, AcOH).[63] Similar chemistry applied to a 6-aldehydo-sugar derivative provided **70**.[64]



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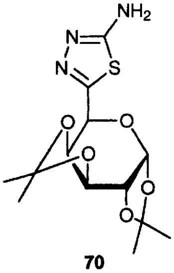
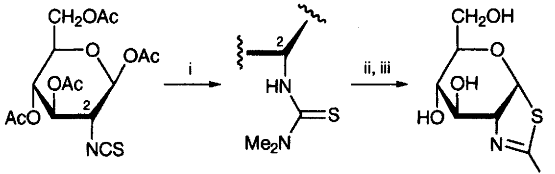


70

7 Other Heterocycles

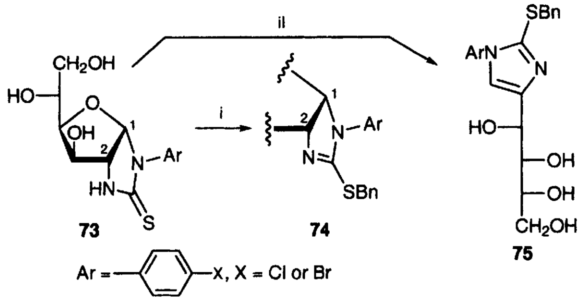
The hexosaminidase inhibitor **72**, with a K_i of 160 μM against the enzyme from jack bean, was synthesized from D-glucosamine *via* the known 2-isothiocyanato-derivative **71** (Scheme 16).[65] Benzylation of the known cyclic thiourea **73** gave the cyclic or acyclic imidazole derivatives **74** or **75** in the presence or absence of base, respectively (Scheme 17).[66] An improved synthesis of the unsaturated epoxide **77** from the D-glucosamine derivative **76** is shown in Scheme 18.[67]



71 **72**

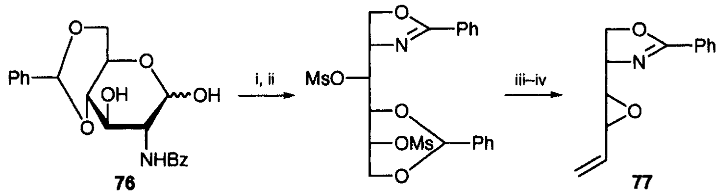
Reagents: i, Me_2NH, H_2O; ii, Et_3SiOTf; iii, NaOMe, MeOH

Scheme 16



Reagents: i, BnCl, NaHCO$_3$, EtOH; ii, BnCl, EtOH

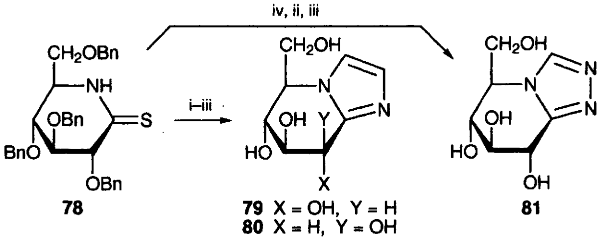
Scheme 17



Reagents: i, NaBH$_4$; ii, MsCl, Et$_3$N, Py; iii, NBS, AIBN, CaCO$_3$; iv, NaI, Na$_2$S$_2$O$_3$, CaCO$_3$; v, K$_2$CO$_3$, MeOH

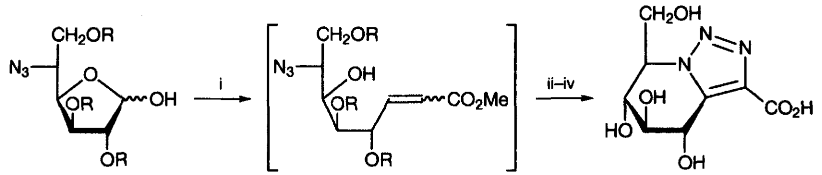
Scheme 18

The fused imidazoles **79** and **80** and the triazole **81** were synthesized from the known thionolactam **78** as shown in Scheme 19, compound **79** being a good inhibitor of two β-glucosidases.[68] The D-*gluco*-fused triazole carboxylic acid **84** was synthesized from D-gluconolactone, the key step being the intramolecular cyclization of the unsaturated azide **83** produced by Wittig chain extension of the 5-azido-hexose **82**, followed by oxidation then deprotection of the initial cyclization product (Scheme 20). The D-*galacto*-analogue was similarly prepared from D-galactonolactone. Neither showed significant glycosidase inhibitory properties.[69] In the synthesis of the racemic 3-fluoro-analogue **85** of 1-azafagomine (Scheme 21), deprotection with hydrazine surprisingly resulted in partial displacement of the fluorine to give hydrazino-derivative **86**. Compound **85** was a weaker glycosidase inhibitor than 1-azafagomine, implicating the 3-OH group in binding to the enzyme.[70]



Reagents: i, H$_2$NCH$_2$CH(OMe)$_2$, Hg(OAc)$_2$; ii, TsOH, PhMe, H$_2$O; iii, H$_2$, Pd(OH)$_2$, AcOH; iv, H$_2$NNCHO, Hg(OAc)$_2$

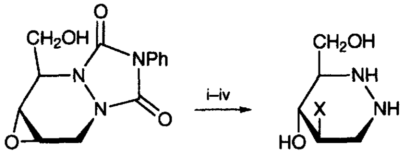
Scheme 19



82 R = Tbdms **83** **84**

Reagents: i, $Ph_3P{=}CHCO_2Me$; ii, Br_2; iii, CF_3CO_2H, H_2O; iv, NaOH, H_2O then Resin(H^+)

Scheme 20

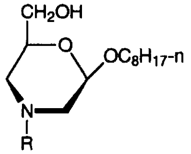


(±)-**85** X = F
(±)-**86** X = $NHNH_2$

Reagents: i, HF, Py; ii, Ac_2O; iii, NaOMe; iv, NH_2NH_2

Scheme 21

Periodate oxidation of the β-D-glucopyranosyl units of octyl β-D-Glc*p* or octyl β-lactosaminide, followed by reductive amination of the resulting dialdehydes with amines or amino acids, provided a range of morpholine-like derivatives such as **87**.[71] Syntheses of nucleobase-substituted anhydroalditols are covered in Chapters 9 and 18. Reactions of β-lactams obtained by cycloadditions of trichloroacetyl isocyanate to glycals are covered in Chapter 24.



87 R = Bn, OH, CH_2OH, $CH_2CH_2NH_2$ or RN = Asp, Phe, Tyr

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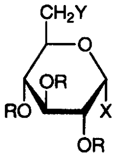
11

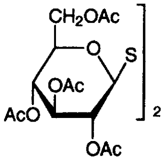
Thio-, Seleno- and Telluro-sugars

A review on recent developments in the chemistry of thiocarbonyl carbohydrate derivatives has been published.[1]

The synthesis of α,ω-dithioalditols is referred to in Chapter 18.



1 R = Ac, X = Br, Y = OAc
2 R = H, X = OMe, Y = Br



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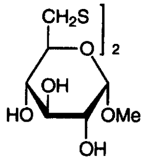
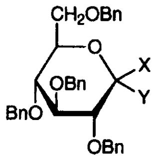
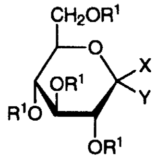


4

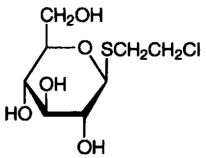
Sugar bromides have been converted to sugar disulfides (*e.g.*, **1**→**3**, **2**→**4**) by treatment with benzyltriethylammonium tetrathiomolybdate in acetonitrile.[2] In connection with the development of new glycosyltransferase inhibitors, *C*-glycosidic sulfones, *e.g.* **6**, have been obtained by radical addition of thioacetic acid to exocyclic methylene derivatives, *e.g.* **5**, followed by de-*S*-acetylation, *S*-methylation and oxidation.[3]



5 X,Y = CH_2
6 X = $CH_2\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}Me$, Y = H



R^1 = Ac, Bz, *p*MeBz
7 X = H, Y = Br
8 X = SeR^2 or TeR^2
R^2 = Me, Ph, Bn

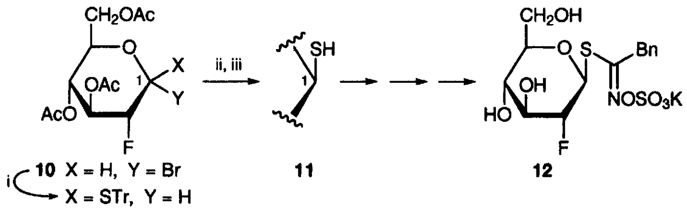


9

New 1-seleno-and 1-telluro-β-D-glucopyranosides **8** have been prepared by reaction of 1-bromides **7** with sodium alkyl selenolates and tellurolates, respectively. The reagents were obtained *in situ* by sodium borohydride-reduction of the appropriate dialkyl- or diaryl-chalcogenides.[4] A facile transformation of benzylated methyl glycosides to the corresponding phenyl 1-thioglycosides has been achieved by use of trimethylsilyl bromide and thiophenol

Carbohydrate Chemistry, Volume 31

in the presence of zinc.[5] A number of 2-chloroethyl 1-thio-β-D-hexopyranosides, such as compound **9**, have been synthesized from the corresponding 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-hexopyranoses by alkylation of the thiol group with $BrCH_2CH_2Cl$ and subsequent deacetylation.[6]

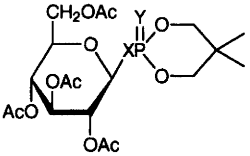


Reagents: i, Bu_4NSTr; ii, PhHgOAc, Ac_2O, Py, H_2S; iii, MeONa, MeOH

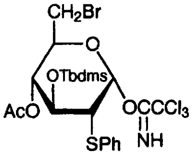
Scheme 1

The thioglucosidase inhibitor **12** has been prepared from tri-O-acetyl-2-deoxy-2-fluoro-1-thio-β-D-glucopyranose (**11**), following the general procedure for the synthesis of glucosinolates (see Vol. 27, Chapter 11, ref. 20). The required 1-thiosugar **11** was obtained in low yield, as shown in Scheme 1, after failure of bromide **10** to react with thiourea.[7] A ^{14}C-labelled glucosinolate analogue has been prepared by the standard route for such compounds.[8]

Glycosylation of triethylammonium phosphoro-thioates, -selenoates and -dithioates with glycosyl halides gave new glycosyl donors, such as compounds **13**.[9] A study on the diastereoselective synthesis and hydrolysis of β-D-galactopyranosyl sulfoxides is referred to in Chapter 3.

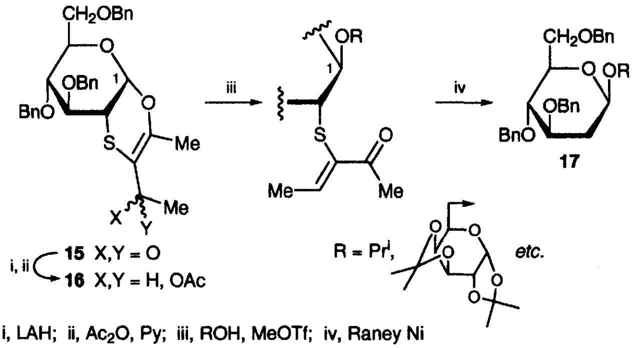


13 X = S, Y = O or X = Y = S or X = Se, Y = O



14

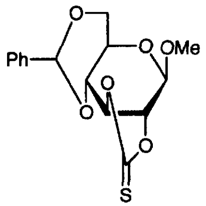
In an approach to the stereoselective synthesis of 2-deoxy-D-glycosides *via* 2-thio-sugar intermediates the influence of the substituents at C-6 and C-4 on the steric course of the addition of PhSCl and PhSeCl to D-glucal derivatives has been examined; it was found that electron-withdrawing groups at the 4- and 6-positions strongly favoured the formation of *gluco*-configured addition products.[10] Amongst a group of closely related 2-thioglucosyl donors, the trichloro-acetimidate **14** with a bulky substituent at O-3 was the most effective and selective for the synthesis of 2-deoxy-β-D-glucosides.[11] The preparation of 2′-deoxy-2′-phenylselenyl nucleosides from furanoid glycals is referred to in Chapter 20. The cycloaddition product **15** of 2,4-dioxopentane-3-thione and tri-*O*-benzyl-D-glucal was converted to oxothiirane **16**, which served as glycosyl donor in the stereoselective preparation of 2-deoxy-β-D-glycosides **17** (Scheme 2).[12]



Reagents: i, LAH; ii, Ac_2O, Py; iii, ROH, MeOTf; iv, Raney Ni

Scheme 2

Full details on the radical-induced *O*,*S*-rearrangement of 3,4- and 5,6-cyclothionocarbonates have been published (see Vol. 21, Chapter 11, refs. 16, 17) in a paper which also includes the rearrangement of *trans*-disposed 2,3-thionocarbonates to *cis*-disposed 2- and/or 3-thiosugar derivatives, for example **18**→**19** + **20**.[13] A full report on the use of the cyclic sulfamidate **21** of allosamine for the introduction of sulfur nucleophiles at C-3 with inversion of configuration has appeared (see Vol. 30, Chapter 11, ref. 11).[14] The synthesis of D-glucose derivatives with thiocarbamoyl and dithiocarbamoyl groups at O-3 and/or O-6 is covered in Chapter 7.



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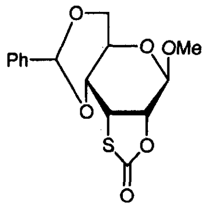

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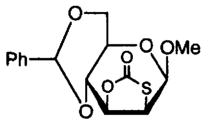

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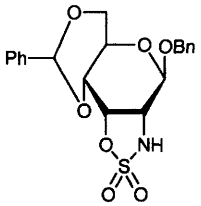

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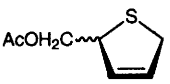

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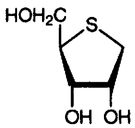
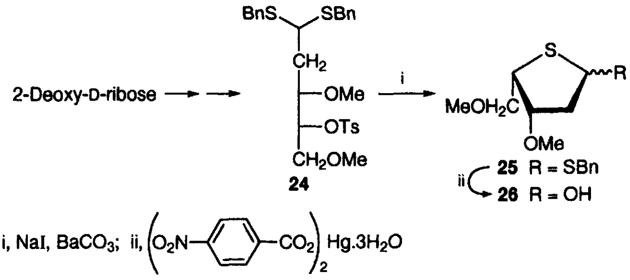


23

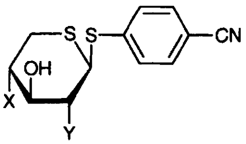
A *de novo* synthesis of 1-deoxy-4-thio-D-ribofuranose (**23**) from methyl 2,5-dihydrothiophene-2-carboxylate has been developed. Key steps were the enzymic resolution of the acetylated reduction product **22** of the starting material and the subsequent *cis*-dihydroxylation without concomitant oxidation at sulfur.[15] 2-Deoxy-D-ribose has been converted to the dimethyl ether **26** of 2-deoxy-4-thio-L-*threo*-pentofuranose in 5 steps *via* dibenzyl dithioacetal derivative **24** and 1,4-dithiosugar derivative **25**, as detailed in Scheme 3. The mechanism of the ring-closure step, which was low-yielding (31%), is briefly discussed.[16]



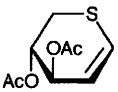
Reagents: i, NaI, $BaCO_3$; ii, $(O_2N-C_6H_4-CO_2)_2Hg.3H_2O$

Scheme 3

Several analogues (compounds **28–30**, **34–36**) of the antithrombotic agent beciparcil (**27**) have been synthesized, using standard reactions. Di-*O*-acetyl-5-thio-D-xylal **31** was the starting compound for making 4-cyanophenyl 2-deoxy-1,5-dithio-β-D-xylopyranoside (**28**)[17] and the 2-azido-2-deoxy derivative **29**,[18] and the 4-azido-4-deoxy analogue **30** was obtained in a multi-step process from L-arabinose diethyl dithioacetal *via* 4-azido-5-benzoylthio-4-deoxy-D-xylose derivative **32**.[19] The thioglucose equivalent **34** of **27** was available from the known *O*-acetyl-protected 5-thio-β-D-glucopyranosyl trichloroacetimidate (**33**), and primary iodination of **34**, followed by acetylation, reduction or elimination, respectively, and deacetylation furnished analogues **35** and **36**.[20] The X-ray analysis of the sulfoxide of beciparcil (**27**) is referred to in Chapter 23.



27 X = Y = OH
28 X = OH, Y = H
29 X = OH, Y = N_3
30 X = N_3, Y = OH



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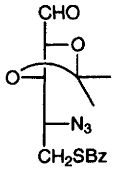

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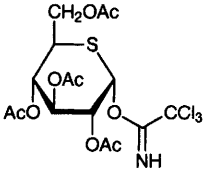

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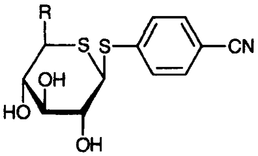
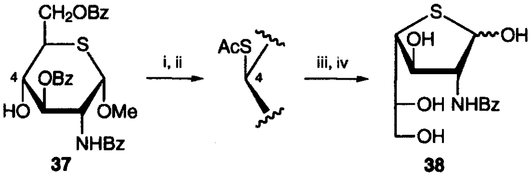


34 R = CH_2OAC
35 R = Me
36 R = $=CH_2$

2-Benzamido-2-deoxy-4-thio-D-galactose **38** has been obtained from methyl 2-benzamido-2-deoxy-β-D-glucopyranoside derivative **37**, as shown in Scheme 4. Following introduction of a sulfur substituent at C-4 *via* a triflate intermediate, Zemplen de-*O*-benzoylation and subsequent acid hydrolysis furnished the free sugar which was present in methanolic solution as an anomeric mixture of thiofuranoses **38**.[21]

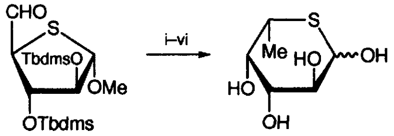


37 **38**

Reagents: i, Tf_2O, Py; ii, KSAc; iii, MeONa, MeOH; iv, H^+, H_2O

Scheme 4

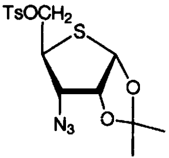
The synthesis of 5-thio-L-fucopyranose (**40**) from dialdopentofuranose derivative **39** involved 1-carbon chain-elongation by use of trimethylaluminium, followed by five conventional reaction steps, including introduction of the sulfur substituent at C-5 by displacement of a triflate with potassium thioacetate (Scheme 5).[22] A similar standard substitution reaction was employed in the preparation of 3-azido-3-deoxy-5-thio-β-D-ribopyranose **42** from 5-*O*-tosylate **41**.[23] 1,5-Dithio-β-D-xylopyranose, as the tri-*O*-acetate **44**, was obtained in a further standard synthesis involving treatment of bromide **43** with thiourea.[24]



39 **40**

Reagents: i, Me_3Al; ii, MsCl, Py; iii, KSAc; iv, LAH; v, Ac_2O, AcOH, H_2SO_4; vi, NaOMe, MeOH

Scheme 5



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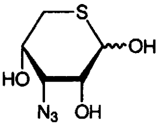

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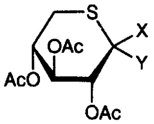
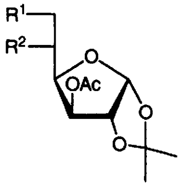
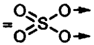


43 X = H, Y = Br
44 X = SH, Y = H

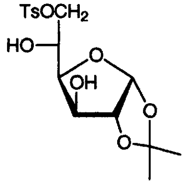
Cyclic sulfates of terminal 1,2-diols were opened with KSAc and KSeCN to give primary thio- and seleno-sugar 5-sulfates, respectively (*e.g.*, **45**→**46** or **47**).[25] In a synthesis of sulfoquinovose (**49**) from D-glucofuranose derivative **48**, the sulfo group was introduced by displacement of the tosylate group at

C-6 with sodium sulfite. Oxidation with iodine, after acid hydrolysis, gave the diacid **50** quantitatively.[26] Monitoring of the regioselective Mitsunobu thiofunctionalization of pentofuranose derivatives by ^{31}P NMR spectroscopy is covered in Chapter 21.



45 R^1 =


46 R^1 = SAc, R^2 = OSO_3Na
47 R^1 = SeCN, R^2 = OSO_3K



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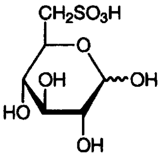

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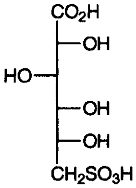

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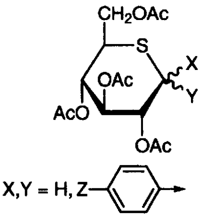
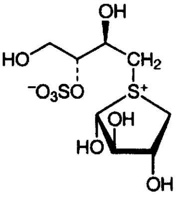


Z = H, OMe, F, Cl, CCl_3, NO_2
51

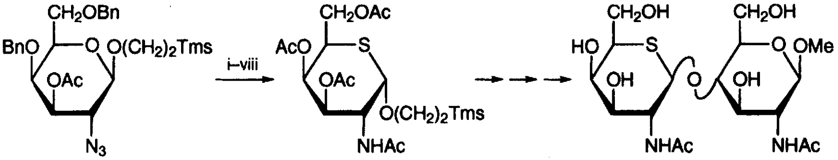


52

The influence of the aglycon structure on the nucleophilicity of the sulfur atoms in aryl 5-thio-α- and β-D-glucopyranoside derivatives has been examined by inspection of Hammett plots of the pseudo-first-order rate constants (k_{obs}) for the oxidation of compounds **51** by MCPBA.[27]

A full report on the reactions of 3,4-*O*-protected 1,2:5,6-dianhydrohexitols with sodium sulfide, producing anhydrothioalditol derivatives with 5-, 6-, and 7-membered rings has been published (see Vol. 29, Chapter 11, ref. 21).[28]

Salacinol (**52**), a natural α-glucosidase inhibitor, is the active principle of a traditional Indian antidiabetic from *Salacia reticulate*.[29]

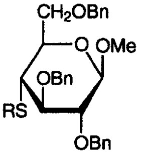


53 **54**

Reagents: i, H_2, Pd/C; ii, Ac_2O, Py; iii, Me_2BBr, Pr^i_2NEt, AcSH; iv, Swern; v, DIBAL; vi, PPh_3, DEAD; vii, Na, NH_3; viii, TFA, CH_2Cl_2

Scheme 6

The 2-acetamido-2-deoxy-5-thio-β-D-galactopyranoside derivative **53**, obtained as shown in Scheme 6, was deprotected and coupled to UDP to serve as donor in the lactase-mediated synthesis of 5′-thio-disaccharide (**54**).[30] In the synthesis of 4-thio-β-cellobioside derivative **55**, the interglycosidic linkage was formed by reaction of tetra-*O*-acetyl-1-thio-β-D-glucopyranose with methyl 2,3,6-tri-*O*-benzyl-4-*O*-triflyl-β-D-galactopyranoside.[31] The same *O*-protected 1-thio-sugar was used in the Michael addition to levoglucosenone to give, after reduction and acetolysis, the 3-deoxy-4-thio-β-cellobioside derivative **56**.[32] Procedures similar to that of ref. 31 have been employed in the synthesis of thio-linked analogues of Lewis x and sialyl Lewis x,[33] and of the ganglioside GM3 epitope,[34] and a series of sulfur-linked oligosaccharides have been prepared chemoenzymically, as inhibitors of 1,3- and 1,4-glucanases.[35] Six easy reaction steps furnished the ganglioside GM1 analogue containing a thioglycosidic bond to ceramide from the natural ganglioside.[36]



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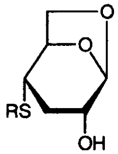

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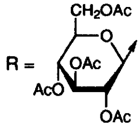

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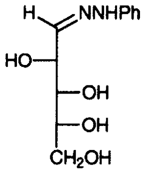
12

Deoxy-sugars

A review on deoxy-sugars and deoxy-sugar oligosaccharides included biological, biochemical and chemical aspects, such as synthesis and chemical as well as enzymic glycoside formation.[1]

Acetylation of aldose phenylhydrazones gave acetylated 1-phenylazoald-1-enitols (*e.g.*, **1**→**2**). On reduction with sodium borohydride these furnished 2-deoxyaldose phenylhydrazones and, after deacetylation and hydrolysis, 2-deoxyaldoses (*e.g.*, **2**→**3**→**4**).[2]



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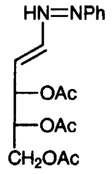

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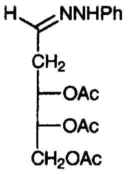

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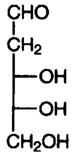

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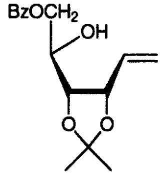

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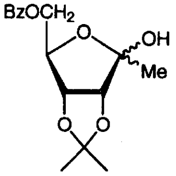


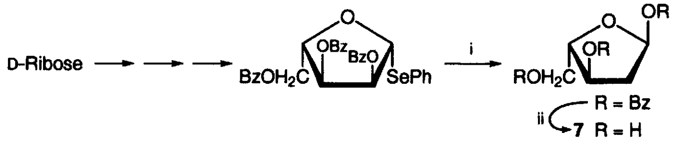
6

Application of the Wacker reaction [Pd(II)-catalysed oxidation of terminal olefins to methyl ketones] to 1,2-dideoxy-hex-1-enitols with unsubstitued OH-5 gave 1-deoxyketofuranoses (*e.g.*, **5**→**6**), the reduction of which to *C*-glycosides on exposure to Et_3SiH is referred to in Chapter 3.[3]

The synthesis of C-3-modified 2-deoxy-D-ribose derivatives is covered in Chapter 2. L-Ribose, obtained from D-ribose *via* 1,2,3,4-tetra-*O*-acetyl-5-*O*-trityl-D-ribitol (see Chapter 2), has been converted to 2-deoxy-L-ribose (**7**) in six steps and 60% overall yield by use of Giese's method, as outlined in Scheme 1.[4]

When 1-xanthates, such as glucose derivative **8**, were heated in cyclohexane in the presence of lauroyl peroxide, clean conversion to 2-deoxy-sugars, in this case compound **9**, took place indicating that, as in Giese's examples, radical migration from C-1 to C-2 had occurred and that the radical at C-2 was capable of abstracting hydrogen from a saturated hydrocarbon.[5]

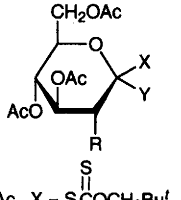
Carbohydrate Chemistry, Volume 31



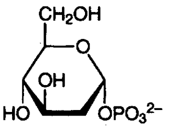
Reagents: i, Bu_3SnH, AIBN; ii, MeO^-, MeOH

Scheme 1

Glycogen phosphorylase in the presence of SiO_2-bound maltopentaose as recyclable primer catalysed the addition of inorganic phosphate to glucal with formation of 2-deoxy-α-D-*arabino*-hexopyranosyl phosphate (**10**).[6]



8 R = OAc, X = $SC(=S)OCH_2Bu^t$, Y = H
9 R = X = H, Y = Ac



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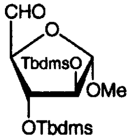
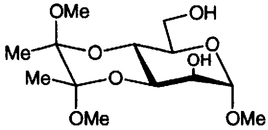


11

L-Fucopyranose has been synthesized from α-D-*arabino*-pentodialdo-1,4-furanoside derivative **11** by reaction with methylmagnesium iodide, followed by deprotection.[7]

The methyl pyranosides of some rare deoxy- and dideoxy-sugars have been obtained from either methyl α-D-manno- or methyl α-D-galactopyranoside *via* the selectively 1,2-diacetal-protected intermediates **12** and **13**, respectively. Deoxygenations at the 6-positions were achieved by iodination/hydrogenation; for the subsequent removal of a secondary hydroxyl group the Barton-McCombie method was employed. An example is given in Scheme 2.[8]



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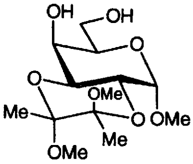

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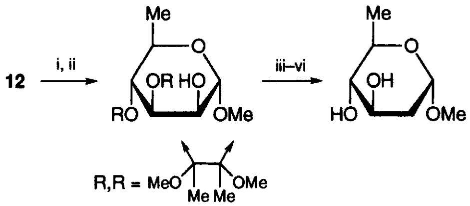
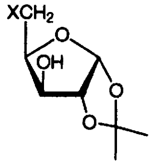
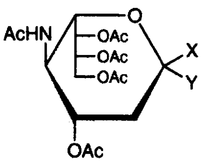


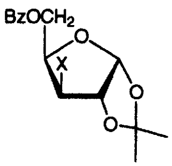
Reagents: i, I_2, PPh_3, Im; ii, H_2, Pd/C; iii, BuLi, CS_2; iv, MeI; v, Bu_3SnH, AIBN; vi, aqu. TFA

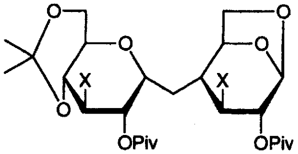
Scheme 2

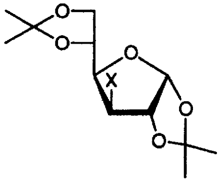
Further deoxygenation of sugars have been carried out by way of iodides (**14**→**15**,[9] **16**→**17**[10]), by photosensitized reductive removal of secondary benzoates (**18**→**19**[11]) and by conventional (**20**→**21**[12]) or catalytic Barton-McCombie reduction (**22**→**23**[13]) which uses Bu_3SnH generated *in situ* using catalytic amounts of $(Bu_3Sn)_2O$ and polymethylhydroxysiloxane as stoichiometric reductant. Routes to 6-deoxy-L-daunosamine from diacetoneglucose using reductive removal of bromine or thionocarbonate groups are covered in Chapter 9.


14 X = I
15 X = H


16 X = I, Y = CO_2Bu^t
17 X = CO_2Bu^t, Y = H


18 X = OBz
19 X = H


20 $X = O\underset{\underset{S}{\|}}{C}OPh$
21 X = H

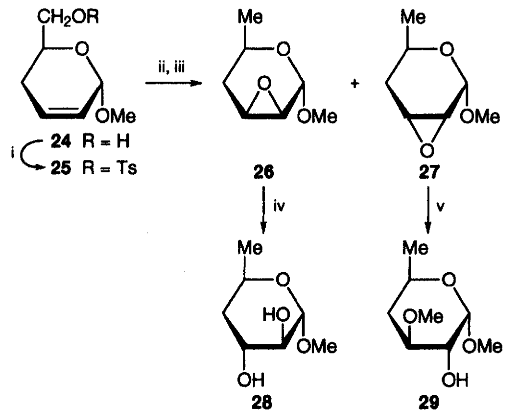

22 $X = O\underset{\underset{S}{\|}}{C}OPh$
23 X = H

Enantiomerically pure 2-hydroxymethyl-2-methoxy-5,6-dihydro-2*H*-pyran (**24**), obtained in a hetero-Diels-Alder reaction with a chiral auxiliary, was first deoxygenated at the primary position *via* tosylate **25**, then epoxidized to give a 2:1 mixture of **26** and **27**. Ring-opening with sodium hydroxide and sodium methoxide, respectively, gave only the *arabino*-product **28** from **26** and mainly the *xylo*-isomer **29** from **27** (Scheme 3).[14]

Attempts to prepare the precursor **30** of rubranitrose (**31**) from the known branched trideoxy-nitrosugar **32** by base-induced epimerization at C-4 *via* a retroaldol process failed, because epimerization occurred also at C-3, producing an isomeric mixture **34**. Inversion of configuration at C-4 was later achieved by way of triflate **33**.[15]

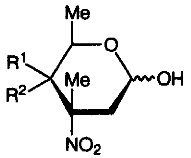
The β,γ-unsaturated α-ketoester **36**, which was readily obtained by reaction of the per-*O*-acetyl-D-gluconic acid-derived Barton ester **35** with ethyl 2-trifluoroacetylacrylate (see D.H.R. Barton *et al*., *Tetrahedron*, 1996, **52**, 2717), has been converted by methoxymercuration to KDO derivative (**37**) and its *gluco*-isomer **38**.[16] The preparation of 2-deoxy- and 2,3-dehydro-2-deoxy-KDN is covered in Chapter 16.

A new route to 6′-deoxy-β-D-glucopyranosyl disaccharides, such as **40**, involved acid-catalysed opening of 1,6-epithio- and 1,6-episeleno-β-D-glucopyranose derivatives, such as **39**, with NIS-triflic acid in the presence of a sugar

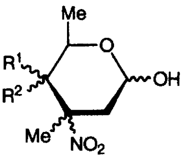


Reagents: i, TsCl, Py; ii, LAH; iii, MCPBA; iv, NaOH, H_2O; v, NaOMe, MeOH

Scheme 3



30 R^1 = OH, R^2 = H
31 R^1 = OMe, R^2 = H
32 R^1 = H, R^2 = OH
33 R^1 = H, R^2 = OTf



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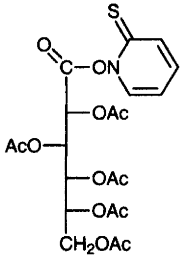

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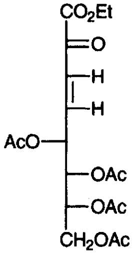

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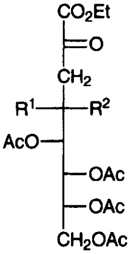
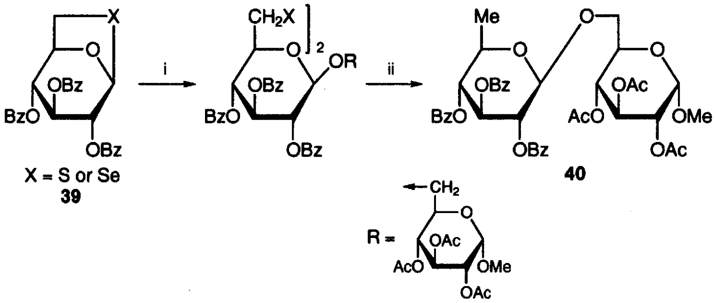


37 R^1 = OMe, R^2 = H
38 R^1 = H, R^2 = OMe

alcohol, followed by reduction of the disulfide- or diselenide-intermediates formed initially (Scheme 4).[17]

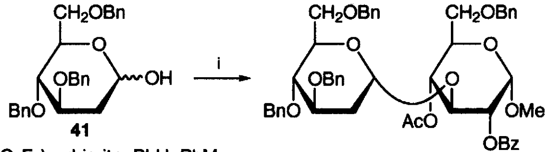
By use of trityl tetrakis(pentfluorophenyl)borate as catalyst, 3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hexopyranose (**41**) has been glycosidated efficiently and with high α-stereoselectivity. An example is given in Scheme 5.[18] The preparation of aryl *C*-2-deoxyglycosides is covered in Chapter 3, and studies on the stereoselective synthesis of 2-deoxy-β-glycosides by way of 2-thiosugar derivatives are referred to in Chapter 11.

6-Deoxy-2-*O*-methyl-β-D-glucopyranosyl residues have been found in toxicariosides B and C, isolated from the latex of *Antiaris toxicaria*.[19] Toxicario-



Reagents: i, ROH, NIS, TfOH; ii, Bu_3SnH, AIBN

Scheme 4



Reagent: i, $TrB(C_6F_5)_4$, drierite, PhH, PhMe

Scheme 5

side A, a dart poison from the same latex, is referred to in Chapter 5. A polyhydroxylated spirostanol saponin from the tubers of *Brodiaea californica* contained a 6-deoxy-β-D-gulopyranosyl residue, the first report of this sugar in a saponin.[20]

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13

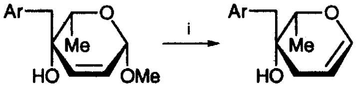
Unsaturated Derivatives

1 General

A review covering the following reactions has appeared: the transition metal (mainly palladium)-catalysed Heck-type couplings of glycals with arenes to give 2,3-unsaturated aryl *C*-glycosides, Stille-type couplings of 1-iodo- or 1-tri-*n*-butylstannyl-glycals with aryl-zinc or -boron compounds to afford 1,2-unsaturated aryl *C*-glycosides and the additions of anions (*e.g.* malonate) to the π-allyl complexes derived from 2,3-unsaturated pyranosides to produce 2,3-unsaturated *C*-glycosides.[1]

2 Pyranoid Derivatives

2.1 1,2-Unsaturated Cyclic Compounds and Related Derivatives – 4-*C*-Substituted hex-2-enopyranosides underwent a reductive rearrangement reaction when treated with lithium aluminium hydride affording good yields of 3-deoxy-glycals (Scheme 1). Several other examples were described and the importance of the tertiary OH group was discussed.[2]



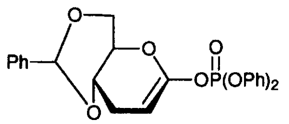
Reagent: i, LAH

Scheme 1

The reaction of 4,6-*O*-benzylidene-2,3-dideoxy-D-*erythro*-hexono-1,5-lactone with strong base followed by quenching with diphenylphosphoryl chloride gave the cyclic ketene acetal phosphate **1**. This latter compound readily underwent a Pd(0)-catalysed coupling with vinyltributylstannane to give the conjugated diene **2**. A similar reaction sequence was also performed on 3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hexono-1,5-lactone.[3]

The glycal-carbene complexes **3** were produced by treating the corresponding 1-lithiated glycal derivative with metal (Cr, Mo, W) hexacarbonyl complexes followed by trimethyloxonium tetrafluoroborate. Compound **3**

Carbohydrate Chemistry, Volume 31



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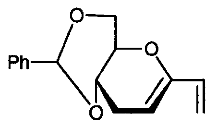

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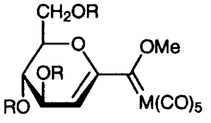
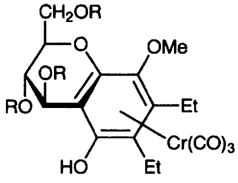


3 M = Cr, Mo, W; R = $SiPr^i_3$



4 R = $SiPr^i_3$

(M = Cr) underwent a benzannulation reaction with 3-hexyne affording a moderate yield of benzoglycal **4**.[4] (See Sections 2.2.2 and 4 for related work).

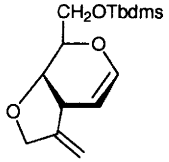
A significantly improved yield of 3,4-di-*O*-acetyl-L-fucal over previously reported methods has been obtained by treating per-acetylated L-fucopyranose with titanium tetrabromide followed by standard reductive elimination of the resulting glycosyl bromide with zinc.[5] (See next Section also for the dimerization of this and other glycals).

A report that the formation of 1-cyano-3,4,6-tri-*O*-acetyl-D-galactal proceeded by a free radical chain mechanism, when the corresponding per-acetylated 1-bromogalactopyranosyl cyanide was treated with zinc in the presence of a N-base, has appeared.[6]

The Pd(0)-promoted Heck-type cyclization of ethyl 4-*O*-(2-bromoprop-2-enyl)-6-*O*-Tbdms-2,3-dideoxy-α,β-D-*erythro*-hex-2-enopyranoside gave the branched-chain glycal **5**. As well as ring closure, double bond migration occurred with ejection of the OEt group. In contrast, the corresponding D-*threo* starting material gave an acyclic derivative (see Section 4) as a result of ejection at O-5 instead of the aglycon. Other examples of these processes were also described.[7] Standard 'one pot' methodology has been used to prepare tri-*O*-acetyl-D-[1,2,3,4,5,6-$^{13}C_6$]glucal from D-[U-^{13}C]glucose. The related, labelled D-[1,2,3,4,5,6-$^{13}C_6$]galactal derivative **6** was also prepared from the same starting material by a sequence of reactions in which the configuration at C-4 was inverted by use of a Mitsunobu process.[8]

The glycal derivative **7** was formed when alkyn-ol **8** was treated with a tungsten- or molybdenum-pentacarbonyl complex. (See also Vol. 30, p. 180, ref. 39 for related work).[9]

Full details of the mechanism of action of bacterial UDP-*N*-acetylglucosa-



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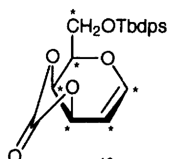
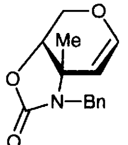


6 * = ^{13}C



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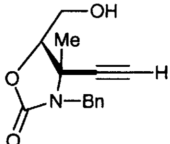

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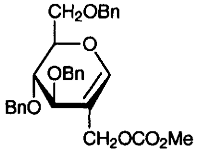
mine-2-epimerase have been elucidated with the aid of kinetic isotope effect measurements. 2-Acetamidoglucal is an enzyme-bound intermediate in the process. (See preliminary report, Vol. 30, p. 174, ref. 13).[10]

Alcohols and activated methylene compounds reacted with the branched glycal-carbonate derivative **9** in the presence of Pd(0) to yield 2-deoxy-2-*C*-methylene *O*- and *C*-glycosides, respectively. For example, with *p*-cresol the aryl glycoside **10** was produced and with dimethyl malonate compound **11** was formed. Secondary hydroxyl groups in sugars also participated in the reaction.[11]



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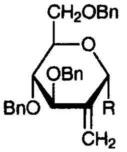
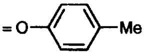
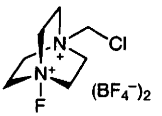


10 R = 

11 R = CH(CO$_2$Me)$_2$



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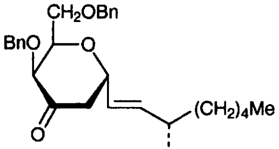

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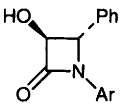

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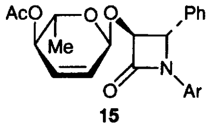

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Pyranoid (and also furanoid, see Section 3.1) glycals underwent a facile reaction with ‘selectfluor’ (**12**) in aqueous or alcoholic media to give 2-deoxy-2-fluoro-pyranoses or -pyranosides, respectively. For example, 3,4-di-*O*-acetyl-L-fucal on treatment with **12** in aqueous DMF gave 3,4-di-*O*-acetyl-2-deoxy-2-fluoro-L-fucopyranose, whereas the same glycal on treatment with **12** and anhydrous benzyl alcohol in acetonitrile afforded benzyl 3,4-di-*O*-acetyl-2-deoxy-2-fluoro-β-L-fucopyranoside.[12]

It has previously been reported that addition of malonyl radicals [formed from dialkyl malonates using Mn(OAc)$_3$ as oxidant] to hexopyranoid glycals in the presence of alcohols yielded 2-*C*-branched-chain-2-deoxypyranosides, but that an undesired Ferrier rearrangement suppressed the yields. Use of CAN as oxidant proved to be superior with no rearrangement observed (See Vol. 30, p. 189, ref. 19 and p. 177, ref. 26) Full details of this reaction have now been published and its scope extended to pyranoid pentoses.[13]

Pyranoid (and also furanoid, see Section 3.1) glycals underwent reaction with the manganese complex, nitrido[*N*,*N*′-(1,1,2,2-tetramethyl)ethylenebis(salicylideneaminato)]manganese(V) and trifluoroacetic anhydride followed by treatment with silica gel or aqueous acid to afford 2-deoxy-2-trifluoroacetamidopyranoses in high yield. Stereoselectivity was observed and resulted in the introduction of the N-function *trans* to the substituents at C-3.[14]

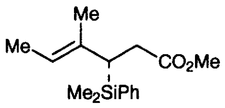
The *C*-glycoside **13**, a potential thromboxane precursor, was conveniently prepared by adding the (*E*)-vinyl cuprate derived from 3-*tert*-butyldiphenylsiloxy-oct-1-ene to 4,6-di-*O*-benzyl-1,2-dideoxy-D-*threo*-hex-1-enopyranos-3-ulose. Studies have also shown that other anions (*e.g.* LiCX(SMe) where X = SMe or $SiMe_3$) add in a similar 1,4-manner. In contrast, the 6-deoxy-5-*epi*-analogue of the enone, accepts anions giving rise to mixtures of 1,2- (to the C=O) and 1,4-products.[15]

The synthesis of 2-deoxy-α-D-*arabino*-hexopyranosyl phosphate from D-glucal and glycogen phosphorylase using a silica bound maltopentaose primer is covered in Chapter 12 and the synthesis of oligosaccharides composed of 2-deoxy-β-D-glucose units from D-glucal and glycogen phosphorylase is mentioned in Chapter 3. The electrophilic addition of various halogen-containing reagents to tri-*O*-benzyl-D-glucal is noted in Chapter 8.

2.2 2,3-Unsaturated Cyclic Compounds

2.2.1 Syntheses Involving Allylic Rearrangements of Glycals. – The racemic β-lactam compound **14** (one enantiomer depicted for clarity) has been resolved by iodine-promoted Ferrier reaction with 3,4-di-*O*-acetyl-L-rhamnal to give **15** (together with the corresponding separable diastereomer) followed by acid-catalysed hydrolysis.[16]

Tri-*O*-acetyl-D-glucal reacted with the chiral (*E*)-crotylsilane **16** in the presence of boron trifluoride etherate to afford unsaturated derivative **17** with a d.e. > 30:1. Examples were also described using other silanes and also involving tri-*O*-acetyl-D-galactal.[17]



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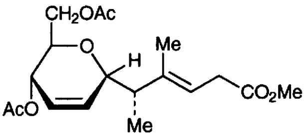

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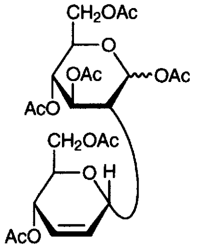
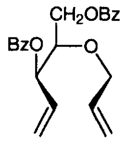


18

Improved methods have been reported for preparing *C*-linked disaccharides by the Lewis-acid catalysed dimerization of tri-*O*-acetyl-D-glucal, -D-galactal and 3,4-di-*O*-acetyl-L-fucal. For example tri-*O*-acetyl-D-glucal gave a 55% yield of the known **18**. In addition, dihydroxylation of the double bond of **18** proceeded unexpectedly with high *allo* selectivity. (See Vol. 30, p. 176, ref. 21 for related work).[5]

2.2.2 Other Syntheses and Reactions. – Alkene metathesis reaction of D-*threo*-derivative **19** catalysed with Grubbs' reagent ($[(C_6H_{11})_3P]_2Cl_2Ru{=}CHPh$) gave a 90% yield of 1,5-anhydro-4,6-di-*O*-benzoyl-2,3-dideoxy-D-*threo*-hex-2-enitol.[18]

The branched-chain α-D-*erythro*-hex-2-enopyranoside **20**, conveniently prepared by Claisen-Meerwein-Eschenmoser rearrangement of methyl 6-*O*-Tbdps-3,4-dideoxy-α-D-*erythro*-hex-3-enopyranoside with $MeC(OMe)_2NMe_2$ (see Vol. 24, p. 157, ref. 18), was selectively epoxidized to the α-D-*allo*-derivative under Payne's conditions (perbenzimidic acid) as a useful intermediate in the preparation of thromboxane A2. The unexpected formation of this epoxide was explained through H-bond interaction of the C=NH group of the epoxidzing agent with the anomeric methoxy or 4-*C*-(*N*,*N'*-dimethylcarboxamido)methyl substituent resulting in a favourable orientation for *allo*-epoxidation. The α-D-*manno*-epoxide expected under these conditions was not observed. In contrast the D-*threo*-derivative **21**, prepared in a similar manner from methyl 6-*O*-Tbdps-3,4-dideoxy-α-D-*threo*-hex-3-enopyranoside, led *via* the presumed D-*gulo*-epoxide only to a low yield of D-*galacto*-lactone **22**.[19]



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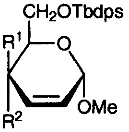
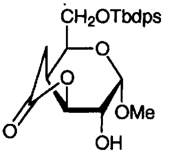


20 $R^1 = H$, $R^2 = CH_2C(O)NMe_2$
21 $R^1 = CH_2C(O)NMe_2$, $R^2 = H$



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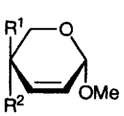
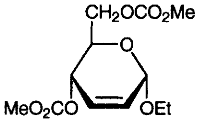


23 $R^1 = CH(CO_2Et)_2$, $R^2 = H$
24 $R^1 = H$, $R^2 = CH(CO_2Et)_2$



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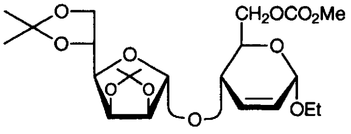
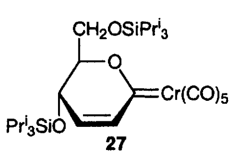


26

It has been observed that reaction of sodio diethyl malonate with methyl 4-*O*-benzoyl-2,3-dideoxy-β-L-*glycero*-pent-2-enopyranoside or methyl 4-*O*-benzoyl-2,3-dideoxy-α-D-*glycero*-pent-2-enopyranoside in the presence of Pd(0) afford the substitution products **23** and **24**, respectively, with overall retention of configuration. (See Section 2.3 for a different outcome when branching groups are present in the C-5 position).[20] In a similar way Pd(0)-catalysed coupling of allylic carbonate **25** with 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose gave unsaturated disaccharide **26**.[21]

The preparation of 4-amino-4,6-dideoxy-D-mannose (D-perosamine) and of vicenisamine (found in the antibiotic vicenistatin) involved in the key step allyl cyanate to allyl isocyanate rearrangements (the double migrating from a 3,4- to a 2,3-position). (See Vol. 30, p. 178, ref. 30 and Vol. 28, p. 178, ref. 32).[22]

The α,β-unsaturated glycosylidene complex **27** was prepared from 1-*C*-lithio-3,4,6-tri-*O*-isopropylsilyl-D-glucal by treatment with a chromium pentacarbonyl complex containing triphenylphosphine ligands. Compound **27** underwent reaction with ethoxyethyne to give **28** in which the OEt group was easily displaced by ammonia. (See also Section 4 for the direct reaction of **27** with ammonia).[4]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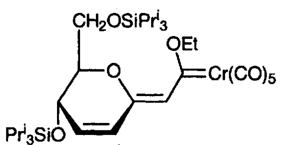
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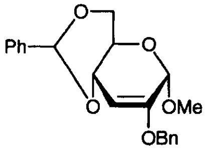
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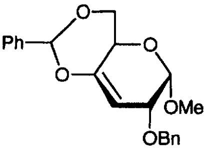
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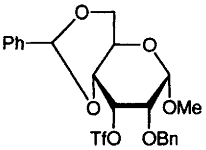
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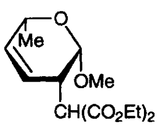

32

In previous reports it has been shown that certain carbohydrate triflates, depending on the configuration of the sugar, reacted with the strong bases methyl- or butyl-lithium to give unsaturated or ketonic products of which the latter reacted further. Although the formation of the unsaturated products appeared to have resulted from an overall β-elimination (E-2 elimination) process, deuterium labelling experiments indicated that a mechanism involving an initial α-hydrogen abstraction at the carbon bearing the OTf group took place first followed by a 1,2-H shift then loss of CF_3SO_3Li. (See Vol. 30, p. 185, ref. 3 and p. 180, ref. 41). Full details and further examples addressing this mechanistically interesting reaction have now appeared. For example deuteration studies have shown that methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-triflyl-α-D-glucopyranoside gave the products **29** and **30**, by a mechanism involving an initial α-hydrogen abstraction. In contrast the *allo*-triflate **31** gave only **30**, but involved a mixture of initial α- and coventional β-hydrogen loss processes.[23] Further investigations by the same group have also demonstrated that when the milder base potassium *tert*-butoxide (KOBu^t) was used a similar pathway operated in the 3-*O*-triflyl-glucopyranoside series as seen with strong bases, affording the same products as above, *i.e.* those arising by an initial α-hydrogen abstraction. With 3-*O*-triflyl-allopyranosides and KOBu^t, products formed by initial β-hydrogen loss predominated. The use of pyridine as base was also investigated but led only to 3-pyridinium derivatives. (See Section 3.2 also).[24]

Reactions at the carbonyl groups of 2,3-unsaturated enones, involving Horner-Wadsworth-Emmons olefination or addition of allyl- or aryl-lithiums resulting in unsaturated branch-chain sugars, is mentioned in Chapter 14. Also covered in Chapter 14 are the preparations of branched 3-*C*-derivatives from protected 2,3-dideoxy-3-*O*-triflyl-hex-2-enpyranoside derivatives and of tricyclic systems formed by cyclization of 4-*O*-(2-propynyl)-2,3-unsaturated sugar derivatives. The preparation of cyclopentane-based compounds from 2,3-unsaturated-aldono-1,4-lactones is noted in Chapter 18.

2.3 3,4-Unsaturated Cyclic Compounds – Reaction of sodio diethyl malonate with methyl 4-*O*-benzoyl-2,3,6-trideoxy-β-L-*threo*-hex-2-enopyranoside afforded a 1:5 mixture of the rearranged branched-chain sugar **32** and the product formed by nucleophilic displacement of the ester group with retention of configuration (see Section 2.2.2) as products. When the reaction was conducted on the substrate lacking the methoxy group, rearrangement became the major pathway.[20]

2.4 5,6-Unsaturated Cyclic Compounds – Full details have been reported on the simple preparation of the ketopyranoside glycal, methyl 5-deoxy-4-*O*-Tbdms-1,3-*O*-isopropylidene-β-D-*threo*-hex-5-en-2-ulopyranoside, used to make the synthetically useful vinylogous lactone **33**. (See Vol. 28, p. 170, ref. 4 for preliminary details).[25]

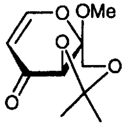
3 Furanoid Derivatives

3.1 1,2-Unsaturated Cyclic Compounds – Two new methods for the synthesis of furanoid glycals have been reported. Various *O*-protected (allyl, benzyl, benzoyl and pivaloyl) D-*allo*-, D-*galacto*-, D-*ribo*- and D-*xylo*-pento- and hexofuranose 1,2 diols were treated with a mixture of triphenylphosphine, imidazole and iodine to give high yields of products. Alternatively, conversion of the 1,2-diols into their respective 1,2-thionocarbonates with thiophosgene followed by heating with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine also gave good yields.[26] Furanoid glycals, prepared by the first method, have been converted into 2-deoxy-2-iodo nucleoside derivatives (see Chapter 20).

Reaction of 1,4-anhydro-2-deoxy-3,5-di-*O*-benzyl-D-*erythro*-pent-1-enitol with 'selectfluor' (**12**) in aqueous media gave a high yield of 3,5-di-*O*-benzyl-2-deoxy-2-fluoro-D-*arabino*-pentofuranose.[12] Furanoid glycals could be converted in a stereoselective way into 2-deoxy-2-trifluoroacetamido-derivatives by use of trifluoroacetic anhydride and a manganese complex followed by treatment with acid. (See Section 2.1 for the same reaction with pyranoid glycals). Overall, yields were higher with the more reactive furanoid glycals as compared with their pyranoid counterparts.[14]

A large scale adaptation of a previously reported method (see Vol. 28, p. 170, ref. 1) for converting *O*-protected-2-deoxy-thymidine derivatives into protected furanoid glycals by use of 1,1,1,3,3,3-hexamethyldisilazane-ammonium sulfate has been described.[27]

3.2 2,3-, 3,4- and 5,6-Unsaturated Cyclic Compounds – In an attempt to react sodio acetophenone with the carbonyl group of 2,3,5-tri-*O*-benzyl-D-*arabino*-pentono-1,4-lactone, elimination product **34** unexpectedly formed (presumably through enolate formation followed by β-elimination). The formation of 2,5-di-*O*-benzyl-3-deoxy-D-*glycero*-pent-2-enono-1,4-lactone was not observed. This unusual type of elimination has been observed before when 2,4,6-tri-*O*-benzyl-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone resulted after 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone was treated with sodio acetophenone. (See S.B. Rosenblum *et al.*, *J. Am. Chem. Soc.*, 1990, **112**, 2746; Y. Tsuda *et. al.*, *Chem. Pharm Bull.*, 1980, **28**, 3223; and R.H. Hall *et. al.*, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2236).[28]



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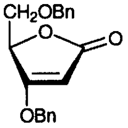

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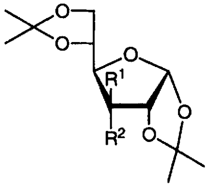
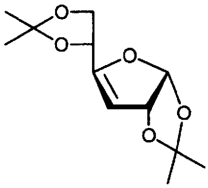


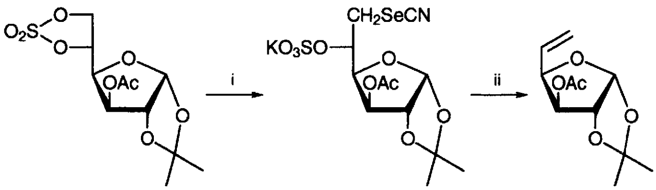
35 R^1 = OTf, R^2 = H
36 R^1 = H, R^2 = OTf



37

It has previously been reported that 3-*O*-triflyl-α-D-glucofuranose derivative **35** reacted with the strong bases methyl- or butyl-lithium affording the corresponding 3,4-elimination product **37**. The formation of **37** appeared to have been formed by an overall β-elimination (E-2 elimination) process but it was shown by deuteration studies to involve an initial α-hydrogen abstraction at the carbon bearing the OTf group followed by a 1,2 hydride shift then loss of CF_3SO_3Li. In contrast, reaction of the α-D-allose-derivative **36** with the same bases gave a 3-oxo product, again by initial abstraction of the α-hydrogen followed by loss of CF_3SO_2Li. (See Vol. 30, p. 185, ref. 3 and p. 180, ref. 4). In an extension of these studies, and by the further use of deuterium labelled compounds, it has been shown that treatment of **35** or **36** with the milder base potassium *tert*-butoxide both gave **37** but by a process involving an initial β-hydrogen loss. The use of other bases such as pyridine or sodium methoxide with **35** gave a preponderance of **37** mainly by β-hydrogen abstraction, but reaction of **36** with pyridine gave only a 3-pyridinium derivative.[24]

A 'one pot' process for converting cyclic sulfates of furanoid 5,6-diols into 5,6-unsaturated sugars is illustrated in Scheme 2. Several other examples were described.[29]



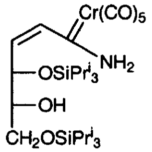
Reagents: i, KSeCN; ii, NaBH$_4$, MeOH

Scheme 2

4 Acyclic Derivatives

The reaction of the α,β-unsaturated glycosylidene complex **27** with ammonia led to the amino carbene complex **38** in high yield.[4]

Ethyl 4-*O*-(2-bromoprop-2-enyl)-6-*O*-Tbdms-2,3-dideoxy-α,β-D-*threo*-hex-2-enopyranoside underwent a Pd(0)-catalysed Heck-type coupling to afford compound **39**. (See Section 2.1 for a different outcome with the *erythro* derivative).[7]



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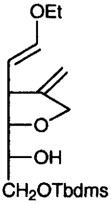

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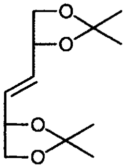
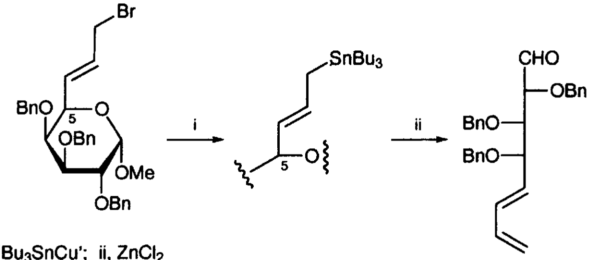


40

Treatment of 1,2:5,6-di-*O*-isopropylidene-3,4-di-*O*-mesyl-D-glucitol with lithium phenyl selenide (PhSeLi) formed *in situ* from a mixture of lithium triethylborohydride and diphenyl diselenide gave (*E*)-alkene **40** in 77% yield The same reagent, however, failed to convert 1,2-*O*-isopropylidene-5,6-di-*O*-mesyl-3-*O*-methyl-α-D-glucofuranose into its 5,6-unsaturated derivative.[30]

Full details of an earlier report (see Vol. 30, p. 180 and p. 182, ref. 36) on the use of tributyltin cuprate as a mild alternative to tributyltin lithium in the preparation of unsaturated derivatives such as that shown in Scheme 3 have been reported.[31]



Reagents: i, 'Bu$_3$SnCu'; ii, ZnCl$_2$

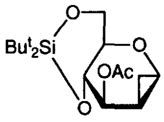
Scheme 3

The diastereoselective addition of azomethine imines to various acyclic 5,6-unsaturated aldehydes affording highly functionalized cyclopentanoids is mentioned in Chapter 18.

5 Miscellaneous Compounds

Addition of diethylzinc-diiodomethane to 4,6-*O*-di-*tert*-butylsilanediyl-D-glucal, followed by reaction with acetic anhydride-pyridine, gave the cyclopropane compound **41**. Trimethylsilyl triflate-catalysed reaction of **41** with various silylated nucleophiles led to mixtures of oxepanes **42** and eliminated product

43. (See Vol. 30, p. 189, ref. 21 and Vol. 29, p. 197, ref. 28 and p. 187, ref. 24 for similar work).[32] In a related paper, oxepane **44** was obtained when the dibromocyclopropane derivative **45** was treated with potassium carbonate-methanol.[33]



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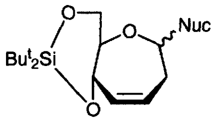
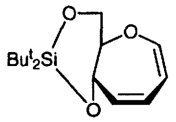


42 Nuc = N_3, CN, H, All, CH_2CO_2Et



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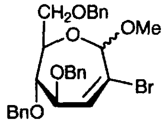

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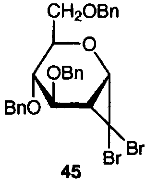

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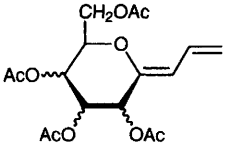

46

Reaction of 2,3,4,6-tetra-*O*-acetyl-1-bromo-β-D-hexopyranosyl chlorides with tributylallyltin then DBU gave *C*-glycodienes **46** in moderate yields.[34]

The addition of the radical generated from thioacetic acid to 2,6-anhydro-1-deoxy-D-*gluco*-hept-1-enitol derivatives is covered in Chapter 11.

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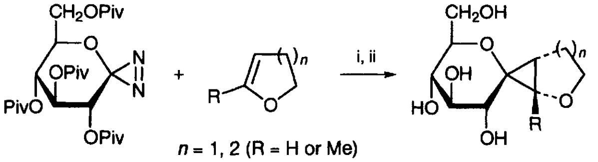
14

Branched-chain Sugars

1 Compounds with a $\mathrm{C{-}\overset{\displaystyle R}{\underset{\displaystyle O}{C}}{-}C}$ Branch-point

1.1 Branch at C-1 or C-2

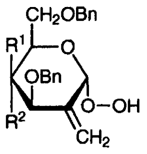
1.1 Branch at C-1 or C-2 – *O*-Pivaloyl-protected glycosyl diazirines reacted with cyclic enol ethers in a higher yield than did the corresponding *O*-benzyl protected derivatives to give *spiro* products, as indicated in Scheme 1.[1]



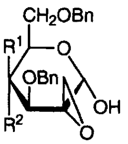
Reagents: i, 45°C or *hν*; ii, Bu_4NOH

Scheme 1

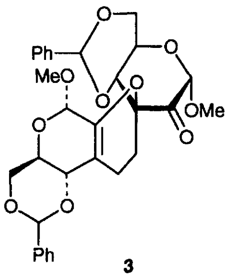
The glycosyl hydroperoxides **1**, prepared from the corresponding methyl glycosides by reaction with hydrogen peroxide-molybdenum(VI) oxide, underwent rearrangement in the presence of titanium(IV) isopropoxide to afford **2** and the pyranose C-1-OH forms of **1**.[2]



1 $R^1 = H$, $R^2 = OBn$
or $R^1 = OBn$, $R^2 = H$



2 $R^1 = H$, $R^2 = OBn$
or $R^1 = OBn$, $R^2 = H$



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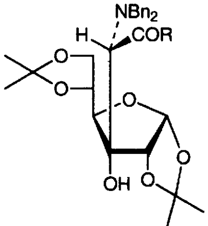
1.2 Branch at C-3 – Dimerization of methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-methylene-α-D-*erythro*-hex-2-ulopyranoside by an inverse demand hetero

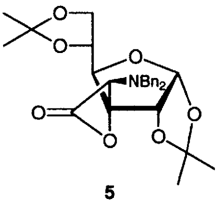
Carbohydrate Chemistry, Volume 31

Diels-Alder reaction gave product **3**.[3] A quantum AM1 study of this reaction was performed to account for the observed regio- and stereo-selectivity.[4]

Common starting materials for the synthesis of C-3 branched sugars are 3-ulose derivatives. Thus the branched-chain amino acid derivative **4** was produced by addition of a protected glycine enolate to the corresponding 3-ulose compound. Saponification of the methyl ester in **4**, followed by intramolecular lactonization, afforded **5**.[5] Further reaction of **5** with glycine methyl ester in dichloromethane containing DMAP gave peptide derivative **6**. This latter step was also performed with derivatives of alanine and phenylalanine.[6]



4 R = OMe
6 R = NHCH$_2$CO$_2$Me



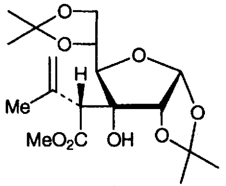
5

Condensation of the anion derived from methyl 3,3-dimethyacrylate with 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hex-3-ulofuranose afforded a mixture of **7** (α-anion attack) and **8** (γ-anion attack). Successive reaction of **8** with hydrogen peroxide, lithium aluminium hydride, aqueous mineral acid and sodium periodate afforded (*R*)-mevalonolactone. A fully deuterated (*R*)-mevalonolactone analogue was also prepared in the same way using $(C^2H_3)_2C{=}C^2HCO_2Me$ and $LiAl^2H_4$ as reagents.[7]

Wittig reaction of 5-azido-6-*O*-Tbdps-5-deoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hexos-3-ulofuranose with (ethoxycarbonylmethylene)triphenylphosphorane, followed by removal of the silyl protecting group, led to the formation of **9** as a precursor of C-3 branched analogues of 3,6-anhydrodeoxynojirimycin.[8]

The 3-*C*-allyl-2-deoxy compounds **10**, **11**[9] and 3-*C*-allyl compound **12** [10,11] were all prepared by initial addition of allylmagnesium bromide to the corresponding 5-*O*-silyl-protected 3-ulose compounds, followed by de-silylation then acetylation or benzylation under standard conditions. Compound **12** was further transformed into the bicyclic derivative **13** by successive treatment with methanolic hydrochloric acid, borane, tosyl chloride-pyridine and potassium hydroxide. Compounds **10** – **12** were useful precursors for the synthesis of nucleoside analogues. The preparation of some 2′-deoxy-3′-*C*-ethynyl-, 2′-deoxy-3′-*C*-difluoromethyl- and 2′,3′-dideoxy-3′-*C*-difluoromethylene-nucleosides are covered in Chapter 20.

The mono lithium salt derived from 2,6-dibromopyridine added smoothly to 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hex-3-ulofuranose affording **14**,[12] and from the same ulose, a wide range of C-3 branched compounds have been made through the intermediacy of the previously reported (Vol. 30, p. 186, ref.



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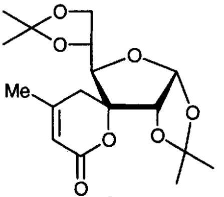

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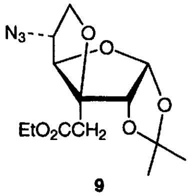

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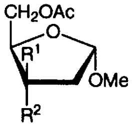
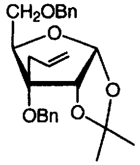


10 R^1 = All, R^2 = OAc
11 R^1 = OAc, R^2 = All



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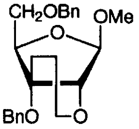

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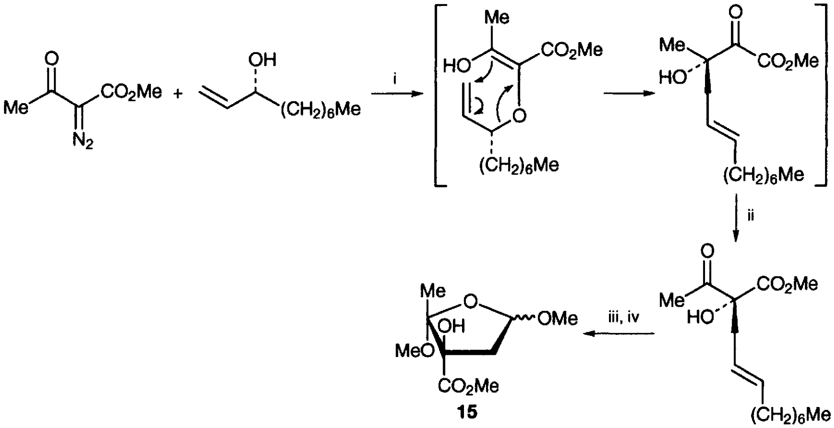
9) 3-deoxy-3-*C*-(dichloromethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose, whose chemistry proceeds *via* a *spiro*-chloro-epoxide intermediate. (See also ref. 27 for related work).[13]

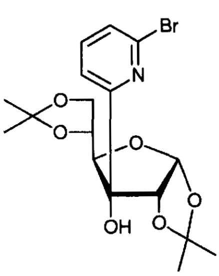
The marine sponge *Callipelta* sp. yielded the bioactive 14-membered ring macrolides callipeltosides B and C containing 4,6-dideoxy-2-*O*-3-*C*-dimethyl-4-formamido-β-talopyranosyl- and 4,6-dideoxy-2-*O*-3-*C*-dimethyl-β-mannopyranosyl-units, respectively. The absolute stereochemistries of the sugars were not determined.[14]



Reagents: i, $Rh_2(OAc)_4$; ii, $BF_3{\cdot}OEt_2$; iii, O_3, DMS; iv, *p*-tsa, MeOH

Scheme 2

In the synthesis of compounds structurally related to staurosporine, an asymmetric approach to branched-chain sugar **15** has been adopted (Scheme 2). The rhodium-catalysed carbene insertion into the chiral decenol, followed by a [3,3] sigmatropic rearrangement and Lewis acid-catalysed 1,2-allyl migration all take place in 'one pot'. Compound **15** was further transformed into the protein kinase C inhibitor (+)-K252a (**16**). The enantiomer of **15** was also



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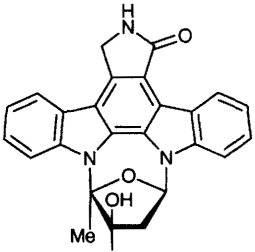
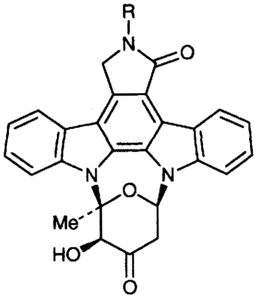
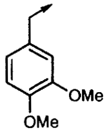


16 R = CO_2Me
18 R = CHO

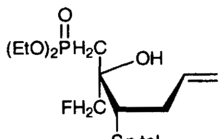


17 R =



prepared by an identical method but (*S*)-(+)-1-buten-3-ol was used as chiral starting material. The enantiomer of **16**, (−)-K252a, was thereby obtained.[15] Furanoid compound **16** was also transformed into the pyranoid derivative **17** by boron trifluoride etherate treatment of the easily prepared derivative **18** (2 steps from **16**). Compound **17** acted as a precursor for the synthesis of (+)-staurosporine and a range of related analogues.[16]

1.3 Branch at C-4 – The chiral, non-carbohydrate derived compound **19** was transformed into **20** by reaction with 'ruthenium tetroxide' then acetic anhydride-pyridine, as an intermediate in the synthesis of branched-chain nucleoside analogues.[17]



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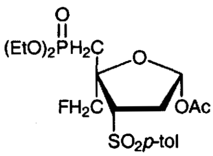

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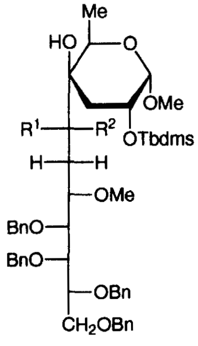
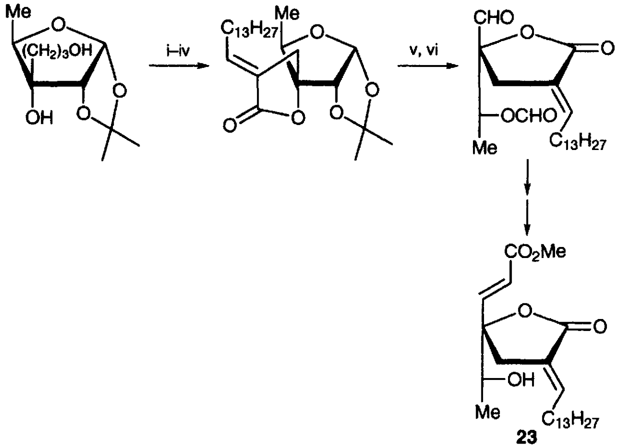


21 $R^1,R^2 = O$
22 $R^1 = H$, $R^2 = OH$

The relative configuration of the recently isolated antigenic lipooligosaccharide LOS (III) from *Mycobacterium gastri* has been established by synthesis. The key step involved the samarium diiodide-promoted coupling of methyl 2-*O*-Tbdms-3,6-dideoxy-α-D-*erythro*-hex-4-ulopyranoside with 2-deoxy-3-*O*-methyl-4,5,6,7-tetra-*O*-benzyl-D-*galacto*-heptonoyl chloride to give the ketone derivative **21**. Protection of the tertiary OH as a Tms ether, then reduction of the ketone with Red-Al (which also resulted in loss of the Tms group) gave **22**, which was methylated at the secondary alcohol, de-benzylated and de-silylated to give the product.[18]

Compound **23**, containing an (*R*)-1-hydroxyethyl branching group was synthesized, as shown in Scheme 3, as a semi rigid lactone with structural similarities to bryostatins and debromophysiatoxin.[19]

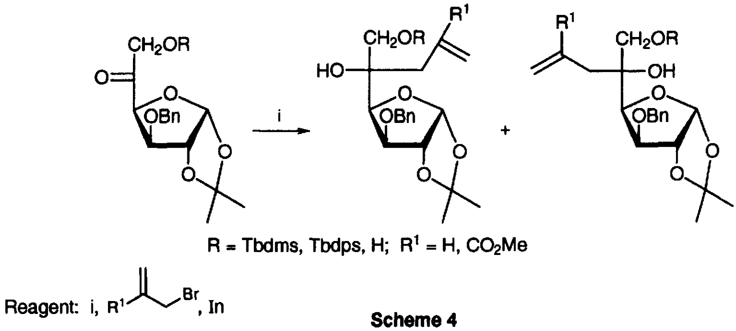


Reagents: i, PCC; ii, LiHMDS, $C_{13}H_{27}CHO$; iii, MsCl, Et_3N; iv, DBU; v, HCl; vi, $NaIO_4$

Scheme 3

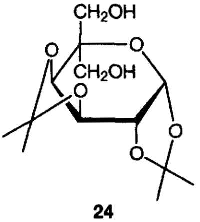
Butyl-, benzyl- and 2,5-dimethyl-4-methylphenyl-lithium added with increased stereoselectivity to the carbonyl groups (1,2-addition) of ethyl 6-*O*-Tbdms-2,3-dideoxy-α-D-*glycero*-hex-2-en-4-ulopyranoside and methyl 2,3,6-trideoxy-α-L-*glycero*-hex-2-en-4-ulopyranoside to give epimeric mixtures of 4-*C*-branched products. In contrast, 2,5-dimethoxybenzyllithium gave a mixture of 1,2- and 1,4-addition (Michael-like) products.[20]

1.4 Branch at C-5 – A new route to chiral tertiary alcohols involving the indium-promoted coupling of a ketone with an allyl bromide is shown in Scheme 4. Selectivities ranged from 80:20 to 98:2 for the D:L isomers.[21]



Scheme 4

The syntheses, involving Cannizzaro reactions, of a series of 5-*C*-hydroxymethyl-hexoses which are resistant to metabolism have been described. For example, treatment of 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose with formaldehyde and aqueous sodium hydroxide solution gave **24**. The aldehyde function in the starting material was introduced by standard chemical oxidation of the corresponding alcohol and the sequence was also applied to D-glucopyranose, D-mannopyranose and D-fructopyranose derivatives. Alternatively, by use of a purified D-galactose oxidase, unprotected *galacto*-sugar derivatives could be oxidized in aqueous solution and in high yield.[22]



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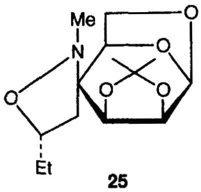

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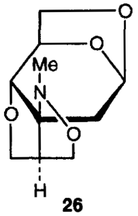

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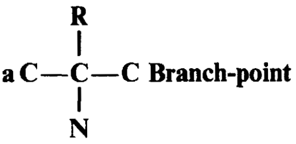
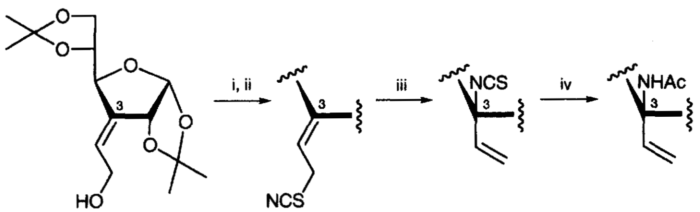


2 Compounds with a $\mathrm{C{-}\overset{R}{\underset{N}{C}}{-}C}$ Branch-point

2.1 Branch at C-3 or C-4 – 3-*C*-Allylic thiocyanates undergo a stereoselective [3,3] sigmatropic rearrangement on heating to give 3-deoxy-3(*S*)-isothiocyanato-3-*C*-vinyl derivatives from which the corresponding acetamido compounds are available as depicted in Scheme 5.[23]

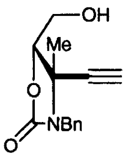


Reagents: i, MsCl, Et_3N; ii, KSCN, MeCN; iii, 70 °C, xylene; iv, MeCOSH, $KOBu^t$

Scheme 5

The keto-nitrone produced by reaction of *N*-methylhydroxylamine with 1,6-anhydro-2,3-*O*-isopropylidene-β-D-*lyxo*-hex-4-ulopyranose underwent a 1,3-dipolar cycloaddition reaction with ethyl vinyl ether and gave **25** in 62% yield together with 11% of its C-4 epimer. Likewise, the nitrone derived from 1,6-anhydro-2-*O*-benzyl-4-*O*-vinyl-β-D-*arabino*-hex-3-ulopyranose and *N*-methylhydroxylamine reacted with ethyl vinyl ether to give **26**. Several other similar examples were also described.[24]

Reaction of alkynol **27** with a tungsten or molybdenum pentacarbonyl complex gave a branched glycal derivative which, on treatment with isopropanol and triphenylphosphine hydrobromide, gave glycoside **28**.[25] The synthesis of a rubranitrose precursor is mentioned in Chapter 10.



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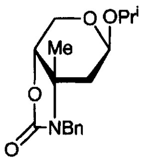

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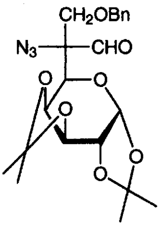

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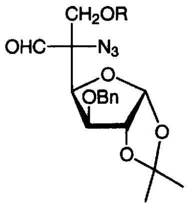


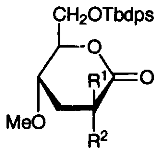
30 R = Tbdms or Bn

2.2 Branch at C-5 or C-6 – Treating 7-*O*-benzyl-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hept-6-ulopyranose with dichloromethyllithium, followed by sodium hydride (to form a *spiro*-chloro-epoxide), then with sodium azide, gave **29**. Elaboration of the azido and aldehyde groups into an acetamido and methyl group, respectively, afforded a lincosamine analogue.[26] In a similar way treating 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*O*-Tbdms-α-D-*xylo*-hex-5-ulofuranose with dichloromethyllithium followed directly with sodium azide, gave exclusively the azido-aldehyde **30** (R = Tbdms). Use of the 6-*O*-benzyl analogue gave a 2:1 mixture of **30** (R = Bn) and its C-5 epimer.[27] Other examples involving the addition of dichloromethyllithium to ketones which react through the intermediacy of *spiro*-chloro-epoxides can be found in ref. 13.

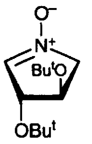
3 Compounds with a $\text{C—}\overset{\overset{\text{R}}{|}}{\text{CH}}\text{—C}$ Branch-point

3.1 Branch at C-2 – This section initially deals with compounds containing a single branch-point at C-2. Those compounds containing additional branch-points are treated at the end of this section.

In studies aimed towards the preparation of the C-10–C-15 portion of the immunosupressant FK 506, a 1:1 mixture of compounds **31**:**32** was prepared by α-methylation of 6-*O*-Tbdps-2,3-dideoxy-4-*O*-methyl-D-*erythro*-hexono-1,5-lactone with methyl iodide-LDA. Equilibration of this mixture with base (DBU or potassium *t*-butoxide) surprisingly led to an increase in the proportion of **32**. NMR experiments on compound **32** indicated that the C-2 methyl group occupied an equatorial orientation with the C-4 and C-5 substituents axially orientated in a half-chair structure. An axial preference for the C-4 and C-5 substituents was also observed in the precursor to **31** and **32**. A conformational analysis of these compounds by molecular mechanics and molecular orbital calculations indicated *gauche* effects and electrostatic interactions as a cause for the preference of axial oriented conformers.[28]



31 $R^1 = H$, $R^2 = Me$
32 $R^1 = Me$, $R^2 = H$



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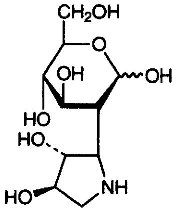

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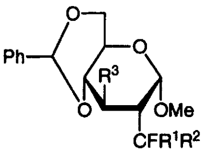
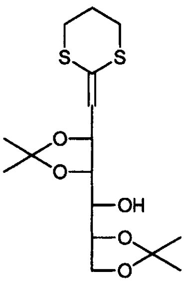
Cycloaddition of *N*-oxide **33** to tri-*O*-acetyl-D-glucal gave an intermediate tricycle which, on treatment with sodium methoxide-methanol, TFA, then hydrogen-Pd/C, afforded **34**.[29]

The fluorinated compounds **35** – **37** have all been prepared from methyl 4,6-*O*-benzylidene-3-*O*-Tbdms-2-*C*-difluoromethylene-α-D-*arabino*-pyranoside, itself derived from the corresponding 2-ulose and dibromodifluoromethane. Thus the difluoromethylene intermediate was transformed into **35** by reaction with Red-Al, then hydrogenolysis, into **36** by hydrogenolysis and into **37** by reaction first with TBAF, then DAST to give methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-trifluoromethyl-α-D-*erythro*-hex-2-enopyranoside, followed by hydrogenation.[30]



35 $R^1 = R^2 = H$, $R^3 = OTbdms$
36 $R^1 = H$, $R^2 = F$, $R^3 = OTbdms$
37 $R^1 = R^2 = F$, $R^3 = H$



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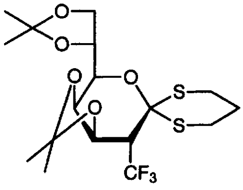

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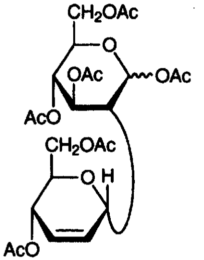

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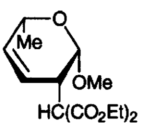

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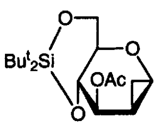

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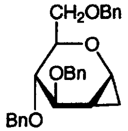


43

The reaction of ketene dithioacetal **38** with iodotrifluoromethane in the presence of sodium formate and sulfur dioxide (conditions that generated a trifluoromethyl radical) produced **39** in 75% yield. Removal of the dithioacetal protecting group gave 2-deoxy-3,4:6,7-di-*O*-isopropylidene-2-*C*-trifluoromethyl-D-*glycero*-D-*galacto*-heptano-1,5-lactone which could be readily epimerized at C-2 to the D-*glycero*-D-*talo*-derivative by treatment with triethylamine. (See Vol. 28, p. 193, ref. 48 for a preliminary account of this work).[31]

Methyl 2,3-anhydro-5-*O*-benzyl (or trityl)-α-D-*ribo*-pentofuranoside and methyl 2,3-anhydro-5,6-*O*-cyclohexylidene-α-D-allofuranoside reacted with 2-propynyl metallic reagents in the C-2 position giving the corresponding 2-deoxy-2-*C*-(2-propynyl)-α-D-*arabino*-pentofuranosides and 2-deoxy-2-*C*-(2-propynyl)-α-D-*altro*-hexofuranosides, respectively. When the β-glycosides were used the reaction was not as successful, but where it did occur the products were 3-deoxy-3-*C*-(2-propynyl)-substituted. (See also Section 3.2).[32]

Lewis-acid-catalysed dimerization of tri-*O*-acetyl-D-glucal gave a 55% yield of **40**. Tri-*O*-acetyl-D-galactal and 3,4-di-*O*-acetyl-D-fucal could be dimerized in the same way.[33]

The Pd(0)-catalysed reaction of sodio diethyl malonate with methyl 4-*O*-benzoyl-2,3,6-trideoxy-α-L-*threo*-hex-2-enopyranoside afforded a 1:5 mixture of rearranged branched sugar **41** and the product formed by substitution of the 4-OBz group (see Section 3.4). This substitution with rearrangement became the major pathway in the absence of a substituent at C-1.[34]

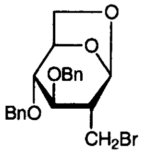
Full details have now appeared on the preparation of 2-deoxy-2-*C*-(diethyl malonate)-branched sugars by reaction of tri-*O*-acetyl-D-glucal with diethyl malonate promoted by CAN. The work has now been extended to include tri-*O*-acetyl-D-galactal and pentose-derived glycals. (See Vol. 30, p. 189, ref. 19 and p. 177, ref. 26 for preliminary details).[35]

Hydroxyl-directed cyclopropanation (CH_2I_2-Et_2Zn) of 4,6-*O*-di-*tert*-butylsilanediyl-D-glucal gave, after *O*-acetylation, cyclopropanoid derivative **42**, a useful precursor in the preparation of oxepanes (see also Chapter 13).[36] In a related way a similar cyclopropanation took place with tri-*O*-benzyl-D-glucal. However addition of dichlorocarbene to the same glycal, followed by treatment with lithium aluminium hydride, gave cyclopropanoid **43**. The latter compound reacted with NBS-methanol to give a 1:4 mixture of methyl 2-*C*-(bromomethyl)-2-deoxy-3,4,6-tri-*O*-benzyl-α-:-β-D-glucopyranosides. The anhydro sugar **44** was produced when 1,5-anhydro-3,4-di-*O*-benzyl-2-deoxy-1,2-*C*-methylene-D-*glycero*-D-*gulo*-hexitol was treated with NBS in acetonitrile.[37] (See also Vol. 30, p. 189, ref. 21 and Vol. 29, p. 197, ref. 28 and p. 187, ref. 24 for related work).

Hydrogenation of the double bond in **45** over a chiral ruthenium catalyst, followed by cyclization with camphor sulfonic acid, gave **46**.[38]

Iodo-glycoside **47** underwent a radical-mediated tandem cyclization when treated with boron trifluoride etherate and oxygen to give **48**.[39] Compound **49** underwent a similar reaction.[40] (See Vol. 29, p. 196, ref. 21 for similar work).

The synthesis of an indolizidine alkaloid skeleton fused onto a sugar template is illustrated in Scheme 6. Cyclization takes place in a 6-*endo*-trig



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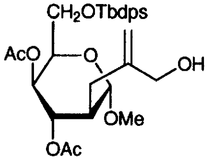

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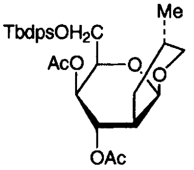

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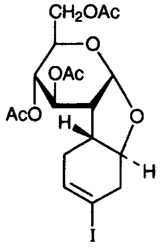

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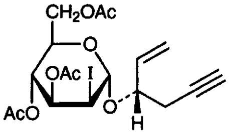

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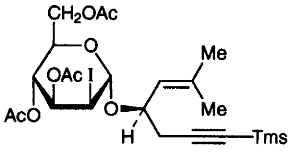
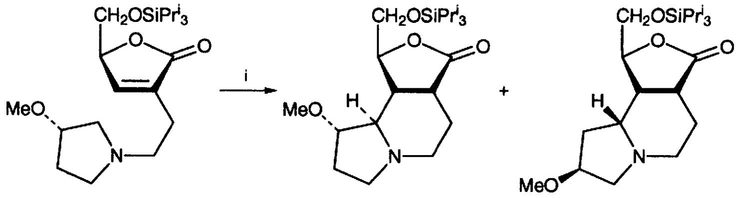


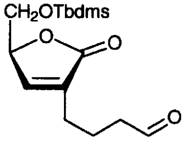
49

mode. (See also Vol. 27, p. 168, ref. 20 for similar work).[41] When unsaturated lactone **50** was subjected to the same reaction conditions as shown in Scheme 6, bicyclic lactone **51** was formed.[42] (See Section 4 also). The same researchers have also prepared the tricyclic derivative **52** by treating lactone-ester **53** with potassium *tert*-butoxide.[43]



Reagents: i, $h\nu$, Ph_2CO, MeCN

Scheme 6



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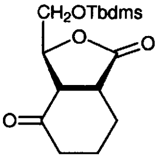

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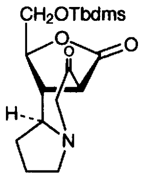

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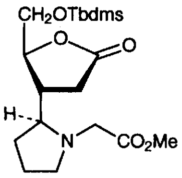
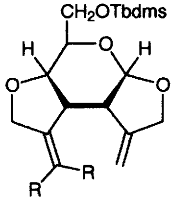
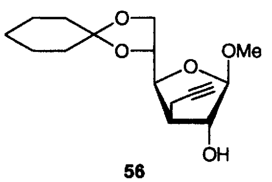


53

The reaction of allyl 6-*O*-Tbdms-2,3-dideoxy-4-*O*-(2-propynyl)-α-D-*erythro*-hex-2-enopyranoside with iodobenzene in the presence of Pd(0), triethylamine and tetrabutylammonium hydrogen sulfate in aqueous acetonitrile at 80 °C produced tricycle **54**.[44] (See Section 3.2 also). In a similar way treatment of allyl 6-*O*-Tbdms-2,3-dideoxy-4-*O*-(2-bromoprop-2-enyl)-α-D-*erythro*-hex-2-enopyranoside under the same reaction conditions but substituting iodobenzene with triphenylphosphine resulted in compound **55**. Many related examples were also described.[45] Scheme 7 shows a similar Pd(0)-catalysed cascade process to produce tricyclic systems. In these cases the starting materials were all prepared from methyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside. Products were also reported from starting materials with a 4-amino-4-deoxy-substituent.[46] The syntheses of some nucleoside derivatives containing a 2,3-cyclopropyl branch group are mentioned in Chapter 20.



54 R = Ph
55 R = H



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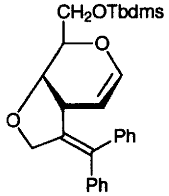

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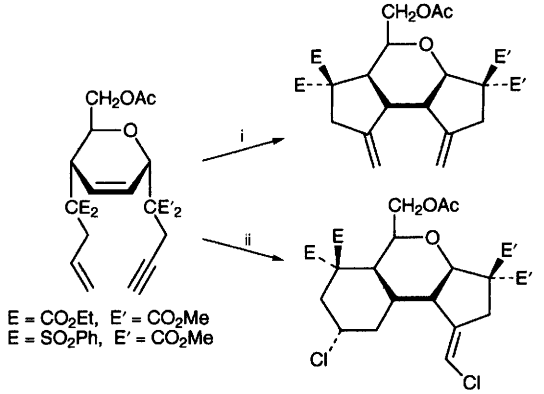


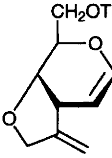
Reagents: i, Pd(0), $(2\text{-}MeC_6H_4)_3P$, AcOH, benzene; ii, Pd(0), $CuCl_2$, LiCl, AcOH, MeCN

Scheme 7

3.2 Branch at C-3 – This section initially deals with compounds containing a single branch-point at C-3. Those compounds containing additional branch-points are treated at the end of this section.

Reaction of 2-propynylmagnesium bromide with methyl 2,3-anhydro-5,6-*O*-cyclohexylidene-β-D-*allo*-hexofuranoside gave an 89% yield of compound **56**. Similar reactions using methyl 2,3-anhydro-5-*O*-benzyl (or trityl)-β-D-*ribo*-pentofuranoside with various 2-propynyl metallating agents did not proceed in such a specific manner. In contrast, the corresponding α-glycosides underwent reaction exclusively at the C-2 position.[33]

Treatment of ethyl 6-*O*-Tbdms-2,3-dideoxy-4-*O*-(2-propynyl)-α-D-*erythro*-hex-2-enopyranoside with iodobenzene in the presence of Pd(0), triethylamine and tetrabutylammonium hydrogen sulfate in aqueous acetonitrile at 80 °C afforded cyclized product **57**.[44] In like fashion, Pd(0)-catalysed cyclization of ethyl 4-*O*-(2-bromoprop-2-enyl)-6-*O*-Tbdms-2,3-dideoxy-D-*erythro*-hex-2-enopyranosides afforded **58** as product as a consequence of cyclization with ejection of the OEt group. When the corresponding D-*threo* derivative was subjected to the same reaction, cyclization took place, but resulted in ejection of the O-5 group to give an acyclic unsaturated compound (see Chapter 13).[47]



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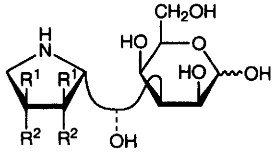
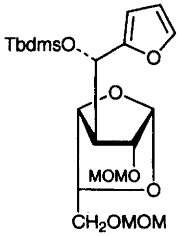


59 $R^1 = OH$, $R^2 = H$
60 $R^1 = H$, $R^2 = OH$



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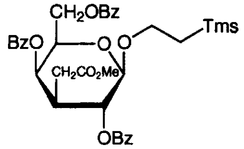

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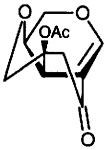

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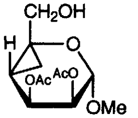

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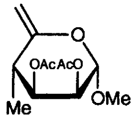


65

The synthesis of 3-deoxy-3-*C*-monofluoromethyl-, difluoromethyl- and trifluoromethyl-D-*allo*-hexopyranoside derivatives from methyl 2-*O*-benzoyl-4,6-*O*-bezylidene-3-deoxy-3-*C*-difluoromethylene-β-D-*ribo*-hexopyranoside, by use of similar chemistry to that described in ref. 30, have been reported.[48]

The racemic disaccharide mimics **59** and **60** have been synthesized and the former shown to be a moderate α-mannosidase inhibitor. The galactose units in these compounds were introduced through manipulation of the known anhydride **61** (see Vol. 29, p. 200, ref. 42).[49]

Olefination of 2-(trimethylsilyl)ethyl 2,4,6-tri-*O*-benzyl-β-D-*xylo*-hex-3-ulopyranoside with diethyl phosphonoacetate catalysed by sodium methoxide, followed by hydrogenation-hydrogenolysis and finally benzolylation, gave **62**, which was further transformed into 3′-*C*-carboxymethyl-3′-deoxy-Lewis x analogue.[50]

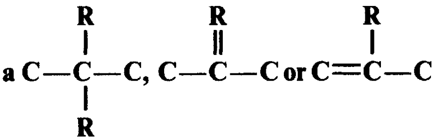
Reaction of the anion derived from methyl methylthiomethyl sulfoxide [$MeS(O)CH_2SMe$] with 2,3-anhydro-4-*O*-triflyl-pyranosides afforded 3,4-cyclopropanated analogues. (See also Vol. 30, p. 194, ref. 38 for related work).[51]

Full details (see Vol. 25, p. 173, ref. 42 for a preliminary report) on the stereoselective Pd(0)-catalysed intramolecular cyclizations of 2,3-unsaturated sugars bearing *C*-, *N*- and *O*-linked alkenyl and alkynyl substituents have been published. For example, tricycle **63** was produced from phenyl 2,3-dideoxy-4-*O*-(2-propynyl)-β-L-*glycero*-pent-2-enopyranoside by Pd(0)-catalysed cyclization with carbon monoxide insertion in the presence of acetic acid and triisopropyl phosphite.[52]

3.3 Branch at C-4 – Substitution with retention of configuration of the 4-*O*-benzoate groups of methyl 4-*O*-benzoyl-2,3-dideoxy-α-D-*glycero*- or β-L-*glycero*-pent-2-enopyranosides, on reaction with sodio diethyl malonate and catalytic Pd(0), afforded the corresponding 4-deoxy-4-*C*-(diethyl malonyl) derivatives.[34]

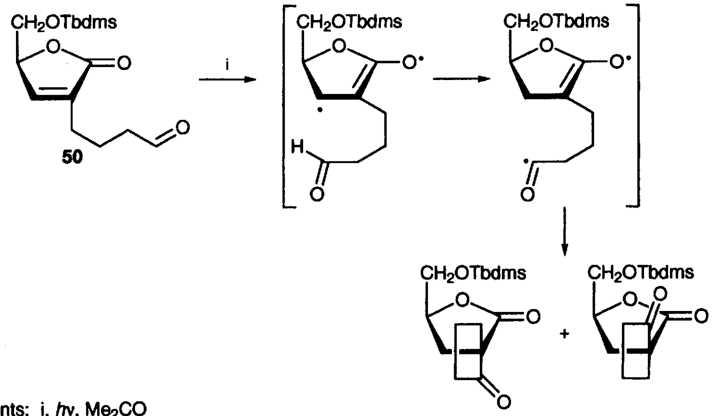
The reaction of methyl 2,3-di-*O*-benzoyl-4-deoxy-4-iodo-α-D-xylopyranoside with an excess of allyl ethyl sulfone ($CH_2{=}CHCH_2SO_2Et$)-AIBN afforded a 1:1 mixture of methyl 4-*C*-allyl-2,3-di-*O*-benzoyl-4-deoxy-α-D-*xylo*- and β-L-*arabino*-pyranosides in a new radical allylation process.[53] Cyclopropanation of methyl 2,3-di-*O*-acetyl-4-deoxy-β-L-*erythro*-hex-4-enopyranoside gave compound **64** together with its stereoisomer. Reaction of **64** with carbon tetrabromide-triphenylphosphine then tributyltin hydride-AIBN gave the 4-deoxy-4-*C*-methyl derivative **65** used to prepare a C-7–C-16 segment of lasonolide A.[54]

Further details on the synthesis (see Vol. 24, p. 157, ref. 18) and unexpected epoxidation products formed from some 4-deoxy-4-*C*-(*N*,*N*′-dimethylcarboxamido)methyl-hex-2-enopyranosides are mentioned in Chapter 13.



4 Compounds with a $C{-}\underset{R}{\overset{R}{C}}{-}C$, $C{-}\overset{R}{\overset{\|}{C}}{-}C$ or $C{=}\overset{R}{C}{-}C$ Branch-point

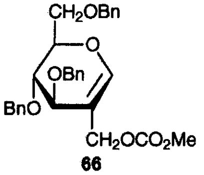
Irradiation of compound **50** in acetone with light afforded low yields of *spiro*-bicyclic lactones (Scheme 8).[42]



Reagents: i, *hv*, Me₂CO

Scheme 8

Alcohols and activated methylene compounds reacted with glycal-carbonate derivative **66** in the presence of Pd(0) to yield 2-deoxy-2-*C*-methylene *O*- and *C*-glycosides, respectively. For example, with *p*-cresol the aryl glycoside **67** was produced and with dimethyl malonate compound **68** was formed. Secondary hydroxyl groups in sugars also participated in this reaction.[55]



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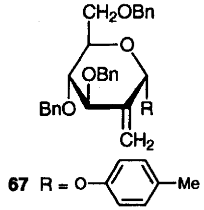

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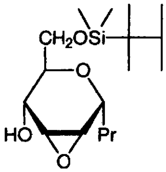
68 R = CH(CO$_2$Me)$_2$



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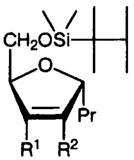
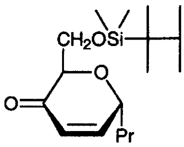
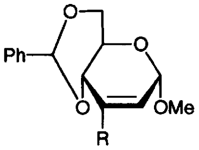


70 R^1 = H, R^2 = CHO
71 R^1 = CHO, R^2 = H

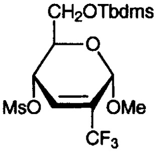


72

Full details have been published on the lithium bromide-initiated ring contraction of 2,3-anhydrohexopyranosides bearing a hydroxyl group at C-4 giving 3-*C*-formyl unsaturated furanosides. (See Vol. 24, p. 168, ref. 30 for a preliminary account). The present work has also been extended to include a range of appropriate starting materials such as *C*-glycosidic derivatives. For example, compound **69** on treatment with lithium bromide and tetramethylurea afforded product **70** in 81% yield, together with **71** and **72** in 18% and 1%,



73 R = CHO
74 R = C(O)CH=CH$_2$



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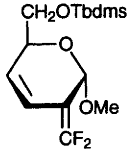

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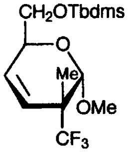

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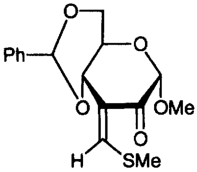

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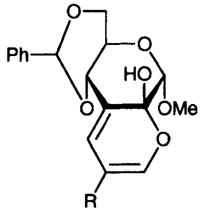
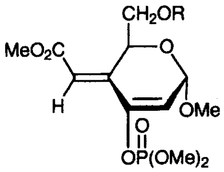


79 R = Me or CO$_2$Et



80 R = Bz
81 R = Tbdps

respectively. By use of the isomeric α-D-*manno*- starting material the same products were obtained but in 71%, 17% and 12% yield.[56]

Methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-triflyl-α-D-*erythro*-hex-2-enopyranoside acted as a useful precursor for the syntheses of the corresponding 3-*C*-alkyl-2,3-dideoxy derivatives. Thus on Pd(0)-catalysed reaction with carbon monoxide and tributyltin hydride, compound **73** was produced and with carbon monoxide and vinyltributyltin, compound **74** was formed. Other similar coupling reactions were also described.[57]

Treatment of mesylate **75** with Me_2CuLi-LiI in ether unexpectedly gave diene **76**, whereas under the same reaction conditions, but with added boron trifluoride etherate or with the reagent $Me_2CuCNLi$, branched-sugar **77** was produced. A related example was also described.[58]

Addition of pentane-2,4-dione or ethyl 2,4-dioxovalerate to **78** gave tricyclic compounds **79**. Cyclic dicarbonyl compounds such as dimedone also reacted affording tetracyclic products, whilst 3-oxoglutarate gave a benzannulated product. (For related work see Vol. 29, p. 201, ref. 49 and 50).[59]

Horner-Wadsworth-Emmons olefination of methyl 3,6-di-*O*-benzoyl-2-deoxy- or 3-*O*-benzoyl-6-*O*-Tbdps-2-deoxy-α-D-*glycero*-hex-2-en-4-ulopyranosides with dimethylphosphonoacetate, unexpectedly produced compounds **80** and **81**, respectively.[60]

The preparation of 3-deoxy-3-*C*-methylene sugar derivatives as masked 3-keto-analogues is covered in Chapter 15. By their use, unwanted reactions that occur with ulose derivatives can be circumvented.

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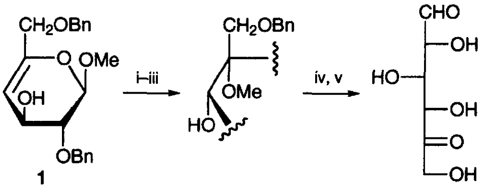
15

Aldosuloses and Other Dicarbonyl Compounds

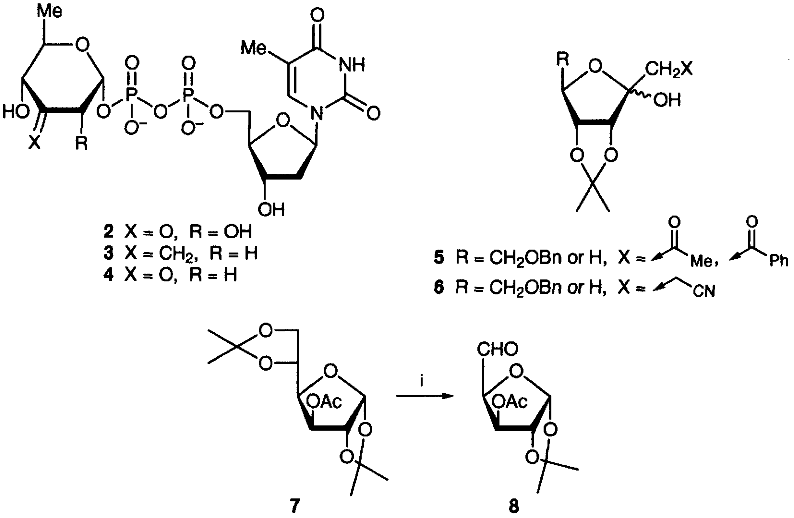
1 Aldosuloses

D-*xylo*-Hexos-5-ulose has been synthesized from the known hex-4-enoside **1** (Scheme 1).[1] Further work on the synthesis of putative biosynthetic intermediates of deoxy sugars has included more details on the synthesis of the thymidine diphospho-6-deoxy-α-D-*ribo*-hexos-3-ulose **2**.[2] Ozonolysis of **3** generated the 2-deoxy analogue **4** of **2**, but it was too unstable for isolation because of elimination of the diphosphate.[3]



Reagents: i, NaH, BnBr; ii, MCPBA; iii, MeOH, TsOH; iv, H_2, Pd/C; v, H_3O^+

Scheme 1



2 X = O, R = OH
3 X = CH_2, R = H
4 X = O, R = H

Reagent: i, $FeCl_3$, $NaIO_4$, THF, H_2O

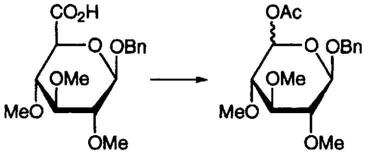
Scheme 2

Carbohydrate Chemistry, Volume 31

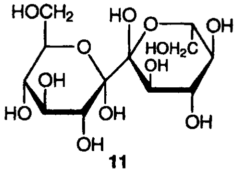
2 Other Dicarbonyl Compounds

The 2,4-diuloses **5** were obtained by condensation of the corresponding aldonolactones with acetone and acetophenone using NaH in THF to generate the required carbanions. Parallel work with acetonitrile afforded the 4-ulosononitriles **6**.[4]

The selective hydrolysis of dioxolane rings on sugars can be accompanied by *in situ* periodate cleavage of the released diols. For example, the dialdose **8** is formed in one pot from **7** (Scheme 2).[5]



9 **10**



11

Irradiation of uronic acid derivatives in acetonitrile in the presence of phenyl iodonium diacetate and iodine affords products of oxidative decarboxylation, *e.g.* **10** from **9**.[6]

Synthesis of the symmetric C–C bonded dicarbonyl analogue **11** of trehalose has been reported.[7]

The use of a 3-keto-fructose derivative as catalyst for the asymmetric epoxidation of olefins is mentioned in Chapter 24.

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16

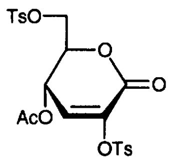
Sugar Acids and Lactones

1 Aldonic and Aldaric Acids and Lactones

The preparation of selectively activated aldonolactones as chiral synthons has been reviewed.[1] Potassium D-idarate has been isolated from the nyctinastic plant *Cassia mimosoides* and was found to cause leaf closing during daytime.[2]

Treatment of unprotected D-ribono-, -arabinono- and -xylono-1,4-lactones with $SOCl_2$ or $SOBr_2$/DMF led to the corresponding 5-deoxy-5-halo derivatives in 70–95% yields. The same conditions applied to D-lyxono-1,4-lactone, however, afforded 2-chloro-2-deoxy-D-xylono-1,4-lactone.[3] Subsequent treatment of the 5-bromo-5-deoxy-lactones with lithium azide and then hydrogenolysis of the resulting 5-azido-5-deoxy compounds led to the corresponding 1,5-lactams.[4]

Tosylation (TsCl, Py) of D-glucono-1,5-lactone followed by *in situ* acetylation gave 70% of **1**, which on hydrogenation gave **2** (93%). More forcing hydrogenation conditions has afforded up to 20% of **3**.[5] D-Glucono-1,5-lactone has been selectively acylated at O-6 using fatty acid esters with *Candida antarctica* lipase in Bu^{t}OH. Treatment of the products in methanol with C_{16} or C_{18} amines precipitated the 6-*O*-alkanoyl-*N*-alkylgluconamides.[6] Per-*O*-alkylated glycono-1,5-lactones are the major products on reaction of the corresponding glycosides with trimethylsilyl azide and stannic chloride. The mechanism proposed involves formation of the glycosyl azide, loss of nitrogen and a hydride shift to give an imine that hydrolyses on work-up.[7] Aldonolactones have been successfully per-*O*-benzylated under acidic conditions by use of benzyl trichloroacetimidate in dioxane.[8]



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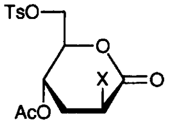
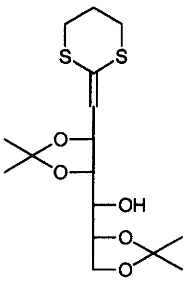


2 X = OTs
3 X = H



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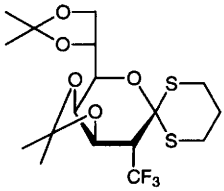

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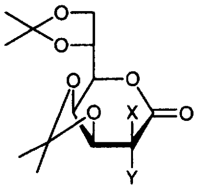
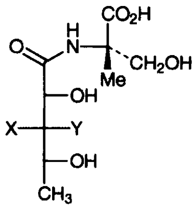
Carbohydrate Chemistry, Volume 31



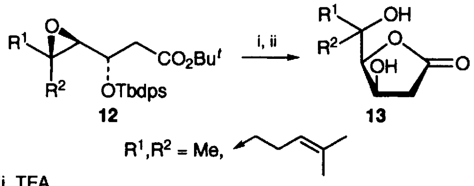
6 X = H, Y = CF_3
7 X = CF_3, Y = H



8 X = H, Y = Me
9 X = Me, Y = OH
10 X = OH, Y = H
11 X = Me, Y = H

Radical trifluoromethylation (CF_3I, HCO_2Na, SO_2) of unsaturated dithioacetal **4** gave **5**, which on hydrolysis gave lactone **6**. Under basic conditions **6** could be epimerized to **7**.[9] Ozonolysis of fully protected sugar hydrazones and subsequent oxidation of the released aldehydes has provided a way of obtaining acyclic aldonic acids.[10] Analogues **8–10** of the immunomodulator conagenin **11** have been synthesized from D-xylose or calcium D-xylonate using standard methods.[11]

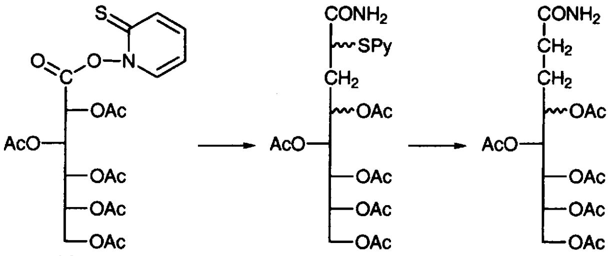
Epoxides such as **12** have undergone intramolecular epoxide opening to form 2-deoxy-5-*C*,*C*-dialkyl-pentonolactones **13** (Scheme 1).[12]



Reagents: i, $ZnCl_2$; ii, TFA

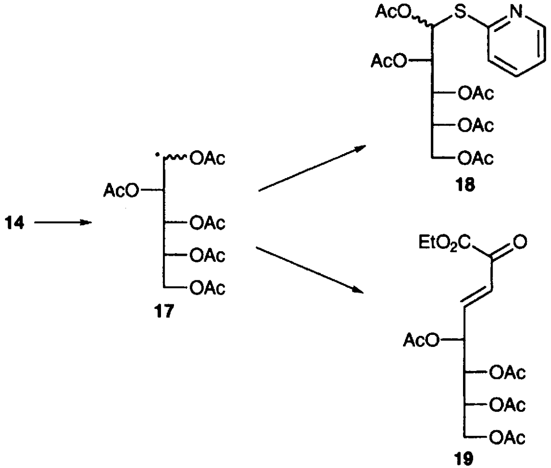
Scheme 1

Photolysis of *N*-hydroxy-2-thiopyridone ester **14** in the presence of acrylamide led to adduct **15**, apparently formed by addition of the C-2 radical **17** to the amide, which on desulfurization with nickel boride gave amide **16** (Scheme 2).[13] Others have reported that attempts to prepare **14** were unsuc-



Scheme 2

cessful and the product isolated was always that of decarboxylation *i.e.* the *O,S*-acetal **18** (Scheme 3), presumably formed *via* the radical intermediate **17**. In the presence of ethyl 2trifluoroacetoxyacrylate this radical was trapped to give α,β-unsaturated keto ester **19**.[14]



Scheme 3

A calix[4]resorcarene derivative containing eight primary amine residues has been treated with excess lactobiono-1,5-lactone to give a molecule with eight glyconamide residues.[15]

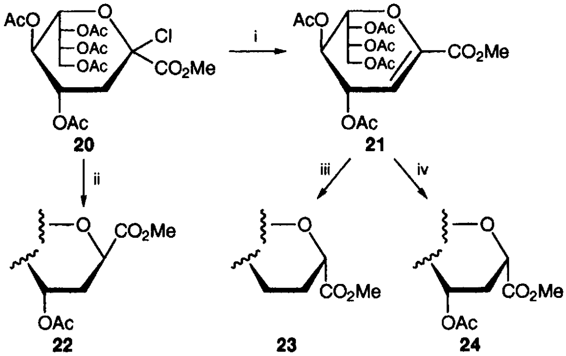
The β-elimination reactions catalysed by D-galactonate dehydratase from *E. coli* and D-glucarate dehydratase from *Pseudomonas putida* have been studied mechanistically focussing on the importance of the pK$_a$s of the protons α- to the carboxylic acid groups of the substrates.[16] The participation of acetate ions in the oxidation of D-galactose by Cu(II) in acetic acid has been studied, with the results confirming that $CuOAc^+$ is the reactive species.[17] The electrooxidation of D-glucose to calcium gluconate in the presence of NaBr and $CaCO_3$ has been optimized. The optimal conditions are those that promote NaOBr formation.[18]

The synthesis of both enantiomers of the chain-extended aldonolactone *epi*-muricatacin is covered in Chapter 24, and the 2-*C*-methylation of 2,3-dideoxy-aldonolactone derivatives is discussed in Chapter 14. The oxidation of glycosylamines by chloramine T to the corresponding aldonic acids is mentioned in Chapter 9.

2 Anhydroaldonic Acids and Lactones

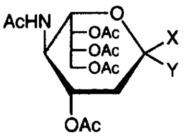
Hydrogenation of Kdn derivatives **20** and **21** has allowed the synthesis of anhydroaldonic acid derivatives **22**–**24** (Scheme 4).[19] The glycosyl iodide **25** in the presence of excess HI/HOAc is reductively cleaved to give exclusively **26**.[20]

A ring contraction of 2-deoxy-2-iodoaldonolactone derivative **27** on reaction with K_2CO_3 or NaOMe/MeOH gave **28**.[21] Syntheses have been reported of analogues **29** of lipid A with anti-inflammatory potential.[22]

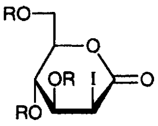


Reagents: i, DBU, CH_2Cl_2; ii, H_2, Pd/C, toluene/py; iii, H_2, Pd/C, MeOH/HOAc; iv, H_2, Pd/C, MeOH

Scheme 4



25 X = I, Y = CO_2Bn
26 X = CO_2Bn, Y = H



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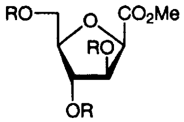
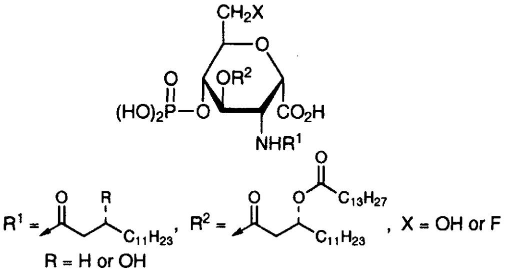


28

R = Tbdms

3 Ulosonic Acids

The preparation and modification of sialic acids and sialyl glycosides has been reviewed,[23] as has the platinum-catalysed oxidation of L-sorbose to 2-keto-L-gulonic acid.[24] The diamino-tetradeoxy-L-*glycero*-D-*talo*-nonulosonic acid derivative **30** is released by mild acid hydrolysis of the *Legionella pneumophilia* seragroup lipopolysaccharide.[25]



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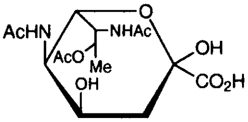
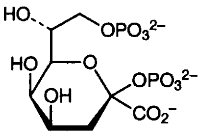


30

The bis-phosphate **31** has been synthesized as a putative intermediate in the biosynthesis of 3-deoxy-D-*manno*-2-octulosonate-8-phosphate by Kdo-8P synthase.[26] It was a poor substrate, however, and the acyclic bis-phosphate **32** has been proposed as an intermediate.[27]

Polyvalent dendrimers of sialic acid thioglycosides have been prepared with even-numbered valencies of between 4 and 12.[28]



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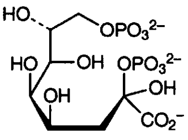

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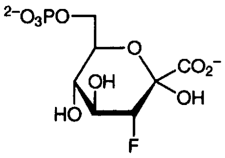


33

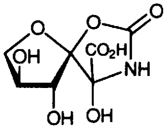
The fluorinated ulosonic acid phosphate **33** has been prepared and shown to be an excellent substrate for dehydroquinate synthase, whereas its C-3 epimer was a relatively poor substrate for the enzyme.[29]

The novel spirocyclic derivative **34** was isolated from the cyanate-producing plant *Solanum tuberosum*, and it has been synthesized by reaction of cyanate with dehydroascorbic acid.[30]

A chemical synthesis has been described of CMP-NeuAc which utilizes phosphite diester coupling; analogues with variation in the NeuAc moiety were also produced.[31]

A non-enzymic synthesis of Kdo-8-phosphate utilized an interesting approach (Scheme 5) that is similar to that proposed for the biosynthetic pathway.[32]

A new method for the homologation of aldonolactones, analogous to a



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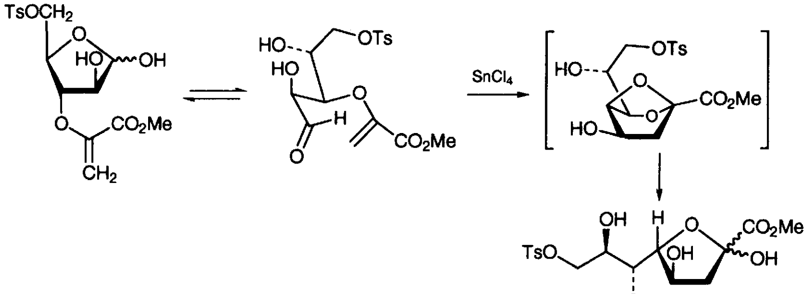
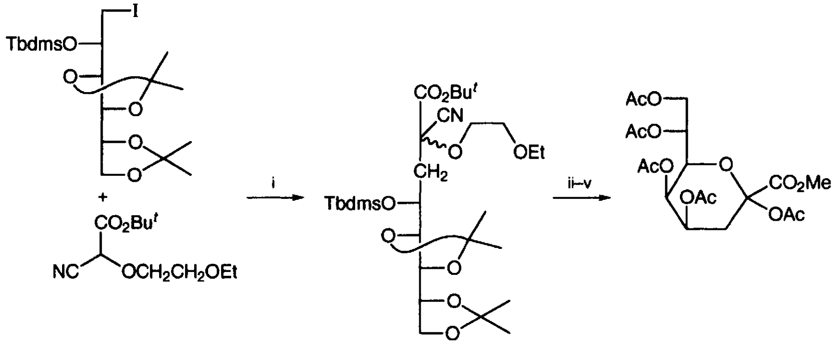


Scheme 5

Reformatsky reaction, involves a magnesium-graphite mediated coupling of an α-halogenated sultam.[33]

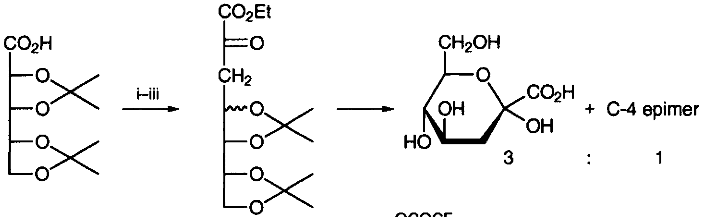
A synthesis of Kdo features the addition of ethyl diazoacetate to an aldehydo-D-mannose derivative followed by extensive synthetic manipulation to release the 3-deoxy-2-keto product.[34] An indium-mediated allylation of D-erythrose in an aqueous solvent system has been used in the synthesis of 3-deoxy-D-*arabino*-2-heptulosonate.[35] The displacement of a primary iodide has been used to effect chain extension in a new synthesis of Kdo (Scheme 6).[36]



Reagents: i, NaH, DMF; ii, CF_3CO_2H; iii, NH_4OH; iv, Ac_2O, DMAP; v, CH_2N_2

Scheme 6

Further work on the radical reactions of *N*-hydroxy-2-thiopyridone esters (see Scheme 3 above) has resulted in the synthesis of 3-deoxy-D-*arabino*-2-heptulosonic acid from D-ribonolactone (Scheme 7).[37,38]



Reagents: i, DCC, *N*-hydroxy-2-thiopyridone; ii, *hν*, $CH_2=C(OCOCF_3)CO_2Et$; iii, $NaHCO_3$

Scheme 7

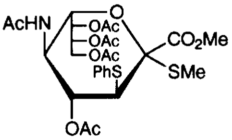
Process improvements for the large scale production of *N*-acetylneuraminic acid using *N*acetylneuraminic acid aldolase have been described,[39] and *N*-glycolylneuraminic acid has been prepared by the action of *N*-acetylneuraminic acid aldolase on *N*-glycolyl-D-mannosamine and pyruvic acid,[40] while similar procedures were used to convert *N*-t-butoxycarbonyl-D-mannosamine to *N*-t-butoxycarbonylneuraminic acid.[41] Others have adopted the same procedure using *N*-acetylneuraminic acid aldolase applied to a number of *N*-acyl-D-mannosamines in which the acyl groups were more complex, including aromatic and long chain aliphatic substituents.[42] ^{13}C-Labelled pyruvate has been used in the same aldolase-catalysed reaction with *N*-acetyl-D-mannosamine to give *N*-acetylneuraminic acid labelled at C-1 and C-2.[43]

A sialylphospholipid has been synthesized using standard sialyl glycosidation techniques,[44] and participation of the sialic acid ester group in the stabilization of the anomeric oxocarbenium ion intermediate has been utilized in the selective formation of α-glycosides of sialic acid.[45] The sialyl donor **35**, when activated with phenyl sulfenyl triflate, affords only α-glycosides with a number of carbohydrate glycosyl acceptors.[46] By use of different deliberately designed donors and acceptors either α- or β-8-*O*-sialylation of neuraminic acid could be achieved.[47] The α- and β-methyl glycosides of 3-deoxy-D-*lyxo*-hept-2-ulosonic acid have been prepared separately.[48]

An unusual furanoside product obtained from a Koenigs-Knorr glycosidation with a Kdn donor is covered in Chapter 3, as is the synthesis of *C*-glycosides from neuraminic acid glycosyl sulfones using samarium iodide.

Intramolecular sialic acid lactones have been treated with ethyl glycinate to give new amide-linked sialic acid-amino acid conjugates.[49]

Allylic displacements applied at C-4 to 2,3-unsaturated sialic acid derivatives have allowed the synthesis of predominantly 4-deoxy-4-*epi*-4-halogeno derivatives.[50] The 4-epimer of the well known 4-azido-4-deoxy-2,3-unsaturated sialic acid has been prepared using a Pd-catalysed allylic displacement.[51]



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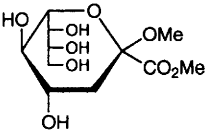

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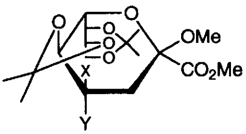


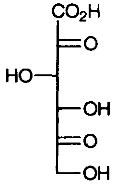
37 X = H, Y = OH
38 X = NHAc, Y = H

Isopropylidenation of Kdn derivative **36** gave the 5,8:7,9-di-*O*-isopropylidene derivative **37** which, after oxidation, oxime formation, reduction and acetylation gave the 4-*N*-acetyl-4-deoxy analogue **38**.[52] Alternative isopropylidenation conditions applied to **36** led to the 8,9-*O*-isopropylidene and/or the 5,7:8,9-di-*O*-isopropylidene derivatives. Oxidation of these, at C-7 and C-4 respectively, led to enone products after β-eliminations.[53]

The known trimethylsilyl triflate-catalysed reaction of acetonitrile with 2,3-unsaturated sialic acid *O*-acetates to give the 4-*N*-acetyl-4-deoxy derivatives has been extended to other nitriles such as benzonitrile and CH_3OCH_2CN.[54]

Methyl 3-deoxy-α- and β-D-*ribo*, -*xylo*, and -*lyxo*-hept-2-ulosonic acids have been prepared from methyl (methyl 3-deoxy-α- and β-D-*arabino*-hept-2-ulopyranosid)onate by controlled triflate displacement with inversion at C-4 and/or C-5 using caesium acetate.[55]

2,5-Diketo-D-*threo*-hexonic acid **39**, an intermediate in the microbial production of ascorbic acid, has been isolated and hydrogenated to give mixtures of **40** and **41**.[56]



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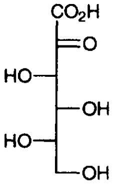

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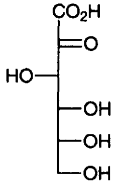

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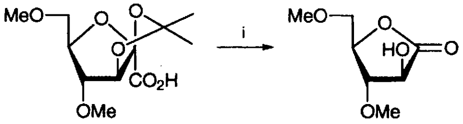
Oxidative decarboxylation of ulosonic acid derivative **42** gave 86% of lactone **43** (Scheme 8).[57]



42 **43**

Reagents: i, $PhI(OAc)_2$, I_2, $h\nu$, MeCN

Scheme 8

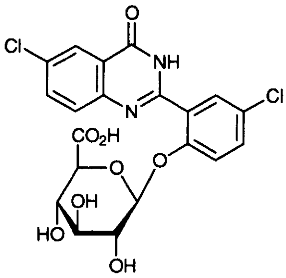
4 Uronic Acids

The colourless glucuronoside **44** has been synthesized as a colorimetric substrate for β-glucuronidase. It releases a strongly fluorescent phenol on hydrolysis and can detect as little as 10^{-3} U/ml of enzymic activity in solution.[58] The 4-nitrophenyl glucuronosides **45**–**47** have been prepared as potential colorimetric substrates for bovine β-glucuronidase, but none was better than 4-nitrophenyl β-D-glucopyranosiduronic acid.[59] A synthesis of 7-hydroxycoumarin glucuronide has also been described.[60]

The glucuronic acid *C*-glycoside derivative **48** has been prepared as a trisubstrate analogue inhibiter for UDP glucuronosyltransferases.[61] Glucuronide metabolites have been prepared of the anti-inflammatory drugs DUP697[62] and ML-3000.[63]

The methyl glucuronate glycoside **49** has been synthesized as a prodrug of a phosphorodiamidic mustard. It is released by a carboxylic esterase followed by a β-glucuronidase.[64]

The TEMPO-catalysed sodium hypochlorite oxidation of α- and β-D-glucopyranosyl phosphate and α-D-glucopyranosyl fluoride has afforded the corresponding glucuronosyl phosphates and fluoride.[65] In a comparative study of the oxidation of methyl and *n*-octyl α-D-glucopyranoside with molecular oxygen over a graphite-supported platinum catalyst, it was found that the *n*-octyl glycoside reacts 10 times more slowly, but with increased selectivity to



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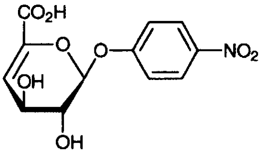

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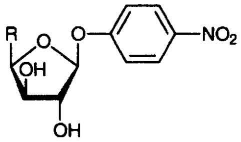
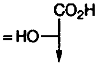
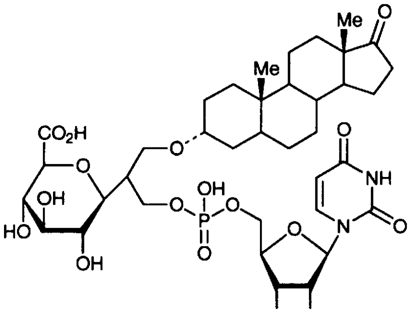


46 R = CO_2H

47 R =





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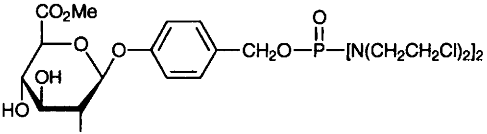
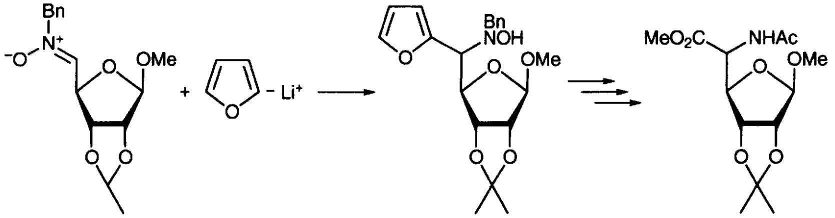


49

give the glucuronoside,[66] and a further study has looked at the effect of particle size of the platinum catalyst on the oxidation products formed.[67]

The addition of 2-furyl anions to sugar nitrones has led to the synthesis of uronic acid derivatives (Scheme 9); a number of other examples were reported.[68]

Uronic acids are oxidized in alkaline media by Chloramine T or Chloramine



Scheme 9

B to the corresponding glycaric acids. A study of the kinetics of these reactions has been reported.[69]

The addition of a propargyl anion to C-5 of a variety of 5-*aldehydo*-pentofuranose derivatives gave *anti*-addition products, generally with high diastereoselectivity. These could be ozonolysed to 6-deoxy-hepturonate derivatives.[70] A synthesis of 2-amino-2-deoxy-L-altruronic acid derivatives is covered in Chapter 9.

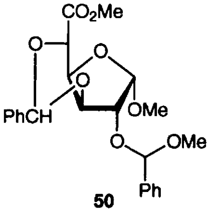
The conversion, over several steps, of D-glucuronic acid esters into L-iduronic acid derivatives has been reported,[71] and L-iduronic acids have been prepared by hydroboration and subsequent oxidation of hex-5-enopyranosides.[72]

Acid hydrolysis of alginic acid from kelp has given D-mannurono-6,3-lactone in 33% yield based on the mannuronic acid content of alginic acid.[73]

Benzyl 2,3,4-tri-*O*-methyl-β-D-glucopyranosiduronic acid has been oxidatively decarboxylated with iodobenzene diacetate to give the corresponding 5-acetoxy-pentopyranoside. Other examples were given.[57]

Some methyl 1-*O*-arylcarbonyl-2,3,4-tri-*O*-acetyl-β-D-glucopyranuronates have been prepared from the corresponding glycosyl bromide under standard conditions.[74]

Novel amphiphilic bis-amides have been prepared with glucuronic or galacturonic acid moieties as polar head groups by the reaction of long chain diamines with *n*-octyl β-D-gluc- or galacturono-6,3-lactones.[75] Amide bonds have also been formed between D-galacturonic acid derivatives and suitably protected amino acids.[76] Some glucuronides with ^{125}I labels (in the aglycon) have been prepared.[77] Treatment of D-glucuronic acid with benzaldehyde dimethyl acetal under acid conditions has given the fully protected furanosiduronate **50**.[78]



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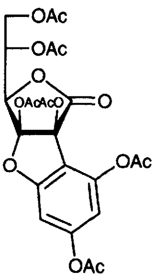
5 Ascorbic Acids

The novel phloroglucinol derivative **51** was isolated from *Sargassum spinuligerum*, a brown seaweed, after acetylation.[79] The preparation of a series of 2-*O*-alkylascorbic acids as oxygen radical scavengers has been reviewed.[80] Isopropylidenation of L-ascorbic acid followed by phosphorylation and deacetalation has afforded magnesium L-ascorbate 2-phosphate.[81] The thermal degradation of lascorbic acid at 300 °C, or 180 °C in propyleneglycol, has been investigated, and the products identified by GC-MS.[82]

The tocopheryl ascorbic acid **52** has been synthesized and shows promise as a prodrug form of vitamin E.[83] Each of the 2-deoxy-2-halo-L-ascorbic acids **53** have been prepared from 2-deoxy-L-ascorbic acid.[84] A kinetic study has been reported on the mechanism of oxidation of L-ascorbic acid by the molybdato-pentamine cobalt(III) ion in aqueous solution.[85]



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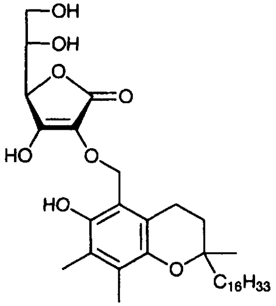

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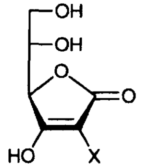

53 X = F, Cl, Br or I

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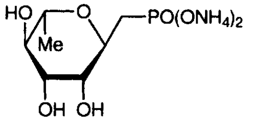
17

Inorganic Derivatives

1 Carbon-bonded Phosphorus Derivatives

A review of the synthesis of enantiomerically pure phosphonates has included some carbohydrate examples.[1] A phosphonate analogue **1** of α- L-rhamnose-1-phosphate has been prepared,[2] as has the protected α-D-glucopyranosyl phosphonate **2**, by standard methods.[3] An indium-mediated addition to D-mannose has furnished vinyl phosphonate **3** from which the *C*-1 phosphonate **4** was prepared (Scheme 1). The same chemistry applied to *N*-acetylmannosamine afforded **5**.[4] These compounds were prepared as potential sialidase inhibitors.



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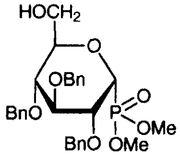

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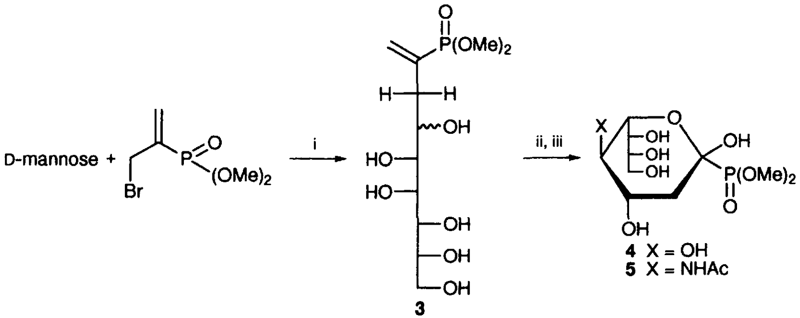


Reagents: i, Indium, H_2O; ii, O_3; iii, Me_2S

Scheme 1

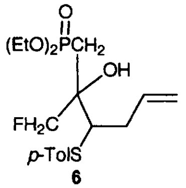
The thymidine 5′-phosphonate analogue **7** has been prepared by way of resolution of the non-carbohydrate precursor **6**.[5] The Diels-Alder reactions of a vinyl phosphonate separately with furan, cyclopentadiene and *E*-1-acetoxy-1,3-butadiene have been utilized as the initial steps in the preparations of racemic *myo*-inositol phosphonate analogues.[6]

Carbohydrate Chemistry, Volume 31

The synthesis of some 2,3-aziridino-D-pentono-1,4-lactone-5-phosphonates is covered in Chapter 9 and the preparation of glycosyl difluorophosphonates is discussed in Chapter 8, while phosphonate analogues of nucleoside di- and tri-phosphates are detailed in Chapter 20.

Full details of the regioselective ring opening of 2,3-anhydro-sugar derivatives by $LiPPh_2$ have appeared (*cf.* Vol. 29, p. 219).[7]

The four stereoisomers of cyclic phosphonate **8** have been prepared[8] and the phospholene-1-oxides **9** and **10** have been converted into **11**, **12** and **13–15**.[9]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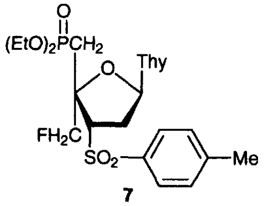
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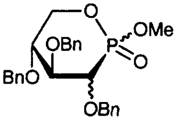
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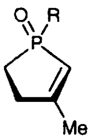
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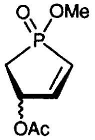
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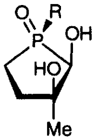
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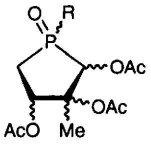
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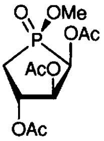
R = OMe, OEt or Ph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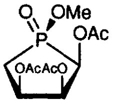
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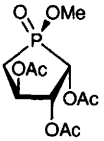
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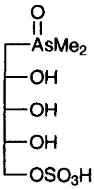
2 Other Carbon-bonded Derivatives

The arsine oxide **16**, a red algal constituent, has been synthesized from ribitol,[10] and the organoiron-complexed derivative **17** was prepared as a racemate.[11]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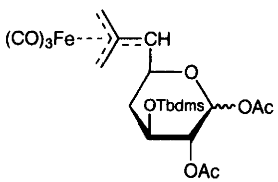
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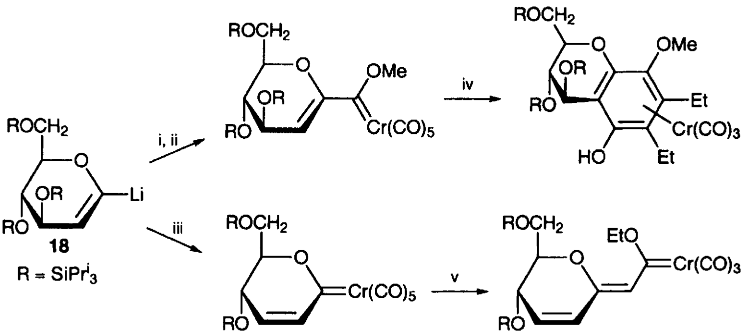
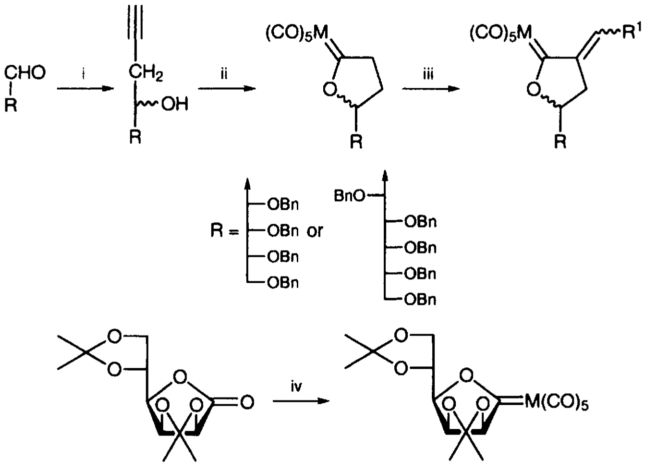


Reagents: i, $Cr(CO)_6$; ii, Me_3OBF_4; iii, $Cr(CO)_5PPh_3$; iv, Et—≡—Et; v, ≡—OEt

Scheme 2



M = Cr or W

Reagents: i, ≡—≡—MgBr; ii, $M(CO)_5.THF$; iii, BuLi then PhCHO or $Me_2\overset{+}{N}=CH_2\ Cl^-$; iv, $(CO)_5M{=}C(Ph)_2$

Scheme 3

Organochromium carbohydrate compounds have been prepared from the lithiated glycal **18** (Scheme 2),[12] and the same group have synthesized 2-oxacyclopentylidene complexes of chromium and tungsten from *aldehydo*-sugars and from sugar lactones (Scheme 3).[13,14]

Various *O*-(3-trialkyl- or triaryl-stannyl)propyl sugar derivatives have been prepared by hydrostannylation of selected *O*-allyl mannose, glucose and lactose derivatives,[15] and a number of trialkyl- or triaryl-stannylmethyl ether derivatives of D-xylose have been synthesized.[16]

Some *C*-tributylstannyl sugar derivatives are mentioned in Chapter 13 and a nucleoside carborane is discussed in Chapter 20.

3 Oxygen-bonded Derivatives

The regioselective manipulation of hydroxyl groups using organotin ether intermediates has been reviewed,[17] as have the interactions between transition metal ions and sugars.[18]

Some sugar alcohols have been treated with chlorophosphines to give phosphinic acid monoesters.[19]

New oxovanadium(IV) complexes of D-glucose, D-fructose, D-ribose and sucrose have been isolated crystalline as their sodium salts and characterized spectroscopically.[20,21]

The equilibrium reactions between deprotonated 4-*O*-β-D-galactopyranosyl-D-gluconic acid and Co(II), Ni(II), Cu(II), Zn(II), CD(II) and Hg(II) ions have been studied by potentiometric and spectrophotometric methods. Compounds of the type $M(X)_2.2H_2O.EtOH$ and $CD(X)_2.2H_2O.\frac{1}{2}EtOH$ have been isolated and characterized (M = Co, Ni, Cu, Zn and X = the disaccharide).[22]

Crystalline cobalt complexes with bis(*N*-D-glucopyranosyl-2-aminoethyl)(2-aminoethyl)amine have been prepared[23] and sugar complexes of Co(II) and Ni(II) with, separately, D-glucose, D-fructose, D-galactose, D-xylose, D-ribose and maltose have been made and characterized by diffuse reflectance, CD, FTIR, EPR and cyclic voltammetry.[24,25] Some Ni(II) complexes of glycosylamine derivatives of glucose, galactose, mannose and talose have been studied by MS (electrospray and CI). Specific cleavage of the sugar C-3– C-4 bond was identified.[26]

The glucose mannose epimerization reaction catalysed by Ni(II) complexes has been studied using different Ni(II)-coordinating ligands.[27]

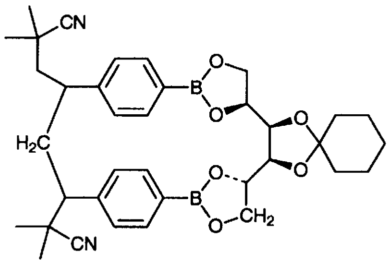
D-Galactonic acid has been found to form four complexes with W(VI) in aqueous solution depending on the pH and concentration. Homologous species were also observed with Mo(VI) under similar conditions as well as four additional complexes.[28] Nine complexes of L-mannonic acid with, separately, W(VI) and Mo(VI) in aqueous solution have been identified using multinuclear NMR spectroscopy.[29]

The interactions of La(III) with D-glucitol and ribitol in aqueous solution have been studied by NMR spectroscopy,[30] and manganese complexes with the adducts of tris(aminoethyl)amine and D-mannose or L-rhamnose have been identified.[31]

The 1,2:5,6-bis-*O*-[(4-vinylphenyl)boronate] of 3,4-*O*-cyclohexylidene-D-mannitol has been intramolecularly cyclized by radical initiation with AIBN to give **19**.[32]

4 Nitrogen-bonded Derivatives

Oxorhenium(V) and oxotechnetium(V) complexes as inhibitors of ribonucleases have been reviewed[33] and the new oxorhenium(V) complexes **20** and **21** have been prepared.[34]



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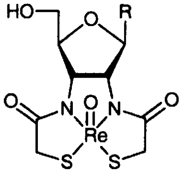

20 R = H
21 R = Uracil-1-yl

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18

Alditols and Cyclitols

1 Alditols and Derivatives

1.1 Alditols – A review on the application of D-(−)-quinic acid in natural product synthesis briefly mentions the synthesis of 2,4-di-*O*-benzoyl-3,5-dideoxy-D-*erythro*-hexitol and that of an epimeric mixture of 3-deoxy-4,5-di-*O*-isopropylidene-6-*O*-(4-methoxybenzyl)-L-*allo*-/L-*altro*-heptitols as intermediates in the synthesis of (+)-negamycin and hepotoxin B_3, respectively.[1]

Stereoselective $(Cp_2ZrCl)_2$-promoted pinacol-like coupling of isopropylidene-D-glyceraldehyde, followed by isopropylidenation, gave an 88:12 mixture of 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol and 1,2:3,4:5,6-tri-*O*-isopropylidene-D-iditol.[2]

A short, multigram synthesis of 1,3,4,6-tetradeoxy-D-*threo*-hexitol has been achieved by treating 1,2:5,6-di-*O*-isopropylidene-D-mannitol successively with tosyl chloride-pyridine, aqueous mineral acid then more tosyl chloride-pyridine (to form 1,3,4,6-tetra-*O*-tosyl-D-mannitol) and finally with lithium aluminium hydride.[3]

Symmetrical diols can be cleanly mono-benzylated with 1.1 equiv. of benzyl chloride in the presence of silver(I) oxide. For example, 1,3:4,6-di-*O*-benzylidene-D-mannitol gave a 92% yield of 2-*O*-benzyl-1,3:4,6-di-*O*-benzylidene-D-mannitol and 1,6-di-*O*-benzyl-3,4-*O*-isopropylidene-D-mannitol gave the corresponding 1,2,6-triether in 93% yield.[4]

Several new, neutral amphiphiles of the type 1,2-di-*O*-alkyl-D-mannitols (alkyl = C_{12}, C_{14}, C_{16} or C_{18}) and derived from 1,2:3,4-di-*O*-isopropylidene-D-mannitol have been prepared. Aggregates formed between these compounds and a lipase functioned in organic solvent as an immobilized enzyme system for the enantioselective-acetylation or -hydrolysis of α-hydroxy esters or α-acetoxy esters, respectively.[5]

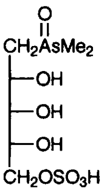
D-Xylose has been converted by standard methods into mono-alkylxylitol derivatives as novel thermotropic liquid crystals. Thus 2-, 3-, 4- and 5-*O*-octyl- or -dodecyl-D-xylitols were prepared.[6] Unprotected pentitols and hexitols have been converted into 1,5- or 1,6-dibromo-peracetylated derivatives, respectively, by treatment with acetyl bromide followed by acetic anhydride-pyridine. Substitution of the dibromides with thioalkyl groups (butyl, octyl, dodecyl and hexadecyl) then de-acetylation gave the corresponding 1,5- or 1,6-alkyldithioalditols.[7]

Carbohydrate Chemistry, Volume 31

Addition of ethyl, allyl, vinyl or isopropenyl Grignard reagents to 4-*O*-protected (ethers, silyl ethers or esters)-1,2:5,6-di-*O*-isopropylidene-D-*arabino*-3-uloses was highly stereoselective in favour of the 3,4-D-*erythro* products. The stereochemistry of the additions were discussed and the Felkin-Anh and chelate transition state models were found not to be applicable in this series.[8]

A short synthesis of the red algal constituent **1** has been reported starting from 1,2:4,5-di-*O*-isopropylideneribitol and involving treatment first with carbon tetrachloride-triphenylphosphine which caused acetal migration and led to 1-chloro-1-deoxy-2,3:4,5-di-*O*-isopropylideneribitol. Substitution of the chloride with sodio dimethylarsine (Me_2AsNa) then oxidation with hydrogen peroxide, acid-catalysed hydrolysis and sulfation gave (±) **1** (one enantiomer drawn for clarity). The absolute configuration of the natural **1** was not determined but is likely to be as drawn since the D-ribofuranosylarsine **2** is also found in the algae.[9]

Sharpless asymmetric dihydroxylation of alkene **3** under the usual conditions with hydroquinine 1,4-phthalazinediyl diether as chiral ligand [$(DHQ)_2PHAL$, matched case] afforded D-galactitol derivative **4** as major product together with D-iditol derivative **5**. The same reaction in the presence of hydroquinidine 3,6-pyridazinediyl diether as chiral ligand [$(DHQD)_2PYDZ$, mis-matched case] gave **5** as major product together with some **4**. In a similar way, 1-*O*-(4-methoxybenzoyl)-D-*galacto*- or D-*ido*-hexitol derivatives were prepared from **6**.[10]



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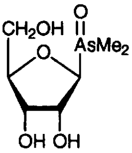

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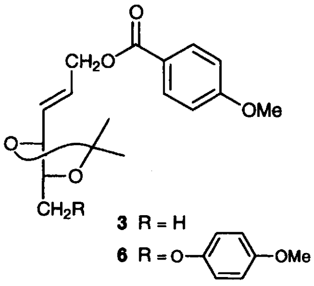
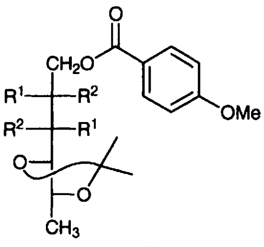
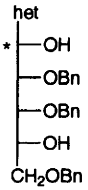




4 $R^1 = H$, $R^2 = OH$
5 $R^1 = OH$, $R^2 = H$



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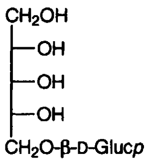

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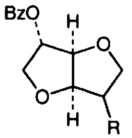
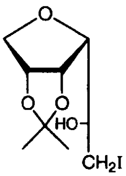
Interaction of lithiated heterocycles with ribofuranose derivatives produced intermediate aldityl heterocycles, for example, **7**, having mainly the *R*-configuration at the indicated carbon. These reacted further by Mitsunobu reaction to give mainly α-*C*-glycosides (*C*-nucleoside analogues) and full details of this work have now been reported. (See Vol. 28, p. 282, ref. 171 for preliminary report). Included also was the use of less basic metallated (Mg, Ce, Cd or Zn) heterocyles from which mainly *S*-configured aldityl heterocyclic intermediates were obtained, the *R*,*S*-ratio depending on the structure of the heterocycle. The *S*-products were further converted into β-*C*-glycosides.[11] Base hydrolysis of scorzoneroside A, a novel hepatoprotective triterpene glycoside isolated from a Chinese plant, generated ribitol glycoside **8**. The structure and absolute configuration of **8** was confirmed by synthesis.[12]

The dipole moment of D-mannitol in aqueous solution has been determined by optical, dielectric and volumetric methods.[13]

1.2 Anhydro-alditols – Treatment of 1,4:3,6-dianhydrohexitol-iodide **9** with allyl ethyl sulfone-AIBN in heptane or a mixture of heptane and chlorobenzene afforded an *endo*:*exo* mixture of *C*-allyl-derivatives **10**, the former being favoured, in a new radical-based allylation reaction.[14] The reaction of 1,4:3,6-dianhydro-D-glucitol (isosorbide) with a mixture of trimethylsilyl chloride, sodium iodide and acetone gave the 3,6-anhydro-1-deoxy-1-iodo-D-*gluco*-compound **11**. The same reaction performed on 1,4:3,6-dianhydro-D-mannitol gave the D-*manno*-equivalent of **11**.[15]



9 R = ---I
10 R = ∿∿All



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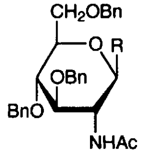


12 R = $SnBu_3$
13 R = H

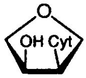
Compound **12**, when treated with 1 equiv. of butyllithium at −78 °C (deprotonates amide NH) then 1 equiv. of butyllithium at −65 °C (tin-lithium exchange, which does not occur at lower temperature) generated a dianion which trapped carbon dioxide at C-1 to give a β-*C*-glycosyl carboxylic acid as a peptide precursor for making derivatives with a reversed amide bond. (See Vol. 30, p. 47, ref. 310). A by-product from this reaction was **13**. Now, NMR-deuteration experiments have established that the new proton at C-1 in **13** originated from the amide NH during treatment of **12** with base. Further, the amide NH could be selectively deprotonated with methyllithium-LiBr without any tin-lithium exchange and, when complete, treatment with BuLi generated a dianion in optimized yield. Hence maximum yields of β-*C*-glycosides could be made.[16]

1,4-Anhydro-2,3:5,6-di-*O*-isopropylidene-D-allitol has been prepared in 63% yield from the corresponding 1-*O*-β-glycofuranosylphenylthionocarbonate by a catalytic Barton-McCombie deoxygenation reaction. The method used a new reagent combination of a catalytic amount of bis(tributyltin)oxide-AIBN with an excess of polymethylhydrosiloxane and *n*-butanol, conditions which generated catalytic amounts of tributyltin hydride *in situ*.[17]

1,4-Anhydro-5-azido-5-deoxy-3-thio-D-*erythro*-pentitol[18] and an *N*-protected 1,4-anhydro-5-deoxy-5-methylamino-3-thio-D-*threo*-pentitol[19] have been prepared from 2-deoxy-D-ribose and coupled with carbapenams to produce novel antibacterial agents.

2,5:3,4-Dianhydro-1-*O*-benzyl-D-ribitol and -L-arabinitol have been prepared by standard means from 2,5-anhydro D-xylose diisobutyldithioacetal, itself prepared by conversion of D-xylose into its diisobutyldithioacetal derivative, followed by 5-*O*-tosylation with concomitant ring closure.[20] The nucleophilic opening of (±)-1,3:2,5-dianhydro-xylitol with 1,2-ethane- or 1,3-propane-diol under basic conditions afforded the corresponding 1-*O*-(2-hydroxyethyl)- and 1-*O*-(3-hydroxypropyl)-derivatives.[21]

Several papers reporting on the synthesis of anhydro-sugar-derived nucleosides have appeared. Thus 1,4-anhydro-erythritol has been converted in several steps into (±)-1,4-anhydro-2-azido-3-*O*-Tbdms-2-deoxy-erythritol and further elaborated into **14**. The *trans*-isomer of **14** was also made, starting from 1,4:2,3-dianhydro-erythritol.[22] Treatment of 1,2-*O*-isopropylidene-3,5-di-*O*-mesyl-α-D-xylofuranose with trifluoroacetic acid then potassium carbonate gave 2,5:3,4-dianhydro-D-ribose dimethylacetal which was treated with azide to open the epoxide then further transformed through standard chemistry into the triazole isonucleoside **15** as well as into related pyrrolo[2,3-d]pyrimidine derivatives.[23] 1,4-Anhydro-D-ribitol has been converted in five straightforward steps into **16** in which the 5-OH group was bonded to a polymer support through a succinyl linker, as a universal solid support for oligonucleotide synthesis.[24] 2-Deoxy-D-ribose has been transformed in six steps into **17** for use in machine-assisted oligonucleotide synthesis.[25]



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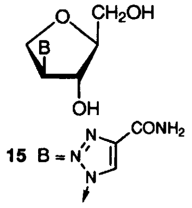

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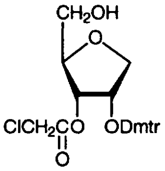

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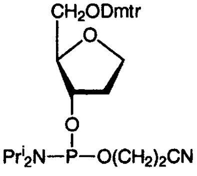

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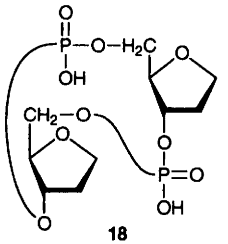

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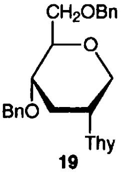

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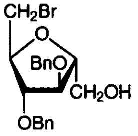
Treatment of methyl 2-deoxy-α,β-D-*erythro*-pentofuranoside with *N*,*O*-bis(Tms)trifluoroacetamide then triethylsilane gave the corresponding 1,4-anhydro sugar which was ultimately converted into the bis-abasic dinucleotide derivative **18** as an inhibitor of HIV-1 integrase.[26] Several examples of α-analogues of 1,5-anhydrohexitol nucleosides have been reported. For example, treatment of 4,6-di-*O*-benzyl-3-deoxy-2-*O*-Thp-D-*arabino*-hexitol with tosyl chloride, sodium hydride-DMF then tosic acid gave 1,5-anhydro-4,6-di-*O*-benzyl-3-deoxy-D-arabinitol. Further reaction of the latter derivative with N^3-benzoylthymine-diethyl diazodicarboxylate-triphenylphosphine, then treatment with sodium hydroxide, gave thymine derivative **19**. Several other purine and pyrimidine analogues were made in the same way and all deprotected. The cytidine equivalent of **19** showed moderate but selective antiviral activity. (See Vol. 30, p. 230, ref. 50 for related work on the synthesis of acyclic alditol nucleoside derivatives).[27]

A facile synthesis of 1,2:5,6-dianhydro-alditols has been reported by treating various 3,4-*O*-acetal-protected-D-mannitol or -D-glucitol derivatives first with trimethyl orthoacetate-pyridinium tosylate then with acetyl bromide (to generate the 2,5-di-*O*-acetyl-1,6-dibromo-1,6-dideoxy derivatives) and finally with methanolic potassium carbonate. When 3,4-di-*O*-benzyl-protected derivatives in the mannitol series were used, the 1,5-anhydro compound **20** and bicyclo-[2.2.2]octane **21** were formed in addition to the expected products. 1,2:4,5-Dianhydro-6-*O*-benzyl-D-glucitol was also prepared from L-ascorbic acid.[28]



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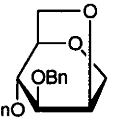

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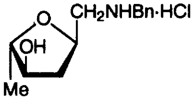


22

3,6-Dideoxy-D-*xylo*-hexono-1,4-lactone on reaction with dimethylamine, borane then aqueous hydrochloric acid gave 1,3,6-trideoxy-1-dimethylamino-D-*xylo*-hexitol hydrochloride. Treatment of this with anhydrous hydrofluoric acid-formic acid generated in the key step a 4,5-*O*-formoxonium ion intermediate which underwent intramolecular S_N2 attack at C-5 by the 2-OH to form a 2,5-anhydro ring. Further treatment with basic ion exchange resin then methyl iodide afforded a facile route to (−)-*allo*-muscarine. Compound **22** was also prepared as an analogue of the latter in a similar way and *ent*-**22** was made from 3,6-dideoxy-L-*xylo*-hexono-1,4-lactone.[29] In a related manner 1-deoxy-1-trifluoroacetamido-hexitol derivatives on treatment with anhydrous hydrofluoric acid gave a reactive 2-trifluoromethyloxazolinium ion intermediate which underwent substitution by the 5-OH at C-2 with inversion of configuration to form a 2,5-anhydro ring. For example 1-deoxy-1-trifluoroacetamido-D-glucitol gave 2,5-anhydro-1-deoxy-1-trifluoroacetamido-D-mannitol as major product together with small amounts of 1-amino-3,6-anhydro-1-deoxy-D-glucitol and 1-amino-1-deoxy-D-glucitol hydrofluoride.[30]

1.3 Amino- and Imino-alditols – Reviews on the chemical and chemoenzymatic syntheses of piperidine- and pyrrolidine-based sugar derivatives[31] and on the chemoenzymatic syntheses of 5-, 6- or 7-membered ring iminoalditols[32] as glycosidase inhibitors have appeared. A review on the preparation of alditols using furan Diels-Alder chemistry has also been reported.[33]

1.3.1 Acyclic Derivatives – Several non-ionic surfactant-like molecules have been prepared from 1-deoxy-1-methylamino-D-glucitol. Thus treatment of the alditol with oleic acid and a *Rhizomucor miehei* lipase in hexane[34] or with oleic acid and a *Candida antarctica* lipase at 90 °C[35] gave 1-amino-1-deoxy-*N*-methyl-*N*-oleoyl-D-glucitol in 50% and 97%, respectively. Similarly, reaction of the same starting amino alditol with a commercially available mixture of fatty acid methyl esters [*e.g.* oleic (59%), linoleic (22%), linolenic (11%), palmitic (5%), *etc.*] and a *Candida antarctica* lipase in *tert*-butanol again gave a mixture of *N*-acylated derivatives as major products in a form suitable for direct use.[36] In all cases, some 6-*O*-acylation took place.

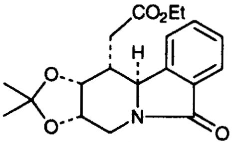
The synthesis of the tacaman indole alkaloid **23** has been accomplished in several steps from the phthalimide derivative **24**. The latter was made by treating 2,3-*O*-isopropylidene-D-ribose with *O*-benzylhydroxylamine and reducing the intermediate oxime ether with lithium aluminium hydride to produce 1-amino-1-deoxy-2,3-*O*-isopropylidene-D-ribitol which on treatment with *N*-ethoxycarbonylphthalimide-triethylamine gave **24**.[37]

Reaction of 1-(*tert*-butyloxycarbonylamino)-1-deoxy-2,3,4-tri-*O*-methyl-L-arabinitol with phthalic anhydride-pyridine followed by pentachlorophenol-dicyclohexylcarbodiimide then hydrochloric acid furnished **25**. Attempts to polycondense **25** by heating in various solvents gave only minor amounts of desired oligomeric materials. The main product was the phthalimide **26**.[38]

The (ribitylamino)uracils **27** have been synthesized as inhibitors of lumazine synthase.[39]

The 1-amino-1-deoxymannitol compound **28** has been prepared, the key steps being treatment of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose first with ethyl glycinate-sodium cyanoborohydride then diethylphosphonomethyl triflate to afford the corresponding 2,3:5,6-di-*O*-isopropylidene triethyl ester. The protonated form of **28** was found to be a potent inhibitor of 3-deoxy-D-*manno*-2-octulosonate-8-phophate (Kdo8P) synthase and believed to be effective by mimicking an intermediate oxycarbenium ion involved in the formation of Kdo8P.[40]

1.3.2 Cyclic Imino Compounds – Six new pyrrolidine alkaloids fitting within the generic structure **29** have been isolated from the branches of the plant *Broussonetia kazinoki* and have displayed potent glycosidase inhibitory activity. In particular, **29** (X = OH, Y = H, Z = OH, m = 8, n = 3, R = H) had IC_{50} values in the nanomolar region versus a β-glucosidase, β-galactosidase and β-mannosidase. The stereochemistry at the carbon where Z = OH remained undefined.[41] Isolated from the same plant also were the new compounds broussonetines C (**29**, X = OH, Y = H, Z = H, m = 8, n = 3) and D



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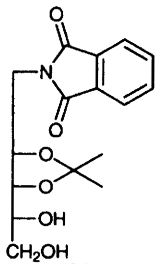

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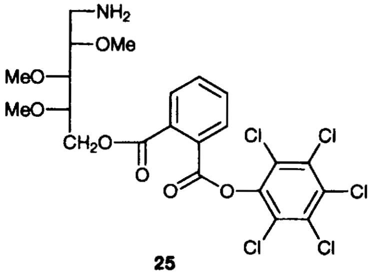

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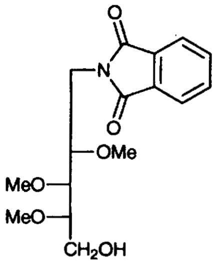

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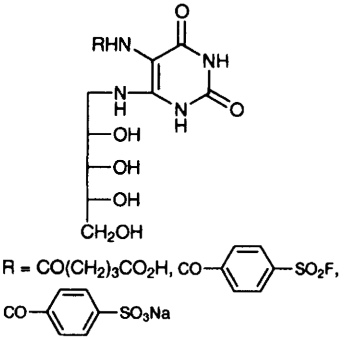

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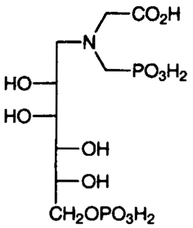

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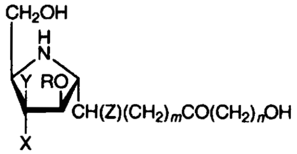
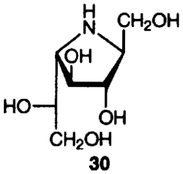
(**29**, X = OH, Y = H, Z = H, m = 7, n = 4) which were also strong β-galactosidase and β-mannosidase inhibitors, but without effect on α- or β-glucosidases.[42] The 'homo DMDP' compound **30** has been isolated from the plant *Hyacinthoides non-scripta* along with its 7-*O*-apiosyl derivative,[43] and the new calystegine C2 (**31**) has been isolated, along with several pentahydroxy-*nor*-tropane alkaloids from *Duboisia leichhardtii* (solanaceae).[44]



29 X,Y = OH, H; Z = H, OH; *m* = 7 or 8; *n* = 3 or 4; R = H, β-D-Glc*p*



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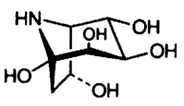

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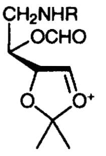
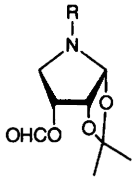


32 R = Boc or PO(OPh)$_2$

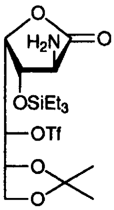


33 R = Boc or PO(OPh)$_2$

Treatment of carbamate or phosphoramidate derivatives of 5-amino-5-deoxy-2,3-*O*-isopropylidene-D-ribofuranose with iodosylbenzene (PhIO) and iodine generated anomeric *O*-alkoxyl radicals which underwent a β-fragmentation-oxidation process leading to the intermediate oxycarbenium ions **32** which were intercepted by the nitrogen group to give pyrrolidines **33**. A similar reaction was observed starting with 6-*tert*-butyloxycarbonylamino-6-deoxy-2,3,4-tri-*O*-methyl-D-glucopyranose and this gave a piperidine derivative.[45]

Displacement with inversion of the 5-*O*-triflyl group by the 2-amino group in **34** (prepared from D-*glycero*-D-*gulo*-heptono-γ-lactone) upon treatment with sodium acetate-methanol gave 2,5-dideoxy-2,5-imino-D-*glycero*-L-*galacto*-heptitol. The product along with two related analogues inhibited UDP-galactose mutase and mycobacterium galactan biosynthesis.[46]

Treating glycosyl enamine **35** with base resulted in displacement of the *O*-mesyl group by nitrogen. The resulting bicycle gave pyrrolidine **36** when treated with acetic anhydride-trimethylsilyl triflate.[47]



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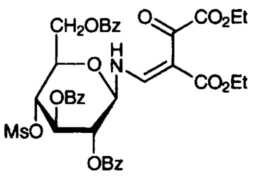

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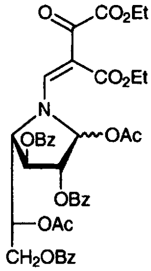

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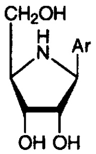
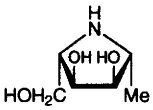


37 Ar = 3-pyridyl or substituted phenyl



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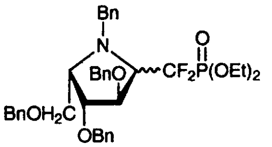

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A facile synthesis has been reported of 1-amino-1,2,5-trideoxy-2,5-imino-D-mannitol by Amadori rearrangement reaction of 5-azido-5-deoxy-D-glucofuranose with dibenzylamine to give 5-azido-1-dibenzylamino-1,5-dideoxy-β-D-fructopyranose which was hydrogenated-hydrogenolysed.[48]

The syntheses of a large range of 1,4-dideoxy-1,4-imino-D-ribitol derivatives **37** as transition state analogue inhibitors of nucleoside hydrolases using a previously reported general method involving addition of lithiated aromatics to a cyclic imine (Vol. 30, p. 230, ref. 51 and Vol. 27, p. 211, ref. 68) have been reported.[49]

The use of 2,3:5,6-di-*O*-isopropylidene-1-*C*-nitroso-β-D-mannofuranosyl chloride as a chiral dienophile for Diels-Alder reactions has been further demonstrated by its cycloaddition reaction with sorbaldehyde in the key step and subsequent transformation into pyrrolidine **38** and its C-5 hydroxymethyl epimer as potential glycosidase inhibitors.[50] The same nitroso-chloride has also been used to prepare 6-deoxy-D-nojirimycin, D-*fuco*-nojirimycin and 6-deoxy-D-*gulo*-nojirimycin and full details of this work are now described. (See Vol. 29, p. 236, ref. 86 for a preliminary account).[51]

Furanosylamines reacted with (diethylphosphinoyl)-difluoromethyllithium followed by treatment with mesyl chloride-triethylamine to afford (difluoroethyl)phosphonate aza sugars such as **39**. The deprotected form of this compound together with a series of differentialy configured derivatives were designed as transition state mimics for glycosyltransferases.[52]

The known methyl 2,3-dideoxy-5,6-*O*-isopropylidene-D-*erythro*-hexonate, derived from D-glucono-1,5-lactone, on successive treatment with tosyl chloride-pyridine, sodium azide, DIBAL and hydrogen-Pd/C afforded 1,4-dideoxy-1,4-imino-5,6-*O*-isopropylidene-D-*threo*-hexitol which was further elaborated into (*R*)-proline *via* manipulation of the side chain. (*S*)-Proline was also prepared by treating the same starting material successively with triphenylphosphine-carbon tetrabromide, lithium azide, DIBAL and hydrogen-Pd/C producing 1,4-dideoxy-1,4-imino-5,6-*O*-isopropylidene-D-*erythro*-hexitol, followed by degradation of the diol side chain.[53] An analogue, 4-hydroxyprolinol, has also been synthesized from the uncommon keto sugar, 3-deoxy-D-*glycero*-pentulose.[54]

Treatment of 6-azido-5,6-dideoxy-5-fluoro-L-idofuranose with 'sweetzyme T', an immobilized glucose isomerase, gave 6-azido-5,6-dideoxy-5-fluoro-L-*xylo*-hex-2-ulose which on hydrogenation gave 2-fluoro-deoxynojirimycin. 1,2,5-Trideoxy-1-fluoro-2,5-imino-D-mannitol and 2,5-dideoxy-2,5-imino-1-*O*-methyl-D-mannitol, for which the key step involved the use of the same glucose isomerase, were also prepared. The fluoro-derivatives were found to be poorer glycosidase inhibitors than the corresponding hydroxy ones.[55]

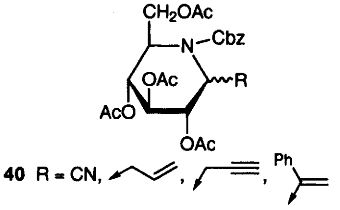
1,5,6,6′-Tetradeoxy-6,6′-difluoro-1,5-imino-D-glucitol has been achieved in a straightforward manner starting from L-sorbose.[56]

Full details on the synthesis of 7-carbonyl homologue derivatives of deoxynojirimycin have been reported. (See Vol. 28, p. 227, ref. 53 for a preliminary account).[57]

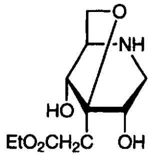
A five-step synthesis of D-nojirimycin and L-*ido*-nojirimycin from readily accessible 3-*O*-acetyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-D-*xylo*-hex-5-enofuranose has been achieved.[58]

The preparations of some *C*-glycoside derivatives of nojirimycin such as **40** have been described in which the key steps involved conversion of a protected 1-methoxy nojirimycin derivative into a 1-deoxy-1-fluoride analogue by treatment first with phenylthiotrimethylsilane-trimethylsilyl triflate then *N*-bromosuccinimide-DAST. The resulting fluorides reacted with various trimethylsilyl *C*-nucleophophiles in the presence of Lewis acids. Compounds **40** were deprotected and all unsaturated groups hydrogenated.[59]

The 3-*C*-branched-3,6-anhydro deoxynojirimycin compound **41** has been synthesized. The route involved treatment of 5-azido-6-*O*-Tbdps-5-deoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hex-3-ulofuranose with (ethoxycarbonylmethylene)-



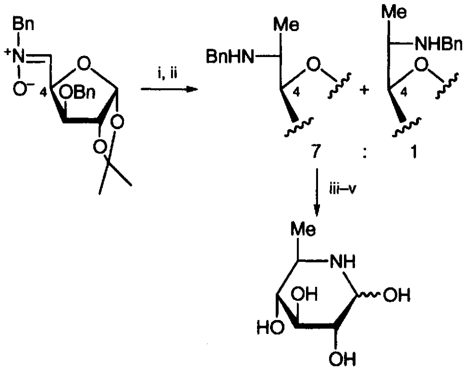
40 R = CN,



41

triphenylphosphorane then TBAF to produce a 3,6-anhydro-3-*C*-branched furanose. Subsequent removal of the acetonide and reductive amination furnished **41**. An analogue of **41** containing a 3-*C*-hydroxyethyl group was also prepared.[60]

A new route to 6-deoxynojirimycin is illustrated in Scheme 1. The nitrone starting material was made by treating the corresponding 5-aldehyde derivative with *N*-benzylhydroxylamine.[61]



Reagents: i, MeMgCl, Tms·OTf; ii, Zn/Cu, AcOH; iii, HCO_2NH_4, Pd/C; iv, SO_2, H_2O; v, HO^-

Scheme 1

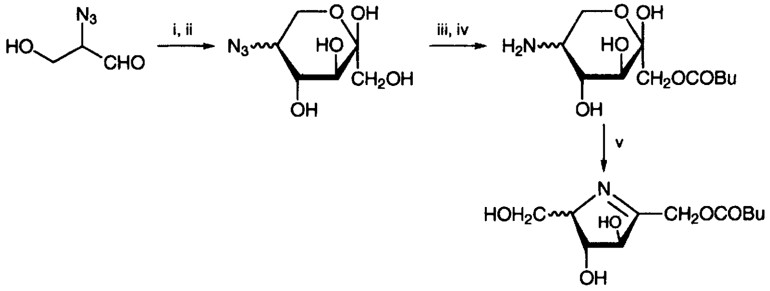
The syntheses of some *N*-alkylsilyl-, *N*-alkenyltrialkylsilyl- and *N*-benzyltrimethylsilyl-deoxynojirimycin derivatives have been described and their inhibitory activities against a range of intestinal glycosidases assessed. It was found that **42** was a potent inhibitor of intestinal sucrase but the (*Z*)-isomer of **42** was only a weak inhibitor.[62]

1-Deoxygalactonojirimycin has been prepared with high diastereoselectivity by double reductive amination of L-*arabino*-hexos-5-ulose with benzhydrylamine followed by hydrogenolysis. In contrast, double reductive amination of 2,6-di-*O*-benzyl-L-*arabino*-hexos-5-ulose with ammonia or methylamine followed by deprotection gave 1-deoxygalactonojirimycin and its *N*-methyl derivative together with 1,5-deoxy-1,5-imino-L-altritol and its *N*-methyl derivative.[63] In a similar way a double reductive amination of 3-*O*-benzyl-6-deoxy-D-*xylo*-hexos-5-ulose with benzhydrylamine was the key step in the formation of 1,6-dideoxynojirimycin.[64]

The synthesis of several 1,5-deoxy-1,5-iminopentitols from 5-bromo-5-

deoxy- or 5-*O*-mesyl-pentonolactones has been reported. For example, treatment of 5-bromo-5-deoxy-D-*arabino*-1,4-lactone with ammonia then 2,2-dimethoxypropane-tosic acid, followed by sodium borohydride-trifluoroacetic acid, gave **43**. The compounds were tested for inhibition of a glycosidase from human liver.[65]

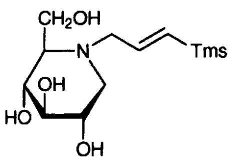
Previous reports have demonstrated the utility of aldolases in the preparation of azido sugars which upon hydrogenation afford aza sugars. (See for example Vol. 30, p. 234, ref. 79 and Vol. 28, p. 231, ref. 67). Scheme 2 illustrates a way in which the latter hydrogenation step can be controlled, allowing the isolation of imine intermediates. The method was also applicable to the formation of 6-membered cyclic analogues. In general, it was found that the cyclic imines were more potent glycosidase inhibitors than their reduced forms.[66]



Reagents: i, Dihydroxyacetone phosphate, aldolase; ii, phosphatase; iii, CH_2=CHOCOBu, Lipase; iv, H_2/Pd/C, HCl; v, NaOH

Scheme 2

A synthesis of 1,7-diamino-1,2,6,7-tetradeoxy-2,6-imino-D-*glycero*-L-*gulo*-heptitol has been described in which the key step involved intramolecular amination of aziridine **44** upon treatment with base to give **45** which was hydrogenated-hydrogenolysed to product.[67]



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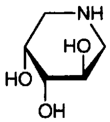

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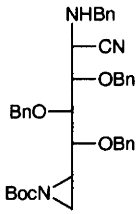

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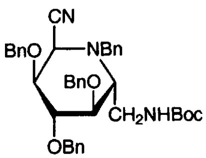

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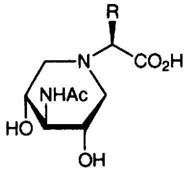
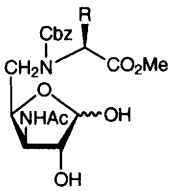
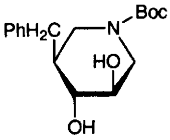


46 R = H or Bn



47 R = H or Bn



48

1,5-Dideoxy-1,5-imino-L-fucitol has been prepared from intermediate methyl 2,3-di-*O*-Tbdms-α-D-*arabino*-pentodialdo-1,4-furanoside in several conventional steps.[68]

The 4-acetamido-3,5-dihydropiperidines **46** have been synthesized and found to inhibit bacterial sialidases. The synthesis involved substitution of 3-azido-3-deoxy-1,2-*O*-isopropylidene-5-*O*-triflyl-α-D-xylofuranose with glycine- or phenylalanine-methyl esters followed by protecting group manipulations to afford intermediates **47** which were hydrogenolysed then saponified.[69]

The *N*-protected 6-deoxy-6-*C*-phenyl analogue **48** of isofagomine has been made as a precursor for an isofagomine-based peptide derivative by treating 1,6:2,3-dianhydro-4-*O*-benzyl-β-D-mannopyranose with benzylmagnesium chloride, hydrochloric acid then benzylamine-sodium cyanoborohydride to give 1-aminobenzyl-2-*C*,4-*O*-dibenzyl-1,2-dideoxy-D-glucitol which was oxidized with periodate, hydrogenolysed and treated with $(Boc)_2O$. (See Vol. 28, p. 229, ref. 58 for related work).[70]

Full details have been reported on the synthesis of 1,4,5-trideoxy-1,5-imino-D-ribitol from L-arabinose. (See Vol. 30, p. 231, ref. 63 for a preliminary report).[71]

The synthesis of some L-iduronic acid-like 1-*N*-imino-sugars from micro-organism-derived siastatin B is covered in Chapter 19 and the synthesis of 5-amino-5-deoxy-D-pentonolactones from unprotected D-pentonolactones is mentioned in Chapters 10 and 16.

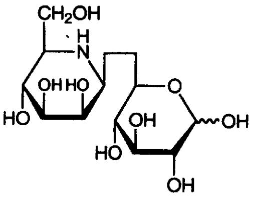
The synthesis of the *C*-linked D-aza-Man*p*-β-(1→6)-D-Glc*p*-OH analogue **49** in which the key step involved a Suzuki-like cross coupling of a cyclitol-derived vinyl bromide with a glucopyranose-derived alkyl borane, followed by conversion of the cyclitol moiety into a 1,5-deoxy-1,5-imino-D-mannitol ring structure, has been described. The method is similar to a previously reported one (Vol. 28, p. 229, ref. 61) and was also applied to the synthesis of analogous D-aza-Man*p*-β-(1→6)-D-Man*p*-OH, D-aza-Man*p*-β-(1→4)-D-Tal*p*-OH and D-aza-Man*p*-β-(1→1)-D-Glc*p*-OH products. The compounds were evaluated as glycosidase and HIV inhibitors.[72]

Compound **50** has been prepared by linking 1,2,6-trideoxy-2,6-imino-3,4-*O*-isopropylidene-D-galactitol (a deoxy-L-fuconojirimycin derivative) with 2-(2-bromobenzyl) 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside and deprotecting. An analogue of **50** was also prepared in which the aromatic linker group was replaced with a *n*-butyl one. The deoxyfuconojirimycin derivative above was prepared from a known 1-*C*-methyl-2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranose.[73]

The aza-*C*-disaccharide **51** has been made by treating tri-*O*-acetyl-D-glucal with nitrone **52** and the resultant cycloadduct successively with sodium methoxide-methanol, trifluoroacetic acid then hydrogen-Pd/C.[74]

Scheme 3 illustrates a route to an aza-*C*-linked disaccharide structure, starting from a known protected imino-octitol (Vol. 30, p. 233, ref. 75, compound **45**).[75]

Several iminoalditols have been prepared from non-carbohydrate sources. Thus (±)-aza-*C*-disaccharide **53** together with an analogue have been made as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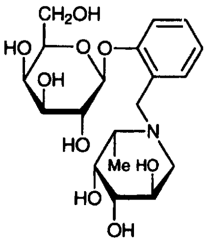
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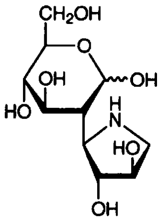
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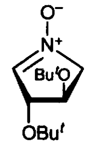
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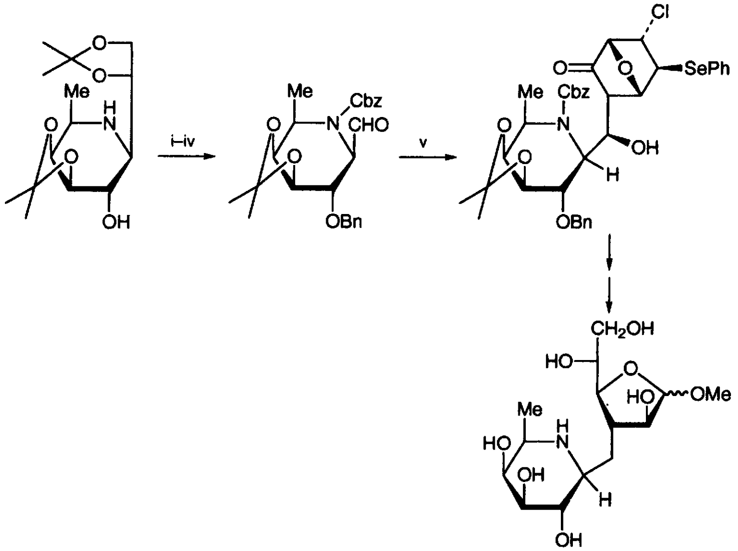
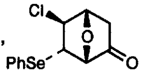
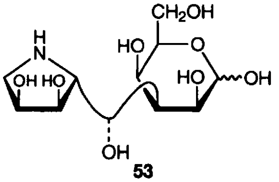


Reagents: i, BnBr, NaH; ii, BnOCOCl; iii, AcOH, H_2O; iv, IO_4^-; v,  , $LiN(Tms)_2$

Scheme 3

moderate α-mannosidase inhibitors from a known bicyclic cycloadduct formed between furan and 1-cyano vinyl acetate.[76] D-Tartaric acid has served as chiral starting material for the synthesis of 1,4-dideoxy-1,4-imino-D-arabinitol[77] and of nectricine and *epi*-nectricine.[78] D-Serine was the starting material for the preparation of nucleoside analogue **54** which when incorporated into an oligonucleotide, followed by conversion of the 6-chloropurine ring into an adenine ring, bound to a base-excision DNA repair enzyme with a K_d < 1pM.[79] *trans*-3-Hydroxyprolinol has been prepared as major product from L-serine and converted to the *N*-acyl derivative **55** for incorporation into oligonucleotides. Likewise the enantiomer of **55** was made from D-serine. *cis*-3-Hydroxyprolinol enantiomers were also formed as minor products.[80]

Addition of allyl bromide to an *N*,*O*-protected D-serinal derivative, mediated by tin(II) chloride-sodium iodide, gave **56** as the major isomer. Successive treatment with triphenylsilyl chloride-pyridine, osmium tetroxide, TEMPO-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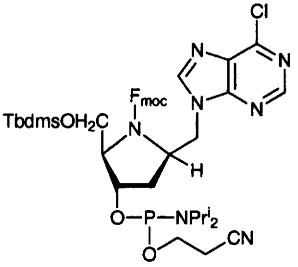
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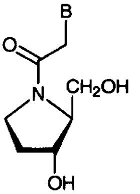
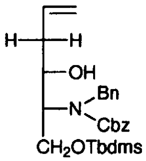

55 B = Thy, Ade^{Bz}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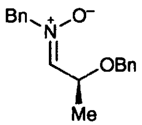
sodium hypochlorite then hydrogen-Pd/C produced 6-*O*-Tbdms-1,3,5-trideoxy-1,5-imino-4-*O*-triphenylsilyl-D-*ribo*-hexitol which, after treatment with TBAF, afforded 1,3-dideoxynojirimycin, offering an alternative route to this system. (See for example Vol. 28, p. 227, ref. 54).[81]

Tin-mediated aldol reactions between L-tartrate-derived 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose and protected alanine and glycine amino acids was the key step in the synthesis of several aza-sugars. For example, 1-deoxy-L-*altro*-nojirimycin was made involving a glycine derivative.[82]

Cycloaddition reaction between 2-trimethylsiloxyfuran and (*S*)-lactaldehyde-derived nitrone **57** gave **58** together with the isomer inverted at the indicated carbons. Hydrogenolysis of **58** gave a lactam which was treated with borane to afford 6-*O*-benzyl-1,2,5,7-tetradeoxy-1,5-imino-L-*altro*-heptitol. Similar treatment of the isomer of **58** gave 2-*O*-benzyl-1,3,6,7-tetradeoxy-3,7-imino-D-*galacto*-heptitol.[83]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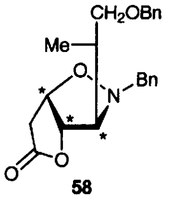
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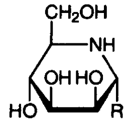
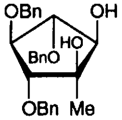

59 R = Ph, $n\text{-}C_8H_{17}$ or $(CH_2)_3OBn$

Full details on the preparation of 1-deoxy-D-mannojirimycin and 1-deoxy-L-altrojirimycin from (2*R*,6*R*)- and (2*S*,6*S*)-6-hydroxy-2-methoxymethyl-*N*-tosyl-1,2,3,6-tetrahyroxypyridin-3-one, respectively, both prepared from an α-furfurylamine, have been published. (See Vol. 30, p. 236, ref. 92).[84] Aryl- and alkyl substituted deoxynojirimycin analogues such as **59** have been prepared from benzene *cis*-diols (microbial oxidation products).[85,86]

2 Cyclitols and Derivatives

The synthesis of carba-sugars, inositols and carba-amino-sugars such as valiolamine from D-(−)-quinic acid has been reviewed.[1] Reviewed also are intramolecular cycloaddition reactions of sugar-based C-centred radicals onto oxime ethers or hydrazones giving amino- and hydrazino-cyclitols, respectively.[87]

2.1 Cyclopentane Derivatives – The involvement of free radicals in the C–C bond forming step in the synthesis of cyclopentane rings has received much attention. Thus the cyclitol moiety found in the natural product caryose (Vol. 30, p. 237, structure **74**) has been prepared by treatment of 2,3,4-tri-*O*-benzyl-6-deoxy-L-*xylo*-hexos-5-ulose with samarium diiodide to give **60**. The synthesis of caryose itself was completed in five standard steps from **60**. (See Vol. 30, p. 237, ref. 101 for the characterization of caryose).[88] The cyclization of 1,5-iodo-oxime ether derivatives with samarium diiodide proceeds to give *trans*-products about the newly formed bonds. Thus for example **61** gave **62**. In this case an O→N migration of a pivaloyl group and breakage of the N-O bond of the oxime ether were observed. Several other examples were described.[89] Many examples of the synthesis of 4-amino-1,2,3-cyclopentanetriol derivatives by reductive couplings of 1,5-halogeno-, keto- or aldehydo-oxime ethers have also been reported.[90] Likewise, the carbocyclic nucleoside precursor **63** has been prepared by an improved procedure (see also Vol. 25, p. 211, ref. 82) using a similar kind of radical-based ring closure of an iodo-oxime ether followed by conventional chemistry.[91] Treatment of unsaturated iodide **64**, available in three steps from 5-deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranose, with samarium diiodide gave cyclopentane **65**, whereas with tributyltin hydride-AIBN, cyclopentane **66** was produced.[92]



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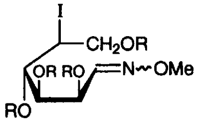
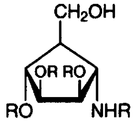
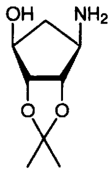


61 R = Piv



62 R = Piv



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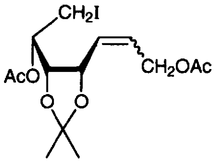

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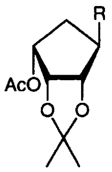
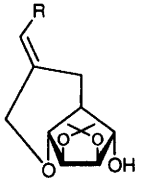


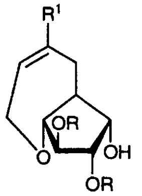
65 R = CH=CH$_2$
66 R = (CH$_2$)$_2$OAc

Grob fragmentation of methyl 6-deoxy-6-iodo-2,3-*O*-isopropylidene-4-*O*-(substituted 2-propynyl)-α-D-mannopyrannoside derivatives, followed by treatment with samarium diiodide, gave the 5:6-bicyclic compounds **67**. When the 2,3-di-*O*-methyl- or benzyl-D-glucopyrannoside equivalent starting materials were used, the 5:7-membered ring products **68** predominated.[93]

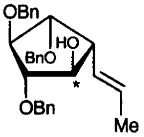
Treatment of 2,3,4-tri-*O*-benzyl-5,6,7,8-tetradeoxy-D-*xylo*-oct-5(*E*),7-dienose (see Vol. 28, p. 8, ref. 30 for its preparation) with tributyltin hydride-AIBN gave compound **69**. Reduction of the aldehyde group in the starting material to an alcohol and conversion of this into a xanthate then treatment with tributyltin hydride gave the deoxy version of **69** at the indicated carbon. Some other similar examples were described.[94]



67 R = H, Me or Tbdms



68 R = Me or Bn, R¹ = H or Me



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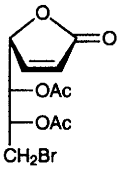

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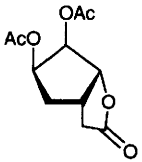

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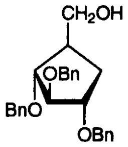


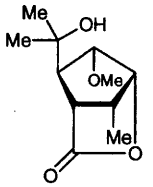
72

Treatment of the bromo-lactone derivative **70** with tributyltin hydride-AIBN gave cyclopentane **71**. The lactone function of **71** was hydrolysed and the carboxylic acid-containing substituent was reduced to a hydroxyethyl group. Other similar examples were also reported.[95]

Treatment of 2,3,4-tri-*O*-benzyl-1,5,6-trideoxy-1-iodo-D-*xylo*-hex-5-enitol with a Co(salicylideneiminato) complex in the presence of sodium hydroxide gave **72** as the major product together with its hydroxymethyl epimer. Many other examples with different sugar configurations were also described.[96]

The bicyclic cyclopentane derivative **73** was produced when 2,3,6,7-tetradeoxy-4-*O*-methyl-D-*erythro*-hept-2,6-dieno-1,5-lactone was irradiated with light in isopropanol.[97]

The preparation of cyclopentane-based bicyclic and tricyclic systems, formed by intramolecular cycloaddition reaction, has been further exploited. For example, addition of the azomethine imine derived by treatment of ethyl *N*-benzylcarbazate ($BnNHNHCO_2Et$) with triethylamine to 2,3,4-tri-*O*-benzyl-5,6-dideoxy-D-*xylo*-hex-5-enose gave **74**. Some similar examples were also described.[98]



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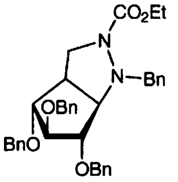

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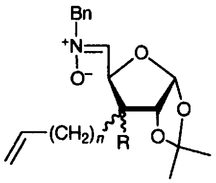

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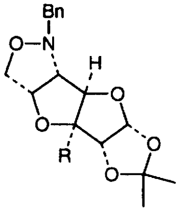
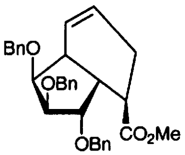


76 R = OH, OMe, OBn or OAll



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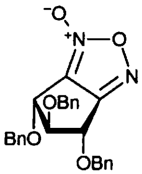


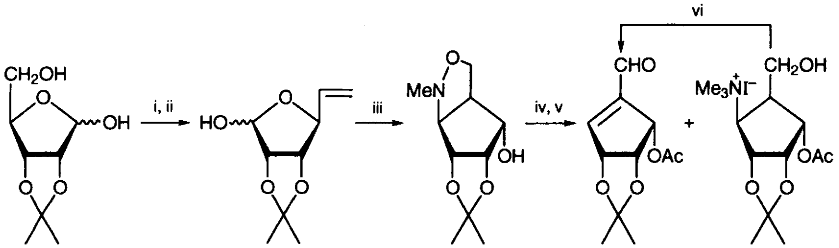
78

The nitrones **75** underwent facile cyclization on heating to give new tricyclic systems. For example **75** ($n = 1$) gave **76**.[99]

Bicyclic derivative **77** was prepared by intramolecular Diels-Alder reaction of (*E*),(*E*)-methyl 4,5,6-tri-*O*-benzyl-2,3,7,8,9,10-hexadeoxy-L-*arabino*-2,7,9-tridecanoate catalysed by aluminium trichloride.[100]

2,3,4-Tri-*O*-benzyl-xylodialdose has been converted into its 1,5-di-oxime derivative and oxidized with *N*-chlorosuccinimide-pyridine to its bis-nitrile oxide which dimerized to give **78** plus its *N*-oxide isomer. Hydrogenolysis of the heterocyclic ring without loss of the *O*-benzyl groups produced the corresponding cyclic bis-oxime derivative.[101]

Full details of a preliminary report (M.P. van Boggelen *et al.*, *Tetrahedron Lett.*, 1995, **36**, 1899) on an efficient, short synthesis of a cyclopentene aldehyde has been published (Scheme 4). The method involved a novel methyl iodide-induced N–O bond cleavage reaction in the key step. A quaternary ammonium iodide alcohol was also produced as shown which could be converted to the cyclopentene aldehyde by oxidation with concomitant elimination of triethylamine [102]

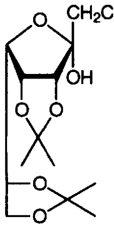


Reagents: i, $CH_2{=}CHMgBr$; ii, $NaIO_4$; iii, MeNHOH, Py; iv, Ac_2O, Py; v, MeI, THF, reflux; vi, $(COCl)_2$, DMSO

Scheme 4

Treating compound **79**, available from a protected D-gulonolactone, with periodic acid gave as intermediate, *N*,*N*-diethyl 5-deoxy-2,3-*O*-isopropylidene-D-*erythro*-hex-4-uluronamide, which cyclized to cyclopentenone **80**.[103]

The carbocyclic analogue of 5-phophoribosyl 1-pyrophosphate has been synthesized by reaction of **81** first with methanol under light irradiation, then reduction with sodium triacetoxyborohydride to give **82** which was phosphorylated and deprotected.[104]



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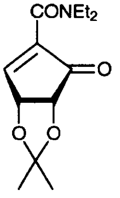

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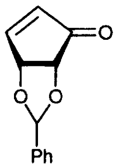

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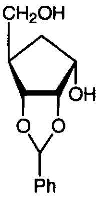

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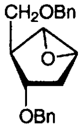

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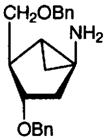

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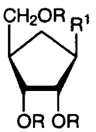
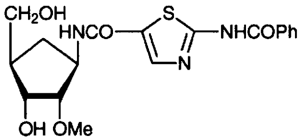


85 R = Bn, R^1 = CO_2Me
86 R = H, R^1 = NH_2
87 R = Bn, R^1 = CH_2NHAc



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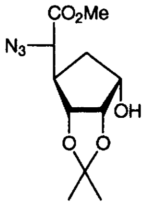


89

A chiral synthesis of the known cyclopentane epoxide **83** has been achieved from sodio cyclopentadiene, as an intermediate useful in the synthesis of carbocyclic nucleosides.[105] The same epoxide was transformed into amine **84** and on into carbocyclic nucleoside derivatives based on adenine, guanine and cytidine in the same way as that described for the thymine analogue in Vol. 29, p. 285, ref. 167.[106]

The chiral ester derivative **85** has been prepared by an initial Diels-Alder reaction and converted into carbocyclic nucleoside precursors **86** and **87**.[107]

(−)-(1*R*,4*S*)-2-Azabicyclo[2.2.1]hept-5-en-3-one was used as starting material for the synthesis of **88**[108] and enantiomerically enriched norborn-5-en-2-yl acetate was used as starting material in the preparation of **89**, a precursor to carbocyclic analogues of the nucleoside antibiotics nikkomycins and polyoxins.[109]

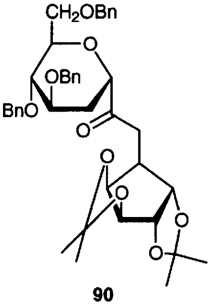
1-Dimethylphenylsilylcyclopenta-2,4-diene was the starting material for the cyclopentane ring found in the carba-disaccharide **90**. Compound **90** in which the cyclopentane ring had the enantiomeric stereochemistry was also prepared.[110]

2.2 Inositols and Other Cyclohexane Derivatives – A review on the stereospecific syntheses of all conduritol isomers derived from appropriate cyclohexa-1,3-dienes has appeared.[111]

Full details on the preparation of (–)-shikimic acid and related compounds involving a novel methyl iodide-induced N–O bond cleavage reaction of isoxazolidine derivatives have been reported. (See M.P. van Boggelen *et al.*, *Tetrahedron Lett.*, 1995, **36**, 1899 for a preliminary account).[102]

The addition of allyl magnesium bromide to 2,3-*O*-isopropylidene-D-ribofuranose gave a mixture of 1,2,3-trideoxy-5,6-*O*-isopropylidene-D-*allo*-oct-1-enitol (major isomer) together with the corresponding D-altritol derivative. Treatment of this mixture with sodium periodate followed by *N*-methylhydroxylamine gave isoxazolidine **91** as the major isomer which was converted into the novel (–)-5-*epi*-shikimic acid, the key step being hydrogenolytic N–O bond cleavage in **91**. In contrast allyl magnesium bromide added to protected D-ribono-1,4-lactone, followed by reduction with DIBAL, to give exclusively 1,2,3-trideoxy-5,6-*O*-isopropylidene-D-*altro*-oct-1-enitol from which (–)-shikimic acid was obtained again *via* a hydrogenolytic N–O bond cleavage reaction of an isoxazolidine intermediate.[112]

(3*R*)-3-Fluoro-Dahp and its C-3 epimer have been made by enzymic methods and used as substrates for dehydroquinate (DHQ) synthase. The (3*R*)-epimer was found to be consumed rapidly to produce (6*R*)-6-fluorodehydroquinate whereas the (3*S*)-epimer was only consumed slowly and gave mixtures of (6*R*/6*S*)-6-fluorodehydroquinates. The results were interpreted to reveal a subtle role for the enzyme in the natural process.[113]



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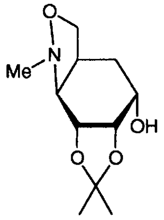

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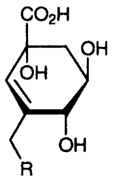
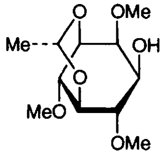


92 R = OPO_3H_2 or $CH(CO_2H)_2$

(–)-Quinic acid has been used to prepare useful biologically active cyclohexitols. For example, unsaturated derivative **92** and related compounds were prepared and found to be very potent DHQ synthase inhibitors; more potent than their saturated equivalents.[114] Carbocyclic analogues of *N*-acetyl-2,3-didehydro-2-deoxy-neuraminic acids in which the trihydroxypropyl unit found in the natural compound was replaced by a range of small linear and branched alkyl groups have been made as very strong influenza neuraminidase inhibitors.[115] Other carbocylclic analogues of sialic acid prepared from quinic acid as well as shikimic acid starting materials have also been reported.[116] An efficient way of making *myo*-inositols with free 1,3-hydroxyl groups *via* a chelation assisted C–O bond cleavage of ortho ester derivatives has been described. For example treatment of 2,4,6-tri-*O*-methyl-*myo*-inositol 1,3,5-orthoformate with two equivalents of methylmagnesium Grignard gave the *exo*-3,5-*O*-ethylidene derivative **93** which on further treatment with excess phenylmagnesium Grignard reagent gave 5-*O*-benzhydryl-2,4,6-tri-*O*-methyl-*myo*-inositol. In a similar way treatment of the corresponding orthobenzoate-derived starting material with excess lithium aluminium hydride-aluminium chloride furnished 3-*O*-benzyl-2,4,6-tri-*O*-methyl-*myo*-inositol.[117] Treatment of 2,4-di-*O*-benzoyl-*myo*-inositol-1,3,5-orthoformate with alkyl halides and silver(I) oxide unusually led to the 4,6-di-*O*-alkylated or 4-*O*-mono-alkylated *myo*-inositol-1,3,5-orthoformate derivatives. The products produced were very dependent on the nature of the reagents and solvent used.[118]

Full details (Vol. 29, p. 239, ref. 104 for preliminary account) on the syntheses of 3-deoxy-L-*chiro*-4-inosose and 6-deoxy-D-*myo*-1-inosose as precursors of 3-deoxy-L-*chiro*- and 6-deoxy-D-*myo*-inositols, respectively, have been reported. The cyclitol ring was made by a Ferrier carbocyclization reaction on a methyl D-galactopyranoside derivative. In addition the synthesis of 2-*O*-benzyl-3,6-dideoxy-3-fluoro-D-*myo*-inositol was also described.[119] A ^{1}H- and ^{13}C-NMR investigation of *myo*-inositol hexaacetate is covered in Chapter 21.

Cyclohexene derivative **94** has been prepared from D-glucose by a Ferrier carbocyclic reaction and converted into its β-epoxide derivative or induced to undergo a thermal Claisen rearrangement with dimethylformamide dimethylacetal. D-Quinic was also converted into unsaturated cyclitol derivatives which also underwent similar epoxidation-rearrangement reactions.[120]



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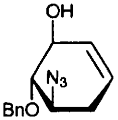

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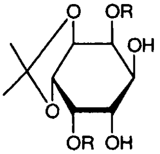
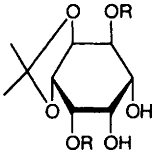


95 R = Bn or Tbdms



96 R = Bn or Tbdms

Treatment of 3,4,5-tri-*O*-benzyl-1,2,7,8-tetradeoxy-D-*gluco*-oct-1,7-dienitol with TbdmsCl-imidazole followed by ozone and samarium diiodide afforded 3,4,5-tri-*O*-benzyl-6-*O*-Tbdms-L-*chiro*-inositol. The dienitol starting material was prepared in three straightforward steps from D-xylose.[121] Oxidation of 2,5-di-*O*-Tbdms- or 2,5-di-*O*-benzyl-3,4-*O*-isopropylidenemannitol followed by treatment with samarium diiodide yielded mixtures of *neo*-inositol derivatives **95** and *allo*-inositol derivatives **96**. The former isomers predominated with the 2,5-di-*O*-Tbdms-alditol starting material whereas the latter was the major isomer with the 2,5-di-*O*-benzyl-alditol. Compound **96** (R = Bn) was also converted into (−)-conduritol E when treated under Corey-Winter conditions.[122] A simple synthesis of a (−)-conduritol E derivative has been achieved by potassium hydroxide treatment of sulfone **97** leading to expulsion of sulfur dioxide (Ramburg-Bäcklund reaction) followed by deacetylation.[123]

(+)-D-Conduritol tetraacetate has been synthesized from 1,2:4,5-di-*O*-cyclohexylidene *myo*-inositol, the key step involving resolution of a dispiroketal intermediate.[124]

Successive treatment of compound **79** first with aqueous acid, sodium periodate then base gave unsaturated derivative **98**.[103]

2,3,4,5-Tetra-*O*-benzyl-D-mannitol has been converted to its corresponding 1,6-di-oxime derivative and oxidized with *N*-chlorosuccinimide-pyridine to its bis-nitrile oxide which dimerized to give **99** plus its *N*-oxide isomer. Hydrogenolysis of the heterocyclic ring without loss of the *O*-benzyl groups produced the corresponding cyclic bis-oxime derivative.[101]

A short synthesis of (±)-pinitol from benzene has been achieved in which the key step involved a catalytic photoinduced charge-transfer osmylation in the presence of sodium bromate. Treatment with acetone-acid then led to the key intermediate, 4-bromo-4-deoxy-1,2:5,6-di-*O*-isopropylidene-*neo*-inositol, together with two other cyclitol derivatives. (See W.B. Motherwell *et al.*, *Angew. Chem. Int. Ed. Eng.*, 1995, **34**, 280 for preliminary work).[125]

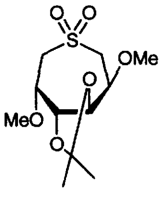
The most common routes to cyclitols derived from benzene are those that involve a microbial oxidation step to produce a *cis*-diol derivative. By use of this method 3-deoxy-3-fluoro-L-*chiro*-inositol, 5-deoxy-5-fluoro-*myo*-inositol,[126] *allo*-inositol[127] and conduritol D[128] have all been prepared from bromobenzene. The formation of the last of these compounds is notable in that in the key step a *syn*-dihydroxylation of the initial *cis*-diol oxidation product was achieved using osmium tetroxide-trimethylamine *N*-oxide. *Anti*-dihydroxylation is more commonly observed in these systems. From benzene itself, (±)-conduritol E,[129] (−)-conduritol E, (−)-conduramine F4[130] and partial *O*-acetyl derivatives of (+)- and (−)-conduritol E[131] have been reported; asymmetry being introduced by lipase-mediated kinetic resolution. Full details on the preparation of mono-epoxy derivatives of various benzene *cis*-diols and their regioselective opening with O, N, C and halogen centred nucleophiles have appeared. (See Vol. 28, p. 242, ref. 142, Vol. 27, p. 218, ref. 112 and 113 for example).[132]

A route to (±)-*trans*-cyclohexa-3,5-diene-1,2-diol derivatives from (±)-*myo*-inositol derivatives has been reported.[133]

Oxidation of (±)-3,4,5-tri-*O*-benzyl-1,2-*O*-isopropylidene-*myo*-inositol gave the corresponding inosose. Reduction of this ketone with sodium borohydride gave an *epi*-inositol derivative, whereas treatment with methylmagnesium iodide gave a 4-*C*-methyl-*epi*-inositol (*iso*-laminitol) derivative. The same inosose, on treatment with diazomethane, gave a *spiro*-epoxide which reacted with lithium aluminium hydride to give a 4-*C*-methyl-*myo*-inositol (laminitol) compound.[134]

The bicyclic cyclohexane derivative **100** was produced when 6-*O*-acetyl-2,3,7,8-tetradeoxy-4-methyl-D-*ribo*-oct-2,7-dieno-1,5-lactone was irradiated with light in isopropanol.[97]

In the area of carba-disaccharides a new inositol glycoside, α-D-Gal*p*-(1→2)-2-*O*-D-*chiro*-inositol has been isolated from the jojoba plant *Simmondsia chinensis* together with known α-D-Gal*p*-(1→1)-1-*O*-L-*myo*-inositol (galactinol).[135] A route to galactinol has also been described by coupling an appropriate L-*myo*-inositol derivative with a protected galactosyl trichloroacetimidate donor.[136] The structure of 'galactosylononitol' has been revised to α-D-Gal*p*-(1→3)-4-*O*-methyl-3-*O*-D-*myo*-inositol.[137] The synthesis of sialyl Le^x mimics containing a cyclitol in place of a galactose or GlcNAc ring is mentioned in Chapter 4.



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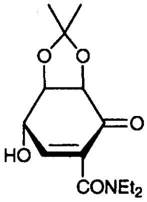

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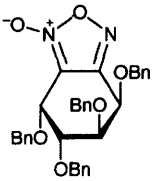

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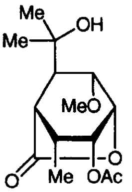

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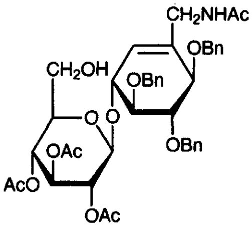

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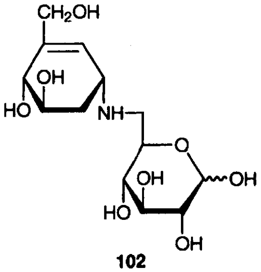


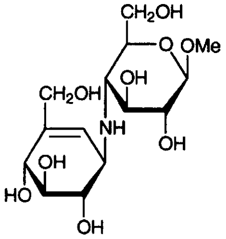
102

The carba-disaccharide **101** has been synthesized by coupling tetra-*O*-acetyl-α-D-glucopyranosyl bromide with the corresponding mono-hydroxy cyclitol derivative under Koenigs-Knorr conditions. The cyclitol portion was made from D-glucose by Ferrier carbocyclization reaction.[138] The cyclitol moiety in **102** (a 2-deoxyisomaltose analogue of acarbose) was made by a similar carbocyclic ring forming reaction applied to methyl 3,4-di-*O*-benzyl-2,6-dideoxy-D-*threo*-hex-5-enopyranoside. The D-glucose unit was attached by displacement of a 6-*O*-triflate by the cyclitol amino group.[139]

The acarbose analogue **103** has also been made by coupling an amino cyclitol to a sugar epoxide.[140] The carbamate compound **104** was surprisingly obtained in 25% yield when benzyl 2,3-di-*O*-benzyl-6-deoxy-4-*O*-triflyl-β-D-galactopyranoside was treated with amino cyclitol **105** and potassium carbonate-HMPA. A similar reaction took place between **105** and a trisaccharide triflate.[141] Improved procedures for the large scale synthesis of **105** have also been described.[142]

The syntheses of some novel carba-disaccharide types of aminocyclitol antibiotic model compounds by glycosylating a suitably protected (azido) deoxy inosose with mono-saccharides derived of D-arabinose, D-ribose, D-glucosamine, L-ristosamine and L-acosamine have been described.[143]

The carbo-lactosaminide **106** and its (1→3)-linked equivalent have been prepared by nucleophilic opening of a cyclitol epoxide with a D-glucosamine-



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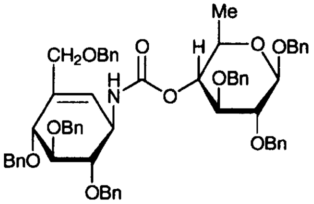

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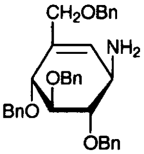


105

based alcohol. Compound **106** was found to be a substrate for human milk fucosyltransferase.[144]

1-*tert*-Butyldimethylsilylcyclohexa-2,5-diene was the starting material for the cylclitol unit found in **107** and was produced in chiral form using Sharpless asymmetric dihydroxylation chemistry.[110] The same dienylsilane, after asymmetric dihydroxylation, was also used to prepare carba-α-D-galactopyranose-, carba-β-L-altropyranose and related-derivatives.[145]

Validamine (carba-α-D-glucopyranosylamine) has been transformed by standard chemistry into its 'manno' and 'galacto' equivalents.[146] The morpholino group in the known glucosylceramide synthase inhibitor, 1-phenyl-2-decanoylamino-3-morpholino-1-propanol, has been replaced with valienamine and validamine. The products were no longer inhibitors of the synthase but were found to be potent inhibitors of a β-glucocerebrosidase.[147]

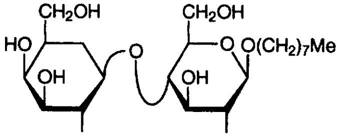
A synthesis of (+)-cyclophellitol by a stereoselective Diels-Alder reaction has been described.[148]

2.3 Inositol Phosphates and Derivatives – A review on the total syntheses of inositol phospholipids involved in signal transduction has been published. It includes the preparation of inositol 3,4,5-trisphosphate, 4,5-bisphosphate and 2,6-dimannopyranosylphosphate and the use of new benzoyl derivatives bearing oxyethyl substituents at the *ortho*-positions as protection for hydroxyl groups. The latter are selectively removable in the presence of OAc groups.[149]

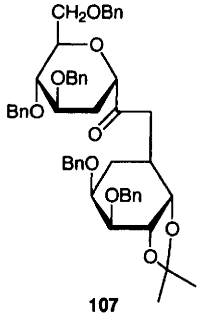
Studies on the elucidation of the catalytic mechanism of phosphatidylinositol-specific phospholipase C (PI-PLC) (converts phosphatidyl inositol into 1-inositol phosphate) and its comparison with that of ribonuclease A have been reported.[150] The synthesis of the [1^{3}H]-labelled form of the potent PI-PLC inhibitor 1-octadecylphosphothiolyl-*myo*-inositol has also been described to help elucidate its mechanism for inhibition.[151]

In the field of phosphatidylinositols, full details on the synthesis of 2,6-di-*O*-α-D-mannopyranosyl-1-*O*-(1,2-di-*O*-heptadecanoylphosphatidyl)-D-*myo*-inositol by coupling of a mannosyl phosphite donor with a (±)-*myo*-inositol diol acceptor, followed by separation of the diastereomers, have been reported. (See Vol. 30, p. 23, ref. 101 for a preliminary account).[152]

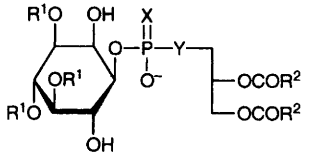
A route to 1-*O*-(1,2-di-*O*-heptadecanoylphosphatidyl)-D-*myo*-inositol 3,4,5-trisphosphate from D-glucose *via* a known 2,3,4,5,6-penta-*O*-(4-methoxybenzyl)-D-*myo*-inositol intermediate has been reported.[153] The syntheses of



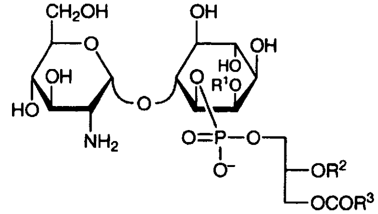
106



107



108 $R^1 = P(S)O_2^{2-}$, X = Y = O, $R^2 = C_{15}H_{31}$
or $R^1 = P(S)O_2^{2-}$, X = S, Y = O, $R^2 = C_{15}H_{31}$
109 R^1 = H, X = O, Y = S, $R^2 = C_7H_{15}$
or R^1 = H, X = O, Y = S, $R^2 = C_{15}H_{31}$



110 R^1 = Me, $R^2 = COC_{15}H_{31}$, $R^3 = C_{15}H_{31}$
R^1 = H, R^2 = Me, $R^3 = C_{16}H_{33}$
R^1 = H, $R^2 = R^3 = C_{18}H_{37}$

2,5,6-tri-*O*-benzyl-1-*O*-(4-methoxybenzyl)-D-*myo*-inositol and 2,6-di-*O*-benzyl-1-*O*-(4-methoxybenzyl)-D-*myo*-inositol from (±)-*myo*-inositol *via* resolution with (1*R*)-(+)-camphor dimethylacetal have been described.[154] These compounds were converted into 1-*O*-(1,2-di-*O*-pentadecanoylphosphatidyl)-D-*myo*-inositol 3,4-bisphosphate and 3,4,5-trisphosphate, respectively. The enantiomers of the products were also prepared.[155] Syntheses of 1-*O*-(1,2-di-*O*-pentadecanoyl)-, (1,2-di-*O*-heptanoyl)-, and (1-*O*-aminooctyl-2-*O*-octanoyl)-(designed to be cross-linkable) phosphatidyl-D-*myo*-inositol 3,4-bisphosphates have been prepared from 1,2:5,6-di-*O*-cyclohexylidene-D-*myo*-inositol[156] or 5,6-di-*O*-benzyl-3,4-di-*O*-(4-methoxybenzyl)-D-*myo*-inositol.[157] It should be noted that the glycerol moieties in the last two references have been drawn in the papers in their wrong enantiomeric forms. 1-*O*-(1,2-Di-*O*-hexadecanoylphosphatidyl)-D-*myo*-inositol 3,4,5-trisphosphate has been synthesized from 3,4,5-tri-*O*-allyl-6-*O*-benzyl-1,2-*O*-cyclohexylidene-D-*myo*-inositol,[158] and 1-*O*-(1-*O*-heptadecanoyl-2-*O*-arachidonoylphosphatidyl)-D-*myo*-inositol 3,4,5-trisphosphate together with three stereoisomers have also been synthesized from a differentially protected D-*myo*-inositol derivative.[159] A synthesis of (±)-1-*O*-(1,2-di-*O*-oleoylphophatidyl)-*myo*-inositol 4,5-bisphosphate which uses a novel 9-fluorenylmethyl phosphate protecting group strategy[160] and a synthesis of phosphorothioate analogues **108** which utilized in the key step a cleavage of an *O*-benzylphosphorothioate triester intermediate with trimethylamine-trimethylsilylchloride[161] have been described. Full details have been reported on the synthesis of 1-*O*-(1,2-di-*O*-pentadecanoylphosphatidyl)-3-deoxy-D-*myo*-inositol from L-quebrachitol (see Vol. 29, p. 244, ref. 148 for preliminary details) together with new material on the synthesis of the 2,3-dideoxy-D-*myo*-inositol equivalent, also from L-quebrachitol.[162]

O,S-Phosphorothioate analogues of phosphatidyl-inositol **109** have been prepared in which a chiral thiophosphoramidite, prepared from (2*R*)-glycidol, was utilized to introduce the glycerol moiety.[163]

Compounds **110** and a related derivative have been made as substrate analogues of 6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-D-*myo*-inositol-(1,2-di-*O*-tetradecanoylphosphatidate), an early intermediate in the biosyntheis of glycosylphosphatidylinositol and tested with an α-(1→4)-D-mannosyltransferase from the protozoan parasite *Trypanosoma brucei*.[164] The related derivatives 6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-D-*myo*-inositol 1-phosphate and the corresponding 1,2-cyclic phosphate have also been prepared employing a D-camphor acetal-resolved inositol and a 2-azido-2-deoxy-glycosyl fluoride donor.[165]

The preparation of (±)-*myo*-inositol 1-*p*-nitrophenylphosphoryl-4,5-bisphosphate[166] and an improved one of *myo*-inositol 1-*p*-nitrophenylphosphate[167] as chromogenic substrates useful in the assaying of PI-PLC have been reported.

The synthesis of D-*myo*-inositol 1-phosphate in which the key step involved use of a chiral phosphorylating reagent to simultaneously monophosphorylate and resolve (±)-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol has been described.[168]

All six isomeric *myo*-inositol pentakisphosphates have been prepared from known regioselctively protected *myo*-inositol derivatives for metabolic studies in a cytosolic extract from calf thymus.[169] D-*myo*-Inositol 1,3,4,5-tetrakisphosphate and its enantiomer D-*myo*-inositol 1,3,5,6-tetrakisphosphate (equivalent to L-*myo*-inositol 1,3,4,5-tetrakisphosphate) have been prepared *via* resolution of (1*S*)-(−)-camphanate esters derived from *myo* inositol 1,3,5-orthoformate.[170]

(±)-*myo*-Inositol 1,2,4,5-tetrakisphosphate has been prepared from 3,6-di-*O*-benzoyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol and tested for its ability to mobilize intracelular Ca^{2+}. Individual enantiomers were also made by conventional processes.[171] *myo*-Inositol 1,2,3-trisphosphate has been prepared from *myo*-inositol by way of regioselective benzoylation[172] and a proposed binding model of *myo*-inositol 1,4,5-trisphosphate kinase based upon the inhibitory effects of all thirty-eight regioisomers of inositol phosphates has been described. The compounds used in the study were prepared using the acyl migration method (see Vol. 30, p. 243, refs. 151-153).[173] The syntheses of *myo*-inositol 1,2,3,5- and 2,4,5,6-tetrakisphosphates as novel *myo*-inositol 1,4,5-trisphosphate kinase inhibitors have been achieved from *myo*-inositol orthoformate intermediates.[174]

D-*myo*-Inositol 1,2,6-trisphosphate (α-trinositol), obtainable from baker's yeast treatment of phytic acid, has been converted into 1,2-*O*-isopropylidene-D-*myo*-inositol and 3,4,5-tri-*O*-benzyl-D-*myo*-inositol as intermediates for the synthesis of optically active *myo*-inositol derivatives.[175]

D-*myo*-Inositol 1,3,4,5,6-pentakisphosphoryl-2-pyrophosphate and D-*myo*-

inositol 1,2,3,4,6-pentakisphosphoryl-5-pyrophosphate have been reported as intracellular mediators.[176]

Five potentially membrane-permeable phosphate ester derivatives of *myo*-inositol have been synthesized. For example the (±)-*myo*-inositol 1,4,5-trisphosphatehexakis(propionyloxymethyl) ester and the hexakis(butyryloxymethyl)ester were effective Ca^{2+} mobilizing agents.[177] Various phosphate ester derivatives of D-*myo*-inositol 1,2,6-trisphosphate have also been prepared as potential analgesics.[178]

myo-Inositol 1,4,5-trisphosphate derivatives having 3-*O*-methyl, -ethyl, -propyl or -glycollyl substituents[179] and *myo*-inositol hexakisphosphate *o*-nitrobenzyl esters which are photolabile[180] have been reported. The synthesis of D-galactopyranosyl-1,2,6-trisphosphate as an analogue of D-*myo*-inositol 1,4,5-trisphosphate is mentioned in Chapter 7. Some phosphate derivatives of 6-*O*-(2-hydroxyethyl)cyclohexane-1,2,4,6-tetraol have been prepared from *cis*/*trans*-cyclohexane-1,4-diol as mechanistic probes for the inositol monophosphatase reaction.[181]

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19

Antibiotics

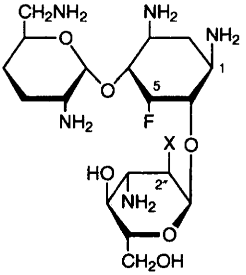
1 Aminoglycosides and Aminocyclitols

Dibekacin has been converted into 5-deoxy-5-epi-5-fluorodibekacin (**1**); the related 2″-keto-compound and the 2″-ketone acylated at N^1 with 4-amino-2-hydroxybutanoic acid were also reported.[1] A 2″-keto-derivative of 5-deoxy-5-epi-5-fluorodibekacin (**1**) was also used as an intermediate in the preparation of the 2″-amino-2″-deoxy-analogue **2** and its 2″-epimer; various 2″-*N*-acylated derivatives of **2** were also synthesised.[2] Amikacin is a semisynthetic antibiotic made from kanamycin by acylation at N^1 of the 2-deoxystreptamine unit with 4-amino-2-hydroxybutanoic acid; it has been found that the major by-products in the synthesis of amikacin are the compounds with an additional acyl unit at the 3″-amino-group and the one with an extra acyl group at the 6′-amino-position.[3]

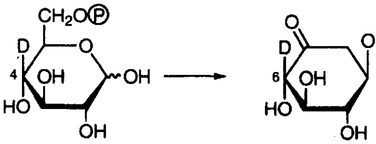
There have been studies reported on the interaction of aminoglycoside antibiotics with RNA. A series of compounds have been made in which two aminoglycoside units are linked together, *via* their primary alcohol groups, by a 14-atom spacer containing four sulfur atoms. These were designed to interact with two similar structural motifs in RNA, and the dimers did indeed display enhanced activity as ribozyme inhibitors relative to their natural counterparts, with the highest inhibition of the hammerhead ribozyme being displayed by the tobramycin-spacer-neomycin B and neomycin-spacer-neomycin dimers.[4] The same workers have also investigated electrostatic interactions in RNA-aminoglycoside binding. On the theory that more basic aminoglycosides should bind more tightly, a comparison was made of kanamycin, tobramycin, and various deoxy-analogues of tobramycin including dibekacin. It was found that dibekacin, 4″-deoxytobramycin and 2″-deoxytobramycin, which each lack one secondary alcohol function of tobramycin, were much better inhibitors of the hammerhead ribozyme than was tobramycin itself. It was also found that 6″-amino-6″-deoxytobramycin was a potent inhibitor.[5] A novel assay has been developed based on surface plasmon resonance that allows the direct observation of interaction between neomycin B and related aminoglycosides with RNA strands, in order to better understand the specificity of these antibiotics for the Rev response element (RRE) of HIV-1 mRNA. The results indicated that neomycin B interacts with three different sites in RRE.[6]

Carbohydrate Chemistry, Volume 31

A novel bifunctional bacterial enzyme that confers resistance to aminoglycoside antibiotics through an ATP-dependent phosphorylation and an acetyl CoA-dependent acetylation has now been purified and characterized. An extensive NMR investigation of the acetylation and phosphorylation products from kanamycin A, and the product of both enzyme activities, led to the identification of the 6′-amino-group as the site of acetylation, and O-2″ as the phosphorylation site. Some kinetic parameters for both the acetylation and phosphorylation reactions were determined with a variety of aminoglycoside substrates.[7]



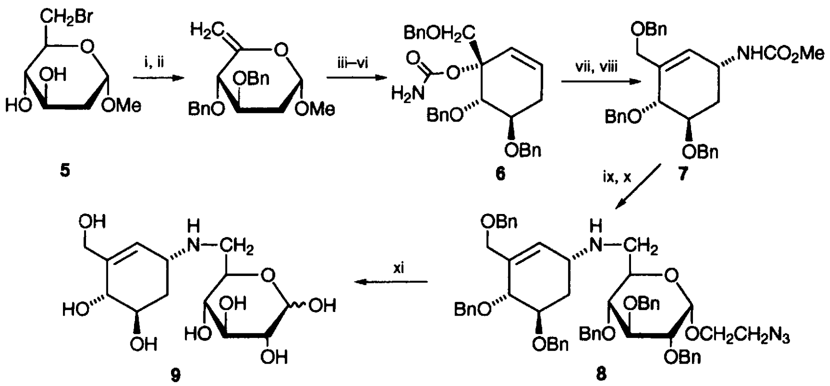
1 X = OH
2 X = NH_2



3 **4**

Further work has been reported on the mechanism of action of 2-deoxy-*scyllo*-inosose synthase, which is involved in the biosynthesis of 2-deoxystreptamine. A deuterium label at C-4 of glucose-6-phosphate (**3**) was retained at C-6 of the product (**4**), relative to ^{18}O at C-3, even though a redox process occurs at C-4 in order to facilitate the elimination of phosphate. The product was isolated as its oxime-Tms ether for identification.[8]

A synthesis has been reported of the 2-deoxyisomaltose analogue **9** related to acarbose (Scheme 1). The 6-bromo-2,6-dideoxy-compound **5** was made from the known 2,6-dibromo-2,6-dideoxy-D-mannono-1,4-lactone by a three-



Reagents: i, $BnOC(N{=}H)CCl_3$, TfOH; ii, NaH, DMF; iii, $HgCl_2$; iv, MsCl, py, DMAP; v, $BnOCH_2Li$, THF, −110°C; vi, $Cl_3CCONCO$, then Al_2O_3; vii, Tf_2O, $EtNPr^i_2$; viii, MeOH; ix, NaOH, DMSO; x, 6-*O*-triflyl-glucoside, $EtNPr^i_2$; xi, Na, NH_3

Scheme 1

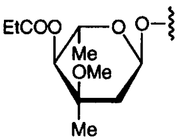
step sequence involving a selective hydrogenolysis of a secondary bromide. In the conversion of **6** to **7**, a cyanate was formed by dehydration, and this underwent a [3,3]-sigmatropic rearrangement to the allylically-rearranged isocyanate. One of the aims of this work was the production of compounds which could be used to create catalytic antibodies for glycoside hydrolysis. The intermediate **8** is of potential use in this respect, and the chemistry of Scheme 1 could also be applicable to the synthesis of valienamine, the 2-deoxy analogue of which was made by deprotection of 7.[9]

2 Macrolide Antibiotics

There have been further reports on 16-membered macrolide antibiotics bearing modified cladinose and mycarose units (see Vol. 30, p. 255). After protection of the macrocycle, alkylation was used to make analogues of leucomycin A_7 with the L-mycarose unit 3,4-di-*O*-alkylated, and containing 4-*O*-alkyl-L-cladinose (*i.e.* with the 3″-position *O*-methylated).[10] Midecamycin A_1, which contains a 4-*O*-propanoyl L-mycarose residue, has been methylated at O-3″ to give the analogue with a 4-*O*-acyl-L-cladinose unit (**10**), which was an enhanced antibacterial agent. Various 9-*O*-acyl derivatives were also prepared, and similar chemistry was carried out on josamycin.[11]

Formamycin, which contains a 24-carbon polyketide chain with a 16-membered macrolide ring, carries a 2,6-dideoxy-β-D-*arabino*-hexopyranose (2-deoxy-β-D-rhamnose) unit (**11**) at O-21.[12]

A new derivative of amphotericin B with low toxicity, *N*-methyl-*N*-(1-deoxy-D-fructos-1-yl)-amphotericin B (with sugar unit **12**), has been reported.[13]



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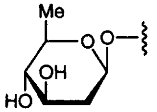

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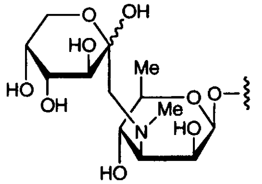

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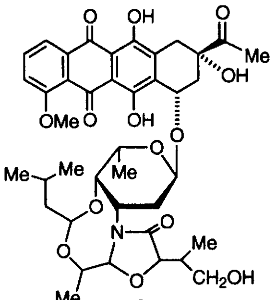
3 Anthracyclines and Other Glycosylated Polycyclic Antibiotics

A new anthracycline antibiotic IT-62-B, which converts the morphology of *ras*-transformed cells back to normal, has been assigned the structure **13** by spectroscopic means, and is a new member of the baumycin class.[14] The compound **14**, related to steffimycin but lacking a methoxy group at C-8, has been isolated; the 10-ketone, and the 2′-*O*-demethyl compound (*i.e.* with L-rhamnose as sugar) were also identified. Genetic engineering techniques were also used to produce 2,8-demethoxy-steffimycins.[15] Nocardicyclins A and B, new antibiotics from *Nocardia pseudobrasiliensis*, have been assigned the structures **15** and **16** respectively. The structure assigned to the aglycon is thus epimeric at C-9 with the steffamycin class, and the sugar in **15** is novel, termed brasiliose, but no evidence is presented for the absolute configuration.[16] 10-*O*-Rhodosaminyl-β-rhodomycinone (**17**, R = H) and obelmycin H (**17**, R = OH) have been isolated from a culture of obelmycin-producing *Streptomyces violaceus* after acid treatment.[17]



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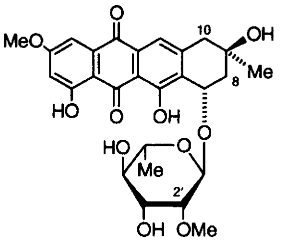

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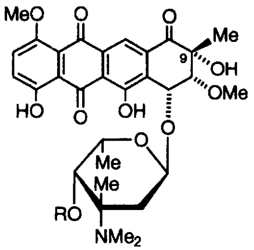
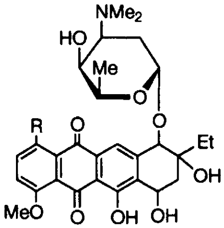


15 R = H
16 R = Ac



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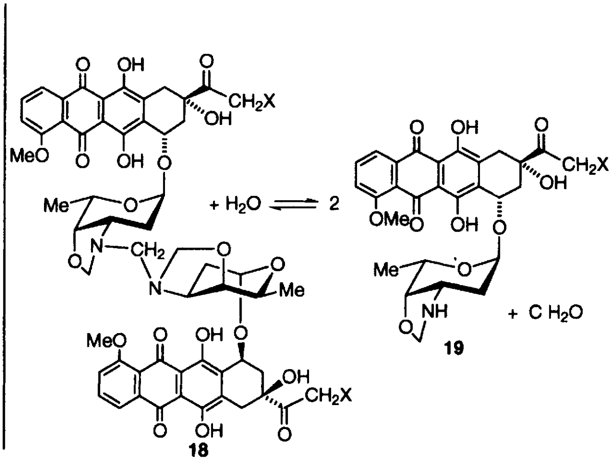
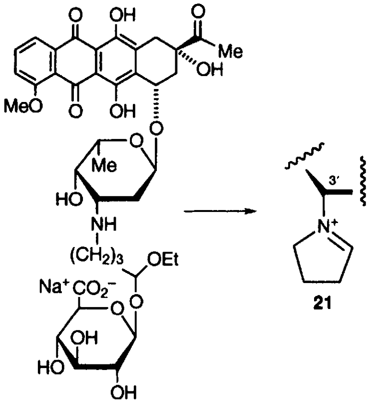


Scheme 2

The theory that doxorubicin and daunorubicin alkylate DNA by catalytic production of formaldehyde prompted an investigation of drug-formaldehyde reactions. It was found that interaction of the drugs with formalin at pH 6 gives 40–50% yields of the condensation products doxoform (**18**, X = OH) and daunoform (**18**, X = H) respectively, the structures of which were determined spectroscopically. These products are labile with respect to hydrolysis, and the oxazolidines **19** are intermediates in the hydrolysis (Scheme 2). Daunoform (**18**, X = H) reacted with the self-complementary deoxyoligonucleotide $(GC)_4$ faster than did daunorubicin and formaldehyde at equivalent concentrations, and doxoform was effective against resistant tumour cells.[18]

The glucuronide **20**, containing an unusual acetal linkage, was prepared from daunorubicin by a sequence involving reductive amination of the anthracycline. It was found that **20** was highly toxic to human A375 melanoma cells in the presence of *E. coli* β-glucuronidase, and it was speculated that hydrolysis led to the species **21** which could act as an alkylating agent.[19] Reductive amination of daunorubicin with nucleoside dialdehydes gave rise to morpholino-derivatives **22** (B = Ade, Gua, Ura, Cyt, Hypoxanthinyl, 6-aza-Ura),[20] and an increase in the lipophilicity of daunorubicin, doxorubicin and carminomycin was achieved by trimethylsilylation of the 4′-hydroxy groups with *N,O*-bis(trimethylsilyl)trifluoroacetamide.[21]



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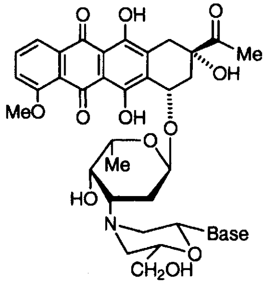

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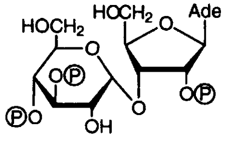
Doxorubicin has been linked *via* spacers to the nitrogen atom of maleimide, the linking either being at the 3′-amino-group or through an *N*-acylhydrazone at the methyl ketone, with a view to subsequent conjugation to proteins.[22]

4 Nucleoside Antibiotics

Full details have been published of a synthesis of the IP_3 receptor agonist adenophostin A (**23**) in which the nucleosidic link is introduced at a late stage (see Vol. 30, p. 258).[23] The same group have also prepared a number of more flexible analogues of adenophostin A, including **24**. For this, the condensation of a 3′-*O*-phosphoryloxymethyl nucleoside with a monohydroxyalditol derivative was a key synthetic step. Analogue **25** was made by imidate glycosylation,[24] and the diphosphates **26** (R = H, CH_2OH) have also been prepared; in these cases coupling of silylated N^6-benzoyladenine with *O*-acetoxymethyl derivatives were employed.[25] Additionally, the same team has described interesting compounds in which two and four units of the triphosphorylated disaccharide found in the adenophostins are connected as glycosides to a benzene core *via* four-atom spacers; these polyvalent compounds were prepared with the intention of allowing cooperative binding to the IP_3 receptor, which has four binding sites for IP_3.[26]

The selectively-protected nucleoside **27** has been prepared by the interaction of silylated thymine and the 1,2-anhydrosugar, as also reported for the uridine analogue;[27] glycosylation of **27** with a derivative of L-fucose was then used to make the analogue **28** of shimofuridin A (Vol. 28, p. 254; for other analogues see Vol. 30, p. 259).[28]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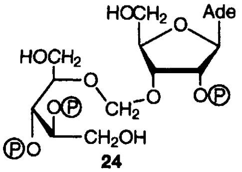
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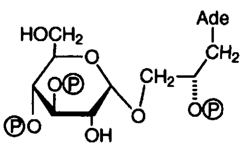
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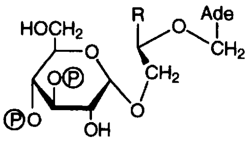
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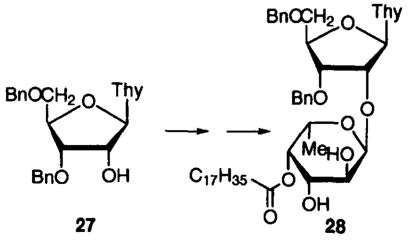
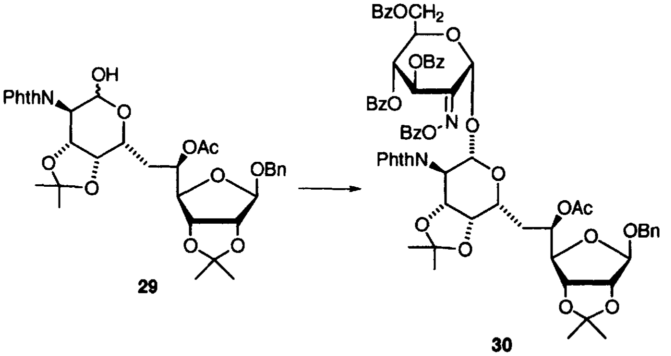
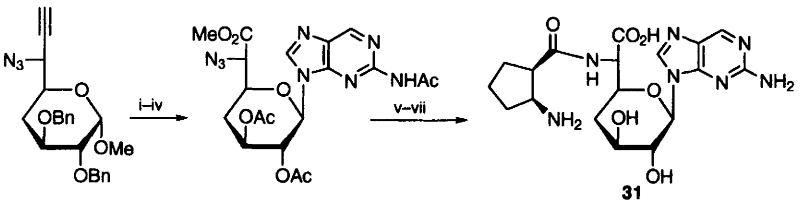

27 **28**

There has been a further report on the synthesis of the sugar unit of tunicamycin, which gives a full account of the synthesis of tunicamine derivative **29** by a Wittig reaction followed by a regio- and stereo-selective hydroboration (Vol. 28, p. 255). The coupling of **29** with a glycosyl bromide gives predominantly the α,β-disaccharide **30**, the stereochemical outcome


29 **30**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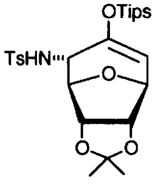
Reagents: i, BCl_3; ii, Ac_2O, AcOH, H_2SO_4; iii, $RuCl_3$, $NaIO_4$, $CCl_4/MeCN/H_2O$, then CH_2N_2; iv, silylated 2-acetamidopurine, $SnCl_4$; v, H_2, Pd/C; vi, *N*-trifluoroacetyl acid anhydride; vii, LiOH

Scheme 3

being a function of the phthalimido- and benzoyloxyimino functions (Vol. 28, p. 125).[29]

A report from Czernecki's laboratory describes the synthesis, from a previously-described alkyne, of a compound **31** (Scheme 3) which is related to amipurimycin. Since the β-aminoacid used was the racemic *cis*-material (the absolute stereochemistry of this part of amipurimycin is not definitely established) a diastereomer of **31** was also produced; the condensation to form the nucleoside was regio- and stereo-selective in the required sense.[30] Amipurimycin itself has a chain-branch at C-3'; for some work from the same group which introduces this feature see Vol. 30, p. 186.

The intermediate **32** was prepared in racemic form by amination of a silyl enol ether derived from the oxabicyclic ketone, and used to make a derivative of thymine polyoxin C (**33**).[31] A report from the laboratories of Dondoni and Merino gives a full account of their synthesis of polyoxin C (**33**) and polyoxin J (**34**) in which both α-aminoacid units are derived by diastereoselective addition of 2-furyllithium to an appropriate nitrone, the reagent acting as a CO_2H synthon.[32] The carbocyclic analogue (**36**) of uracil polyoxin C has been made in racemic form, the Pd-catalysed *cis*-allylic substitution reaction of (±)-**35** with uracil, and *cis*-dihydroxylation with OsO_4-NMNO being key steps.[33]



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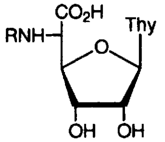
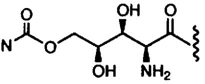
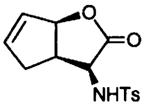


33 R = H

34 R =





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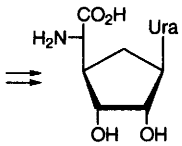

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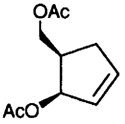

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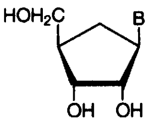

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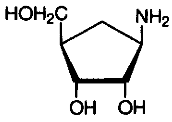
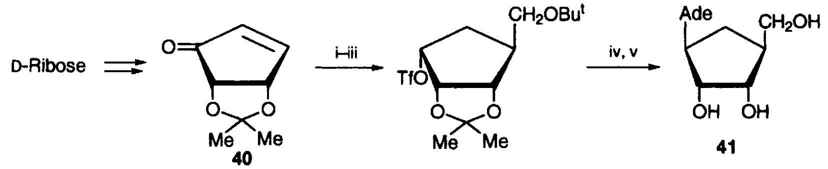


39

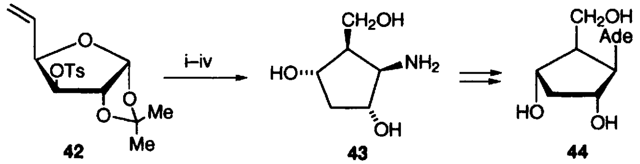
These key transformations in the synthesis of carbocyclic nucleosides were also applied to **37**, readily available in chiral form by a resolution procedure, to give (–)-aristeromycin (**38**, B = Ade) and (–)-carbodine (**38**, B = Cyt); in the latter case, the use of the Cs salt of *N*-benzoylcytosine was necessary to ensure a good yield.[34] A new route has been described, using an asymmetric Diels-Alder reaction, to make the amine **39** which has previously been used to prepare aristeromycin.[35] The (+)-enantiomer **41** of aristeromycin has been made as indicated in Scheme 4, the cyclopentenone **40** being accessible in three steps from D-ribose (Vol. 24, p. 302). A variation on this sequence led to the thymine analogue.[36] A synthesis of (±)-aristeromycin and its 5'-homo-derivative has been carried out from norborn-5-en-2-one.[37]



Reagents: i, $(Bu^tOCH_2)_2CuLi$; ii, DIBAL; iii, Tf_2O; iv, adenine, NaH; v, TFA, H_2O

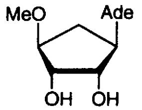
Scheme 4

The glucose-derived alkene **42** was converted as indicated in Scheme 5 into the cyclopentane **43** using an intramolecular nitrone-alkene cycloaddition, after which standard transformations were used to make the analogue **44** of aristeromycin.[38] The methylated derivative **45** of 5′-noraristeromycin has been prepared in enantiopure form from a chiral allylic alcohol using organopalladium chemistry,[39] and the (+)-enantiomer **46** of 7-deaza-5′-noraristeromycin was similarly prepared and shown to have anti-trypanosomal activity (for the enantiomer see Vol. 27, p. 235).[40] Various 8-aza-7-deaza-5′-noraristeromycin derivatives such as **47** and its enantiomer, have also been prepared; the anti-trypanosomal activity of these was not high, but compounds of the L-series performed better than their enantiomers.[41]



Reagents: i, H_2SO_4, $MeCN\text{-}H_2O$; ii, BnNHOH; iii, LAH; iv, Pd/C, cyclohexene

Scheme 5



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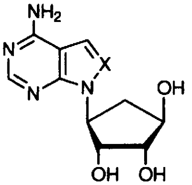
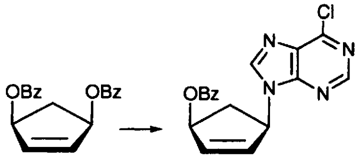
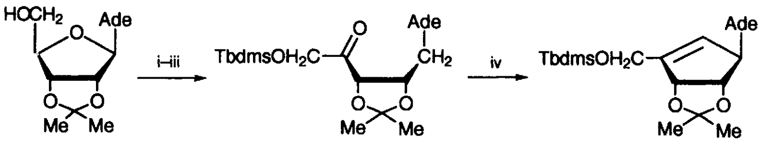


46 X = CH
47 X = N



48 **49**

Trost's group have applied their technique of Pd(0)-catalysed desymmetrization in the presence of a chiral catalyst to convert **48** into **49** of high e.e., which was subsequently transformed into neplanocin A.[42] Another synthesis of the derivative **50** of neplanocin A, using the reductive cleavage of isopropylidene adenosine with excess DIBAL (Vol. 27, p. 270; see also Chapter 20) as the initial step, is indicated in Scheme 6; the desired β-'anomer' was the major product (4:1) in the insertion reaction.[43] An improved synthesis of the antiviral *C*-methylated neplanocin A analogue **51** of *R*-chirality (RMPNA) involved the diastereoselective transformation of the *S*-epimer using adenosine deaminase,[44]



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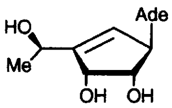
Reagents: i, DIBAL; ii, TbdmsCl, Im; iii, Dess-Martin reagent; iv, TmsC(Li)N_2

Scheme 6



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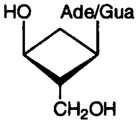

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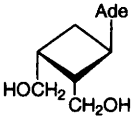


53

and a number of related epimeric *C*-ethynyl, -ethenyl and -ethyl derivatives of neplanocin A were made by Grignard reactions with an aldehyde.[45]

The nor-analogues **52**,[46] and the diastereoisomer **53**[47] of carbocyclic oxetanocin have been prepared as racemates.

Some analogues of the *C*-nucleoside antibiotic showdomycin are mentioned in Chapter 20.

5 Miscellaneous Antibiotics

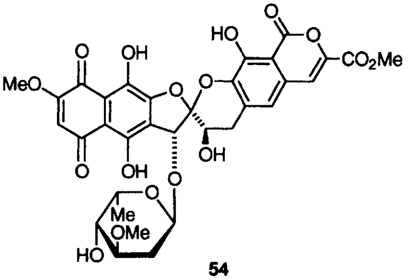
Heliquinomycin, a new inhibitor of DNA helicase isolated from a Streptomyces species, has been assigned the structure **54** by X-ray crystallography. Heliquinomycin contains the sugar L-cymarose, and the absolute configuration of the antibiotic was determined by hydrolysis and measurement of the optical rotation of the sugar.[48] The absolute configurations of the pyralomycins (Vol. 30, p. 261) have now been determined as being based upon D-glucose, by X-ray crystallography of heavy-atom derivatives of pyralomycins 1a and 2a.[49]

Oxidation of lincomycin with dimethyldioxirane gives two diastereomeric sulfoxides, which with OsO_4-NMNO give the same sulfone. An unsaturated analogue of clindamycin has also been made by elimination between C-6 and C-7.[50]

The indolocarbazoles **55** (D-*gluco*- and D-*galacto*-), related to rebeccamycin and AT 2433-A1 and -B1, were prepared by reaction of the heterocycle with glycosyl bromides, which also gave the α-anomers. The L-fucosyl analogues were also synthesised.[51] A similar glucosylation was also used during the synthesis of the related topoisomerase inhibitor and anticancer agent NB-506; conditions for obtaining good β-selectivity in the glucosylation were defined.[52]

Siastatin B (**56**) has been converted into a number of analogues epimeric at C-3 such as **57** and its 5-epimer. A 3,4-ene was involved as an intermediate in this chemistry, and compounds with a trifluoroacetyl group at N-6 were also described.[53]

A report from Ganguly's laboratory has established unambiguously for the



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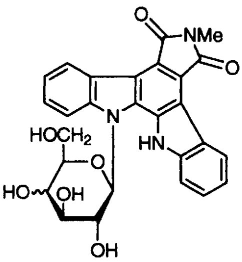

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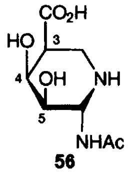

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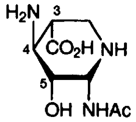
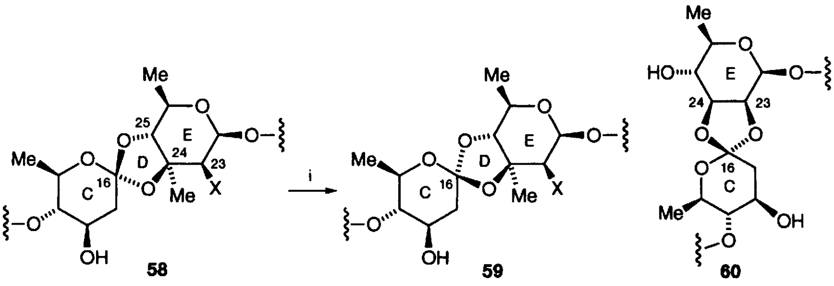


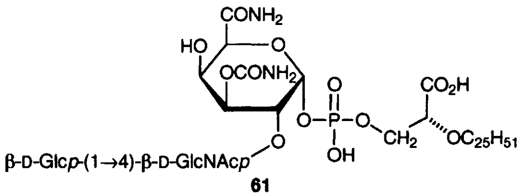
57

first time the stereochemistry of the everninomycin antibiotics at the C-16 orthoester (Scheme 7). Treatment with acid of compounds such as ziracin, with a hydroxy group at C-23 (part-structure **58**, X = OH), led to a mixture of the C-16 epimer **59** (X = OH) and the O-23, O-24-orthoester **60**, with more of **60** after longer reaction times. Treatment of everninomycin D (part-structure **58**, X = H) gave the epimer **59** (X = H). Detailed NMR studies, including NOE work, allowed assignment of stereochemistry.[54] Complete ^{1}H- and ^{13}C-NMR assignments of the oligosaccharide antibiotic Sch 27899 have been reported.[55]



Reagents: i, *p*-nitrobenzoic acid, THF, reflux

Scheme 7



61

Corynandecin is a new antifungal glycolipid of the papulacandin type, which contains the commonly-occurring β-D-Gal*p*-(1→4)-β-D-Glc*p*-*C*-glycoside unit with a novel fatty acid esterified at O-3′.[56]

A series of papers have described the synthesis of analogues of the phosphoglycolipid antibiotic moenomycin A$_{12}$. A trisaccharide was prepared as its allyl glycoside from peracetylcellobial and a galacturonamide derivative using Danishefsky's sulfonamidoglycosylation procedure,[57] and then converted into the moenomycin analogue **61**. This structure differs from the smallest antibiotically-active fragment of moenomycin A_{12} in having a glucose unit at the non-reducing terminus in place of an *N*-acetylglucosamine residue, but **61** was not active.[58] The analogue **61**, but with a galactopyranose unit replacing the glucose moiety, was also made, using an oxazoline derived from lactosamine as a glycosyl donor and an allyl galactosiduronamide derivative as aceptor, but again the modification led to loss of antibiotic activity.[59] Moenomycin A has been linked to various reporter groups (*e.g.* biotin and the dansyl group), the linkage being *via* the 2-amino-cyclopentanedione ring (ring A) of the antibiotic.[60]

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Nucleosides

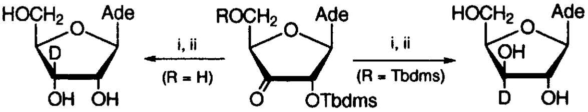
1 General

Structure-activity relationships of novel nucleosides for the treatment of AIDS have been reviewed,[1] and reviews have also appeared on *seco*-nucleosides[2] and *di-seco*-nucleosides.[3] The synthesis and reactions of nucleosides and nucleotides under conditions relevant to early evolution have been incorporated into a review on prebiotic chemistry.[4]

A glycosylated zeatin has been identified as the compound in coconut milk responsible for over 20% of its potent cytokinin activity.[5]

2 Synthesis

Sodium triacetoxyborohydride in acetic acid reduces 2′- and 3′-ketonucleosides with high stereoselectivity, 5′-*O*-Tbdms-protected derivatives being reduced from the α-face, whereas 5′-unprotected compounds are reduced from the β-face. Use of $NaBD(OAc)_3$ gave rise to stereoselectively deuteriated species, as in the cases illustrated in Scheme 1.[6]



Reagents: i, $NaBD(OAc)_3$, HOAc; ii, NH_4F, MeOH

Scheme 1

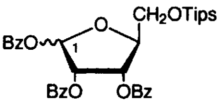
Ribonucleosides uniformly-labelled with ^{13}C in the sugar unit have been prepared from $[^{13}C]_6$-di-*O*-isopropylidene-D-glucofuranose by a sequence in which a ribofuranose derivative was made by configurational inversion at C-3, followed by periodate cleavage of C-6 and coupling to the nucleobase.[7] Di-*O*-isopropylidene-D-glucofuranose has also been converted, again *via* the D-*allo*-epimer, into the L-ribose derivative **1**, C-5 of D-glucose becoming C-1 of **1**. β-L-Ribonucleosides were then made, and incorporated into oligonucleotides.[8]

Conventional base-sugar coupling procedures have been used to make hydroxamic acids related to uridine,[9] 5-carboranyluracil nucleosides,[10] 5-(alkyl/arylthioethyl)thio-6-azauridines,[11] and 6-methyl-5-aza-cytidine (**2**),

Carbohydrate Chemistry, Volume 31

which could also be prepared by reaction of tri-*O*-benzoyl-β-D-ribofuranosyl isocyanate with monoacetylguanidine and subsequent cyclization.[12] A condensation promoted by ultrasound was used in an improved synthesis of the 1′-cyano-nucleoside **3**.[13] The protected nucleosides **4** (R = Ph, Bn) were made by base-sugar condensation, but debenzoylation with methanolic ammonia led to the pyrazole nucleosides **5**.[14]

Ribavirin has been prepared from inosine in good overall yield by acetolysis, condensation with the triazole and ammonolysis.[15] Ribosylation of 3-mercapto-1,2,4-triazole with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose gave three nucleosides, including the N^4-regioisomer,[16] whilst in similar work, condensation of isothiocyanate **6** with hydrazine, followed by cyclization with acyl derivatives, gave thio-substituted 1,3,4-triazole nucleosides of type **7**.[17,18] The thiadiazole nucleoside **8**, and its N^3-regioisomer, were both obtained using a base-sugar condensation.[18]



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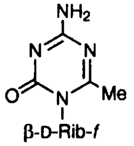

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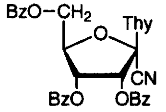

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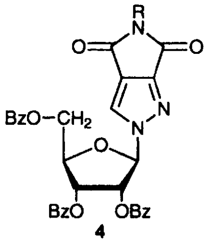

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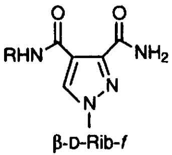

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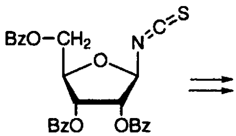

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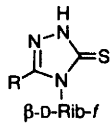

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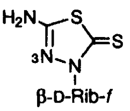

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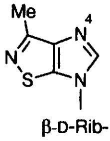
The imidazo[4,5-*d*]isothiazole nucleoside **9**, and the 4-ribosylated analogue, have been prepared by coupling using the silylated base; 2′-deoxy- and D-arabinofuranosyl nucleosides were made similarly.[19] *N*-β-D-Ribofuranosyl derivatives of ergot alkaloids have been reported,[20] as have 2-substituted-4,6-dichloro- and -4,5-dichloro-benzimidazole nucleosides such as **10**.[21] The analogues **11** (X = F, Br, I) of the anti-cytomegaloviral agent TCRB (**11**, X = Cl) have also been described.[22] Some 4-thioalkyl-imidazo- and triazolo-[4,5-*d*]pyridazine nucleosides such as **12** have been prepared as inhibitors of nucleoside transport into human erythrocytes, but were less active than known inhibitors.[23] Some novel 1-β-D-ribofuranosyl-pyrido[2,3-*d*]pyrimidin-2,4-(1*H*,3*H*)-diones have been described,[24] and the pyrimido[4,5-*d*]pyrimidine-2,4-dione **13** has been made by base-sugar condensation, as has the α-D-*arabino*-analogue.[25] A paper describing a route to 3′,5′-di-*O*-benzylthymidine is mentioned in Chapter 19.

In the area of pyranosyl nucleosides, solid-state glycosylation has been reported. Peracetylated glycopyranosyl bromides were separately ground with

AgOTf, silylated uracil or thymine was added, and after a further period of grinding in a ball mill, the acetylated β-D-gluco-, β-D-ribo- or α-L-arabinopyranosyl nucleosides could be obtained in moderate yield.[26]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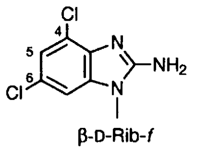
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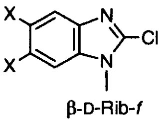
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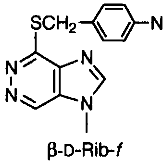
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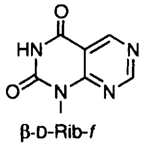

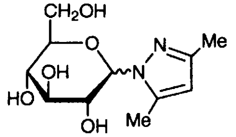
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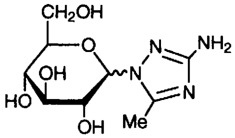
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Treatment of aldoses with hydrazine gave the hydrazones, mainly as the acyclic isomers: subsequent treatment with pentane-2,4-dione gave isomeric glycopyranosyl-3,5-dimethylpyrazoles (*e.g.* **14**), together with the furanosyl nucleosides.[27] Triazole nucleosides such as **15** have been made by the cyclization of peracetylated glycopyranosylaminoguanidines (Vol. 29, p. 146), which occurs on heating in ethanol, followed by deacetylation.[28] Coupling procedures have been used to prepare 1-β-D-glucopyranosyl-5-methyl-2-methylthio- and 2-morpholino-pyrimidin-4(3*H*)-one and related compounds,[29] some 2-substituted-5-fluorouracil xylopyranosides,[30] some 3-glycopyranosyl-2,4-dioxypyrimidines,[31] 3-β-D-glucopyranosyl-6-methyl-2-methylthio-pyrimidin-4-one,[32] some glycopyranosylated pyrazolo[5,4-*e*]-1,2,4-triazines,[33] and various β-D-hexopyranosylated 7,8-dihydrobenzo[*f*]quinoline-3(2*H*)-thiones.[34]

3 Anhydro- and Cyclo-nucleosides

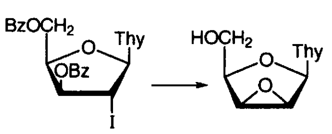
Reaction of furanoid glycals with silylated pyrimidine bases and NIS gave products such as **16**; subsequent base treatment of this compound gave the D-*lyxo*-epoxide **17**.[35] A similar intramolecular displacement of 2′-*O*-tosyl groups also gives rise to 2′,3′-anhydrolyxofuranosyl pyrimidine nucleosides.[36] The 2′,3′-anhydride of 2-aminoadenosine has been made from the parent nucleoside, and was converted to the guanosine analogue by use of adenosine deaminase.[37]

Spiro-uracil nucleosides have been prepared using hypoiodite-induced cyclizations. When **18** was photolysed in the presence of $Pb(OAc)_4$ and iodine, the β-anomer **19** was the major isomer formed (β:α, 7:1), whereas the 7-epimer gave the α-product almost exclusively.[38] The compound lacking the methyl group gave similar amounts of both anomers,[38,39] and these results could be rationalized on a model of the transition state. In the D-*ribo*-series, similar reactions on 2′,3′-*O*-isopropylidene derivatives[38] or on the tris(Tbdms) ether of 6-hydroxymethyluridine[39] were β-selective.

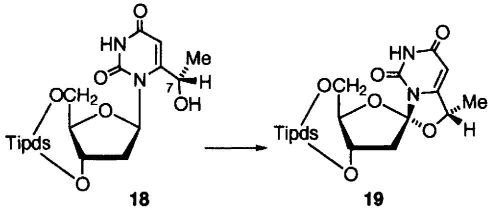
Treatment of the alkyne **20** (Vol. 29, p. 281) with Bu_3SnH/AIBN gave the cyclonucleoside **21**.[40]

When the 5′-thionucleoside derivative **22** was treated with NaOH in ethanol, followed by acid hydrolysis, $S^{5'}$,6-methano-5′-thiouridine (**23**) was obtained, *via* an allylic substitution on the tautomer of **22**. A route similar to that used to make the oxygen-containing analogue of **23** (Vol. 26, p. 227) was less successful for the sulfur compound.[41]

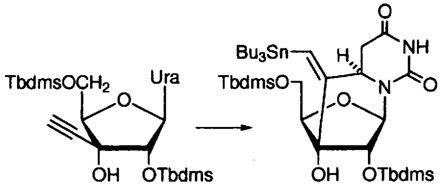
Some uses of anhydro- and cyclo-nucleosides in the synthesis of other types of nucleoside are mentioned later in this Chapter.



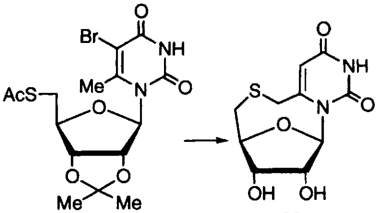
16 **17**



18 **19**



20 **21**

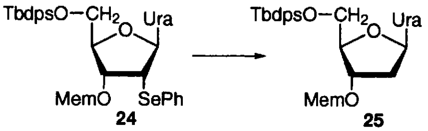


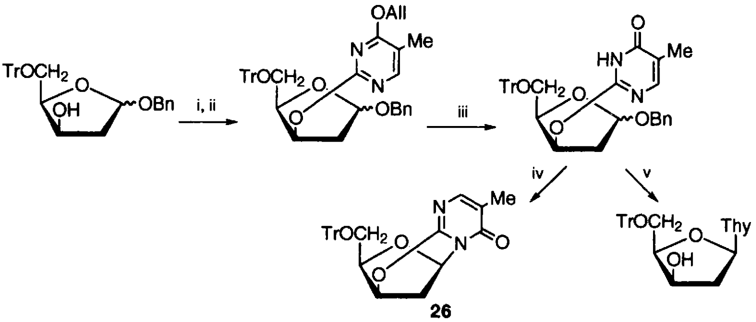
22 **23**

4 Deoxynucleosides

2′-Deoxy-2′-phenylselenyl nucleosides such as **24** can be obtained by reaction of glycals with PhSeCl, AgOTf and a silylated base; these products can be converted to 2-deoxynucleosides (*e.g.* **25**) by radical reduction using Bu_3SnH.[42] A similar reduction of 2′-deoxy-2′-iodocompounds of type **16** gave 2′-deoxy-β-D-*threo*-pentofuranosyl pyrimidine nucleosides,[35] and an approach to the same type of compound using intramolecular glycosidation is outlined in Scheme 2; this work also gave a route to the N^3-linked cyclonucleoside **26**.[43]

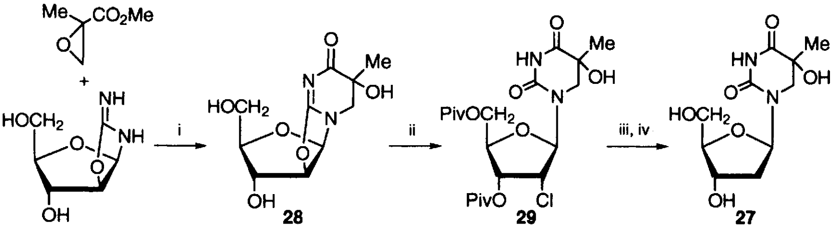
The synthesis of 5,6-dihydro-5-hydroxythymidine (**27**) is indicated in Scheme 3; the hydroxylated cyclonucleoside **28** could also be prepared by oxygenation of a previously-reported intermediate (Vol. 29, pp. 270–271), and the chlorocompound **29** could be dehydrated prior to reductive dehalogenation to provide a route to 2′-deoxy-pyrimidine nucleosides.[44] A new route to 2-deoxy-5-ethyluridine also involves a 2,2′-anhydronucleoside as an intermediate.[45]





Reagents: i, NaH; ii, 6-allyloxy-2-chloro-5-methylpyrimidine; iii, $Rh(PPh_3)_3Cl$; iv, TmsOTf; v, HF, py

Scheme 2



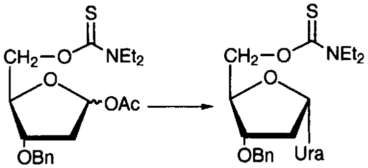
Reagents: i, $MeCONMe_2$; ii, PivCl; iii, H_2, Pd/C or Bu_3SnH; iv, NaOMe

Scheme 3

A route to 2′-deoxy-β-D-ribonucleosides reported last year (Vol. 30, ref. 50) has now been applied to the synthesis of the α-isomers by the use of an arabinofuranosyl precursor,[46] whilst an alternative method for stereoselective synthesis of 2′-deoxy-α-ribonucleosides involves condensation of the 5-*O*-diethylthiocarbamoyl compound **30** with a silylated pyrimidine in the presence of 20 mol% of $SiCl_2(OTf)_2$, to give, for example, **31** as a 93:7 mixture with the β-anomer.[47]

2′-Deoxyuridine stereoselectively deuteriated at C-2′ (**33**) can be prepared by reduction of the bromocompound **32** with $(Tms)_3SiD$ and triethylborane in perdeuteriated THF; if the deuterium was already present in the bromocompound, then the β-deuteriated product was obtained using non-deuteriated reagents.[48] Aldehyde **34**, uniformly labelled with ^{13}C, was made from $[^{13}C_6]$-D-glucose; reduction of **34** with $[2\text{-}^2H_1]$isobornyloxymagnesium bromide gave a stereoselectively-deuteriated alcohol which could be converted to the thymidine isotopomer **35**, also with ^{13}C in all sugar positions.[49] Various 2′-deoxyribonucleosides deuteriated at C-5′ have also been made by reduction of 5′-*O*-acetyl-5′-phenylselenyl-compounds with Bu_3SnD and Et_3B.[50]

Base-sugar condensation methods have been used in a new stereoselective route to 2′-deoxycytidine,[51] to prepare hydrophilic carborane-containing uridine derivatives,[52] and various 5-(3-substituted-phenyl)-2-deoxyuridines.[53] Condensation under phase-transfer conditions gives significant quantities of the N^7-isomer **36**, which was used in the preparation of oligodeoxynucleotides containing N^7-linked guanine.[54] A better route, by base-sugar condensation, has been reported to 7-deaza-2′-deoxy-isoguanosine;[55] 7-deaza-2′-deoxy-7-methylguanosine analogues have been similarly made, and again incorporated into oligonucleotides.[56] The pyrrolo[2,3-*d*]pyridazin-7-one **37** has been made by a procedure in which a pyrrole 2′-deoxy-nucleoside was prepared by condensation, and the second ring built on by reaction with hydrazine; the 2′,3′-dideoxy-compound was also made by subsequent deoxygenation.[57] When the pyrazolo[3,4-*d*]pyrimidine **38** was prepared by anion glycosylation, a major by-product was an N^2-nucleoside which had lost bromine, and an addition-elimination mechanism after glycosylation was proposed.[58] Some *N*-(2′-deoxy-α- and -β-D-ribofuranosyl)-quinazoline-2,4-diones, variously substituted in the phenyl ring, have been described,[59] and synthetic routes have been developed to the isoxanthopterin nucleoside **39** and its 6-phenyl derivative, along with forms suitable for incorporation into oligodeoxynucleotides.[60] 2-Deoxyribonucleosides have also been made from lumazine, 6,7-diphenyllumazine, alloxazine, naphtho[2,3,*g*]lumazine, naphtho[1,2-*g*]lumazine and anthra[1,2-*g*]lumazine, and incorporated into oligonucleotides.[61]



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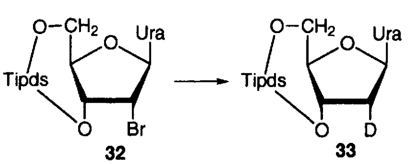

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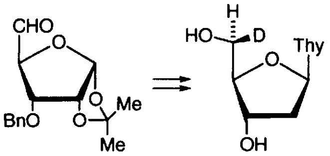

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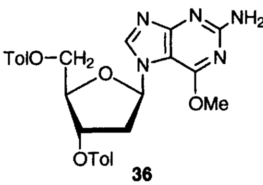

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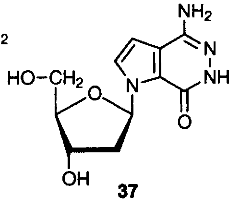

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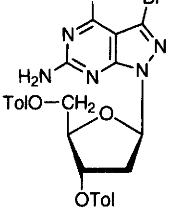

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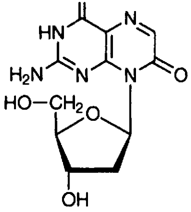

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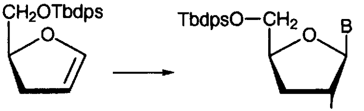
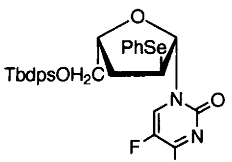


40 **41**

In the area of 2′,3′-dideoxy-compounds, it has been found that when 2′,3′-dimesylates of ribofuranosyl pyrimidines, protected at *O*-5′, are treated with

PhSeLi, the 2′,3′-didehydro-2′,3′-dideoxy-compounds are produced in high yield; this gives an alternative to the use of telluride anion to accomplish the same transformation (Vol. 30, ref. 78).[62] A method noted above for the formation of 2′-deoxycompounds[42] can also be adapted to the synthesis of dideoxy- and didehydro-dideoxy-systems. Thus, treatment of the glycal **40**, itself made by selenoxide elimination, with PhSeCl, AgOTf and a silylated base, gives compounds of type **41** (B = Thy, Ura, 6-chloropurine) with high β-selectivity; reductive removal of the selenium then gives the dideoxy-compound, whilst selenoxide elimination produces the dideoxy-didehydro-system.[63] A phenylselenyl group was also used to direct glycosidation in the formation of **42**; oxidation and elimination then gave the potent antiviral agent β-L-Fd4C (Vol. 30, ref. 84), whilst reductive deselenation gave β-L-FddC (Vol. 28, pp. 269–270).[64] The L-enantiomers of β-L-ddA and β-L-d4A had better substrate activities towards deoxycytidine kinase than did the D-forms.[65] Condensation of 2-*t*-butyldimethylsilyloxyfuran with the enantiomers of isopropylidene glyceraldehyde, followed by further manipulations including side-chain degradation gave **43** (from the D-glyceraldehyde derivative) and its enantiomer, and these were used to make dideoxynucleosides in both enantiomeric series, but without control over the orientation (α/β) of the base.[66] A further report has appeared on the synthesis of d4T from D-xylose,[67], and there have been descriptions of d4T[68] and d4U[69] by opening of 2,2′-anhydronucleosides with iodide ion.

The adenosine kinase inhibitor GP 3269 (**44**) has been made by base-sugar condensation,[70] and various 2′,5′-dideoxy-purine nucleosides were made on a small scale by transglycosylation between 5′-dideoxythymidine and the purine base catalysed by purine nucleoside phosphorylase; pyrazolo[3,2-*d*]pyrimidine and 1-deazapurine 2′,5′-dideoxynucleosides could also be made in this way.[71] Thymidine has been converted into the extended system **45** for incorporation into homologated DNA.[72]



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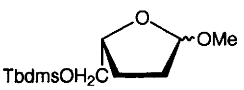

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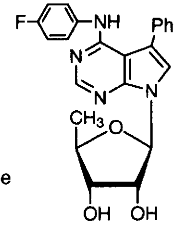

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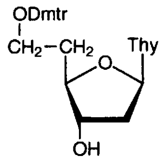

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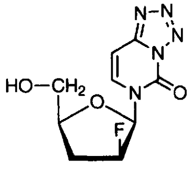

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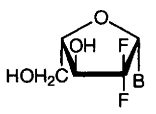

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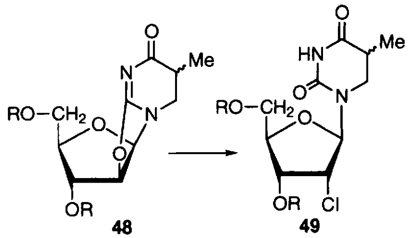


48 **49**

5 Halogenonucleosides

9-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)purine nucleosides have been made by a coupling procedure; the adenosine and hypoxanthine analogues had significant anti-HBV activity without significant toxicity.[73] (2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine has also been prepared by base-sugar coupling,[74] as has the 3′-deoxy-compound **46**; during this work, the analogous tetrazole-fused derivative of ara-C was also made as a potential prodrug.[75] A series of 2′,2′-difluorocompounds of type **47**, in the L-series, have been prepared from a difluoro-sugar (Chapter 8) and the appropriate base; the cytidine analogue is the enantiomer of gemcytabine, but these compounds did not show useful antiviral activity.[76]

When the anhydronucleosides **48** (R = *p*-toluoyl or Piv) were treated with DDQ, substantial amounts of the 2′-chlorocompounds **49** were formed, as well as the dehydrogenated cyclonucleoside, which was itself inert to the conditions. A mechanism was proposed involving attack by chloride ion derived from the reduced form of DDQ.[77] The formation of 2′-deoxy-2′-iodo-compounds such as **16** was mentioned above.[35]

The racemic difluoronucleoside **51** has been made from an oxabicyclo[2.2.1]-heptene, *via* the intermediate **50**.[78]

Methyl 2,3-dideoxy-3-fluoro-5-*O*-(4-phenylbenzoyl)-β-D-*erythro*-pentofuranoside whas been condensed with silylated 2-(methylthio)pyridine-4(1*H*)-one in the presence of TmsOTf to give the corresponding nucleosides.[79] In an improved route to the fluorinated adenosine analogue **52**, fluorine was inserted into 2′,5′-di-*O*-tosyladenosine using DAST, and the tosyl groups were then removed reductively using sodium naphthalenide.[80]

All four 5′-deoxy-5′-halo-derivatives of the anticytomegaloviral agent TCRB (**11**) (X = Cl) have been described.[81] 5′-Deoxy-5′-iodothymidine has been converted into a phosphoramidite for incorporation at the 5′-end of deoxyoligonucleotides. When such an oligonucleotide and another one bearing a phosphorothioate at the 3′-end were brought together on a complementary template, non-enzymic ligation could be demonstrated.[82]

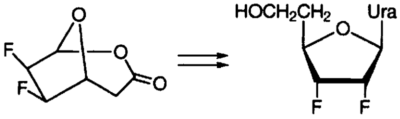
6 Nucleosides with Nitrogen-substituted Sugars

To prepare a fluorescent probe for incorporation into oligonucleotides, 2′-amino-2′-deoxyuridine has been converted into its 6-dimethylamino-2-naphthylamide.[83] 1-(*N*-Acetyl-2-amino-2-deoxy-β-D-glucopyranosyl)-derivatives of uracil and 5-halo-uracils have been synthesized by silyl coupling procedures.[84]

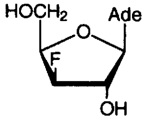
Isocyanato-derivatives of nucleosides have been prepared using various synthetic procedures. Thus, for example, AZT was treated with PPh_3 and the resultant phosphinimine allowed to react with CS_2 to give **53**, and 2′-deoxy-2′-isocyanatouridine was similarly prepared. An attempt to simultaneously reduce the azide to an amine and to deoxygenate C-3′ of uridine derivative **54** formed the cyclic compound **55** instead.[85]

A review from Janda's laboratory discusses the synthesis of complexes of type **56** (M = Re or Tc) as inhibitors of ribonucleases and for the generation of catalytic antibodies,[86] and the same group has also reported on the use of **56** (M = Re, B = Ura) in eliciting antibodies able to catalyse the cleavage of uridine 3′-(*p*-nitrophenylphosphate). An anhydroribitol derivative lacking the base unit was also effective, implying that the nucleobase is not essential, in contrast to earlier studies on RNase U_2 (Vol. 30, p. 279), in which the presence of the base was important.[87]

A number of N^6-cyclopentyl-3′-acylamino-3′-deoxy-xylofuranosyladenines have been prepared, providing a new class of non-xanthine adenosine A_1 receptor antagonists.[88] 1-(3′-Amino-2′,3′-dideoxy-β-D-*erythro*-pentofuranosyl)thieno[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione has been described,[89] and there has been a further report on the synthesis of AZT from thymidine (3 steps, 61% overall).[90]



50 **51**



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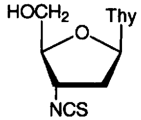

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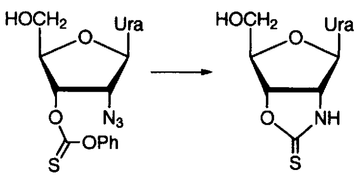
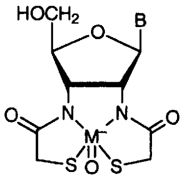


54 **55**



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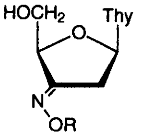

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Oximes **57** (R = H, Me, Ac) have been described, along with the *Z*-isomers (R = Me or Ac). Oxidation of **57** (R = H), protected at O-5′, gave after deprotection a new route to 3′-deoxy-3′-nitrothymidine. Some of the oximes had significant antiviral activity.[91]

Oximes at C-5′ of adenine nucleosides have also been prepared. As well as **58**, various oxime ethers were made, as were the 2′- and 3′-deoxy- and D-*arabino*-analogues of **58**. The compounds were investigated as antiviral and antitumour agents, and **58** was a potent inhibitor of SAH hydrolase.[92]

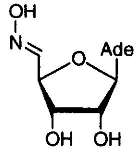
Amides have been prepared by reaction of 5′-amino-5′-deoxythymidine with activated esters of quinaldic acid and 4-(quinoline-2-carbonylamino)butyric acid, and interactions with DNA were studied.[93]

7 Thio- and Seleno-nucleosides

Nucleoside 2′-thionitrites **59** (B = Ura, Cyt) have been synthesized by reaction of the 2′-thiocompounds with *t*-butyl nitrite, and the ability of these compounds to generate NO was studied.[94] A paper dealing with some branched-chain 2′-phenylthio-nucleosides is mentioned in the next Section.

A series of novel 3′-alkylthio-2′,3′-dideoxynucleosides were made by Michael addition of alkylthiols to an α,β-unsaturated hexose aldehyde, followed by acetylation, nucleoside coupling and deprotection, forming the basis for a combinatorial synthesis of libraries of 3′-substituted 2′,3′-dideoxynucleosides.[95]

In the area of sulfur-in-ring analogues, a review has been given of the synthesis and antiviral activity of 4′-thio-2′-deoxyribonucleosides.[96] There has been a fuller account of the synthesis of the 4′-thio-analogues of gemcytabine and 2′-deoxy-2′-methylenecytosine (see Vol. 30, p. 281), and this work was extended to the preparation of the azide **60**.[97] The same group have also used related intermediates to make various 5-substituted uracil 4′-thionucleosides **61** (R = *e.g.* Et, Me, I, CH = CHBr), and the adenine, guanine and 2,6-diaminopurine analogues were also reported.[98] A fuller account has been given of the preparation of compounds of type **62**, their enantiomers and the α-anomers, from the condensation of 2-*t*-butyldimethylsilyloxythiophene and the enantiomers of isopropylidene glyceraldehyde (see Vol. 29, p. 279).[66] A route has been developed for the synthesis of 3-azido-2,3-dideoxy-4-thio-α/β-D-*erythro*-pentofuranose derivatives from D-xylose, which led to the synthesis of the 4′-thio-analogue of AZT and related pyrimidine nucleosides.[99] The doubly-branched 4′-thionucleoside analogue **63** (X = S) has been made by base-'sugar' coupling, although the condensation gave more of the α-anomer (α:β, 2.5:1); the 'sugar' unit was made from L-tartrate.[100]



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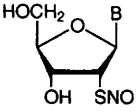

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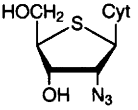

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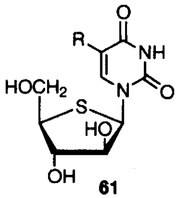

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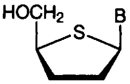

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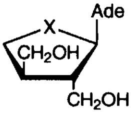

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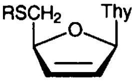

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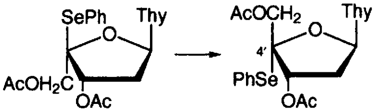


65 **66**

5′-Thiopentofuranosylpyrimidines such as **64** (R = Me, Et), together with sulfoxides and sulfones, and 2′,3′-saturated compounds, have been prepared from d4T.[101]

In previous work (see Vol. 28, pp. 275 and 280), the phenylselenyl pyrimidine nucleoside **65** was produced as essentially the only epimer through reaction of the 5′-aldehyde with PhSeCl and Et_3N. It has now been found that **65** can be epimerized to **66** by photolysis in the presence of diphenyl diselenide to give an equilibrium mixture **66**:**65** of about 2.5:1. Epimer **66** was incorporated into modified oligonucleotides, in which it can provide a source of radicals at C-4′ for chain scission.[102] Some papers on the stereoselective formation of 2′-phenylselenyl nucleosides from glycals, followed by removal of the PhSe group, were mentioned above[42, 63] (see also the next Section).

8 Nucleosides with Branched-chain Sugars

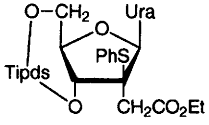
There has been a full account of the synthesis of 2′-*C*-methyl ribonucleosides by addition of $MeTiCl_3$ to a 2-keto-sugar, followed by nucleoside formation (see Vol. 29, pp. 191 and 280), and the method has been extended, using organocerium reagents, to *C*-allyl and *C*-ethynyl systems.[103] A multistep synthesis of 2′,3′-dideoxy-2′-(hydroxymethyl)nucleosides from isopropylideneglycerol has been reported.[104] A full account has also appeared of the synthesis of 2′-deoxyribonucleosides with a two-carbon branch at C-2′ (see Vol. 29, pp. 280–281; for the incorporation of such structures into a dinucleotide analogue, see Section 13).[105] The branched-chain thionucleoside derivative **67** was produced stereoselectively by addition of LiSPh to the 2′-enoate; interestingly, addition of KSPh to the analogous *t*-butyl enoate gave predominantly the opposite epimer at C-2′, a result attributed to different chelation patterns in the two cases.[106]

In work based on earlier precedent (Vol. 23, pp. 218–219), reaction of the selenone **68** with the anion of benzyl (phenylthio)acetate, followed by reductive removal of the PhS group, gave the separable isomers of the cyclopropyl-fused system **69**; for the use of these in making conformationally-restricted dinucleotide analogues, see Section 13.[107]

As regards compounds with the branch at C-3′, the selenoester **70** was made by a sequence involving oxidative cleavage of a 3′-*C*-vinyl compound, which had been prepared through stereoselective addition of a vinylcerium species to a 3′-keto-nucleoside in which O-5′ was protected as a Tbdms ether. Photolysis of **70** gave a 3′-radical of the type implicated in the mechanism of ribonucleotide reductase.[108] There has been a fuller report (see Vol. 29, p. 281) on the synthesis of the 3′-*C*-ethynyl compounds **71**, again through addition of an organocerium species to a 3′-one; here the reaction was highly β-selective, since the substrate had the 5′-hydroxyl group unprotected. The 2′-deoxy analogues of **71** were made by Barton deoxygenation of the 3′,5′-*O*-Tipds derivatives.[109]

Wengel's laboratory has reported the synthesis of the conformationally-restricted nucleoside **72**. This was made from the intermediate **73**, prepared from 1,2-*O*-isopropylidene-α-D-xylofuranose, in a sequence involving stereoselective glycosidation of thymine, inversion of stereochemistry at C-2′ *via* an anhydronucleoside, and then formation of the extra ring after oxidative cleavage of the alkene. Inclusion of thirteen of these modified units into an almost completely modified oligonucleotide gave a duplex with complementary RNA that was considerably more stable than the unmodified RNA-DNA duplex.[110,111] The intermediate **73** was also used to form the *trans*-fused bicyclic nucleoside **74**.[111] The same group has also described the 3′-*C*-allyl-2′-deoxy-compound **75**, as well as the α-anomer, the compounds with opposite stereochemistry at C-3′, and aminopropyl compounds prepared from the *C*-allylated nucleosides.[112]

Workers at Eli Lilly have developed two efficient routes to the promising antiviral agent **77**. In one of these, the key step was hydroformylation [$Rh(CO)_2acac$, Ph_3P, CO (40 psi), H_2] of the 2′-ene **76**, itself easily accessible from cytosine by literature procedures,[113,114] whilst in the other approach stereoselective borohydride reduction of the alkene **78**, made from the D-*lyxo*-epoxide, was a feature.[114] A report from Mann's laboratory has described the application of their method of photochemical addition of methanol to butenolides (see Vol. 26, p. 242 and Vol. 28, p. 278) to the preparation of the enantiomer of **77** and some related compounds.[115]



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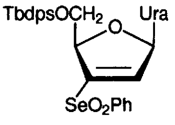

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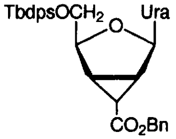

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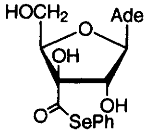

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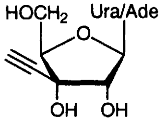

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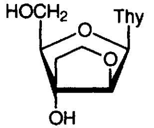

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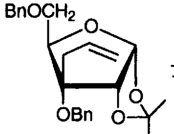

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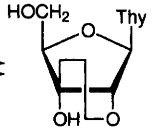

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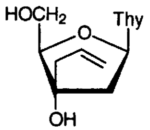

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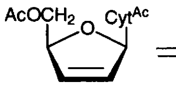

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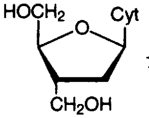

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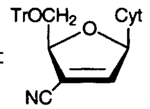

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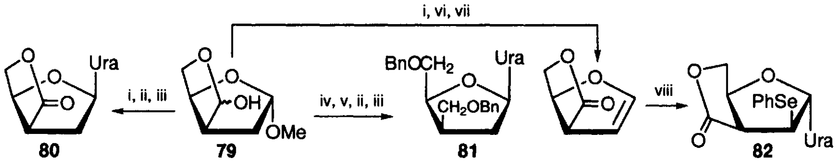
Access to compounds with an 'up' hydroxymethyl group, and related bicyclic systems, comes from the chemistry of Scheme 4. The cyclic lactol **79** was made by ring-contraction of a 3-*O*-triflyl hexopyranoside (Vol. 29, p. 199); the routes to both **80** and **81** were β-selective, but the sequence to **82** gave the α-product, due possibly to delivery of the electrophilic PhSe group to the β-face by association with the carbonyl oxygen atom.[116]

The 3′-*C*-aminomethylthymidine derivative **83** ($R = NH_2$), and also 3′-*C*-methylthymidine, have been made from the previously-known hydroxymethyl compound **83** ($R = OH$) (Vol. 38, p. 278), *via* an epoxide as intermediate.[117]

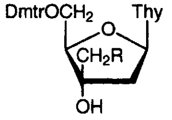
A two-carbon branch has also been introduced in the β-orientation on uridine using an intramolecular Reformatsky-type reaction to give a bicyclic intermediate, as outlined in Scheme 5.[118]

3′-Deoxy-3′-difluoromethylenethymine has been made by a method previously applied to the uridine analogue (Vol. 30, ref. 145), and the difluoromethyl compound **84** was prepared by addition of the anion of difluoromethyl phenyl sulfone to the 3′-keto-group, followed by desulfonation using SmI_2.[119] New analogues of TSAO-T, either of L-*lyxo*-configuration or 5′-deoxy-5′-modified, have been described,[120] and 3′-*C*-isoxazoline, -isoxazolidine and -alkoxyimine derivatives have been prepared from 3′-deoxy-3′-*C*-formylthymidine, the heterocyclic cases being made using cycloadditions of nitrile oxides and nitrones respectively.[121]



Reagents: i, PCC; ii, PhSH, BF$_3$.Et$_2$O; iii, (Tms)$_2$uracil, NBS; iv, LiAlH$_4$; v, BnBr, NaH; vi, PhSeH, BF$_3$; vii, Bu^{t}OOH, Ti(OPr^i)$_4$; viii, PhSeCl, (Tms)$_2$uracil, AgOTf

Scheme 4



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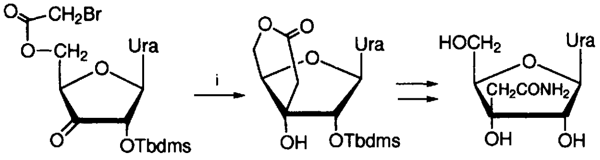
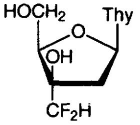


Reagents: i, SmI$_2$, THF

Scheme 5

The doubly-branched adenosine analogue **63** (X = O) has been made by coupling silylated 6-chloropurine to a sugar acetate derived from L-tartrate.[100]

A number of reports have appeared concerning systems with a branch at C-4′. The fused oxetan **86** has been prepared by base-induced cyclization of **85** followed by acidic deprotection; the cytidine analogue was also reported.[122] When O-3′ was protected, then cyclization proceeded with O-2′ as the nucleophile to give after deprotection the interesting bicyclic system **87**, in which the furanose ring is fixed in a C-3′-*endo*-conformation.[123] A preparation has been described of 1-(2-deoxy-4-*C*-hydroxymethyl-α-L-*threo*-pentofuranosyl)uracil,[124] and chloro and sulfanyl derivatives of this have also been reported.[125] Thymidine-4′-*C*-carboxylic acid and derivatives have been prepared by oxidation of a 4′-*C*-hydroxymethyl-compound.[126] The 4′-*C*-fluoromethyl nucleosides **88** (X, Y = H, OH and X = Y = H) have been prepared from a known 4′-*C*-hydroxymethylribose derivative,[127] and the 4′-*C*-fluoromethylthymidine 5′-phosphonate **89** has been prepared from a non-carbohydrate source.[128]



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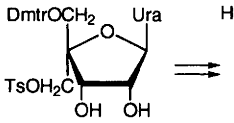

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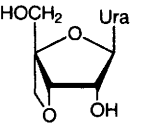

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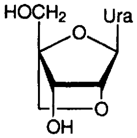

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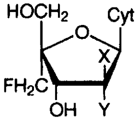

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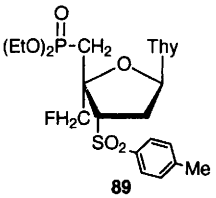

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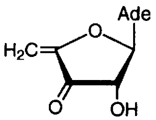

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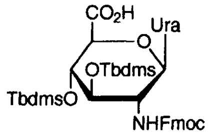

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9 Nucleosides of Unsaturated Sugars, Aldosuloses and Uronic Acids

As in previous volumes, 2′,3′-didehydro-2′,3′-dideoxyfuranosyl nucleosides (d4 systems) are discussed in Section 4, together with their saturated analogues.

The mechanism of the time-dependent inactivation of *S*-adenosylhomocysteine hydrolase by 5′-deoxy-5′-difluoromethylthioadenosine (preparation, Vol. 25, p. 254) has been studied, and evidence was adduced that the mechanism involves the generation of the enone **90** and the powerful acylating agent HFC = S.[129]

A convenient route has been described to convert cytidine into the 2′-ketonucleoside, acetylated at O-3′, O-5′ and N-4, in which formation of a 2,2′-anhydronucleoside was used to differentiate the hydroxyl groups.[130]

Conjugates of adenosine- and 2-chloroadenosine-5′-carboxylic acids with tetra-aspartate and with the pentapeptides Pro-$(Asp)_4$ and Sar-$(Asp)_4$ have been made by solid-phase synthesis. The compounds can be viewed as highly-charged ATP analogues.[131] The *N*-2′-amino-2′-deoxy-glucuronic acid nucleosides **91** (B = Thy, Cyt, Ade, Gua) have been made as building blocks for oligonucleotide amide-linked analogues (see Section 13); oxidation of the primary alcohol to the acid using NaOCl catalysed by TEMPO was the final step in the synthetic sequence.[132] *N*-β-D-Glucuronides of the cytokinins N^6-benzyladenine and isopentenyladenine have been prepared by Koenigs-Knorr chemistry for use in selecting plant cells transformed with a β-glucuronidase gene.[133]

10 *C*-Nucleosides

A review has appeared on the synthesis of *C*-nucleosides of monocyclic heterocycles,[134] and the preparation of pseudouridine under prebiotic conditions has been discussed in a review article.[135] The ionization constant of 9-deazainosine (pK_a 6.0, for protonation at N^3) has been determined for the first time, and a third ionisation constant (pK_a 1.3, for protonation at N^3) was identified for formycin.[136]

'Selenophenfurin' (**92**) has been made by a method analogous to those used for the thiophene and furan compounds (Vol. 29, p. 283), and it was found to inhibit IMP dehydrogenase and to have antitumour activity.[137]

There have been further reports on pyridine *C*-nucleosides. The preparation of **93** (R = X = H) has been described in detail, as have routes to **93** (R = Me, X = H, and R = H, X = OMe); these were made as more basic analogues of cytidine, and the incorporation of these into DNA was studied.[138] An improved route to the pyrimidinone **94** has been described,[139] and the isomer **95** has also been made, using addition of a lithiated pyridine to 2,3,5-tri-*O*-benzylribonolactone, followed by stereoselective reduction with Et_3SiH and $BF_3.Et_2O$.[140] A similar approach was used to make the imidazo[1,2-*a*]pyridine **96**, where the site of ribosylation (C-3) was unexpected.[141]

There has been an extended report on the synthesis of ribofuranosyl and 2′-

deoxyribofuranosyl heterocycles by reaction of protected (deoxy)ribose derivatives with metallated heterocycles, followed by Mitsunobu cyclization (see Vol. 28, p. 282). Use of less basic organometallics tended to give more of the β-product.[142]

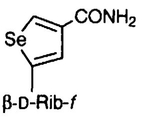
Palladium-catalysed cross-couplings have been used to make some new 2′-deoxypyrazine *C*-nucleosides such as **97**,[143] and the 2′-deoxypyrazofurin analogues **98** (X = Br, CO_2Me).[144] 3-β-D-Ribofuranosylpyrazole-4-carboxamide has been made by cyclization of a previously-reported intermediate.[145]

The L-enantiomer of 9-deazaadenosine has been prepared using methods similar to those employed for the D-form, and 4-amino-8-β-L-ribofuranosylpyrazolo[1,5-*a*]-1,3,5-triazine was also synthesized from one of the intermediates in this work.[146]

Dehydrative cyclization was used to make some 2-tetrosylbenzimidazoles such as **99**,[147] and some 2-(D-erythrosyl)furans have been described, with additional nitrogen heterocycles attached to the furan *via* a carbon spacer.[148,149]

2-(α-D-Mannofuranosyl)maleimide, an analogue of showdomycin, has been reported,[150] and two routes have been developed for the synthesis of the apiofuranosyl maleimide **100**, a showdomycin analogue with a transposed hydroxymethyl group, both proceeding from 2,3-*O*-isopropylidene-D-apio-β-D-furanose, itself available from D-mannose in good yield (*Liebigs Ann. Chem.*, 1995, 551).[151, 152]

The homo-*C*-nucleoside **101**, with a 'split' 8-azapurine system, has been prepared; the triazole was made by cycloaddition of Tms-acetylene and an azide, which was assembled by Wittig reaction-cyclization involving 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranose.[153]



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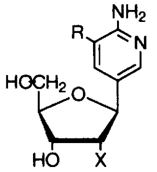

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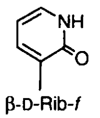

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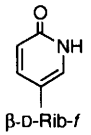

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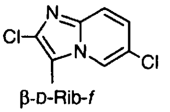

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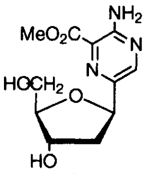

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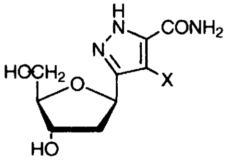

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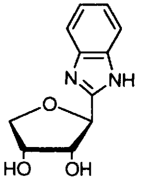

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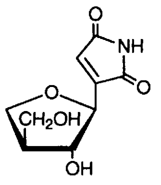

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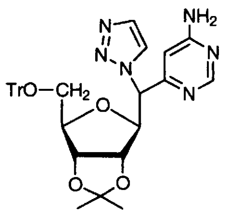
11 Carbocyclic Nucleosides

The carbocyclic ribosylamine **102** has been used to prepare **103** (X = CH_2 and X = O), which, when cyclized *via* a diphosphate unit will give carbocyclic analogues of cADPR in which the labile N^1-ribose link has been stabilized by the presence of the methylene unit.[154] A new synthesis of the antiherpetic agent (+)-cyclaradine (**104**) has been reported,[155] and ring-opening of an epoxide with various nucleobases in the presence of Et_3Al has been used to make a number of racemic carbocyclic nucleosides of *xylo*-configuration.[156] The racemic compound **105** has been made from carbomethoxycyclopentanone.[157]



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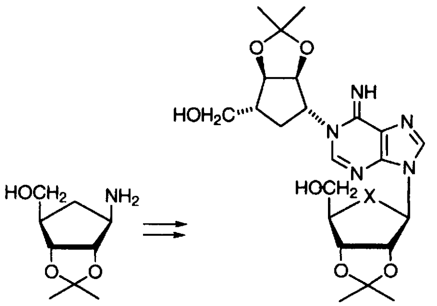
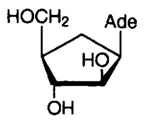


102 **103**



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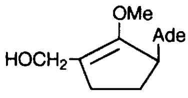

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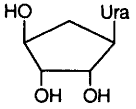

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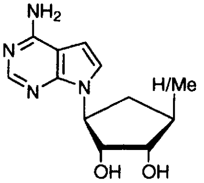

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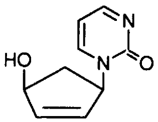


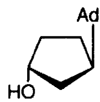
108

The racemic nor-analogue **106** related to aristeromycin has been prepared using the cycloaddition of α-chloronitrosocyclohexane and cyclopentadiene to establish the 1,3-*cis*-stereochemistry of nitrogen and oxygen.[158] The L-type aristeromycin analogues **107**, their enantiomers and a related alkene have been prepared as potential antitrypanosomal agents,[159] several racemic compounds of type **108** have been made by Pd(0)-catalysed reactions of the bases with cyclopentadiene monoepoxide,[160] and the chiral iso-nucleoside analogue **109** was prepared by alkylation of adenine; N^4- and N^9-alkylated products were also formed, and the N^4-product could be selectively extracted from the mixture by an acid wash due to its higher basicity.[161]

The 5′-homo-systems **110** (B = Purine) have been prepared enantioselectively, again using Pd(0) chemistry to add the base,[162] and analogues have been made in which the carbocycle and base are separated by a two-carbon chain.[163]

Some racemic bicyclic dideoxynucleoside analogues such as **111** have been prepared.[164] A report from Marquez's laboratory has described an alternative route to the anti-HSV agent **113**, in which a key step was the formation of the azidoselenide **112** from the enantiopure alkene (*J. Chem. Soc., Perkin Trans. 1*, 1988, 549),[165] and the same group have also given an extended account of the synthesis of the isomeric systems **114** (B = Thy, Cyt, Ade, Gua) (see Vol. 29, p. 285) from the same chiral alkene.[166] Other workers have used very similar intermediates, made in the same way, to produce the methylene-substituted compounds **115** (B = Ade, Gua, Thy, 5-iodoUra), and the Gua analogue showed particularly good activity against hepatitis B virus.[167] The chiral cyclopentanone **116** has been used to produce the fluoronucleosides **117**, and also isomers with the fluorine 'down', and the two epimers where the fluorine is at C-2'. Introduction of fluorine was by electrophilic fluorination of the Tms enol ether of **116**.[168] The iridoid glycoside aucubin has been used as a chiral precursor for the doubly-branched carbanucleoside **118**,[169] and **119** and related purines and 8-azapurines have been prepared in chiral form.[170]

The cyclobutyl derivatives **120** have been synthesized.[171]



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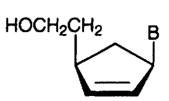

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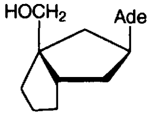

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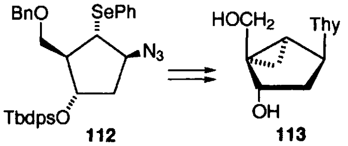
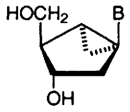


112 **113**



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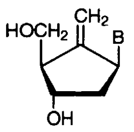

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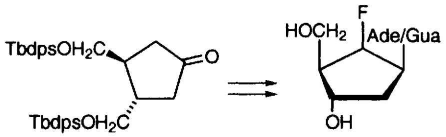
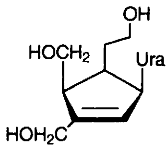


116 **117**



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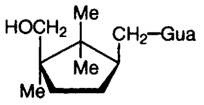

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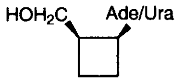

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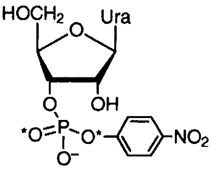


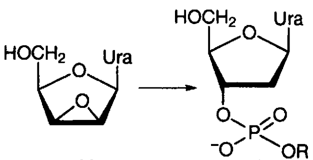
121

Some references to phosphates and phosphonates of carbocyclic nucleosides are mentioned in the next Section, some references to cyclopropyl nucleoside analogues are given in Section 15, and a number of papers on aristeromycin, neplanocin and their close analogues are covered in Chapter 19, along with carbocyclic analogues of oxetanocin.

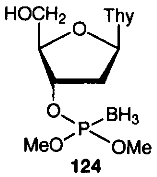
12 Nucleoside Phosphates and Phosphonates

12.1 Nucleoside Mono-phosphates and -phosphonates and Their Analogues – A review on the synthesis of non-racemic phosphonates discusses a number of examples from the nucleoside field.[172] Thymidine 5'-*O*-diphenylphosphate has been prepared by the reaction of thymidine and diphenyl phosphate in the presence of a polystyryl diphenylphosphine–iodine complex. The 3'-*O*-diphenylphosphate was formed if O-5' was protected as the Dmtr ether.[173] The 3'-phosphate **121** has been prepared labelled both with ^{15}N and with ^{18}O at, separately, either of the positions asterisked, for use in studies of isotope effects in the mechanism of ribonuclease A.[174]

When the *lyxo*-epoxide **122** was treated with disodium hydrogen phosphate, the 3′-phosphate **123** (R = H) was formed as the major (5:1) product of epoxide opening, and use of UMP as nucleophile led to the formation of the dinucleotide (**123**) (R = uridyl-5′-yl).[175] A new route to the nucleoside boranophosphate **124** involves the reaction of 5′-*O*-Dmtr-thymidine with *t*-BuLi followed by tetramethylboranopyrophosphate (**125**), and then acidic deprotection.[176] The phosphorothioate **126** has been prepared by the reaction of the corresponding phosphite with propylene sulfide in the presence of $ReOCl_3(PPh_3)_2$ as catalyst.[177] A study has been reported of the acid-base properties of adenosine-5′-*O*-thiomonophosphate in aqueous solution; in the monoanion, the thiophosphate-protonated species dominates (3:1) over the N^1-protonated species, and calculations locate the proton in the former species mainly on oxygen.[178] Nucleoside 5′-phosphorodithioates have been prepared from 2-thio-1,3,2-dithiaphospholanes (Vol. 28, pp. 288–289) as indicated in Scheme 6, and 3′-phosphorodithioates could be made in the same way.[179]



122 **123**



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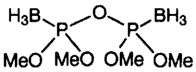

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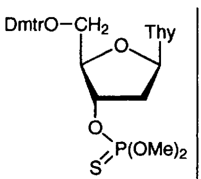

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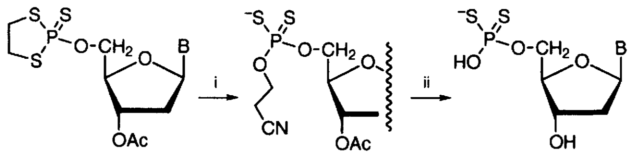


Reagents: i, $HOCH_2CH_2CN$, DBU; ii, NH_3, H_2O

Scheme 6

Carbocyclic analogues of the four 2′-deoxyribonucleoside 5′-monophosphates have been prepared by methods involving Mitsunobu reactions to link the base to a chiral cyclopentane unit.[180]

Adenine-activated nucleosides such as **127**, and related species derived from adenine itself (N^9-phosphorylated) and N^3-methyladenine (N^7-phosphorylated) have been prepared. These compounds underwent oligomerization catalysed by montmorillonite to give products in which 3′,5′-links predominated.[181]

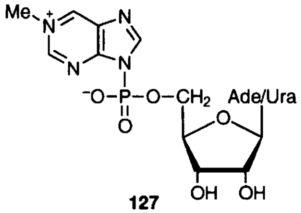
A 3′-phosphoramidite derived from 5-hydroxy-2′-deoxycytidine has been prepared, and used to incorporate the modified base into oligonucleotides.[182]

The 5′-phosphonate of 2′,3′-dideoxythymidine has been prepared, as has the regioisomer **128** in which the positions of the base and the phosphonate are reversed.[183]

Flavin has been linked *via* short chains of methylene groups so as to form a phosphodiester with thymidine-5′-phosphate, and a phosphorothioate diester and an *O*-methyl phosphotriester were also prepared.[184]

There have been a number of further reports (see Vol. 30, p. 294) from Meier and co-workers on a new type of lipophilic prodrug designed to deliver nucleoside 5′-monophosphates. These cyclosaligenyl (*cyclo*Sal) phosphotriesters have been described for d4T (**129**, X = Cl, H, Me, NO_2),[185] ddA,[186] FdU,[187] and AZT.[188] In each case the nucleoside monophosphate can be generated under physiological conditions by initial hydrolysis of the phenyl phosphate, which then leads to a more rapid cleavage of the benzylic phosphate. The derivatives of d4T[185] and ddA[186] were more active against HIV than were the parent nucleosides. A range of phosphoramidates related to AZT and to FLT (3′-fluoro-3′-deoxythymidine) have been reported, including ones which are phosphomonoesters (*e.g.* **130**). The mechanism of enzymic hydrolysis was investigated, and it was found that initial hydrolysis of the CO_2Me group was not involved, unlike the situation for aromatic phosphodiesters.[189] Various long-chain alkyl phosphonoformate esters of AZT have been prepared,[190] and ara-C has been linked *via* a 5′-phosphate to L-1,2-diacylglycerols.[191]

β-D-Lactose has been linked through a 3-hydroxypropyl glycoside to ara-C and ara-A *via* 5′-phosphodiesters,[192] and in related work, the anti-hepatitis B agent IdU monophosphate has been linked to a trivalent lactose array recognised by a receptor on the liver; the structure **131** uses tris and 6-hydroxyhexanoic acid to link the units.[193]



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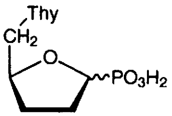

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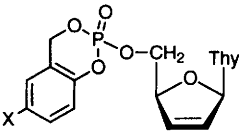

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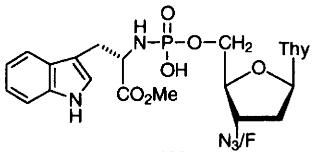

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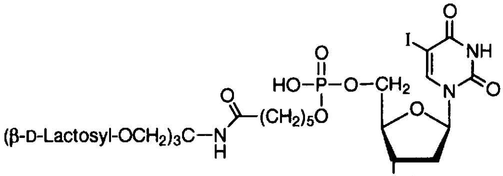

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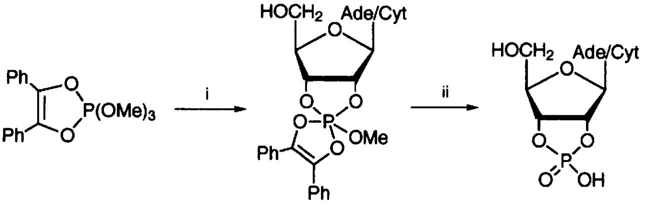
12.2 Cyclic Monophosphates and Related Phosphonates

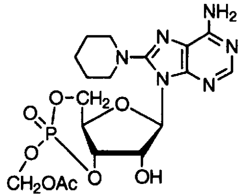
– The sequence of Scheme 7 has been used to prepare the 2′,3′-cyclic phosphates of adenosine and cytosine. Deoxyribonucleosides gave the benzoin phosphodiesters, predominantly at O-5′.[194] Uridine 2′,3′-cyclic phosphite has been prepared, and the diastereomers were analysed by 2D-NMR techniques to assign configuration.[195]

Membrane-permeant but bioactivatable triesters of 8-substituted cyclic AMP derivatives, such as **132**, have been made by reaction of the cyclic diester with $AcOCH_2Br$.[196] The 5′-nor-aristeromycin derivative **133** (Vol. 27, p. 235) has been converted into various racemic carbocyclic phosphonate analogues of cAMP such as **134** (X = NH_2, OH).[197]



Reagents: i, cytosine or adenosine; ii, H_2O, r.t.

Scheme 7



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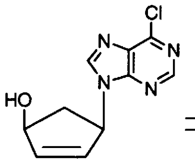

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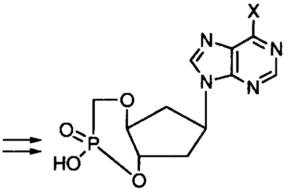

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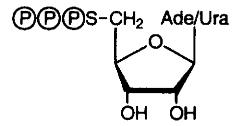
12.3 Nucleoside Triphosphates and Their Analogues – Nucleoside triphosphates have been prepared from the corresponding 5′-monophosphates by treatment with TFAA and tertiary amines, followed by *N*-methylimidazole and inorganic pyrophosphate.[198] $^{13}C_6$-D-Glucose, $^{2}H_7$-D-glucose, and $^{13}C_6,^{2}H_7$-D-glucose have been converted enzymically into multiply-labelled ribonucleoside triphosphates, which were incorporated into oligomers for NMR studies.[199] 4′-*C*-Acylthymidines (Vol. 30, p. 285) have been converted into their 5′-triphosphates and incorporated into deoxyoligonucleotides which underwent chain-scission on photolysis.[200] The 5′-thioribonucleoside 5′-triphosphates **135** have been prepared from the 5′-deoxy-5′-iodonucleosides, either by diplacement of iodide by monothiophosphate followed by formation of the triphosphate, or by direct substitution of iodide by monothiotriphosphate. The products were not substrates for *E. coli* DNA-dependent RNA polymerase, but were weak competitive inhibitors.[201]

A number of analogues of deoxynucleoside triphosphates have been made, in which the α,β- P-O-P unit is replaced by P-NH-P; they were prepared by the reaction of the 5′-imidodiphosphates with phosphoenolpyruvate in the presence of pyruvate kinase, and were inhibitors of HIV reverse transcriptase.[202] The ATP analogue in which the β,γ-oxygen is replaced by a difluoromethylene unit has been made, as has the related arsenic species **136**, the products being competitive inhibitors of glycerol kinase.[203]

The 3′-triphosphate of 2′,5′-dideoxyadenosine is an inhibitor of adenyl cyclases. The species **137** has now been made and used, linked to Affi-Gel 10, for affinity chromatography. Similar derivatives of nucleoside 5′-triphosphates were also prepared.[204]

p-Hydroxyphenacyl esters at the γ-phosphate of nucleoside triphosphates have been made as photolabile protecting groups,[205] and a good synthetic method has been described for P^1-methyl-P^3-(5′-guanosyl)triphosphate (CH_3pppG), in which GDP reacts with methyl phosphorimidazolate.[206]



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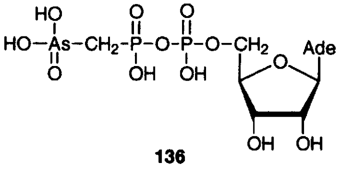

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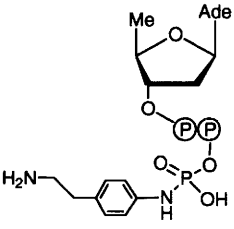

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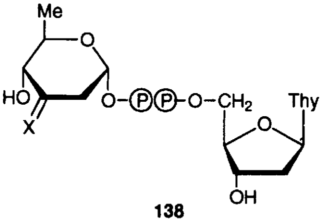

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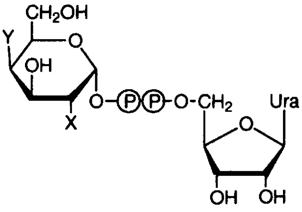
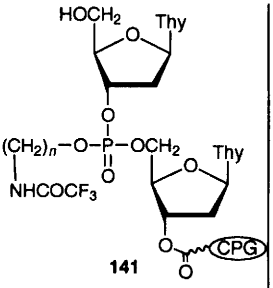


139 X = F, Y = OH
140 X = OH, Y = F

12.4 Nucleoside Mono- and Di-phosphosugars – An enzymic synthesis of CMP-NeuNAc has been reported, using CMP-NeuNAc synthetase.[207] Khorana's original synthesis of nucleoside diphosphosugars from sugar 1-phosphates and nucleoside 5′-monophosphomorpholidates has now been shown to proceed in higher yields and in shorter times if tetrazole is present; UDP-Gal, GDP-Fuc, and GDP-Man were prepared in high yields using this method.[208] The phosphomorpholidate method was used to make the TDP-sugar derivative **138** ($X = CH_2$). Ozonolysis gave the aldosulose derivative **138** ($X = O$), a potential intermediate in the biosynthesis of rare sugars, but the product was too unstable to be isolated due to β-elimination.[209] Various analogues of GDP-fucose have been prepared,[210] as have the UDP-Gal analogues **139** and **140**. These compounds were prepared as potential inhibitors of UDP-galactopyranose mutase, and were found to be fairly weak inhibitors of the reaction in the direction UDP-Gal*f*→UDP-Gal*p*.[211] The analogue **139** has also been prepared in Wong's laboratory by a chemoenzymatic sequence, and it was found to be an inhibitor of β-1,4-galactosyl transferase, providing support that the mechanism of this enzyme proceeds through a transition state with sp^2 character at the anomeric centre.[212]

12.5 Di- and Tri-nucleotides and Their Analogues – *12.5.1 3′→5′-Linked systems* – A new protecting group has been developed for use during phosphodiester synthesis. The triesters **141** (n = 4, 5) were made by phosphoramidite chemistry, and, on treatment with NH_3, TpT was formed. The alkyl group is lost, after hydrolysis of the trifluoroacetyl group, by cyclization producing piperidine or pyrrolidine.[213]

Selective *O*-phosphonylation of 5′-*O*-Dmtr-2′-deoxy-adenosine, -cytidine and -guanosine, without reaction on nitrogen, can be achieved using P–H reagents such as pyrophosphonate and diphenyl phosphonate. The method was further developed to make H-phosphonate internucleotidic links, followed by oxidation to phosphates using an *N*-sulfonyloxaziridine.[214] A report from Reese's laboratory describes a new approach to the solution-phase synthesis of dinucleoside phosphates and phosphorothioates. The method involves H-phosphonate coupling, followed by formation of a P–S bond, as indicated in Scheme 8. The products of type **142** could be very cleanly deprotected without side reactions to give dinucleotides, whilst if a 2-cyanoethyl group was used instead of the *p*-chlorophenyl unit dinucleoside phosphorothioates could be obtained.[215]



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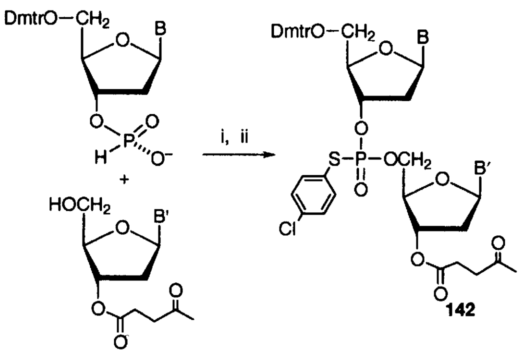
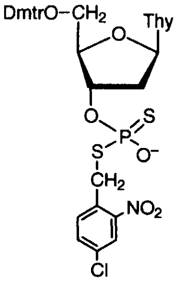


Reagents: i, di(2-chlorophenyl)phosphorochloridate, py;
ii, Phth-S-*p*-C_6H_4-Cl, CH_2Cl_2, py, −40°C, then py, H_2O

Scheme 8

Stawinski and Kraszewski have reviewed recent work from their laboratories, including the preparation of dinucleoside H-phosphonates and H-phosphonothioates, work on 5′-methylenephosphonate analogues, and routes to P–F compounds from H-phosphonates and related compounds.[216] A solution-phase synthesis of dithymidine phosphorodithioate uses a chemoselective coupling reagent PyNOP [6-nitrobenzotriazol-1-yl-oxy-tris-(pyrrolidino)phosphonium hexafluorophosphate], which activates the intermediate **143** selectively at oxygen for coupling with 3′-*O*-acetylthymidine; the use of the 4-chloro-2-nitrobenzyl protecting group on sulfur led to less of the competing attack at C-5′ when it was removed using phenylthiolate anion, as compared with earlier work (Vol. 24, p. 243).[217] The same team has also applied similar chemistry to the synthesis of dithymidine phosphorothioate.[218]

A report from Just's laboratory describes some improvements on their previous work (Vol. 30, pp. 290–291) in which a xylose-based chiral auxiliary was used to prepare dithymidine phosphorothioate with good diastereomeric excess; in the new work, the xylose derivative used has a base-labile protecting group at O-2, so that the auxiliary can be removed using ammonia.[219] The same group has also described the use of an indolic chiral auxiliary for



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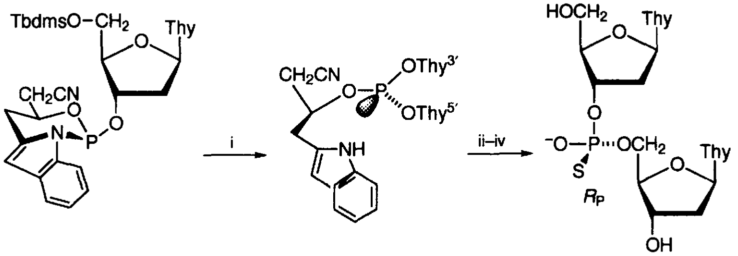


Reagents: i, 3′-*O*-Tbdps-thymidine; ii, Beaucage's reagent; iii, NH_3, H_2O; iv, TBAF

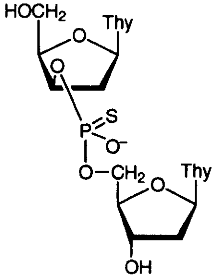
Scheme 9

producing dithymidine phosphorothioate in high diastereomeric excess, as outlined in Scheme 9, where again the removal of the auxiliary under basic conditions is advantageous.[220] The phosphorothioate **144** has been prepared; the diastereomers were separated by reverse-phase HPLC, the absolute configurations being deduced from their behaviour towards snake-venom phosphodiesterase, and incorporated into oligonucleotides.[221]

There has been interest in protecting groups for internucleosidic phosphates, phosphorothioates and phosphorodithioates that are removable under physiological conditions. The glucuronic acid derivatives **145** (X = O, S) have been prepared, and similar systems in which the glucuronic acid was attached by a thioester were also described.[222] The same team has also reported on a series of six triesters of TpT and its mono- and di-thioanalogues, of which **146** and **147** proved best in releasing the phosphodiester and phosphorothioate respectively.[223] Other workers have prepared the trinucleoside analogues **148** (X = O, S), in which the phosphorothioate could be unveiled by esterases.[224]

Various dinucleoside phosphorofluoridates have been prepared using 3′-phosphoramidites with a P–F unit present,[225] and a new method for forming the P–F bond involves the synthesis of dinucleosidyl phosphorofluoridates and phosphorofluoridothioates from phosphorothioates and phosphorodithioates respectively, when they are subjected to desulfurization with iodine in the presence of triethylamine tris(hydrofluoride). Phosphoroselenoates and phosphoroselenothioates undergo loss of Se under these conditions, again forming the P–F species.[226]

A P(III) coupling reagent containing an indole unit has been used to prepare



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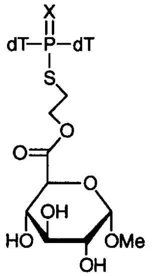

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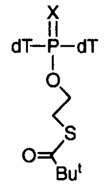
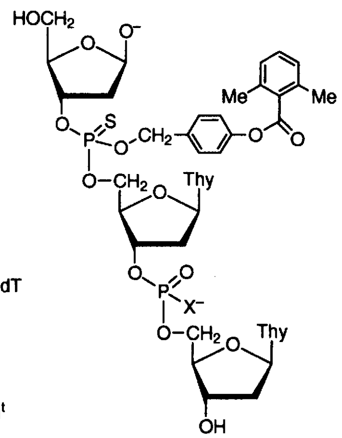


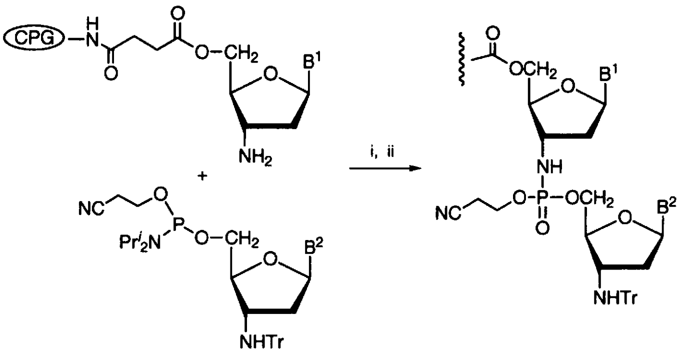
146 X = O
147 X = S



148

deoxyoligonucleotide methylphosphonates and methylthiophosphonates,[227] and there have been reports on diastereoselective syntheses of 2′-deoxy-[228-230] and 2′-*O*-methyl dinucleoside 3′,5′-methylphosphonates.[229,230]

A new method for the synthesis of N3′→-5′ phosphoramidate oligonucleotides is illustrated in Scheme 10. This procedure follows a 5′→3′ strategy, with phosphoramidite-amine exchange as a key step. Removal of the *N*-trityl group with dichloroacetic acid permits repetition of the cycle.[231,232] A similar phosphoramidite-amine exchange was used to prepare the phosphoramidate **149**, from which the *o*-nitrobenzyl group could be removed on photolysis. An alternative route to the same type of link was also developed, involving dinucleosidyl H-phosphonate diesters as intermediates, and this was applied to the synthesis of isomers of **149** with the bases α-oriented.[233]



Reagents: i, 1H-tetrazole; ii, I_2, H_2O, py, THF

Scheme 10

Treatment of 2′-deoxynucleosides with phosphoryl chloride in DMF leads to cyclic dinucleoside dipyrophosphates **150** as major products.[234]

Some chemistry concerning protecting groups used in oligonucletide work is mentioned in Section 14 below.

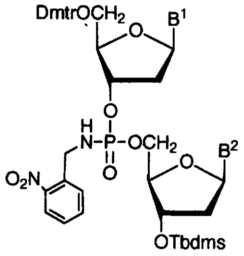
12.5.2 5′→5′-Linked systems – The methylene bis-phosphonate analogue of benzamide adenine dinucleotide (BAD) has been prepared,[235] and a similar analogue **151** in which adenosine is replaced by 2′-deoxy-2′-fluoro-ara-A has also been described. The similar tiazofurin adenine dinucleotide (TAD) analogue was also prepared, and in this case the compound with CH_2 replaced by CF_2 was also made.[236] These methylene bisphosphonates were prepared by activating a 2′,3′-*O*-isopropylidene nucleoside-5′-methylenebisphosphonate with DCC in pyridine, prior to the addition of a second 2′,3′-*O*-isopropylidene nucleoside. The mechanism of such reactions has been investigated, and found to involve bicyclic tris-anhydride intermediates.[237]

In the area of cyclic ADP-ribose (cADPR), a chemoenzymatic approach was used in Sih's laboratory to prepare cATPR, which is more stable and of higher bioactivity, carrying a (6-aminohexyl)amino-substituent at C-8 of the adenosine. The compound is of application as an affinity probe for cADPR-binding proteins.[238] Potter's group have described the synthesis of **152**, a carbocyclic inosine analogue of *seco*-cADPR.[239]

12.5.3 2′→5′-Linked systems – The 2′-5′-adenylate trimer has been prepared with a positively-charged (4-aminobutyl)amino group at C-8 of the 2′(3′)-terminal adenosine unit,[240] with 2′,3′-dideoxy-3′-fluoro-derivatives of adenosine at the 2′-end,[241] and with the triazole base of ribavirin and with N^6-benzyladenine at all three locations in the trimer.[242] The 3′-deoxy trimer (cordycepin trimer) has been made with ω-hydroxyalkyl chains attached at O-3 of the 2′(3′)-end (this unit being adenosine rather than cordycepin), and a cholesterol conjugate was also made, which showed appreciable anti-HIV activity.[243] The cordycepin trimer has also been attached to fatty acids, and to folic acid, at either the 5′- or the 2′-end, the acids being linked to the core by a 6-aminohexanoyl spacer.[244]

13 Oligonucleotide Analogues with Phosphorus-free Linkages

Amide replacements continue to attract attention. De Mesmaeker's group has described thioamides of type **153** (X = S), together with amides in which the furanose rings are linked by the three-atom chains $-NHCOCH_2-$, $-CH_2CONH-$ and $-CONHCH_2-$, and also by a five-atom link previously developed by others (Vol . 29, p. 293).[245] A dithymidyl unit with the four-atom amide link (**153**) (X = O) has been made with an intercalating anthraquinone unit attached to the nitrogen *via* a short chain, and incorporated into oligonucleotides.[246] The same team have also made the dimer **154**; inclusion in oligomers led to improved T_ms with complementary RNA of up to 4.4 °C per modification.[247] Other workers have prepared the 2′-5′ four-atom amide replacement **155** through reaction of a fused butyrolactone with 5′-amino-5′-deoxythymidine.[105]



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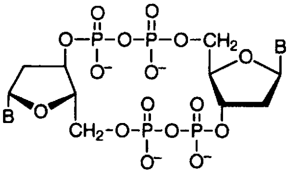

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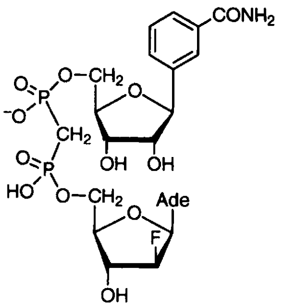

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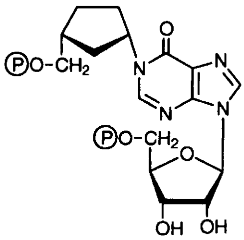

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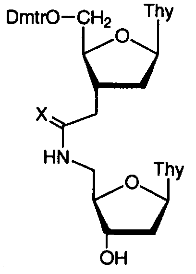

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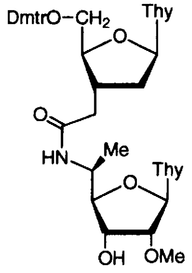

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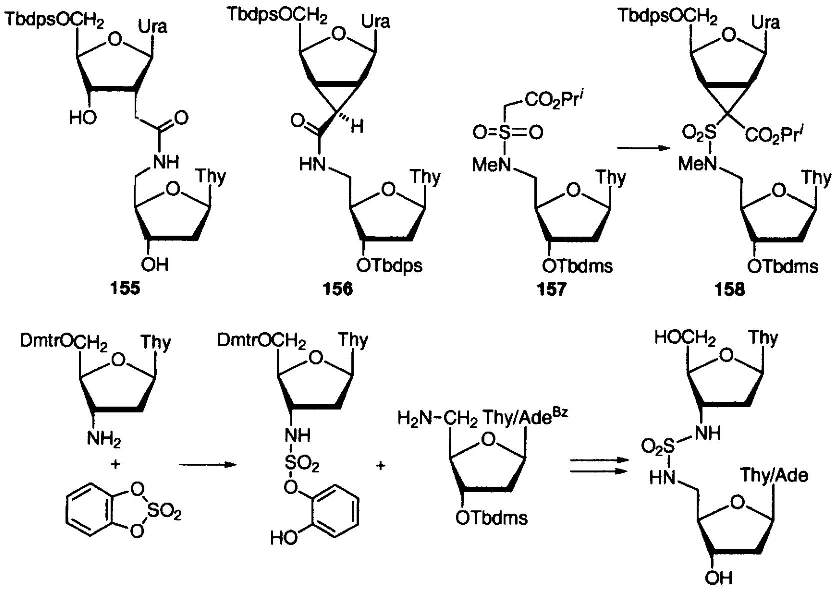
The conformationally-restricted amide **156**, and its diastereomer at the cyclopropyl carbon, have been prepared from **69**, and reaction of the unsaturated selenone **68** with **157** in the presence of *t*-BuOK gave the sulfonamide-linked dimer **158**.[107]

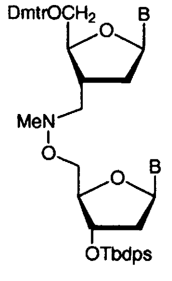
A novel linkage which has now been reported is the sulfamide **159**, prepared as indicated in Scheme 11. The 5′-furanose ring exists predominantly in an N-type conformation, which should be favourable for forming heteroduplexes.[248]

The group at Isis Pharmaceuticals have given an overview of their work on the MMI [methylene(methylimino)] linkage,[249] and also described an improved route to this system (**160**) involving reductive amination between a C-3′-aldehyde and the *N*-methylhydroxylamine.[250] Formacetal-linked systems have now been made in cases where both bases are purines; the synthesis involves the reaction of the 3′-*O*-methylthiomethyl ether with the 5′-OH group in the presence of NIS and 2.5 equivalents of TfOH,[251] and a similar procedure has been used to make formacetal-linked analogues in the ribo-series; the unit **161** was made for incorporation into oligonucleotides using solid-phase H-phosphonate methods.[252] The novel isosteric disulfide **164** has been prepared from the building blocks **162** and **163**, and the shorter 3-atom link **165** was made in a similar way.[253]

Altmann and colleagues have made the *cis*-alkene **166** by a Wittig reaction, and have also prepared the triazoles **167** and **168**, in each case assembling the heterocycle by a cycloaddition-elimination reaction between an azide and a stabilized phosphorane.[254] The related imidazoles **169** and **170** were also prepared; the imidazole ring was made by reaction of an appropriate aldehyde



Scheme 11



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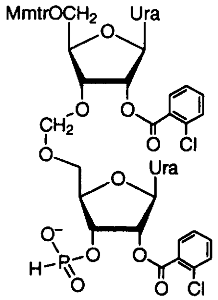

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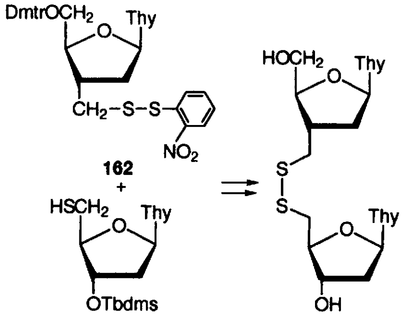
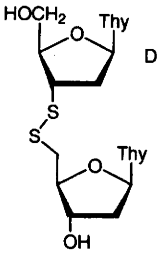


163 **164**

with glyoxal and ammonia, and the *N*-nucleosidyl unit was introduced by alkylation of the imidazole.[255] All of these analogues were incorporated into oligomers by phosphoramidite methods. Matteucci's laboratory has prepared the hemiacetal **171** by oxidative cleavage of a 2′-*O*-allyl group, and hence made the dinucleotide analogue **172**, and its epimer at the acetal carbon. These were incorporated into oligonucleotides by H-phosphonate technology.[256]

Workers at Roche have used solid-phase methods to incorporate building blocks of type **91** into glucopyranosyl nucleic amides (GNA, **173**), capped by a lysine unit. A homopyrimidine 13-mer complementary to a homopurine sequence in the HIV *gag* gene was prepared, and also a decamer containing all four DNA bases. Complementarity studies with RNA and DNA were reported.[257]



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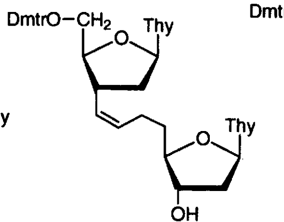

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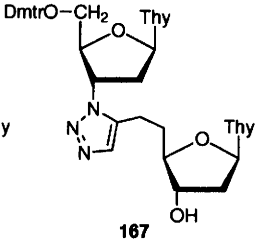

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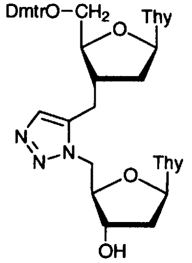

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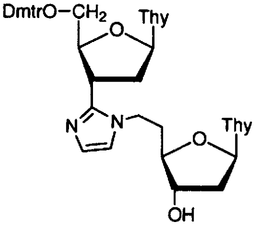

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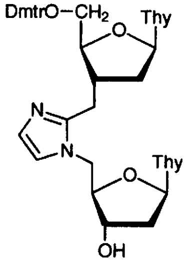

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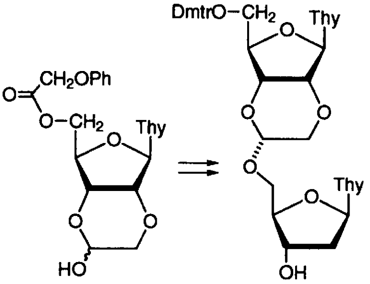


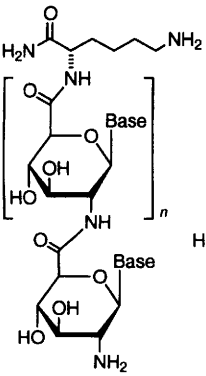
171 **172**

14 Ethers, Esters and Acetals of Nucleosides

The problem of effecting alkylation at O-2′ of guanosine without alkylating the purine has been solved in a new way which involves silylation of 3′,5′-*O*-Tipds-guanosine selectively at O-6, followed by alkylation at O-2′ using an alkyl halide and a strong, sterically-hindered organic base.[258,259] Alternatively, O-6 can be protected as its *o*-nitrophenyl ether.[259] A different solution to the same problem emerged in work designed to make guanosines with pendant alkylthiol chains at O-2′; it was found that alkylation of 2,6-diamino-9-(β-D-ribofuranosyl)purine with NaH and the appropriate alkyl bromide gave mostly (~50% yield) the 2′-*O*-alkyl derivatives **174** (n = 2, 3), which could be deaminated with adenosine deaminase and then converted to the targets **175**.[260] 2′-*O*-Allyl-β-D-arabinofuranosyl-uracil, -cytosine and -adenine have been made as potential inhibitors of ribonucleotide reductase, in the cases of the pyrimidines *via* the 2,2′-anhydronucleoside,[261] which was also involved in a route to 3′,5′-di-*O*-trityl-β-D-arabinofuranosyluracil from uridine.[262] 2,2′-Anhydro-α-uridine was used to prepare 5′-*O*-dimethoxytrityl-α-uridine.[263]

Tetra-*n*-butylammonium peroxydisulfate has been used for the removal of trityl groups from nucleoside derivatives without affecting the glycosidic bond.[264]

Silylation of a mixture of 5′-*O*-dimethoxytrityl-nucleoside-2′- and -3′-H-phosphonates gives selectively the O-2′-silylated 3′-H-phosphonates **176**.[265] Lithium bromide and 18-crown-6 have been used to remove selectively the



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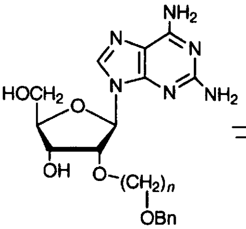

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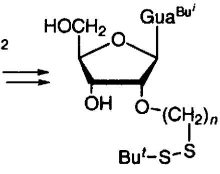

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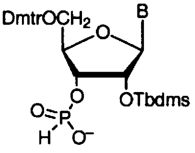

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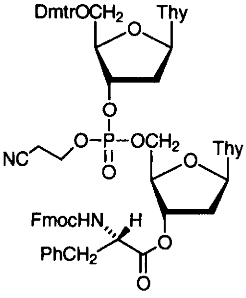
primary Tbdms group from 3′,5′-di-*O*-Tbdms-thymidine and -2′-deoxyuridine.[266]

In a dual-targetting approach to antitumour agents, the ester of retinoic acid at O-2′ of ara-A has been prepared.[267] In an extension of earlier work (Vol. 30, p. 299), the aminoacylated dinucleotide **177** has been made using an Fmoc aminoacid fluoride; the product **177** could be deprotected by removal of both the β-cyanoethyl and the Fmoc groups with oximate anion, which did not affect the ester, followed by detritylation.[268] Anthranilic acid esters of adenosine at O-2′- and O-3′ have been used as mimics of the t-RNA terminus with an attached aminoacid,[269] and 3′(2′)-*O*-(*p*-azidobenzoyl)-adenosine-5′-triphosphate has been prepared as a photoaffinity label for the catalytic subunit of protein kinase C.[270] Fluorescent thymidine 3′-urethanes have been made from the corresponding 3′-carbonylimidazolide and aminoalkyl derivatives of fluorescein or pyrene.[271]

Selective 5′-*O*-acetylation of nucleosides and 2′-deoxynucleosides has been accomplished in high yield by a modified version of Mitsunobu's original procedure. In the new method, DEAD is added to a mixture of the (deoxy)-nucleoside and PPh_3 in acetic acid and dioxane. This adaptation was not however successful for guanosine.[272] *N*-Protected L-aminoacids have been coupled to O-5′ of isopropylidene adenosine. The products after deprotection were tested as potential inhibitors against UDP-glucuronosyl transferase.[273] When the ester **178** of thymidine and 2′-carboxypsoralen was photolysed, followed by methanolysis of the products, the 'furan-side' furocoumarin-thymidine photoproduct **179** was obtained. This reaction has the potential to place such a photo-adduct selectively in mutational 'hot spots' in proto-oncogenes and tumour-suppressor genes.[274] The citrate ester of d4T has been synthesized as a mimic for the triphosphate, and the amide from the corresponding 5′-amino-5′-deoxynucleoside was also described.[275]

There have been reports on new ester protecting groups for the 5′-hydroxyl group during oligonucleotide synthesis. The 2-(levulinyloxymethyl)-5-nitrobenzoyl group (**180**) has been used in solid-phase synthesis of ribonucleotides,



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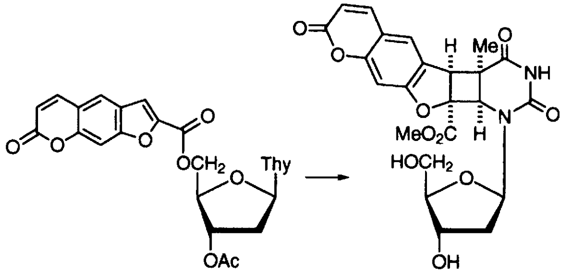
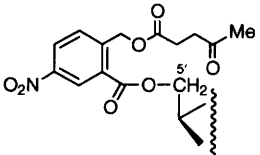


178 **179**



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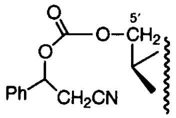

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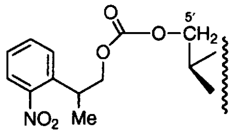

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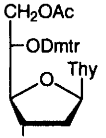
in conjunction with 2′-*O*-Thp ethers; it is removable by treatment with 0.5M hydrazine hydrate in acetic acid:pyridine, followed by imidazole in MeCN.[276] The (2-cyano-1-phenyl)ethoxycarbonyl (Cpeoc) group (**181**) has also been advocated as a base-labile unit for use in the phosphoramidite approach to oligoribonucleotides, using the 4-methoxytetrahydropyran-4-yl group at O-2′.[277] The rates of photo-deprotection of 5′-*O*-(*o*-nitrobenzyloxycarbonyl)thymidine and a number of related derivatives, such as *o*-nitrophenylethoxycarbonyl compounds, were found to vary quite widely. One of the most rapidly removed is the system as in **182**.[278]

The photolabile (*o*-nitrobenzyloxy)methyl (Npm) group was used in work on the synthesis of oligoribonucleosides to protect O-2′, and the protecting group was introduced with higher regioselectivity than previously by using modified conditions.[8] Treatment of 3′,5′-*O*-Tipds-uridine with DMSO and Ac_2O gave the 2′-*O*-methylthiomethyl ether, which with NIS, MeOH and catalytic TfOH gave the methoxymethyl ether. Subsequently, 2′-*O*-Mom-uridine was incorporated into oligoribonucleotides.[279] Some 2′-*O*-β-D-ribofuranosyl-nucleosides (disaccharide nucleosides), made by glycosylation of 3′,5′-*O*-Tipds-nucleosides, have been reported.[280]

15 Miscellaneous Nucleoside Analogues

The chain-extended thymidine derivatives **183** and **184** have been prepared and incorporated into oligonucleotides *via* phosphamidites. A related compound with a two-carbon extension was also described.[281] The bicyclic compound **185** has been made by intramolecular cycloaddition between a nitrone at C-5′ and a 3′-*O*-allyl ether, followed by N–O bond cleavage. Related structures in which the annulated ring is carbocyclic were prepared from similar products of intramolecular cycloadditions (see Vol. 30, pp. 237 and 240), after attachment of the nucleobase.[282]

Some isonucleosides with a 7-deazapurine base, such as **186**, have been prepared, along with some related 1,2,3-triazoles,[283] and similar structures of (*S,S*)-stereochemistry, such as **187**, have also been described.[284]



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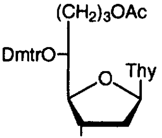

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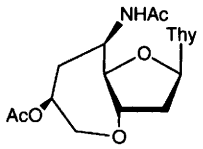

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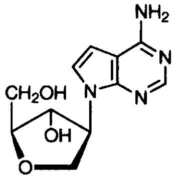

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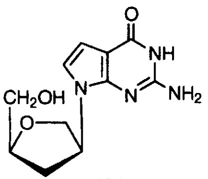

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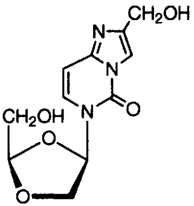

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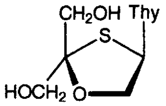

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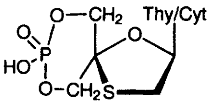

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In the area of 1,3-dioxolanes and related analogues, **188** has been prepared by base-'sugar' coupling, and related compounds including 1,3-oxathiolanes were also made by chemistry on compounds with a monocyclic aglycone.[285] A number of 2,3-dioxolanyl, 1,3-oxathiolanyl (both regiochemistries) and 1,3-dithiolanyl nucleoside analogues with an additional 2′-hydroxymethyl group (*e.g.* **189**) have been reported,[286] and other workers have also made two compounds of this type, and converted them into the cyclic phosphates **190**.[287] The same type of cyclic phosphates, which can be regarded as acyclonucleoside phosphates with a conformationally-restraining thiomethylene tether, were also independently prepared, including the guanosine analogue, in a third laboratory.[288] The oxaselenolane nucleosides **191** (B = Cyt, 5-fluoro-Cyt) have been synthesized and shown to have good anti-HIV activities,[289] and 3′-aza-4′-thia-2′,3′-dideoxynucleosides such as **192** have been made by $SnCl_4$-catalysed coupling of bases to *N*-protected 1,3-thiazolidines.[290] 2′-Thia-2′,3′-dideoxycytidine (**193**) has been prepared, as have the enantiomer and the α-anomers of both enantiomers, starting from 2,3-*O*-isopropylidene-D- and -L-glycerol; **193** had the best anti-HBV activity of the four isomers.[291]

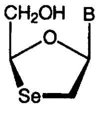
Isoxazolidines **194** (R = H, CO_2H) have been made by cycloadditions of nitrones to 9-vinyladenine, in a manner similar to that described earlier (*Tetrahedron Lett.*, 1996, **37**, 1277) for *N*-vinylthymine. The cycloadduct **194**, (R = CO_2H) could be resolved to give the (−)-enantiomer using pig liver esterase.[292] In an asymmetric route to such systems, the isoxazolidinone **195** was prepared by diastereoselective addition of *N*-methylhydroxylamine to an α,β-unsaturated ester, and could be transformed into the nucleoside analogues **196** (B = Thy, Ura, Ade, Cyt).[293]

Some further chemistry of 1,5-anhydrohexitol nucleoside analogues has been reported, along with studies on their incorporation into oligonucleotides,[294] and a route has been developed for the preparation of the α-anomers **197**.[295] The 1,3-dioxane analogues **198**, and the *trans*-isomers, have been prepared,[296] and the hemiacetal **199**, obtained from uridine by periodate cleavage followed by borohydride reduction in the presence of boric and acetic acids, was coupled to another nucleobase to give the product **200** (both epimers).[297]

There has been a fuller account, extended to other bases, of the asymmetric synthesis of cyclopropyl systems **201** (see Vol. 29, pp. 298–299),[298] and the oxetanocin-like analogue **202** has been prepared.[299]

Interaction of adenosine derivatives with $VOCl_3$ has been used to make two types of vanadyl nucleotide, one of which was a bis-vanadyl equivalent of ADP, and one of which was a 2′,3′-cyclic vanadyl chloride.[300]

Some other references to anhydro- and -imino-alditols with attached nucleobases are given in Chapter 18.



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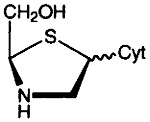

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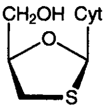

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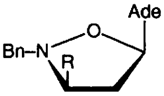

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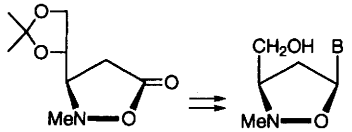

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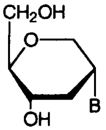

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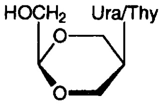

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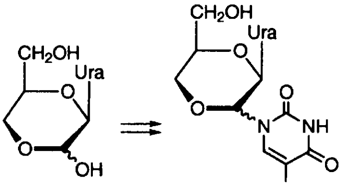
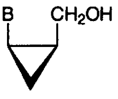


199 **200**



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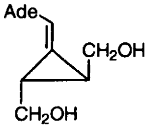

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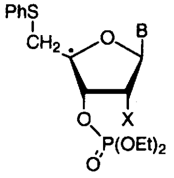
16 Reactions

An interesting study by Crich and Mo has shown that, when B = Ade^{Bz}, the radical **203** (X = H), formed by addition of PhS to the C-4′-ene, fragments to give **204** *via* the 3′,4′-radical cation, but when X = OMe, the equivalent reaction does not occur, implying that the rate of fragmentation is much slower. This result has implications for the mode of action of antitumour agents of the bleomycin type that cleave DNA *via* a C-4′-radical, but which cleave RNA much more slowly.[301] The same workers have also studied the dependence of the conversion of **203** (X = H) to **204** on the nature of the base, with the faster rates being found for bases best able to support a resonance structure of type **205**.[302]

A report from R.K. Robins's laboratory describes further model experiments designed to probe the mechanism of action of ribonucleoside diphosphate reductase, building on their earlier studies (Vol. 30, pp. 275 and 304). The radical **206** (Scheme 12) was generated by Bu_3SnD reduction of the nitrate ester, and gave the C-3′-radical **207** by 1,5-translocation. The enone **208** was formed in good overall yield, and contained about 30% deuterium, implying the sequence of events shown, with loss of tosylate as an anion. The earlier similar experiment with the 2′-chlorocompound (Vol. 30, p. 304) had given **208** with no deuterium, implying loss of chlorine as a radical.[303] The mechanism by which 2′-azido-2′-deoxy-β-D-arabinofuranosyl adenosine triphosphate inhibits bacterial ribonucleside triphosphate reductase has been examind by the use of radiolabelled inhibitors and the observation of paramagnetic intermediates.[304]



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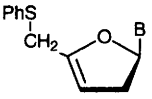

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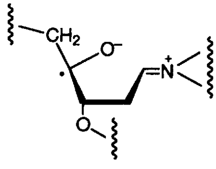

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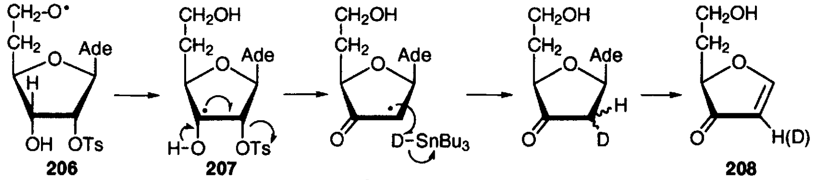


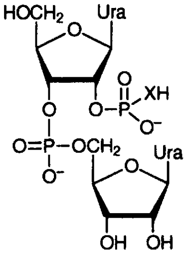
Scheme 12

There has been a further report on the formation of 1′-*C*-acyl-2′-deoxyuridines from 3′-deoxypsicofuranosyluracil, and the photolysis of these compounds to give α,β-2′-deoxyuridine *via* a radical at C-1′ (Vol. 30, p. 304).[305]

Hydrolysis of nucleoside monophosphates catalysed by Ce(IV) ions occurs under physiological conditions, and much more rapidly than for diesters. Thus d(pApA) undergoes selective hydrolysis of the terminal monophosphate.[306] In aqueous acid, various phosphodiesters at the 3′-position of uridine isomerize to the 2′-esters and give rise to the 2′,3′-cyclic phosphate. In alkali, only the latter reaction occurs, and the reaction rate is very sensitive to the nature of the leaving group, whilst the acidic reaction is rather insensitive to the nature of the alkyl group.[307] The hydrolysis and transesterification of the 2′- and 3′-dimethylphosphorothioates of 5′-*O*-methyluridine has been studied from pH 9 to strong acid. Two reactions were found to compete, namely the mutual interconversion of the 2′- and 3′-isomers, and phosphoester hydrolysis to the 2′,3′-cyclic thiophosphate and the 2′- and 3′-monomethyl thiophosphates. It was suggested that all reactions proceed *via* a pentacoordinated thiophosphorane.[308] The kinetics and mechanism of the hydrolysis of **209** ($X = O$ or S) have been studied. Both species underwent specific 2′-dephosphorylation much faster than did thymidine 3′-phosphate and -phosphorothiate, with acid catalysis due to the presence of the neighbouring phosphodiester. The effect of divalent metal ions in inhibiting the process was also investigated.[309] The hydrolysis of the phenyl ester **210** has been studied over a wide pH range. At pH 2–7, the reaction is pH-independent, and from methanolysis experiments the main product appears to arise from cleavage of the C-5′–oxygen bond, whilst at higher pH values the P–O bonds rupture. At pH <4, glycosidic bond cleavage competes with P–O cleavage.[310] A study has been reported on the correlation between the nature of the nitrogen-based ligand and the catalytic effect of Co(III) complexes on the hydrolysis of 3′,5′-cyclic AMP, the cyclen complex giving a 10^{10}-fold acceleration as compared with the uncatalysed reaction.[311] The hydrolysis of dinucleotides catalysed by Eu^{3+} and Co^{3+} has also been investigated, with rate enhancements $>10^7$ being observed.[312]

The transpurination of acetylated guanosine and its N^7-regioisomer with 1-acetoxy-2-(acetoxymethyl)ethane has been studied, and a mechanism involving ions carrying the acetylated sugar and $AcOCH_2CH_2OCH_2$- groups on N^7 and N^9 was proposed.[313]

Quantum mechanical methods have been used to study the transition state for uridine phosphorolysis. It was concluded that enzymic uridine phosphorolysis takes place by an acid-catalysed S_N2 process.[314] Oxidative cleavage of the glycosidic bond of AMP and dAMP can occur in a heme-catalysed reaction with cumene hydroperoxide.[315]



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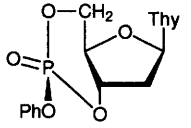

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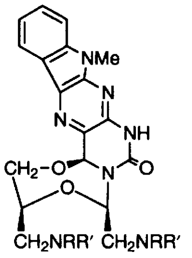

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Full details and further examples have been given of the reduction of 2′,3′-*O*-isopropylidene purine ribonucleosides with DIBAL to give 9-D-ribitylpurines (see Vol. 27, p. 270),[316] and an interesting application of this reaction for the synthesis of neplanocin A from adenosine is mentioned in Chapter 19. A novel cyclization product derived from 5-aminocytidine and *N*-methylisatin (Vol. 30, p. 272) has been subjected to periodate cleavage and reductive amination to give compounds of type **211**, which had antitumour activity.[317] Products from interaction of seco-nucleosides and daunomycin are mentioned in Chapter 19.

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21

NMR Spectroscopy and Conformational Features

1 General Aspects

Reviews on the development of force fields for saccharides[1] and on optimized force field parameters for the application of AMBER to carbohydrates[2] have been published.

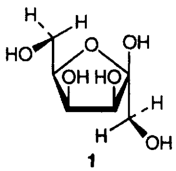
A new, empirical molecular mechanics force field for alcohols and carbohydrates (PEF95SAC) which addresses, in particular, flexibility, the presence of hydrogen-bonding hydroxyl groups and the combination of energetic, structural and kinetic effects at the anomeric centre has been reported.[3] Papers on new force field parameters for application of the SPASIBA potential energy function to saccharides[4] and on a force field model suitable for studying *N*- and *O*-sulfated sugars[5] have appeared, and new software for a database of ^{13}C-NMR spectra of sugars has been described.[6]

Monte Carlo/stochastic dynamics simulations have been used in new conformational analyses of saccharides.[7] Theoretical and experimental evidence suggests that, contrary to widely held beliefs, internal motion and overall motion in carbohydrates, even those of moderate size, occur on similar time scales.[8] The free energy differences between three conformations of D-glucose and of D-galactose have been calculated from molecular mechanics simulations using two versions of the GROMOS force field. The study showed how comparison of the theoretical findings with NMR data resulted in improvements in the force field.[9]

A MM3 investigation of the tautomeric equilibrium of D-fructose included an evaluation of the hydrogen-bond strength for the various tautomeric forms.[10] Seven tautomers of D-*lyxo*-hexos-5-ulose in D_2O have been observed by ^{1}H- and ^{13}C-NMR spectroscopy, with furanose **1** as the most abundant form.[11] The 2-aminoethylimines and 3-aminopropylimines of several aldoses,[12] as well as the 1-glycosyl-2-acetylhydrazines of all D-hexoses, all D-pentoses, 2-acetamido-2-deoxy-D-glucose, 2-acetamido-2-deoxy-D-galactose and L-fucose[13] have been subjected to similar analyses. In the hydrazine derivatives *cis*/*trans*-isomerism caused by the substantial double bond character of the NHC(O) bond was also examined, and the ^{1}H-NMR spectroscopic data of the most abundant forms were reported.

The absolute configuration of monosaccharides can be determined from the

Carbohydrate Chemistry, Volume 31



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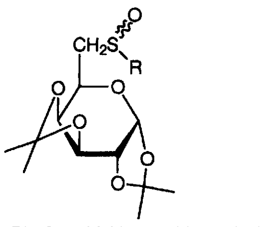
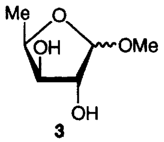


2 R = Me, Ph, 2-pyridyl benzothiazol-2-yl

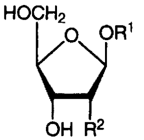


3

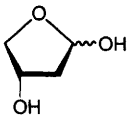
high-field ^{1}H-NMR spectra of their per-*O*-(*S*)-2-methylbutyrates; the method has been applied to the constituent sugars of three complex glycans.[14] (*S*)-α-Methoxyphenylacetic acid has been used as an NMR shift reagent to determine the absolute configuration of a number of D-galactose-derived sulfoxides **2**.[15] The conformations of some nitro-sugar derivatives have been determined by semi-empirical MO calculations.[16]

2 Furanose Systems

A novel method for determining the absolute configuration of secondary alcohols, the so-called 'fucofuranoside method', is based on the characteristic chemical shifts in their ^{1}H- and ^{13}C-NMR spectra induced by β-D- and β-L-fucofuranosylation, using L-fucose tetraacetate as glycosylating agent in the presence of TmsOTf.[17] A best-fit conformational analysis between calculated and experimental coupling constants has been undertaken with both anomers of methyl 5-deoxy-D-xylofuranoside (**3**).[18] *Ab initio* molecular calculations performed on glycosides **4** and **5** with specific ^{13}C-labelling at each carbon atom, combined with NMR data on the free sugars **6** and **7**, hold promise as a tool for determining furanose ring conformations applicable, for example, to DNA and RNA structures.[19] 2-Deoxy-β-D-*glycero*-tetrofuranose (**8**) served as model in an investigation by ^{1}H-NMR spectroscopy and *ab initio* molecular orbital calculations on the effect exerted by protonation of the ring oxygen atoms on the conformations of furanosyl rings.[20]



4 R^1 = Me, R^2 = OH
5 R^1 = Me, R^2 = H
6 R^1 = H, R^2 = OH
7 R^1 = R^2 = H



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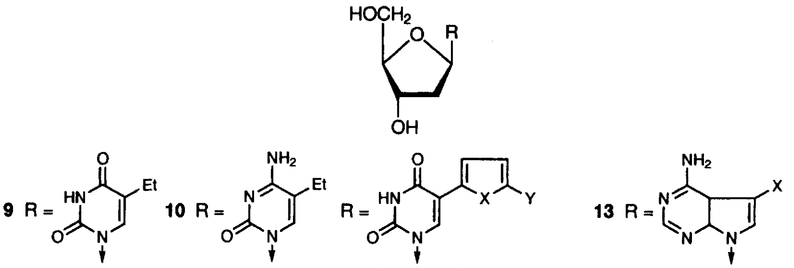
The medium-dependent anomeric effects in nucleosides[21] and in *C*-nucleosides[22] have been investigated in thermodynamic studies employing ^{1}H-NMR spectroscopy and PSEUDOROT conformational analyses, and similar techniques furnished the first experimental evidence that β-D-2′,3′-dideoxynucleosides have greater medium-dependent flexibilities than their α-counterparts.[23] These and related findings have been summarized in a report on the intramolecular stereoelectronic forces that drive the sugar conformations in nucleosides and *C*-nucleosides.[24]

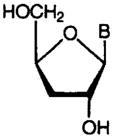
The 1-, 2- and 3-bond ^{1}H-^{13}C and ^{13}C-^{13}C spin-coupling constants involving C-2′ of thymidine, 2′-deoxyadenosine and 2′-deoxycytidine, singly enriched in ^{13}C at C-2′, have been measured; these data may be useful for analysing the conformations of oligonucleotides in solution.[25]



11 X = O or S, Y = H

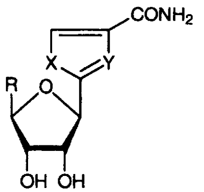
12 X = O or S, Y = Br

X = H, Me, Cl, Br, I, CN, NO2 *etc.*



14

B = Ade, Gua, Cyt, Thy

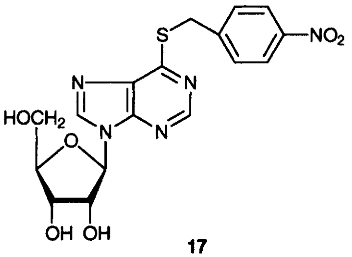


15 R = CH2OH, X = S, Y = N

16 R = CH2OH or H

X = S Se, O or NH

Y = N or CH

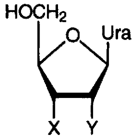


17

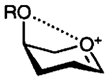
Conformational studies by use of computational techniques and/or NMR spectroscopy have been reported for the following nucleosides: 5-ethyl-2′-deoxyuridine **9** and 5-ethyl-2′-deoxycytidine **10**;[26] 5-(2-furanyl)- and 5-(2-thienyl)-2′-deoxyuridine **11** and their brominated analogues **12**;[27] 7-deaza-2′-deoxy-adenosine derivatives **13** and similarly substituted guanosines;[28,29] C-7 substituted 8-aza-7-deazapurines and 8-azapurines;[29] 3′-deoxy-β-D-ribonucleosides **14**;[30] thiazofurin (**15**), an important inhibitor of inosine 5′-monophosphate dehydrogenase and thiazofurin analogues, such as compounds **16**;[31] S^6-(4-nitrobenzyl)mercaptopurine riboside (**17**), a potent nucleoside transport inhibitor;[32] and a series of uridine 2′,3′-dideoxy-2′- or 3′-fluoronucleosides **18**.[33]

3 Pyranose and Related Systems

Electrostatic stabilization of glycosyl oxocarbonium ions by axial O-4, as indicated in structure **19**, has been introduced as an important new stereoelectronic effect under the term 'through-space electrostatic stabilization'. The effect is greatest in the *galacto*-series, where acetolysis rates decrease from ether **20** to ester **21** to amide **22**.[34]



18 X = H, Y = F or X = F, Y = H



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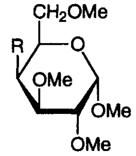
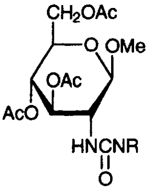


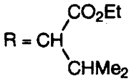
20 R = OMe
21 R = OAc
22 R = NHAc

The chemical shifts and spin-spin coupling constants of methyl β-D-xylopyranoside in solution and in the solid state have been calculated.[35] The solid state ^{13}C-NMR spectra of ureido sugar derivatives **23**[36] and **24**[37] have been recorded, as well as the high resolution ^{1}H- and ^{13}C-NMR spectra of compounds **24** in solution. A ^{1}H-NMR study of 2-amino-2-deoxy-α- and β-D-glucose, -galactose and -mannose as their ammonium ions in D_2O was aimed at determining their acid dissociation constants.[38]

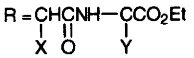
Computational techniques and/or NMR spectroscopy have been used in the conformational analyses of a set of alkyl α-D-glucopyranosides (with emphasis on the rotamer population around the C-5–C-6 bond,[39] penta-*O*-acetyl-α-D-idopyranose,[40] methyl 6-*O*-[(*R*)- and (*S*)-1-carboxyethyl]-α-D-galactopyranosides **25**,[41] sialic acid, sialyl-1,4-lactone and sialyl-1,7-lactone,[42] 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol,[43] and in a detailed structural analysis of *myo*-inositol hexaacetate.[44]

Ab initio calculations on the pyranosyl oxocarbenium ion **26** support a transition state model for the solvolysis of CMP-NeuAc involving a nearly fully formed, nearly planar sialyl cation considerably stabilized by the carboxylate group in the same plane.[45]



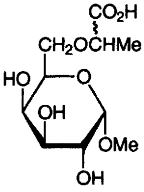


23 $R = CH(CO_2Et)CHMe_2$



24 $R = \underset{X}{CH}\underset{\overset{\|}{O}}{C}NH{-}\underset{Y}{C}CO_2Et$

X,Y = H, Me; H, Pr^i; H, Bn *etc.*



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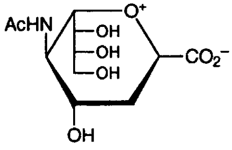


26

The reaction of α- and β-D-glucosyl azides with PPh_3 and CO_2 furnishing 1,2-cyclic carbamates has been investigated by PM3 semi-empirical quantum chemistry computations.[46]

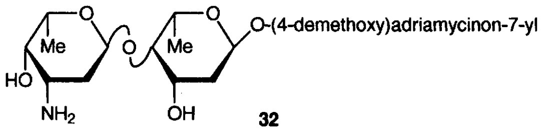
4 Disaccharides

Several molecular mechanics programs were compared for their efficiency in the molecular modelling of methyl α-lactoside; MM3 and CVFF gave satisfactory predictions of the solution NMR spectra, and a good fit with the expected X-ray crystal distances and angles was furnished by CVFF, whereas AM1, ESFF and CFF91 performed poorly.[47] Application of the PEF95SAC force field (see ref. 3 above) to an analysis of β-lactose demonstrated the excellent extrapolative power of this modelling method and led to the proposal of a new linkage geometry region for β-lactose in both the solid state and in aqueous solution.[48]

The complete assignment of the ^{1}H- and ^{13}C-NMR spectra of permethylated sucrose has been reported.[49] The solid state ^{13}C-NMR spectra for hydrated and anhydrous α,α-trehalose, including data for a new anhydrous crystalline form, have been published,[50] and NOEs between chemically equivalent protons in α,α-trehalose-containing molecules have been measured by use of selective DANTE-Z-based ^{13}C-NMR editing experiments.[51]

The following disaccharides have been examined by NMR spectroscopy and/or computational methods: *N,N'*-diacetyl-chitobiose,[52] compounds **27**,[53] **28** and **29** (as hyaluronan models),[54] deoxy- and deoxyfluoro analogues of compound **30** (a constituent of the O-polysaccharide of *Shigella dysenteriae*),[55] disaccharide **31** (which was used as model compound in the conformational analysis of a bacterial peptidoglycan),[56] the disaccharide moiety of the new doxorubicin analogue **32**,[57] and the constituent disaccharides of trisaccharides **34** and **35**, shown in Section 5 below.

27 β-D-Glc*p*NAc-(1→3)-β-D-Gal*p*-OMe
28 β-D-Glc*p*A-(1→3)-β-D-Glc*p*NAc
29 β-D-Glc*p*NAc-(1→4)-β-D-Glc*p*A
30 α-L-Rha*p*-(1→2)-α-D-Man*p*-OMe
31 β-D-Glc*p*NAc-(1→4)-α-MurNAc



32

The low-energy conformations of isomaltose and several of its monodeoxy analogues have been determined in a study of their interactions with the active site of glucoamylase.[58]

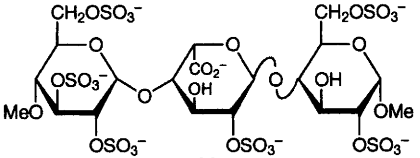
5 Oligosaccharides

Current modelling techniques for the conformational analysis of oligosaccharides have been reviewed. [59,60,61] Review articles have also appeared on the conformational analysis of asparagine-linked oligosaccharides by molecular dynamics simulations[62] and on the NMR assignments of laminarapentaose peracetate and dodecyl laminarapentaoside peracetate,[63] and a paper dealing with the development of a quantum mechanically-derived all atom force field for pyranose oligosaccharides has been published.[64]

β-D-Glc*p*-(1→2)-β-D-Glc*p*-(1→3)-β-D-Glc*p*-OMe
33

Gly*p*-(1→3)[Gly*p*-(1→4)]-β-L-Rha*p*-OMe
Gly = α-D-Man, β-D-Glc, α-L-Rha, β-L-Fuc
34

α-L-Rha*p*-(1→2)-α-L-Rha*p*-(1→3)-α-L-Rha*p*-OMe
35

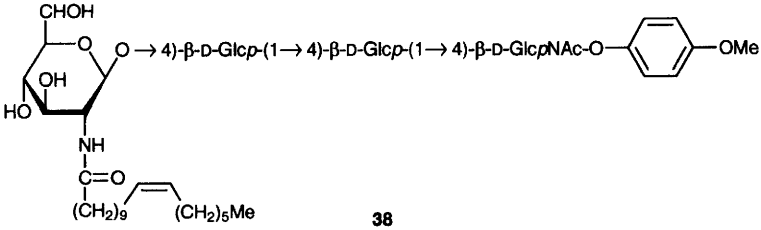


36

The following compounds have been examined by NMR and/or computational methods: 1-kestose and nystose;[49] trisaccharides **33**,[65] **34**,[66] **35**,[67] and **36** (a heparin fragment analogue);[68] tetrasaccharide **37**[69] the sialyl Lewis x tetrasaccharide,[70] a (2→8)-α-linked tetramer of sialic acid,[71] the asialo-GM1 ganglioside,[72] the lipotetrasaccharide glycoside **38**,[73] and a series of inulin-type oligosaccharides.[74]

A solid complex of C_{60} with γ-cyclodextrin has been investigated by NMR-spectroscopy.[75]

α-D-Gal*p*NAc-(1→3)-β-D-Gal*p*-(1→4)[α-L-Fuc*p*-(1→3)]-β-D-Glc*p*-OMe
37



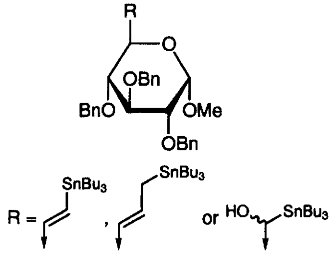
38

6 NMR of Nuclei Other than ^{1}H and ^{13}C

^{19}F-NMR spectroscopy has been used in the analysis of 2-deoxy-2-fluoronucleosides.[76]

Phosphorylation sites in small to medium-sized oligosaccharides have been identified easily and reliably by a combination of ^{31}P decoupling and TOCSY experiments.[77] ^{31}P-NMR spectroscopy has also been used in a study on cyclic ADP-ribose and 2′-phosphocyclic ADP-ribose.[78]

Tris-(1-butyl)stannyl D-gluconate[79] and a series of sugar-tin derivatives, such as compounds **39**, with tin attached to vinylic, allylic or carbinol centres,[80] have been examined by ^{119}Sn-NMR spectroscopy, and a multinuclear approach (^{1}H, ^{13}C, ^{17}O, ^{95}Mo and ^{183}W) has been employed to investigate the complexation of D-gluconic acid with tungsten(VI) and molybdenum(VI).[81]



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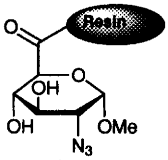
22

Other Physical Methods

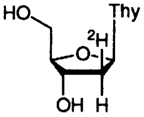
1 IR Spectroscopy

Solid-phase reactions can be monitored on-bead, at high throughput rates, using diffusion reflectance infrared Fourier transform spectroscopy (DRIFTS). Specifically, the reduction of the azido group in the resin-supported 2-azo sugar **1** was monitored in this way.[1]

Vibrational Raman optical spectroscopy has been employed to study the conformational flexibility of a series of β-cyclodextrins. Parameters explored in this study were the effect of solvent (DMSO *vs.* water) and 2,6-di- or 2,3,6-trimethylation of the cyclodextrin. The effect of different guests was evaluated leading to the conclusion that tighter-bound guests lead to greater reduction of conformational mobility.[2]



1



2

IR spectroscopy of crystalline *meso*-erythritol and D,L-threitol at 20 K and 300 K, as both OH and O^2H systems, showed that all the H-bonds in the crystalline *meso*-erythritol are strong, while there are additional weak H-bonds in the crystals of D,L-threitol.[3] The complete vibrational (IR and Raman) spectra of pentaerythritol have been obtained.[4]

The influence of grinding and thermal treatment on anhydrous mono- and di-hydrated lactitol has been investigated using IR, and also by DSC and X-ray diffraction (powder) methods.[5]

Surface-enhanced Raman scattering (SERS) spectra have been reported, with assignments, for several *N*-acetylneuraminic acid glycosides and derivatives.[6]

The C–O–S vibrational bands of the potassium salt of D-galactose 3-sulfate observed using FT-IR spectroscopy are dependent on the anomeric configuration and on hydration. The differences are proposed to be of potential use in

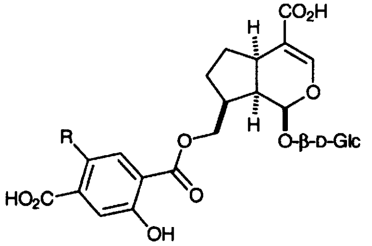
Carbohydrate Chemistry, Volume 31

determination of configuration of biologically significant galactose 3-sulfate units.[7]

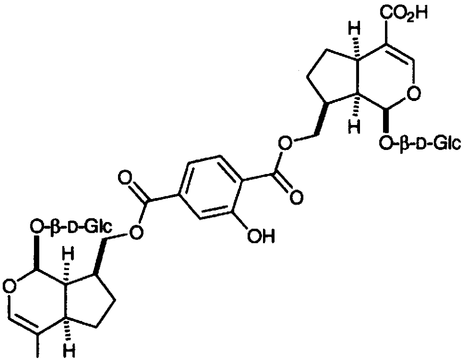
IR and Raman spectra of crystalline powders of (2′*S*)-[2′-^{2}H]thymidine **2** were recorded and the data compared with the non-deuterated system.[8] Raman spectra can be used to differentiate between 2′- and 3′-*O*-silylated *N*-benzyl-cytidine, -adenosine and -guanosine derivatives.[9] The FT-IR and FT-Raman spectra of cytidine 3′-monophosphate and its deuterated derivative have been reported.[10] Far IR spectral characterization of mono- and disaccharides and some metal complexes have been described.[11] A separate IR study of metal ion interactions with galactose and xylose has been reported.[12]

2 Mass Spectrometry

A number of mass spectrometric techniques (CI-MS, liquid SIMS with tandem MS) have been applied to characterization of furanose compounds containing 1,2-*O*-isopropylidene groups.[13] The rare loss of a neutral fragment (CH_4O_2) from a nucleoside derivative was observed using FAB- and electrospray MS.[14] Studies of acyclic 2′,3′-dideoxy nucleoside analogues bearing 8-azapurine bases, using EI MS, have indicated that a nitrogen in the 8-position strongly inhibits fragmentation.[15] A novel quantitative electrospray MS method has been developed for identifying (azasugar) glycosidase inhibitors.[16] FAB-tandem MS has been employed in the investigation of sulfoquinovosyl diacylglycerol and mono- and di-galactosyl diacylglycerols.[17] FAB MS has also been used in the structural characterization of the glycosides **3** and **4**, isolated from the stem-bark of *Fagraea blumei*.[18]



3 R = H, OH



4

A series of peptide conjugated oligonucleotides (up to 8-mers in solution and 15-mers on solid support) have been characterized by MALDI-TOF, and capillary gel electrophoresis,[19] and a number of 2′,5′-dinucleotides (C-G, G-C and T-C) have been characterized using negative ion FAB MS.[20]

Collision-induced dissociation (CID) mass spectra of $[M+Na]^+$ ions produced by FAB MS of glycosylsphingolipids gave fatty acid chain length information on ceramide moieties,[21] Delayed extraction MALDI-TOF MS has been applied to various lysoglycosphingolipids.[22] Complexation of polysulfated oligosaccharides with basic peptides or proteins facilitates analysis by electrospray negative ion MS.[23] A MALDI- based technique using a time-lag focusing TOF spectrometer has been developed for analysis of monosulfated oligosaccharides.[24]

Oligosaccharide alditols with a deuterium on C-1 can be used to obtain information about the masses and linkages of the various residues using high energy CID spectra.[25] EI and tandem MS have been used in the analysis of metal-containing oligosaccharides, specifically α-D-Man-(1→6)-[α-D-Man-(1→3)]-D-Man trisaccharide and this trisaccharide attached to chitobiose, with coordination to Cu^{2+}, Mn^{2+}, Zn^{2+} and Ca^{2+}. The optimium conditions for observing $[M+Met]^{2+}$, $[M+MetCl]^{+}$ and $[M+Met-H]^{+}$ were determined.[26]

The liquid SIMS spectra of methyl glycosides of oligoxylans show intense cluster ions corresponding to protein-bound hetero-dimers when an aliphatic carboximide in glycerol is used as the liquid matrix.[27] The fragmentation patterns of $[M+H]^{+}$ ions of a series of (1→6) linked trisaccharides with one or two deoxy or deoxyfluoro residues were observed using CID FAB MS, and showed an unusual rearrangement process.[28] A new method for combining sequential exoglycosidase digestion with MALDI-TOF MS permits structural characterization of underivatized oligosaccharides in picamole amounts of material.[29] The structural elucidation of 2-aminopyridine-derivatized sialyloligosaccharides by ESI MS has been described.[30] Fragments from glycosidic and cross-ring cleavage were observed from MALDI-TOF MS of complex oligosaccharides.[31] The linkage positions of a series of underivatized linkage-isomeric oligosaccharides have been detected using FAB MS.[32] Dissolution of malto-oligosaccharides with α-(1→4) links in *N*,*N*-dimethylacetamide/lithium chloride produces multiple neutral alkali halide attachments which enable easier ES MS characterization.[33] ES tandem MS coupled to reverse phase HPLC has been used for characterization of permethylated oligosaccharides.[34] The heptasaccharide, α-D-Ara-*p*-(1→6)-β-D-Glc-(1→4)-[α-D-Ara-*p*-(1→6)-]-β-D-Glc-(1→4)-[α-D-Ara-*p*-(1→6)-]-β-D-Glc-(1→4)-glucitol, from tamarind seeds, was analysed using post-source decay fragmentation from MALDI-TOF MS. This identified eleven sodium-adduct fragment ions and a precursor ion. Almost all the fragment ions from species larger than trisaccharide fragments were detected; therefore such information enables structural determination of xyloglucan oligosaccharides.[35]

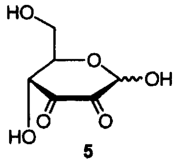
ES MS has aided the characterization of a series of amphipathic functionalized ether-linked di- and trisaccharides (units of alkyl derivatives of glucofuranose and either glucofuranose or diacetyl galactose). A novel eight-membered macrocyclic ether linked trisaccharide was also characterized using ES MS. Low energy CID MS/MS analysis of the $[M+H]^{+}$ precursor ion proved to be a sensitive method of characterization.[36]

MALDI-TOF MS has been employed in the characterization of cyclodextrins. Analysis of post-source decay fragment spectra showed this to be a powerful technique for analysis of sugar-substituted cyclodextrins.[37] Differentially ethylated β-cyclodextrins have been characterized by EI MS.[38]

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 – 3-Acetamido-5-*O*-acetyl-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose,[39] 3-deoxy-β-D-*erythro*-hexulose (3-deoxy-D-fructose),[40] D-*erythro*-hexos-2,3-diulose dihydrate (**5**).[41] Crystallization of maltopentaose has been studied by X-ray analysis,[42] and an *ab initio* calculation of the crystal structure of α- and β-D-glucose has been reported using the Car-Parrinello method.[43]



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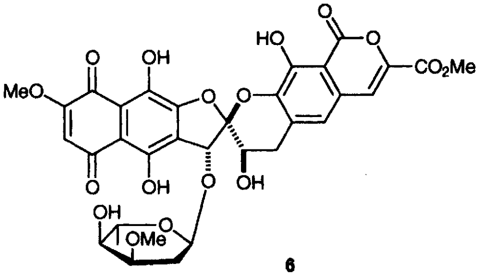

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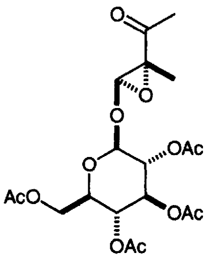
3.2 Glycosides, Disaccharides and Derivatives Thereof – Monosaccharides: *p*-nitrophenyl tetra-*O*-acetyl-β-D-glucopyranoside,[44] *p*-nitrophenyl α-D-mannopyranoside,[45] methyl 3-deoxy-α-D-*arabino*-hexopyranoside,[46] estronyl β-D-glucopyranosidic uronic acid.[47] The *C*-glycoside isopropyl [4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl] methylmalonate.[48] DNA helicase inhibitor heliquinomycin (**6**), isolated from *Streptomyces sp.* MJ929-SF2 (the component sugar is L-cymarose).[49] Epoxide **7**[50] and aldehyde **8**[51] (see Chapter 24 for chemistry). The structure of benzyl 2,6-di-*O*-(β-anthracenylsulfonyl) glucopyranoside bound in the thrombin active site.[52]



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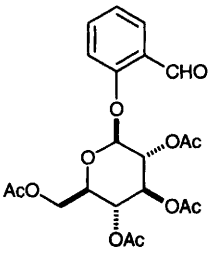

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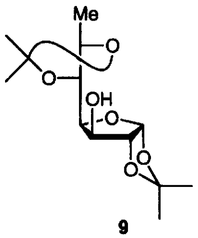
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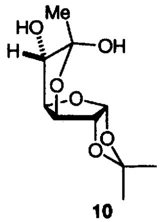
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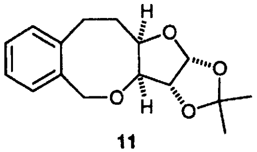
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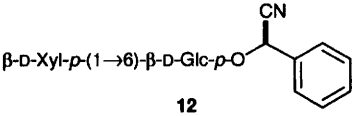
7-Deoxy-1,2:5,6-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-heptofuranose (**9**) and related bicyclic derivative **10**.[53] The glucose-derived oxepin-fused system **11** (see Chapter 24 for synthesis).[54]

Disaccharides: 2,3,4,3′,4′-penta-*O*-benzyl-6,6′-dichloro-6,6′-dideoxysucrose,[55] nitrile-containing glycoside **12**,[56] 3,3′,4,4′,6,6′-hexa-*O*-acetyl-2,1′-anhydro-2-*O*-α-D-glucosyl-D-glucose (**13**),[57] methyl (2-*O*-α-D-mannopyranosyl)-β-D-glucopyranoside,[58] *p*-nitrophenyl 4-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2,3-di-*O*-benzoyl-6-*O*-pivaloyl-β-D-glucopyranoside (**14**),[59] α,β-trehalose,[60] and α,α-trehalose.[61]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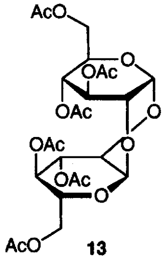
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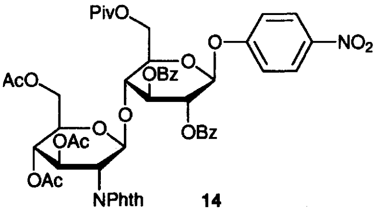
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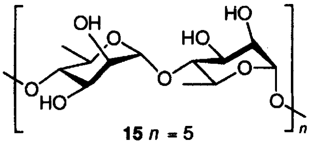
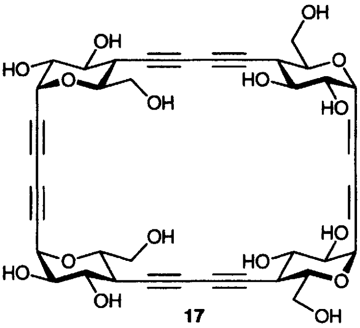
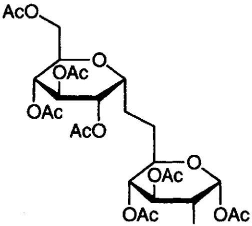

15 *n* = 5
16 *n* = 4


17

3.3 Higher Oligosaccharides and *C*-Glycosides – Most reports in this area have related to cyclic oligosaccharides (cyclodextrins) or related cyclic carbon-linked systems. Stoddart and co-workers have reported X-ray structural analyses showing that **15**[62] and **16**[63] form nanotubes. The latter forms a C_2 symmetric system with the internal nanotube diameter being 1 nm. The inclusion complex of heptakis-(2,6-di-*O*-methyl)-β-cyclodextrin with AcOH,[64] a cyclodextrin constituted of alternating L-rhamnose and D-mannose, and 6-deoxy-6-{4-[2-(*N*-t-butoxycarbonyl)aminoethyl]imidazolyl}cyclomaltoheptaose[66] have been structurally characterized.

Comparison of X-ray data on havamine (a plant chitinase-lysozyme)-chitotetraose and chitinase A-chitobiose with the published data for hevamine-allosamidin and chitobiase-chitobiose indicates that the enzymes are stereochemically retaining because of the involvement of C-2 NAc and also a protein carboxylate in the reaction. The X-ray analysis also shows how the substrate is bound in the active site and how a sugar ring is distorted.[67]

The X-ray structures of cyclic tetrameric acetylene linked saccharide **17**,[68] *C*-disaccharides **18**[69] and **19**,[70] and of the bis-acetylenic *C*-disaccharide **20**,[71] and furan *C*-glycoside **21**[72] have been reported.



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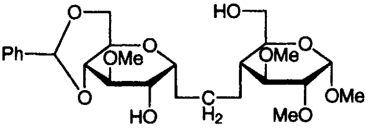

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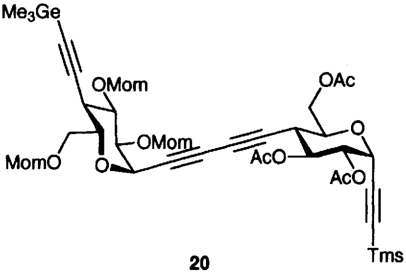

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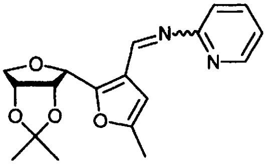

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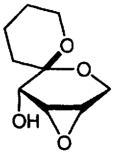
3.4 Anhydro-sugars – 1,4:3,6-Dianhydro-2-*O*-*p*-tosyl-D-mannitol[73] and sugar-derived *spiro*-acetals **22**–**24**.[74]



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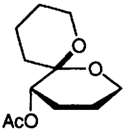

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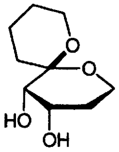

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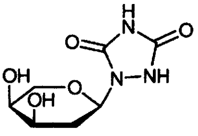
3.5 Halogen, Phosphorus, Sulfur, Selenium and Nitrogen-containing Compounds – D-Galactonic acid hydrazide and its hemihydrate,[75] 2-(2-deoxy-α-L-*erythro*-pentopyranosyl)urazole (**25**),[76] 2-(2-deoxy-α-D-*erythro*-pentopyranosyl)-4-methylurazole (**26**),[77] *N*-(β-D-lactopyranosyl)urea,[78] *N*-acetyl β-D-glucopyranosylamine,[79] *N*-acetyl-2,3,4,6-tetra-*O*-acetyl-*N*-benzyl-β-D-glucopyranosylamine,[80] and 5-deoxy-5-*C*-(5-ethoxycarbonyl-1,2,3-tetrazol-1-yl)-1,2-*O*-isopropylidene-α-D-xylofuranose.[81]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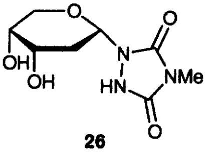
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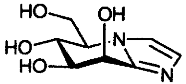
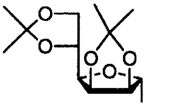

27

The glucosidase inhibitor **27**,[82] 1-amino-2,5-anhydro-1-deoxy-D-glucitol hydrochloride,[83] *N*-benzyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannopyranosyl hydroxylamine **28**,[84] the aza-Diels Alder adduct **29**,[85] the amide linked disaccharide analogues **30** and **31**,[86,87] and **32**.[88]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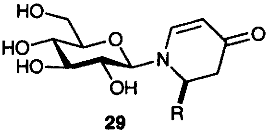
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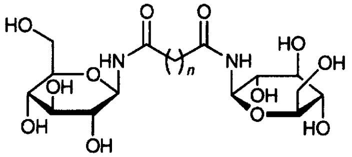
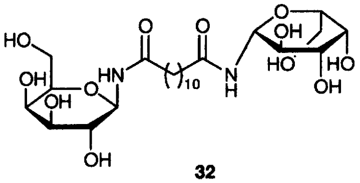

30 $n = 11$
31 $n = 12, 13$ or 14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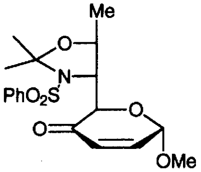
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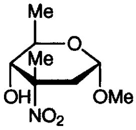
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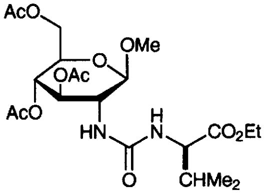
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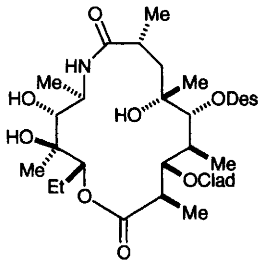
Sulfonamide **33**,[89] 1-(3,4-di-*O*-acetyl-2-deoxy-2-hydroxyimino-α-D-*erythro*-pentopyranosyl)pyrazole and ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-hydroxyimino-α-D-*arabino*-hexopyranoside,[90] 3-nitro-branched chain glycoside **34**,[91] the glucosamine-valine conjugate *N*-(methyl 3,4,6-tri-*O*-acetyl-β-D-glucopyranos-2-yl)-*N*′-carbamoyl-D-valine ethyl ester (**35**).[92]

The macrocyclic lactam **36**,[93] sugar-fused oxazolidinone **37**, aziridine **38** and compound **39**,[94] tricylic **40**,[95] spirocyclic **41**,[96] Oppolzer sultam adduct **42**,[97] 7-*epi*-7-*C*-methyl-castanospermine **43** and 1-*C*-methyl-castanospermine **44**.[98] The C_2-symmetric system **45**,[99] spirocyclic oxazolidinone **46**,[100] the 1,4-imino-arabinitol **47**,[101] pyralomycin 1a **48** and 2a **49**.[102]



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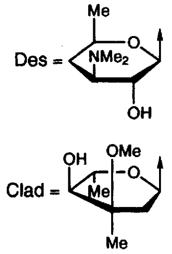

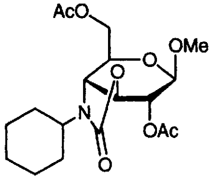

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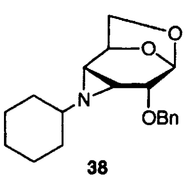

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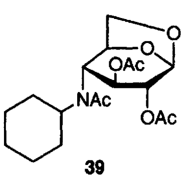

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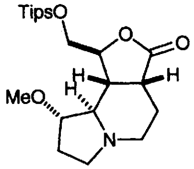

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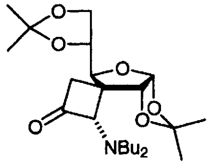

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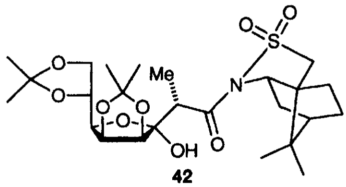

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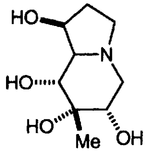

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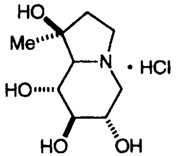

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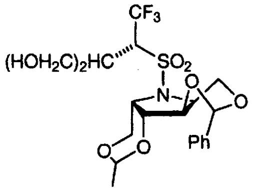

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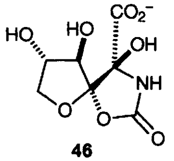

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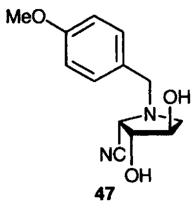

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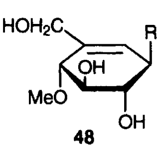

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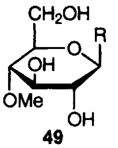

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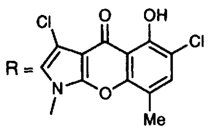
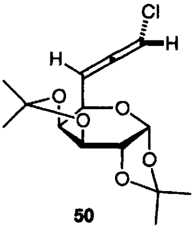


4,6-*O*-Ethylidene-2,3-di-*O*-methanesulfonyl-α-D-glucopyranosyl chloride,[103] methyl 3-deoxy-3-fluoro-β-D-allopyranoside,[104] (6*S*)-8-*C*-chloro-6,7,8-trideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-octa-6,7-dienopyranose (**50**),[105] diphenyl-(methyl 4′,6′-*O*-benzylidene-2′-deoxy-α-D-altropyranosid-2-yl)-phosphine oxide,[106] methyl 4,6-*O*-benzylidene-3-deoxy-3-(diphenylphosphino)-α-D-altropyranoside,[107] 1,6-anhydro-4-deoxy-4-(diphenylphosphine oxide)-D-glucopyranose,[108] cyclic phosphonate **51**,[109] chiral phosphine oxide **52**.[110]



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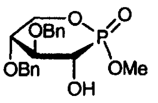

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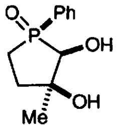

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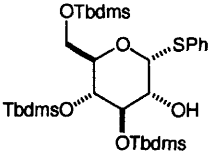
Thioglycoside **53**,[111] disulfide **54**,[112] methyl 4,6-*O*-benzylidene-2,3-*O*,*S*-carbonyl-3-thio-β-D-allopyranoside (**55**) and methyl 4,6-*O*-benzylidene-2,3-*O*,*S*-carbonyl-3-thio-β-D-mannopyranoside **56**,[113] and the natural α-glucosidase inhibitor **57** isolated from the traditional antidiabetic medicinal plant *Salacia reticulata* (no definitive evidence of absolute configuration).[114]



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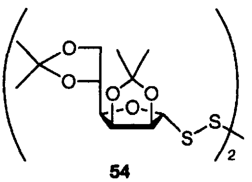

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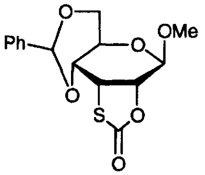

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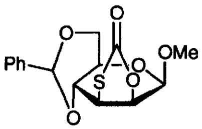

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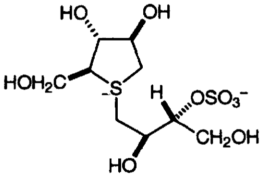

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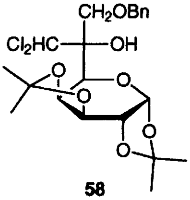
3.6 Branched-chain Sugars – The unusual branched chain dichloromethyl sugar **58**,[115] spirocyclic cyclopropanes **59** and **60**,[116] exocyclic alkene **61** and *spiro*-epoxide **62**,[117] spirocycle **63**,[118] C-4 branched system **64**[119] and the interesting diaryl system **65**.[120]

3.7 Inorganic Derivatives – $[\{Co[D\text{-}Glc]_2tren]\}_2O_2]X_3.H_2)$, where tren = bis-(*N*-glucosyl-2-aminoethyl)(2-aminoethyl)amine), showing cobalts bridged by peroxo ligands and each metal ligated by four nitrogens and the C-2 oxygens of a sugar, with the other D-Glc anchored by only the *N*-glycosidic atom.[121] Chromium carbene **66**,[122] $[(MnL_2)_2Mn(H_2O)][NO_3]_3$ with L = carbohydrate[123] and triphenylstannane **67**.[124]



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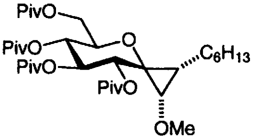

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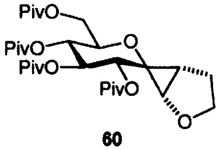

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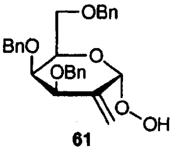

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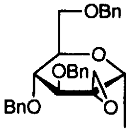

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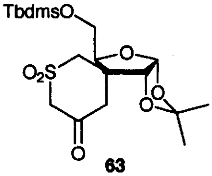

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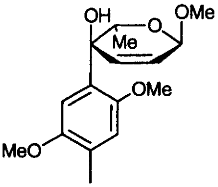

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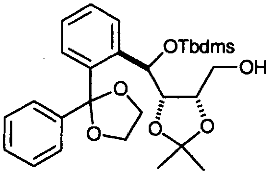

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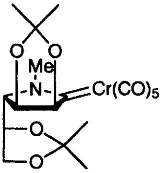

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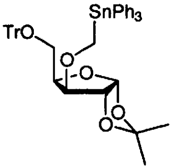

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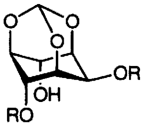
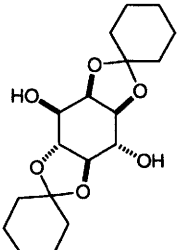


68 R = (–)-camph



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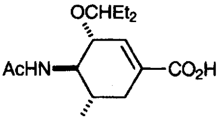

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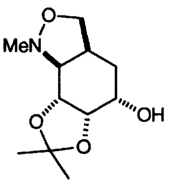

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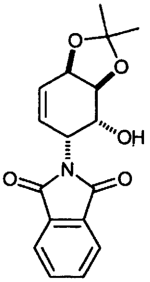

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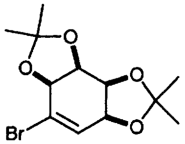

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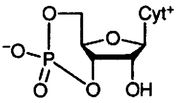
3.8 Alditols and Cyclitols and Derivatives Thereof – Potter's group prepared bis-camphanate **68**,[125] and Freeman's group reported the structure of (±)-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol (**69**), in which some unusual H-bonding features are evident.[126] (3*R*,4*R*,5*S*)-4-Acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid (**70**),[127] the (−)-5-*epi*-shikimic acid precursor **71** (from D-ribose),[128] **72**,[129] and conduritol precursor **73**.[130]

3.9 Nucleosides and Their Analogues and Derivatives Thereof – 3′-Deoxyadenosine,[131] 3′-deoxycytidine (shows C-3′-*endo* sugar ring puckering and *anti*-conformation about glycosidic bond),[132] cytidine 3′,5′-cyclic phosphate **74** (furanose ring has northern conformation – $^3T_2$, C3′-*endo* – which is notably different from other 3′,5′-cyclic nucleoside phosphates reported),[133] *trans*-adenosine 3′,5′-cyclic-*N*,*N*-dimethylphosphoramidate **75** (ribose ring is $^3T_4$, and the phosphoramidate ring is a flattened chair with an equatorial, planar dimethylamino group),[134] bicyclic [2.2.1] nucleoside analogue **76**.[135] The 3′,3′-difluoro L-nucleoside analogue **77**,[136] *E*- and *Z*- isomeric oxime ethers **78** and **79**,[137] carbocyclic nucleoside **80**,[138] and the dioxane nucleoside analogue **81**,[139] 5-(5-methylthien-2-yl)-2′-deoxyuridine, 5-(5-thien-2-yl)-2′-deoxyuridine and 5-(5-bromothien-2-yl)-2′-deoxyuridine,[140] and the spirocyclic system **82**.[141]

3,4-Etheno-5-methoxymethyl-2′-deoxycytidine **83**,[142] the interesting bis-thiophenyl substituted base analogue **84**,[143] 5-formylamino-1-(β-D-ribofuranosyl)-imidazole **85**,[144] the 5-carboranyl-2′,3′-dideoxy-3′-thiauridine **86**,[145] 3-carbamoyl-4-(*N*-phenylcarbamoyl)-1-(β-D-ribofuranosyl) pyrazole **87**.[146] A number of *C*-nucleoside analogues have been reported: pseudouridine **88**,[147] the selenium system **89**,[148] and **90**,[149] prepared as a cimetidine analogue. The 2′-(β-D-ribofuranosyl) nucleoside **91** (note: ether replacing phosphate link).[150]



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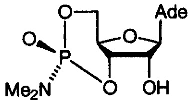

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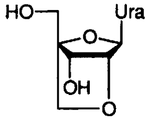

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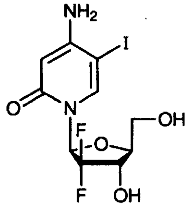

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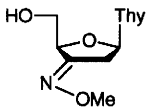

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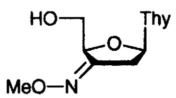

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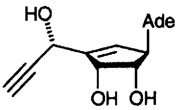

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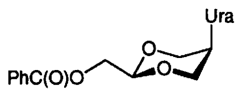

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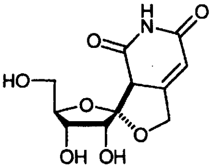
3.10 Neutron Diffraction – Neutron scattering has been used to determine the H-bond structure in glassy and liquid glucose.[151]

4 Polarimetry, Circular Dichroism, Calorimetry and Related Studies

The luminescent decay times of several γ-irradiated saccharides (including glucose, mannose, lactose and maltose) have been studied using a photon



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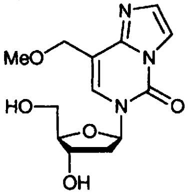

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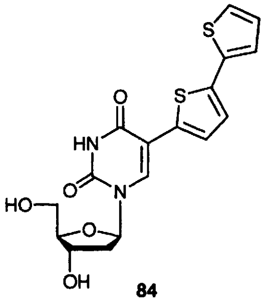

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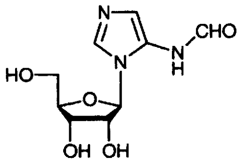

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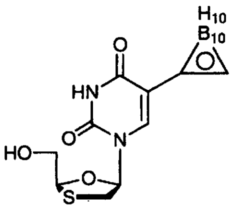

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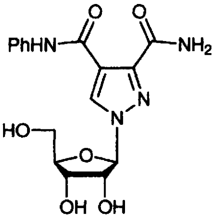

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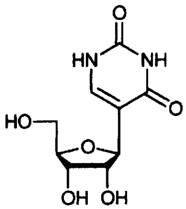

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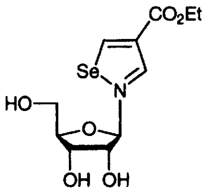

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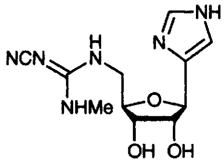

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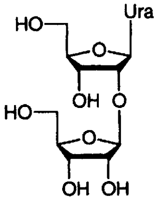

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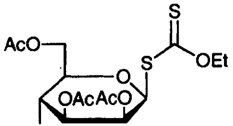
counting technique.[152] The absolute configuration of the acyclic side chain of heptopyranosides and heptofuranosides has been determined by exciton coupled CD (employing the strongly fluorescent 2-anthroate chromophore).[153] The enthalpies and heat capacities of aqueous solutions of a range of saccharides (ribose, mannose, galactose, glucose, fructose, α-D-lactose monohydrate and saccharose) have been recorded.[154] Solvent effect rotatory dispersion, CD and UV spectra of monosaccharide xanthates (*e.g.* **92**) have been correlated with stereochemistry.[155]



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The conformational properties and *gauche* effect of the C-6 CH_2OH and CH_2OMe groups of sugars have been examined using *ab initio* methods (on unsubstituted methyl pyranoside models).[156] ESR has been used to study photo- and sonic bromination of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide with NBS in non-aqueous solution.[157]

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23

Separatory and Analytical Methods

Contrary to an undertaking given in Volume 30, it has, regrettably, not proved possible to include in the current Volume 1996 material published in *The Journal of Chromatography.*

1 Chromatographic Methods

1.1 Gas–liquid Chromatography – Quantitative analyses of the following compounds present in biological samples have been carried out: glucitol as its trifluoroacetylated derivative with [U-^{13}C] as internal standard,[1] ascorbate and dehydroascorbate by isotope dilution (with the [1-^{13}C]-labelled compound) as the Tbdms perethers,[2] and the sugars present in apricots as their trimethylsilyl derivatives.[3]

A Tbdms ether of β-cyclodextrin, which is used as a GLC stationary phase, has been shown by MS methods to contain homologues with 7–10 ether groups.[4]

The members of eight of eleven pairs of enantiomers of trifluoroacetylated alditols and aldose diethyl dithioacetals were separable on permethylated α-, β- and γ-cyclodextrins as capillary stationary phases,[5] and various ethers of β- and γ-cyclodextrins were used to resolve the enantiomers of permethylated sugars and 1,5-anhydroalditols.[6] A successful alternative method involved the separation of the peracetylated or persilylated di-(+)-or di-(−)-1-phenylethyl dithioacetals of enantiomeric sugars and affords a means of obtaining absolute configurations.[7]

1.2 Thin-layer Chromatography – Methods involving the use of high pressure have been reported for the separation and analysis of gentamicin components in urine and plasma,[8] ascorbigen and its 1′-methyl ether[9] and saturated and unsaturated oligogalacturonic acids.[10]

1.3 High-pressure Liquid Chromatography – A further method for determining the absolute configuration of monosaccharides depends on separation of their acetylated aldononitriles on a Chiracel OD-H column.[11] Several separations of sugars,[12-15] alditols,[13-15] and glucuronic acid[14] have used anion exchange resins and pulsed amperometric detection. Other related methods

Carbohydrate Chemistry, Volume 31

have also employed anionic resin-based separations, but the quantitative methods used involved pyranose oxidase followed by colorimetric determination of H_2O_2,[16,17] while a different approach has involved reductive amination and separation of 1-deoxy-1-[(*p*-ethoxycarbonyl)phenylamino]alditols.[18]

Simple sugar derivatives to have been analysed by HPLC are ascorbic acid and isoascorbic acid (on basic polymer-coated silica),[19] unsulfated or partially sulfated unsaturated disaccharides (ion-pair, reverse phase)[20] and unsaturated disaccharides (also from heparin and its sulfate; TSK gel-Amide 80 column).[21]

Analysis of methyl β-cyclodextrin in plasma and cell lysates was carried out by use of size-exclusion HPLC,[22] and oligosaccharides (DP up to 27) have been detected in sea water by application of reverse phase HPLC with mass spectrometric detection and size determination.[23]

HPLC analyses have also been applied to the following carbohydrate-containing compounds: long chain alkyl glycosides (on porous graphitized carbon with evaporative light-scattering detection),[24] glucosinolates (reverse phase, MS),[25] saponins from soya flour (reverse phase, MS),[26] the glucuronide of 25-hydroxyvitamin D_3 (UV detection)[27] and the glucuronides of morphine and codeine (reverse phase, MS).[28]

The following medicinal chemistry applications have been reported: amiprilose [3-*O*-(3′-aminopropyl)-1,2-*O*-isopropylidene-D-glucofuranose] (an immunomodulatory compound, reverse phase, fluorimetry),[29] the eight components of commercial kanamycin sulfate (two new components were observed for the first time; pulsed amperometric detection),[30] several aminoglycoside antibiotics including neomycin, netilmicin, sisomycin (fluorimetry)[31] and paromycin.[32]

Glycolipid compounds to have been examined are octyl, dodecyl, hexadecyl and 3,6,9-trioxapentacosyl β-D-glucopyranosides (reverse phase, MS),[33] and monophosphoryl lipid A immunostimulants from a *Salmonella* which are based on β-D-Glc*N*Ac-(1→6)-D-Glc*N*Ac (where Ac = long chain acyloxy groups; reverse phase, ion-pair HPLC).[34] Glycopeptide-based compounds to have been submitted to HPLC are galactosyl- and glucosylgalactosyl-lysine from collagen (reverse phase, fluorimetry)[35] and the synthetic peptide hormones dalargin and desmopressin coupled to sugars by reductive amination or reaction with 2-chloroethyl-1-thiogalactoside (reverse phase).[36]

Nucleosides and related compounds to have been separated by HPLC methods are carbocyclic nucleoside antitumour agents in biological fluids[37] and 16 urinary ribonucleosides which were separated on a phenylboronic acid column then by reverse phase HPLC. The method was intended for the detection of modified nucleosides originating from degradation of RNA produced by patients with malignant tumours.[38] Various reverse phase HPLC and detection methods have been applied in the examination of nucleotides (as well as nucleosides),[39-42] one giving good differentiation of mono-, di- and triphosphates[41] and another allowing identification of adenine nucleotide metabolites of bisphosphonate drugs, for example ADP having the $H_2O_3P\text{-}CCl_2\text{-}PHO_2\text{-}O\text{-}PHO_2$- group bonded to O-5′.[42] Ion pair reverse phase HPLC and negative ion MS were employed in the separation and identification of cyclic nucleotides in biological samples.[43]

1.4 Column Chromatography – Affinity chromatography using a Gal*N*Ac-specific lectin immobilized on agarose beads resolved Gal*N*Ac, its α-1-phosphate and UDP-Gal*N*Ac, the last being the most strongly bound.[44] In similar fashion lysozyme and α-lactalbumin, both of which have carbohydrate binding sites, bound on a column have been used in the isolation of the aminoglycoside antibiotic hygromycin B from biological samples.[45]

Atmospheric pressure anion exchange methods have been used in the separation of ribonucleotides derived from ribosomal RNA constituents.[46]

Relatively novel sub-critical fluid chromatography operating at 200 bar and 40–60 °C has been applied to the separation of aldoses, ketoses and alditols as well as various glycolipids. Silica and trimethylsilyl silica were the stationary phases; CO_2-methanol with water and triethylamine as additional components were the eluants.[47]

2 Electrophoresis

2.1 Capillary Electrophoresis – Capillary zone electrophoresis is the simplest form of capillary electrophoresis, but the two names are sometimes used interchangeably. They will now be dealt with together, but work specified as having been done under capillary zone conditions will be identified by use of 'CZE'.

Methods have been developed for the use of CZE in measuring ionization constants of sugars,[48] and aldoses have been examined as their 3-methyl-1-phenyl-5-pyrazolone derivatives,[49] and (for those derived from glycoproteins) following reductive amination with 8-aminopyrene-1,3,6-trisulfonate or, in the case of sialic acids, with 9-aminoacridine.[50] The isomeric disaccharides β-D-Gal-(1→3)-D-Glc*N*Ac and β-D-Gal-(1→4)-β-D-Glc*N*Ac and compounds derived by enzymic action on them in human carcinoma cells have been examined as their tetramethylrhodamine derivatives,[51] and oligosaccharides have been sequenced by exo-glycosidase step-wise degradation followed by capillary electrophoresis of 8-aminopyrene-1,3,6-trisulfonate-labelled products.[52] Other dextran- and malto-oligosaccharides have been examined (CZE) following reductive amination with the charged and UV-absorbing 4-aminobenzoyl-L-glutamic acid. Detection was possible at the sub-picomole level.[53]

Two reports have appeared on the simultaneous analysis of ascorbic acid and dehydroascorbic acid in foods and plant tissues,[54,55] and several sugar acids and ganglioside-derived sialo-oligosaccharides have been analysed as their 7-aminonaphthalene-1,3-disulfonic acid derivatives.[56] Another report describes the examination of gangliosides themselves (CZE).[57]

Other relevant compounds to have been examined are inositol phosphates in fermentation broths and blood plasma (by on-line concentration by electrodialysis, capillary electrophoresis, MS),[58] and acarbose and its metabolites (as their 7-aminonaphthalene-1,3-disulfonic acid derivatives) in human urine (CZE).[59]

Purine bases, ribonucleosides and ribonucleotides have been simultaneously determined by capillary electrophoresis with consistent potential amperometric detection with a copper electrode under alkaline conditions.[60] Related studies have been carried out on all the common ribonucleotides,[61] ATP in blood plasma and inositol phosphates in fermentation broth (CZE),[62] twelve ribonucleotides (mono-, di- and tri-phosphates),[63] deoxyribonucleotides in the presence of β-cyclodextrin[64] and twelve deoxyribonucleotides (mono, di- and tri-phosphates) in the presence of a soluble polymer (CZE).[65]

2.2 Other Electrophoretic Methods – Micellar electrokinetic chromatography (MEKC) has been used for analysing for common anti-AIDS drugs (AZT, ddA, ddC, ddI and d4T) and AZT glucuronide,[65] and for monitoring the phospholipase C cleavage of phosphatidylinositol into diacylglycerol and inositol 1,2-cyclic phosphate.[66] For the separation of the relatively hydrophobic cardiac glycosides microemulsion electrokinetic chromatography (MEEKC) was superior to MEKC,[67] and was also used with *N*,*N*-diphenylhydrazones of dicarbonyl sugar compounds *e.g.* D-xylosone, D-glucosone, D-galactosone, and D-*threo*-hex-2,5-diulose.[68]

Capillary isotachophoresis was the method selected for the determination of alditols in pharmaceutical preparations[69] and aldonic acids produced on $PdCl_2$ oxidation of aldoses in alkaline solution. Unexpectedly at pH 9 only mannonic acid was produced from mannose or glucose.[70]

3 Other Analytical Methods

A subnanomol colorimetric method for determining sugars is based on dark violet derived with Fe(II) 2,4,6-tri-2-pyridyl-*s*-triazine which is stoichiometrically destroyed by periodate ion. Excess ion can therefore be determined following the oxidation of the carbohydrates.[71] 1,5-Anhydro-D-*arabino*-hex-2-ulose can be specifically assayed by treatment with alkaline dinitrosalicylic acid under defined conditions.[72] A spectrophotometric determination of ascorbic acid at 10^{-8} M levels depends on its interference in the diazotization of 5,10,15,20-tetrakis(4-aminophenyl)porphine and was applied to analyses in soft drinks and pharmaceuticals.[73]

A new electrode [TEMPO bound to a poly(phenylene oxide) film on glassy carbon] is suitable for the electrochemical determination of sugars by flow injection methods,[74] and a further electrochemical method for post-HPLC separation of carbohydrates depends on periodate oxidation and determination of derived iodate.[75] A novel simultaneous potentiometric determination of carboxylic acids and amperometric assay of sugars has been described.[76]

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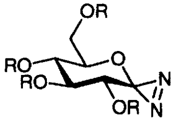
24

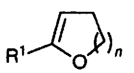
Synthesis of Enantiomerically Pure Non-carbohydrate Compounds

1 Carbocyclic Compounds

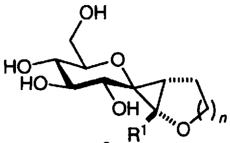
Glucosylidene carbene reactions with enol ethers provides a route to cyclopropane spiro-fused glucose derivatives. Thus, compounds **1** react with cyclic enol ethers **2** to give, after deprotection, **3**, whilst **1** react with acyclic enol ether **4** to afford a mixture of the possible regio- and diastereomeric outcomes (**5**–**8**).[1] Quinic acid has been converted into the fused cyclobutane δ-lactone **9** in 15 steps and leads to an intermediate which has previously been converted into (+)-grandisol (**10**).[2]



1 R = Piv, Bn



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



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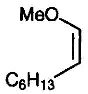

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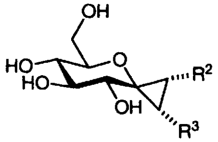
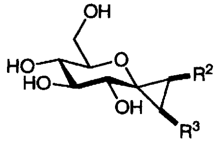
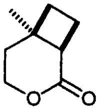


5 $R^2 = C_6H_{13}$, R^3 = OMe
6 R^2 = OMe, $R^3 = C_6H_{13}$



7 $R^2 = C_6H_{13}$, R^3 = OMe
8 R^2 = OMe, $R^3 = C_6H_{13}$



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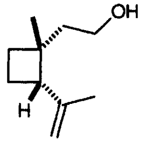
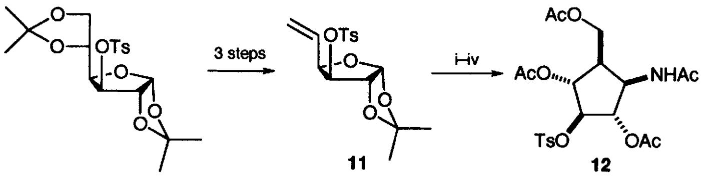


10

The cyclopentane **12** has been synthesized *via* **11** starting, ultimately, from D-glucose (Scheme 1).[3] Highly functionalized cyclopentanes have also been prepared by other carbohydrate-based procedures, as have *C*-nucleosides (see Chapter 20). Radical cyclization was employed in the synthesis of **15**, starting from **13** and proceeding *via* final radical deiodination of **14** (Scheme 2). Analogous chemistry provided a route from **16** to **17**. Both routes furnish the products in 42–48% overall yields (Scheme 2).[4]

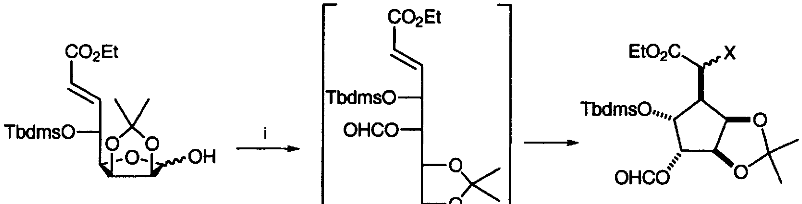
Samarium diiodide mediates the cyclization of carbohydrate-derived oxime ethers **18** and **20** to cyclopentanes **19** and **21**, respectively.[5]

Carbohydrate Chemistry, Volume 31



Reagents: i, H_2SO_4, $MeCN\text{-}H_2O$; ii, $PhCH_2NHOH$; iii, Pd-C, EtOH, C_6H_{10}; iv, Ac_2O, Py.

Scheme 1



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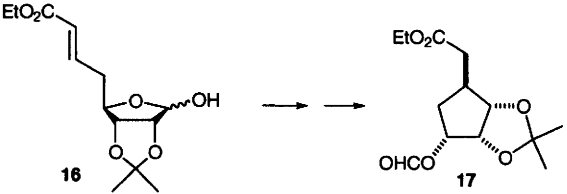
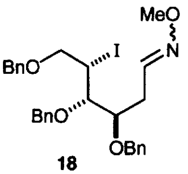
Reagents: i, PhIO, I_2; ii, Bu_3SnH, AIBN.

14 X = I
15 X = H ii



Scheme 2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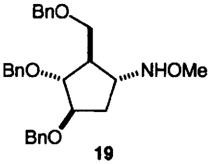
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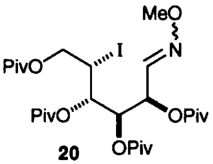
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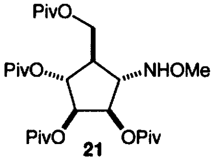
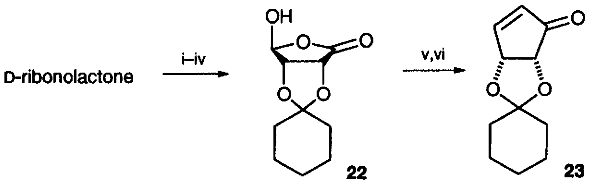
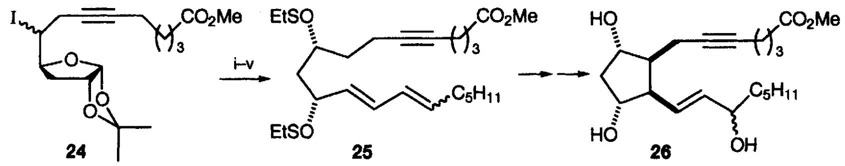

21

D-Ribonolactone was converted into hemiacetal lactone **22**, which was further elaborated to cyclopentenone **23** (Scheme 3).[6] Carbohydrate-derived starting material **24** has been elaborated into 15(*RS*)-5,6-dehydro-8-*epi*-prostaglandin $F_{2\alpha}$ (**26**) *via* intermediate **25** (Scheme 4).[7]



Reagents: i, $C_6H_{10}O$, $FeCl_3$; ii, KOH, H_2O, Δ; iii, KIO_4, H_2O; iv, 2M HCl; v, PPTS, *i*-PrOH, vi, $MePO(OMe)_2$, BuLi.

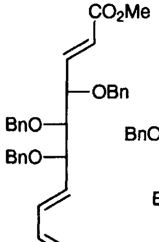
Scheme 3



Reagents: i, $ZnCl_2$, EtSH; ii, Et_3SiCl, Py; iii, HgO, $HgCl_2$, Me_2CO, H_2O; iv, $Ph_3P{=}CHCHO$; v, $Ph_3P{=}CHC_5H_{11}$.

Scheme 4

A number of syntheses of fused ring systems containing five- and/or six-membered carbocylic rings have been reported this year. The trieneoate **27** (see Vol. 28, p. 8, Chapter 2 for synthesis) undergoes an intramolecular Diels-Alder reaction catalysed by $AlCl_3$ to yield bicyclic product **28** and other examples of such cycloadditions were described.[8] Trieneones **29** (from L-arabinose) and **30** (from L-ascorbic acid) undergo IMDA reactions to yield bicyclics **31** and **32**, respectively, in 75–79% yield. The isopropylidene groups provide conformational restriction to direct stereocontrol *via* chair-like and boat-like *endo*-transition states for **31** and **32**, respectively.[9]



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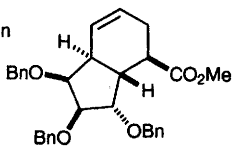

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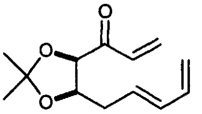

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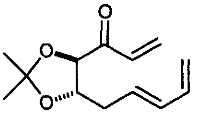

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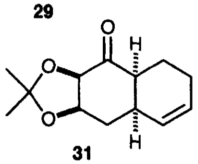

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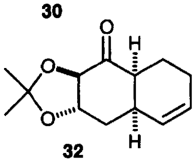


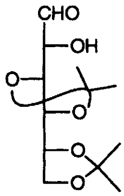
32

A tandem Wittig-Intramolecular Diels-Alder reaction provides a useful entry to highly oxygenated, carbohydrate-bearing decalin systems. Thus, reaction of **33** with **34** generated **35**. Analogous chemistry using other carbohydrate-derived aldehydes gave **36** and **37** (isomeric mixture).[10]

Intramolecular Diels-Alder chemistry (conversion of **38** to **39**) was also the key step in a synthesis of the skeleton of the forskolin analogue **40** from 3,4,6-tri-*O*-acetyl-D-galactal (Scheme 5).[11]

Methyl α-D-xylopyranoside derivative **41** was converted into the acyclic chiral unit **42**, which was treated with two equivalents of methyl acetoacetate to afford (*via* double Claisen chemistry) the chiral α-tetralone **43** (an intermediate related to benanomycinone, the aglycon of benanomycin A) (Scheme 6).[12]

Levoglucosan was converted to the tricyclic system **46** in a number of steps (Scheme 7), *via* derivative **44**, the key reaction being the introduction of the five-membered ring (to give **45**) by means of an intramolecular Horner-Wadsworth-Emmons type olefination. Compound **1AE** is an advanced intermediate towards synthesis of (−)-quadrone.[13]



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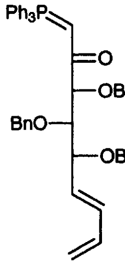

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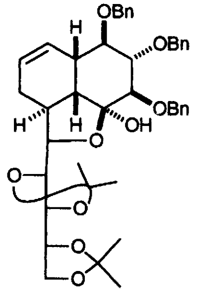

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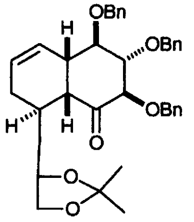

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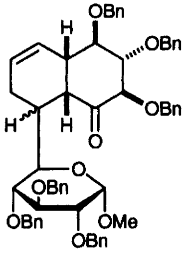

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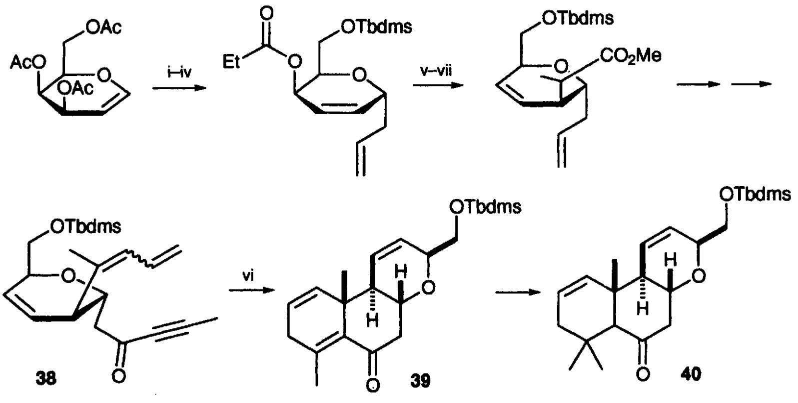
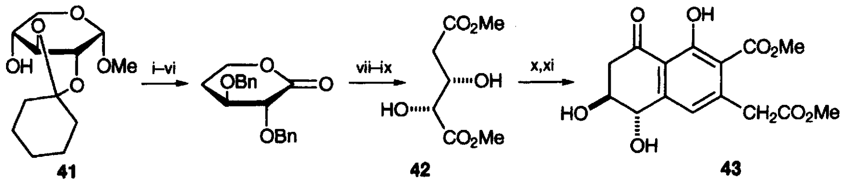


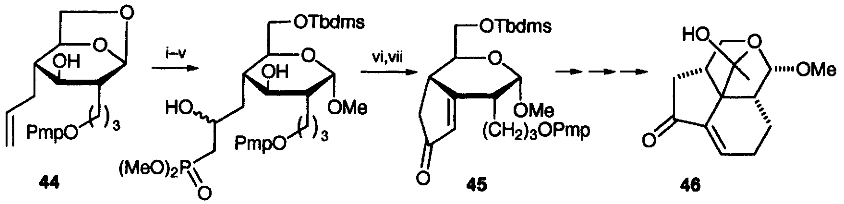
Reagents: i, AllylTms, BF_3; ii, MeOH, Et_3N, H_2O; iii, TbdmsCl; iv, $MeCH_2CO_2H$, DCC; v, HMDS, BuLi, TbdmsCl; vi, Δ; vii, KF, MeI, $KHCO_3$.

Scheme 5



Reagents: i, $SOCl_2$; ii, Bu_3SnH, AIBN; iii, HCl, dioxane, H_2O, r.t.; iv, BnBr; v, HCl, dioxane, H_2O, 100 °C; vi, PDC; vii, TsOH, MeOH; viii, PDC, CH_2Cl_2; ix, PDC, MeOH, DMF; x, $Pd(OH)_2$, cyclohexene; xi, NaH, BuLi, THF, $MeC(O)CH_2CO_2Me$

Scheme 6

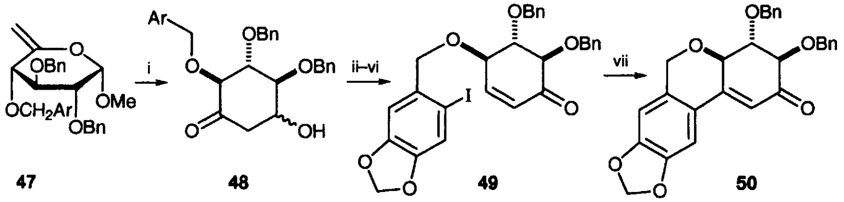


Reagents: i, MeOH, H^+ resin; ii, TbdmsCl, Py; iii, NMNO, OsO_4; iv, IO_4^-; v, $(MeO)_2P(O)CH_2Li$; vi, Dess-Martin; vii, LiCl, i-Pr_2NEt.

Scheme 7

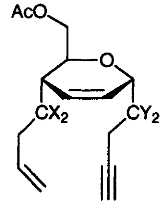
Palladium chemistry was instrumental in two other syntheses of tricyclic systems. Firstly, D-glucose derivative **47** was converted into the pancratistatin C-ring precursor **50**, *via* rearrangement to **48** and elaboration to **49** which then underwent intramolecular Heck closure (to yield **50**) (Scheme 8).[14]

Palladium-catalysed conditions were employed to convert **51** to **52** [$Pd_2(dba)_3.CHCl_3$, tri-*O*-tolylphosphine in acetic acid/benzene]; or to **53** [$PdCl_2(MeCN)_2$, $CuCl_2$, LiCl, in acetic acid/MeCN]. The second set of conditions also converted **54** to the *N*-containing system **55**.[15]

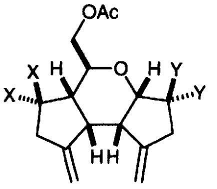


Reagents: i, $HgOTf_2$, aq. Me_2CO; ii, TbdmsOTf; iii, LAH; iv, MsCl, Et_3N; v, Bu_4NF; vi, DMSO, $(COCl)_2$; vii, $Pd(OAc)_2$, Ph_3P, Et_3N, $AgNO_3$.

Scheme 8



51 (a) X = CO_2Et, Y = CO_2Me
(b) X = SO_2Ph, Y = CO_2Me



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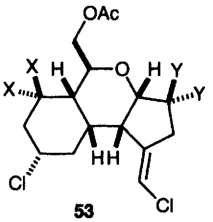

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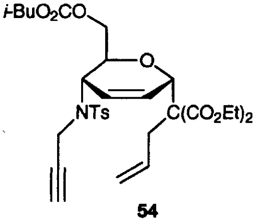

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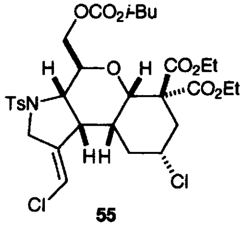

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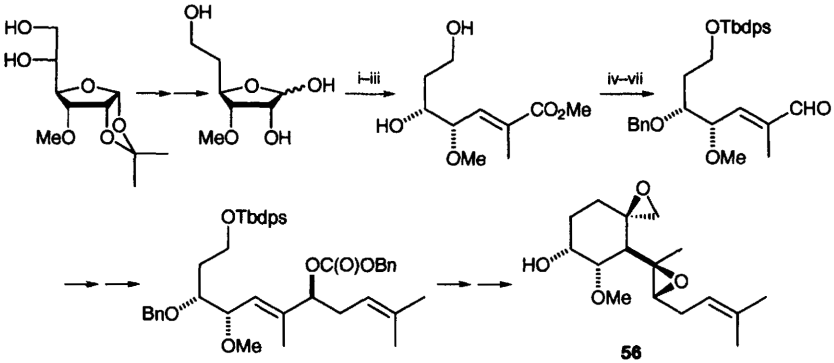
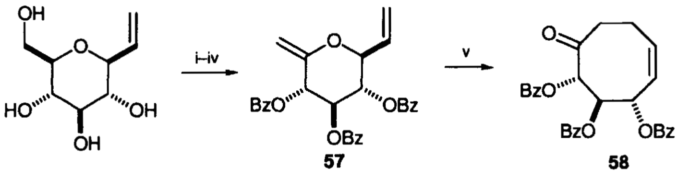


Reagents: i, IO_4^-; ii, $Ph_3P{=}C(Me)CO_2Me$; iii, K_2CO_3, MeOH; iv, TbdpsCl, DMAP; v, $CCl_3C({=}NH)OBn$, CF_3SO_3H; vi, DIBAL; vii, MnO_2.

Scheme 9

D-Glucose has been converted into (−)-fumagillol **56** (Scheme 9).[16]

An interesting synthesis of the cyclooctenone **58** utilizes the (thermally induced) sigmatropic rearrangement (*via* $^1C_4$ chair) of **57** (derived from D-glucose) (Scheme 10).[17]

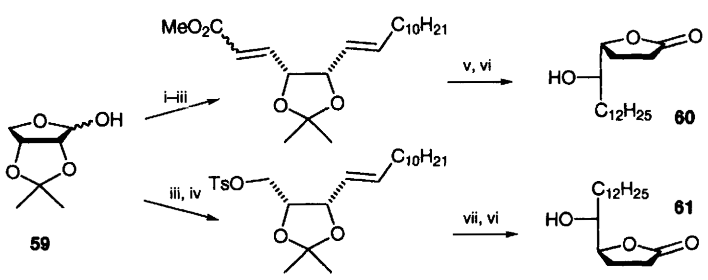


Reagents: i, TsCl, Py; ii, BzCl, Py; iii, DMSO, Δ; iv, NaI, Bu_4NI, DBU; v, xylene, Δ.

Scheme 10

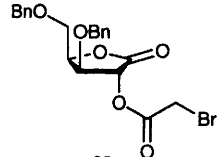
2 Lactones

Both enantiomers, **60** and **61**, of *epi*-muricatacin have been prepared from furanose **59** (Scheme 11).[18] Intramolecular Wittig reaction was the key



Reagents: i, $C_{11}H_{23}PPh_3Br$, KOBu-*t*, Py; ii, DMSO, DCC, Py; iii, $PPh_3P{=}CHCO_2Me$; iv, TsCl, Et_3N; v, H_2, Pd-C; vi, HCl, THF; vii, $(C_{11}H_{23})_2CuLi$.

Scheme 11



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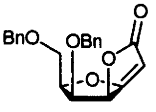

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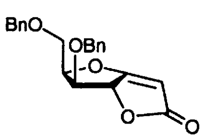

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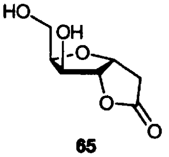
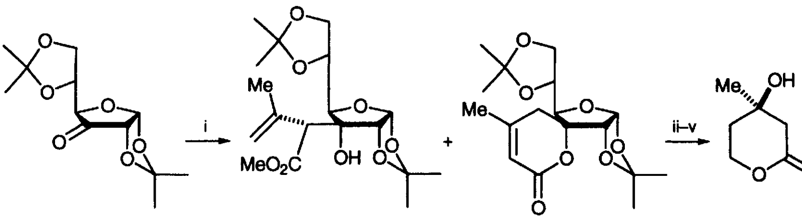


65

chemistry in a synthesis of the bicyclic *C*-glycosidic lactone **65**. Treatment of **62** with Ph_3P and less than an equivalent of DBU generates only **64**, hydrogenation being employed to take this to **65**. If more than an equivalent of DBU is used, epimerization occurs at C-2 and both **63** and **64** are produced.[19]

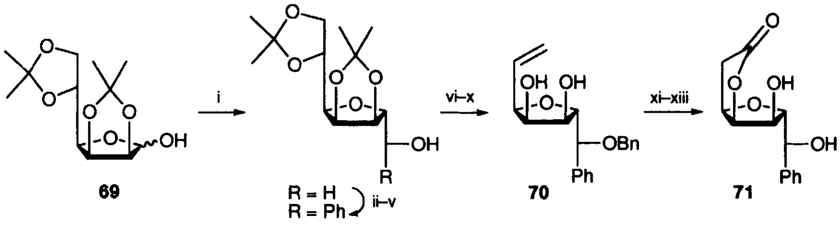
A synthesis of (*R*)-mevalonolactone **68** and its perdeuterated analogue (*R*)-$[^2H_9]$mevalonolactone [using $(C^2H_3)_2C{=}C^2HCO_2Me$ and $LiAl^2H_4$], has been reported based on diacetone-D-glucose as a template,[20] only one of the carbons (the lactone carbonyl) of the final product coming from the sugar. The key C–C bond forming reaction involves addition of an allylic anion to the sugar C-3 carbonyl group to give **67** (30%) (and the alternative allylic anion addition product **66** in 51% yield) and a key step is the diastereoselective epoxidation of the C=C bond of **66** (Scheme 12).



Reagents: i, $(Me)_2C{=}CHCO_2Me$, LDA; ii, H_2O_2; iii, LAH; iv, H^+; v, $NaIO_4$.

Scheme 12

The bicyclic lactone **71** was prepared in 13 steps from carbohydrate starting material **69**. The first step involved epoxidation of the sugar aldehyde followed by ring close ring opening of the epoxide to re-establish the five-membered ring (5-exo-tet). A later key step involved the oxidative Pd-catalysed cyclization of **70** followed by lactol oxidation and debenzylation to give **71** (Scheme 13).[21]

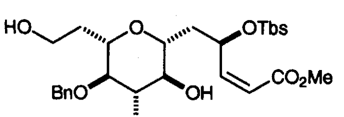


Reagents: i, trimethylsulfoxonium iodide, KOBu-*t*, DMSO; ii, Swern; iii, PhMgBr; iv, PDC; v, $NaBH_4$; vi, BnBr, NaH; vii, 60% AcOH; viii, MsCl, TEA; ix, NaI; x, 5% H_2SO_4, dioxane; xi, $PdCl_2$, CuCl, O_2; xii, PDC; xiii, H_2, $PdSO_4$.

Scheme 13

3 Macrolides, Macrocyclic Lactams, Polyether Ionophores and Their Constituent Segments

This year has seen a variety of reports of syntheses of components of a range of well known bioactive marine systems. Full details of the synthesis of the C-1–C-15 component of halichondrin B, a potent antitumour polyether macrolide, have been reported (preliminary communication see: Vol. 28, p. 361, ref. 58).[22] A companion paper from the same group reported synthesis of two C-27–C-36 units from dimethyl L-tartrate.[23]



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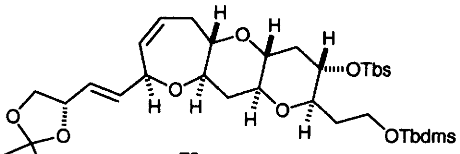
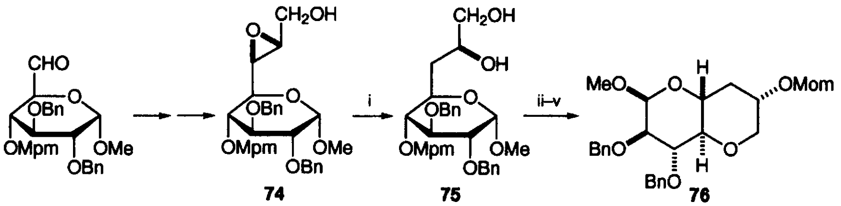


73

Ciguatoxin, the algal red-tide toxin, again proves to be a continuing target for synthetic efforts, with full details of the synthesis of AB ring fragments having been published (preliminary communciation: Vol. 29, p. 379, ref. 59). Proof of the C-2 configuration (of both ciguatoxin and synthetic fragments) as *S* was obtained from exciton chirality method applied to the *p*-bromobenzoate esters.[24] Another Japanese group reported the synthesis of an ABC ring fragment (**73**) of ciguatoxin. The starting material was D-glucose, which was converted into **72** in 17 relatively routine steps and thence to the tricyclic **73**.[25]

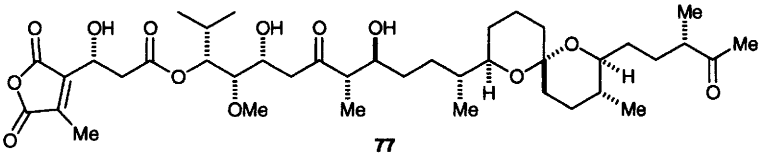
A synthesis of the BC ring system (**76**) of ciguatoxin has also been reported starting from methyl α-D-glucopyranoside. Key steps include the diastereoselective epoxidation with MCPBA yielding **74** and a final intramolecular *O*-alkylation *via* tosylate displacement (Scheme 14).[26]



Reagents: i, DIBAL; ii, TsCl, DMAP; iii, MomCl, DIPEA; iv, DDQ; v, NaH, 15-crown-5

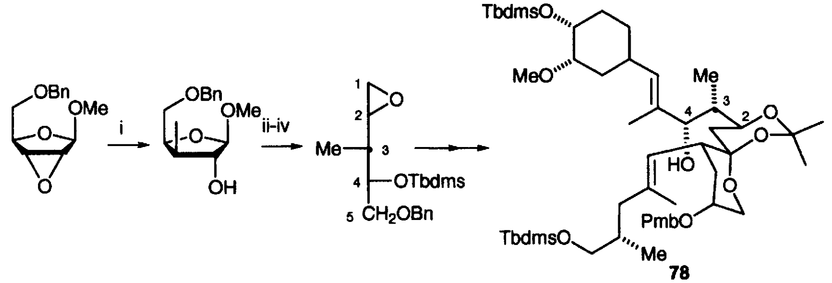
Scheme 14

Full details of the synthesis of the spiroacetal section of tautomycin (**77**) have been reported (preliminary report: Vol. 29, p. 369, ref. 33),[27] with a second paper by the same group describing the total synthesis (only the spiroacetal section is carbohydrate-derived).[28]



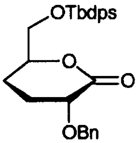
77

Ireland and co-workers have completed a total synthesis of the immunosuppressant FK-506,[29] the synthesis of a carbohydrate-derived section (**78**) being described in an adjoining paper (Scheme 15).[30]



Reagents: i, MeMgCl, CuBr.SMe$_2$; ii, EtSH, H$^+$; iii, TbdmsCl; iv, HgCl$_2$, CaCO$_3$, H$_2$O; v, NaBH$_4$; vi, TsIm, NaH

Scheme 15



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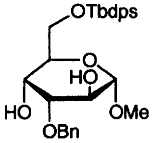

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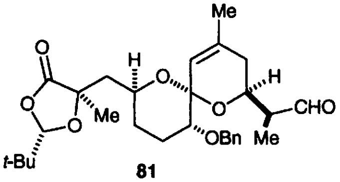

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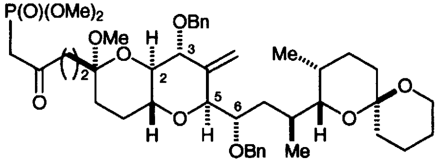
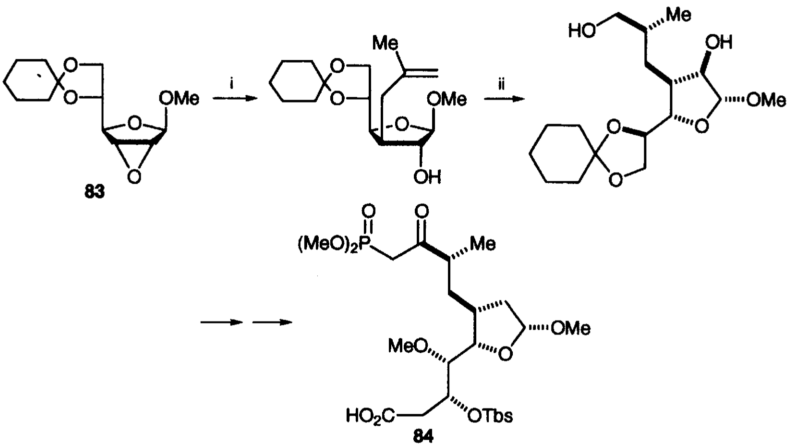


82

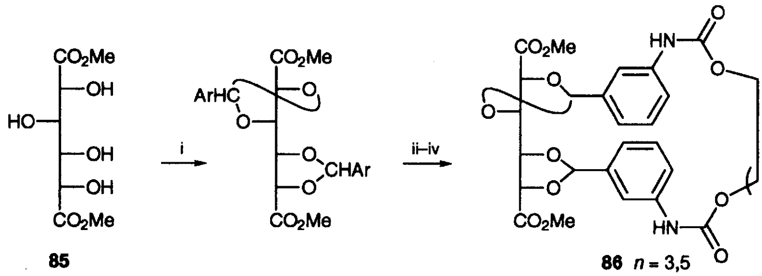
Forsyth's group have completed a total synthesis of okadaic acid from carbohydrate-based starting materials **79** and **80**. Complex elaboration of **79** provided spiroketal **81** and **82** was derived from **80** in a multi-step procedure. Convergent coupling of these components (generating the *trans*-olefin isomer) and further manipulations led to the natural product.[31]

Carbohydrate epoxide **83** was the starting point for a synthesis of the C-1–C-10 fragment of carbonolide B, in the form of intermediate **84** (Scheme 16), which has already been converted into carbonolide A.[32]

The supramolecular host systems **86**, macrocylic bis-lactams, have been prepared from carbohydrate-derived **85** (Scheme 17).[33]



Reagents: i, $CH_2{=}C(Me)CH_2MgCl$; ii, $BH_3.SMe_2$ then H_2O_2.
Scheme 16

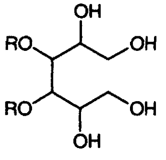


Reagents: i, m-$NO_2C_6H_4CHO$, H_2SO_4; ii, H_2/Pd-C; iii, $(COCl)_2$, iv, $HO(CH_2CH_2)_nOH$ (n = 2, 3).
Scheme 17

4 Other Oxygen Heterocycles

A series of 3,4-*O*-diprotected hexitols **87** (mannitol or glucitol-derived) were converted into 1,2:5,6-bis-epoxides **88** in three steps (61–85% yields), by reaction with PPTS and trimethyl orthoformate, then acetyl bromide/triethylamine and finally potassium carbonate in methanol. In the case of the mannitol-derived starting material, when the diols were protected as benzyl ethers (R = Bn) the furan **89** (10%) and bicyclic system **90** (24%) were also obtained. [The reaction involves the conversion of intermediate orthoacetals into bromohydrins from the action of AcBr, leading to ring closure to epoxides or alternative pathways for **89** and **90**]. When the alternatively bis-protected hexitol **91** (from L-ascorbic acid) was exposed to the same sequence, bis-epoxide **92** and furan **93** were obtained. Galactitol-derived **94** gave rise to bis-epoxide **95** (68%).[34]

Full details have been reported (preliminary report: Vol. 29, p. 376, ref. 52) of iododetherification reactions (with IDCP) of C-6-allylated pyranosides to



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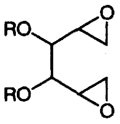

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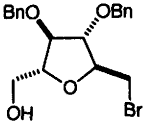

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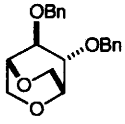

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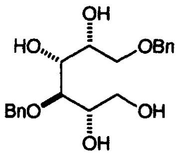

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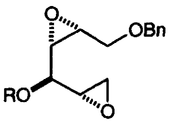

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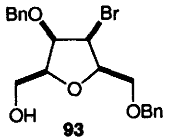

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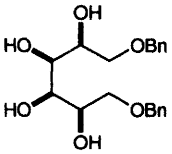

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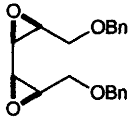

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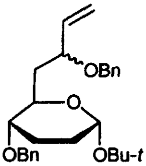

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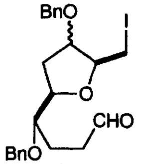

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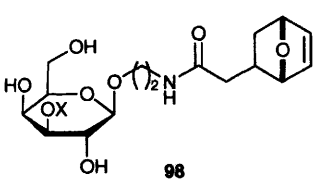

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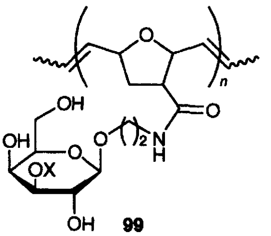
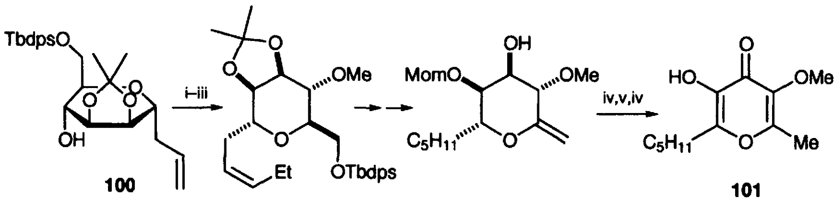


99

afford 2,5-dialkyl-3-alkyloxy tetrahydrofurans, by which, for example, **96** is converted into **97**.[35]

The tetrahydrofuran-based oligomer **99**, bearing sulfated D-galactoside units ($X = SO_3H$), was obtained by olefin metathesis polymerization of **98**. The attached starting bicyclic olefin was racemic.[36]

The known *C*-allyl glycoside **100** (Nicolaou *et al.*, *J. Am. Chem. Soc.* 1989, **111**, 6682) has been elaborated into allixin (**101**), providing the first synthesis of this antitumour promoter found in garlic. It is noteworthy that ALL the carbohydrate chiral centres are lost (Scheme 18).[37]

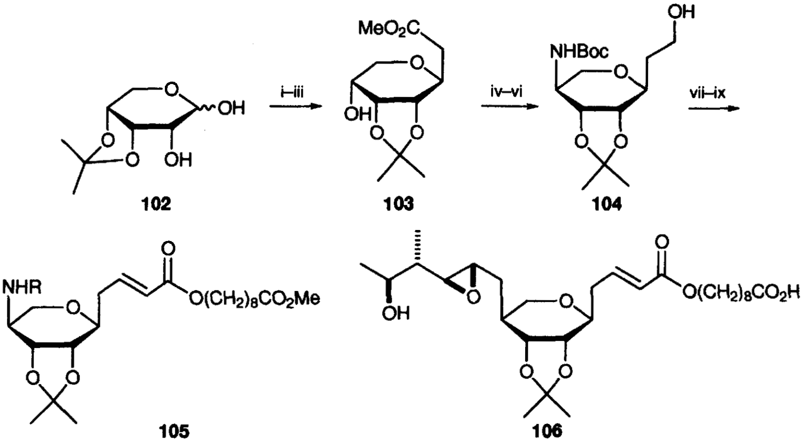


Reagents: i, NaH, MeI; ii, OsO_4, $NaIO_4$; iii, Ph_3PCH_2EtI, NaHMDS; iv, $SO_3.Py$, Et_3N; v, TMSBr.

Scheme 18

Novel analogues (**105**) of the antibiotic pseudomonic acid A (**106**), with the C-9–C-14 unit removed, have been prepared (Scheme 19). The key approach involves elaborating sugar **102** through Wittig reaction, intramolecular conjugate addition and acetal migration, followed by Mitsunobu azidation of **103** to give, after azide and ester reduction and selective *N*-protection, **104**.

A further Wittig homologation completes the natural product functionality on the 'right hand side'. The amino function then provides a common point for reaction with various actived acids, sulfonyl chlorides, isocyanates and aldehydes to afford a range of analogues. Analogue **105** (R = $SO_2(CH_2)_3Cl$) was the most active compound tested against isoleucyl tRNA synthetase (though about two orders of magnitude less active than the natural product **106**).[38]



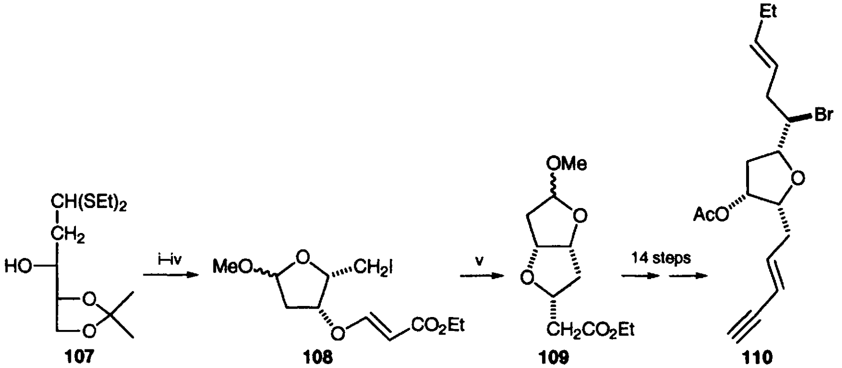
Reagents: i, $Ph_3P{=}CHCO_2H$; ii, NaOMe; iii, $(MeO)_2CMe_2$, H^+; iv, Ph_3P, DEAD, $(PhO)_2P(O)N_3$; v, LAH; vi, $(Boc)_2O$; vii, TEMPO, NaOCl; viii, $(EtO)_2P(O)CH_2C(O)O(CH_2)_8CO_2Me$, $LiN(Tms)_2$; ix, TFA.

Scheme 19

D-Xylose is the starting material (providing known **107**) for a synthesis of (−)-*trans*-kumausyne (**110**), by way of a stereoselective radical cyclization of **108** to **109** (Scheme 20).[39]

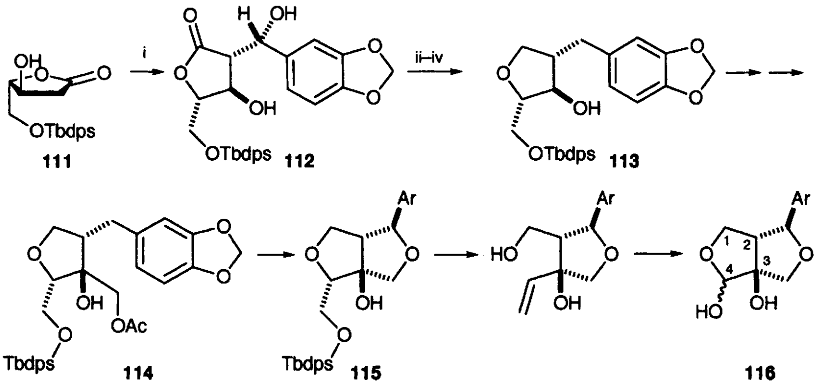
L-Arabinose-derived **111** provided **112** as the major epimer from ester enolate addition to piperonal, which was elaborated to **113**. Subsequent oxidation, Tebbe reaction, osmylation and acetylation led to **114**, which was then converted into bicycle **115**, which then underwent bromination, Zn-promoted fragmentation and oxidative cleavage to afford **116**, (+)-(1*S*,2*S*,5*R*,6*S*)-1-hydroxysamin (Scheme 21).[40]

The furan **118** was prepared by reaction of **117** with iodine. A mechanism was proposed as shown and **118** was converted further into **119**. The related starting material **120** was converted into **121** by treatment with potassium butoxide and then refluxing in benzene.[41]



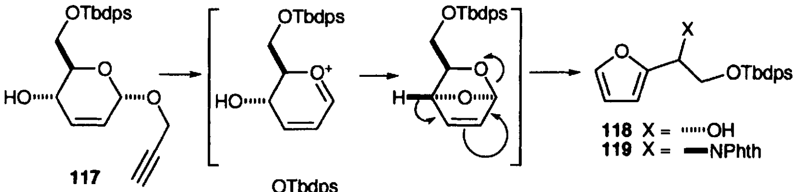
Reagents: i, $HCCCO_2Et$, NMM; ii, TsOH, MeOH then $PhI(Tfa)_2$; iii, TsCl, py; iv, Bu_4NI; v, Bu_3SnH, AIBN.

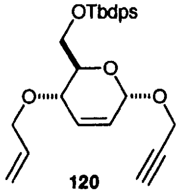
Scheme 20



Reagents: i, LDA, piperonal; ii, TbdmsOTf; iii, DIBAL, –78 °C; iv, Et_3SiH, $BF_3.Et_2O$.

Scheme 21





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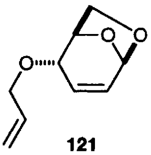
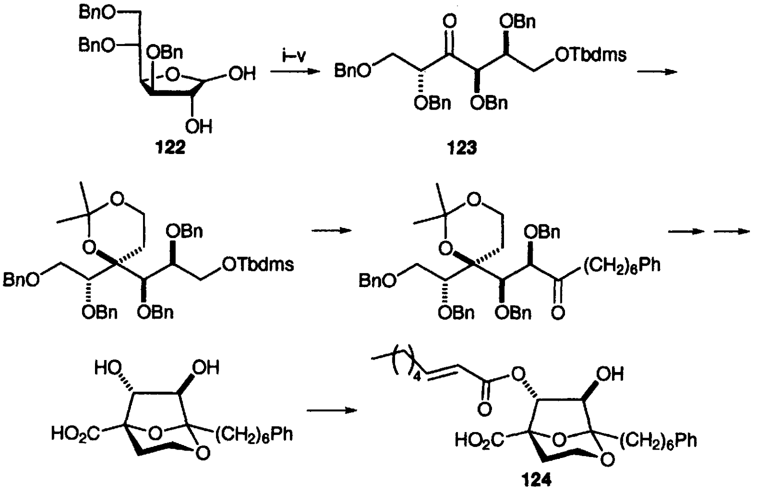


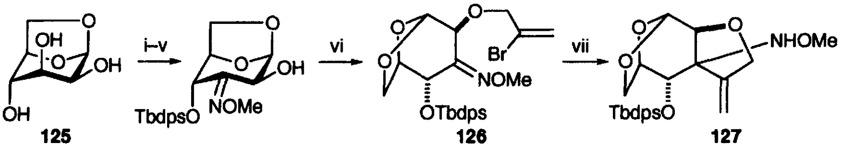
121

A simplified core analogue (**124**) of zaragozic acid has been prepared starting from **122**. Key steps include a diastereoselective vinylation of ketone **123** and subsequent hydroboration (Scheme 22).[42] An intermediate (**127**) towards another complex natural product, tetrodotoxin, has also been prepared from 1,6-anhydro-D-mannose (**125**). The key step involved a vinyl radical cyclization of **126** onto a oxime ether (Scheme 23).[43]



Reagents: i, NaH, BnBr; ii, 2M H_2SO_4, AcOH; iii, $LiAlH_4$; iv, TbdmsCl, ImH; v, Swern.

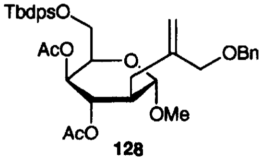
Scheme 22



Reagents: i, TbdpsCl, ImH; ii, H_2O, AcOH; iii, Bu_2SnO; iv, Br_2; v, $MeONH_2$; vi, NaH, $BrCH_2C(Br)=CH_2$; vii, Bu_3SnCl, AIBN, $NaCNBH_3$.

Scheme 23

Asymmetric hydrogenation (chiral ruthenium catalyst) of **128** yielded **129**, a precursor towards **130**.[44]



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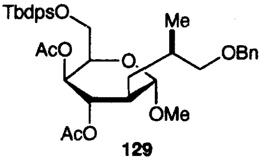

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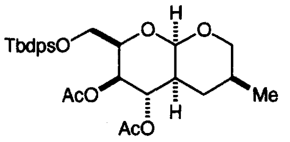
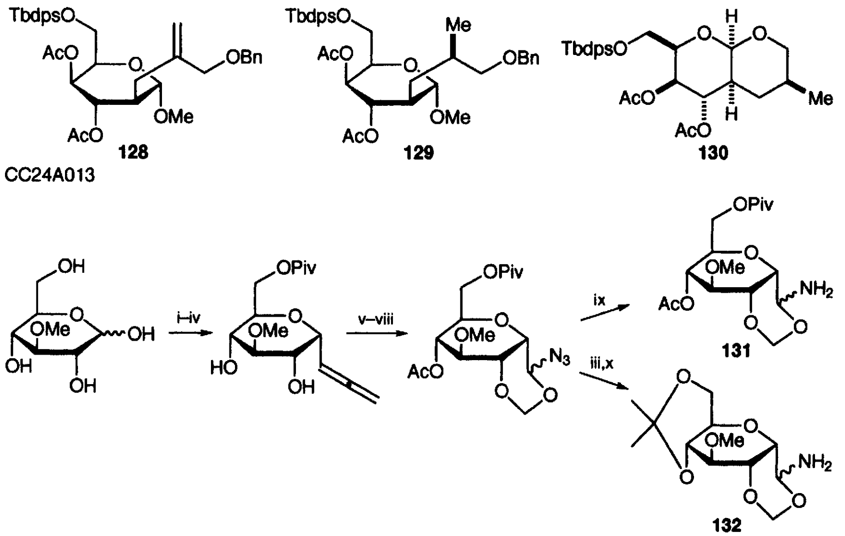


130

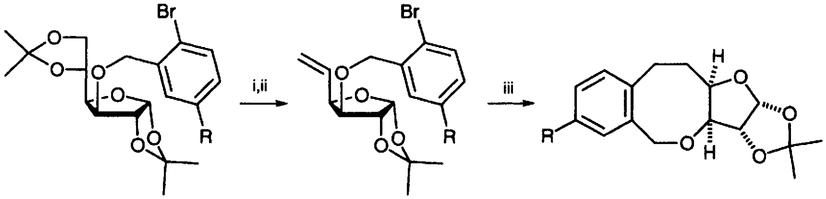
D-Glucose was converted into both **131** and **132**, which were incorporated into analogues of mycalamide A (the natural product contains a 1,2-dihydroxypropyl instead of the C-5 hydroxymethyl group and a geminal dimethyl group at C-4) (Scheme 24).[45] The azido intermediate was obtained as a mixture of isomers and the derived amine was also a mixture of isomers (the natural product has this centre with *R* configuration).



Reagents: i, Ac_2O, Py; ii, TMSOTf, $HCC\text{-}CH_2Tms$; iii, MeOH, K_2CO_3; iv, PivCl; v, MeOH, O_3; vi, CSA, $(CH_2O)_n$; vii, Ac_2O, Py; viii, $TMSN_3$, TMSOTf, ix, Pd/C, H_2; x, $Me_2C(OMe)_2$.

Scheme 24

D-Glucose was also the starting material for a synthesis of chiral furo[3,2-*c*]-[2]benzoxacines **135**, *via* 8-*endo*-trig radical cyclization of **134**. Alkylation of diacetone-D-glucose provides **133**, which was converted into **134** by selective deprotection and then elimination using triphenylphosphine, iodine and imidazole (Scheme 25).[46]

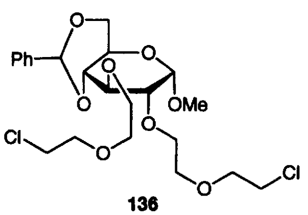


133 R = H, OMe **134** **135**

Reagents: i, AcOH; ii, PPh_3, I_2, ImH, Δ; iii, Bu_3SnH, AIBN, *hν*.

Scheme 25

Carbohydrate-fused bicyclic crown ethers were also prepared from D-glucose, *via* the known derivative **136**, treatment of which with potassium carbonate and tosylamine yielded **137**. Further desulfonylation gave **138**. Other analogues were similarly prepared and the products were examined as chiral phase-transfer catalysts (see Section 7).[47]



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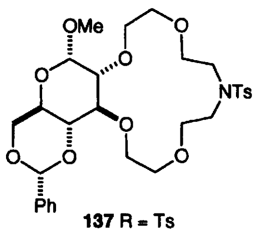
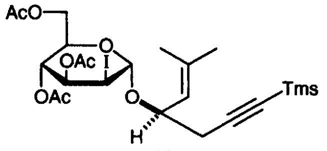


137 R = Ts
138 R = H



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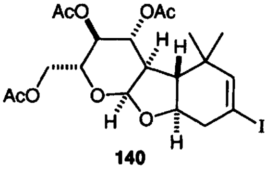
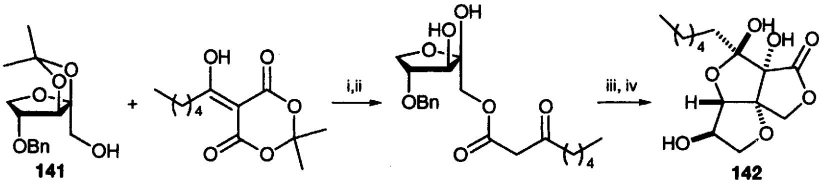


140

An iodoglycosylation of tri-*O*-acetyl-D-glucal gave **139**, which was desilylated then tandem radical cyclized to the tricyclic system **140**.[48]



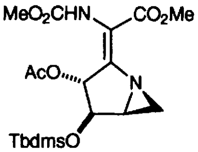
Reagents: i, toluene, reflux; ii, H^+, H_2O; iii, H^+, MeOH; iv, Pd/C, H_2.
Scheme 26

Syntheses of (+)- (**142**) and (−)-syringolide 1 and (−)-Δ^7- syringolide 1 have been achieved starting from D-xylose [(−)-enantiomer) or L-xylose, (+)-isomer] *via* xylulose-derived **141** (Scheme 26).[49]

5 N- and S-Heterocycles

Full details have been reported of the synthesis of the bicyclic aziridine **143**, a component of the azinomycins, from D-glucosamine (preliminary report: Vol. 26).[50] A number of syntheses of azetidine and azetidinone-containing compounds have been described. The carbohydrate-fused azetidine **144** (see: *Carbohydr. Res.*, 1997, **299**, 253) was converted into polyhydroxylated azetidine **145**.[51]

The 1-oxa-cephems **146** and **147** have been prepared *via* [2+2] cycloadditions of chlorosulfonyl isocyanate to precursor D-arabinal and L-rhamnal derivatives, as the key step.[52] Related work has been reported by the same group, with the conversion of glycal **148** to azetidinone **149**, followed by elaboration



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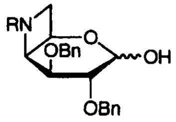

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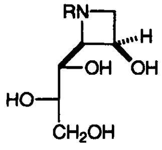

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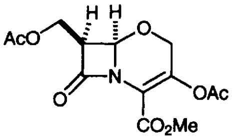

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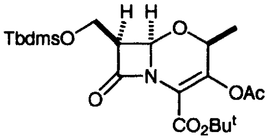

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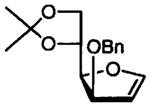

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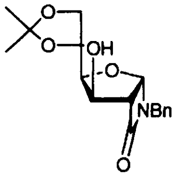

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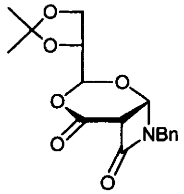

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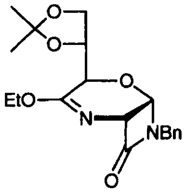
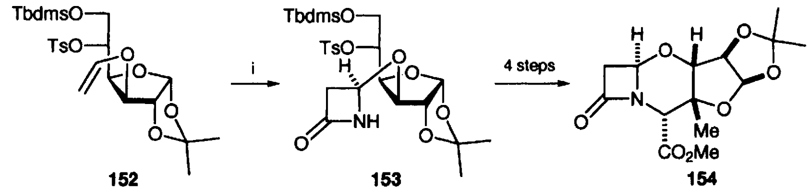


151

to **150** (oxidation and Baeyer-Villiger rearrangement) or to **151** (Beckmann-type rearrangement).[53]

The same group also described another [2+2] cycloaddition of chlorosulfonylisocyanate to an enol ether – on this occasion exocyclic as a substituent of **152** – and obtained the azetidinones **153** and thence **154** in four further steps (Scheme 27).[54]

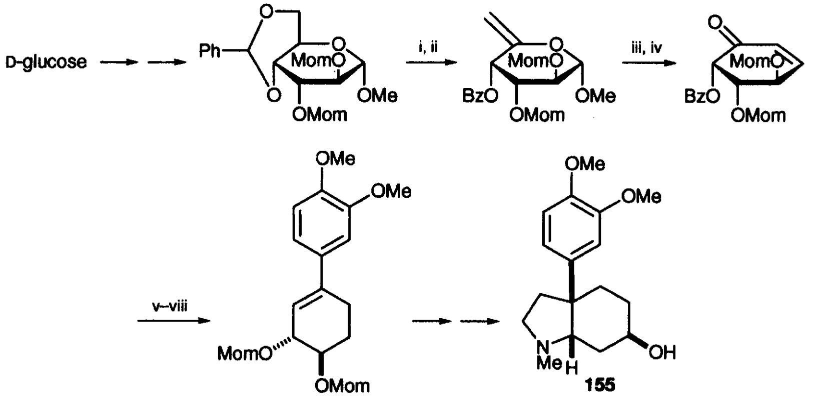


Reagents: i, $ClSO_2NCO$, Na_2CO_3 then Red-Al

Scheme 27

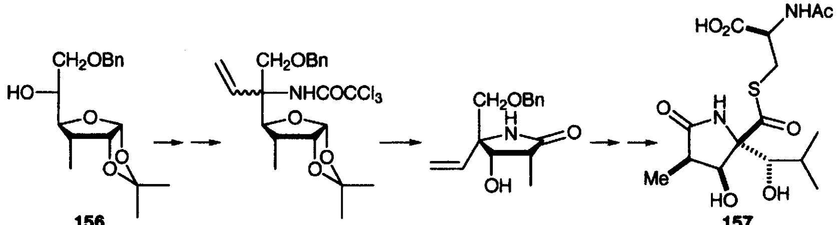
D-Glucose was the starting material in a synthesis of (−)-mesembranol (**155**), which involves Ferrier carbocyclization as a key step (Scheme 28).[55] The same group have reported full details (preliminary report: Vol. 29, p. 385) of the synthesis of (+)-lactacystin (**157**) also starting from D-glucose and proceeding *via* the known branched sugar **156** (Scheme 29).[56]

L-Arabinose was converted into 2-*C*-methyl-1,2,5-trideoxy-1,5-imino-L-ribitol (**159**) in nine steps overall *via* stereospecific reduction of the known



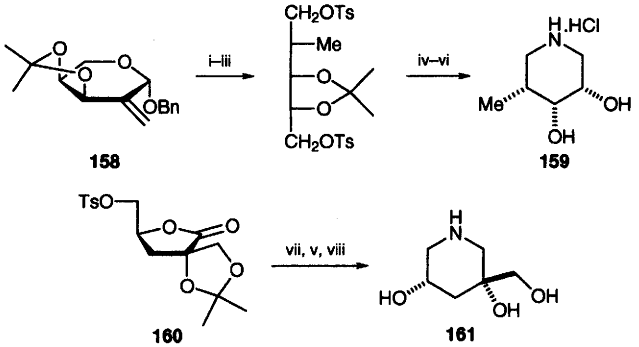
Reagents: i, NBS, $BaCO_3$; ii, DBU; iii, Hg^{2+}; iv, MsCl; v, 3,4-dimethoxy-C_6H_3Li; vi, NaOMe; vii, $Im_2C{=}S$; viii, $P(OMe)_3$.

Scheme 28



Scheme 29

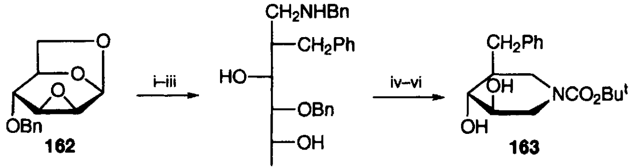
alkene **158**. In addition, lactose was converted into methyl-1,3,5-trideoxy-2-*C*-hydroxymethyl-1,5-imino-L-*erythro*-pentitol (**161**) *via* the known isosaccharinic acid derivative **160** (Scheme 30).[57]



Reagents: i, H_2, Pd/C, NH_3; ii, Na, NH_3; iii, TsCl, Py; iv, $BnNH_2$; v, H_3O^+; vi, H_2, Pd/C, HCl; vii, $NH_3(l)$; viii, BH_3, Me_2S.

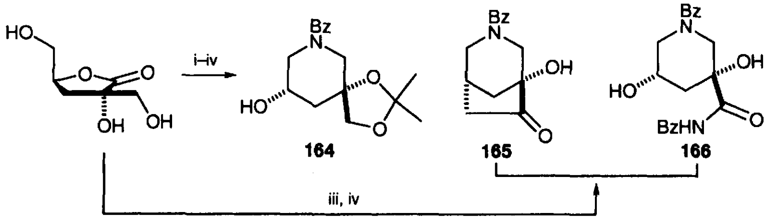
Scheme 30

The 6-deoxy-6-phenyl analogue (**163**) of isofagomine has been synthesized from dianhydro sugar **152**, for inclusion in and isofagmine-based peptide (Scheme 31).[58] α-D-Isosaccharino-1,4-lactone has been converted into the spirocyclic piperidine **164** or into the bridged system **165** and piperidine **166** (Scheme 32).[59]



Reagents: i, BnMgCl, NH_3; ii, H_3O^+, dioxane; iii, $BnNH_2$, HOAc, $NaBH_3CN$; iv, $NaIO_4$; v, H_2, Pd/C, HCl; vi, $(Bu^tOCO)_2O$.

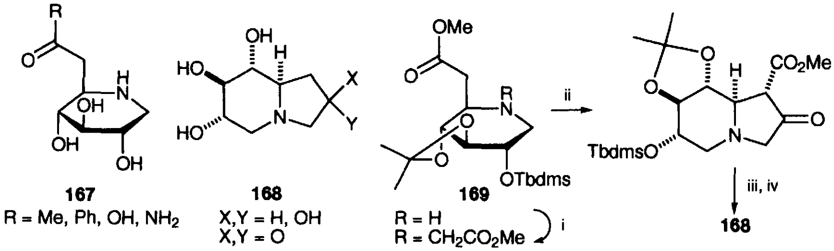
Scheme 31



Reagents: i, Me_2CO, H^+; ii, $NaBH_4$; iii, TsCl, Py; iv, NH_2Bz, Δ.

Scheme 32

Deoxynojirimycin and castanospermine analogues **167** and **168**, respectively, have been prepared from 1-amino-1-deoxy-D-glucitol. A preliminary communication has been reviewed previously (Vol. 28, p. 227, refs. 52 and 53). In this current paper, new work describes the cyclization of **169** ($R = CH_2CO_2Me$) and elaboration to **168** (Scheme 33).[60]



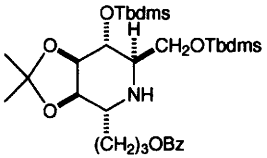
Reagents: i, $BrCH_2CO_2Me$, K_2CO_3; ii, $KOBu^t$; iii, 6M HCl; iv, $NaBH_4$.

Scheme 33

The α-1-*C*-substituted deoxymannonojirimycin **171** has been prepared from **170**, whose synthesis is described in Chapter 18.[61]

A synthesis of four diastereomers of casuarine (pentahydroxy pyrrolizidines) (*e.g.* **172**) involves reduction of acyclic azido dimesylates with sodium hydrogen telluride (Scheme 34).[62]

Two syntheses of pyrrolizidines have been reported both using intermolecular nitrone cycloadditions. Thus, **175** was prepared from 2,3-*O*-isopropylid-



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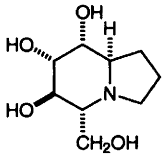

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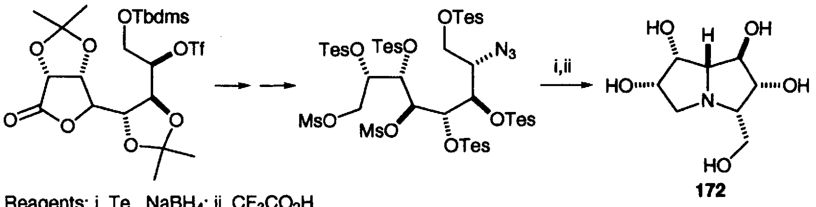
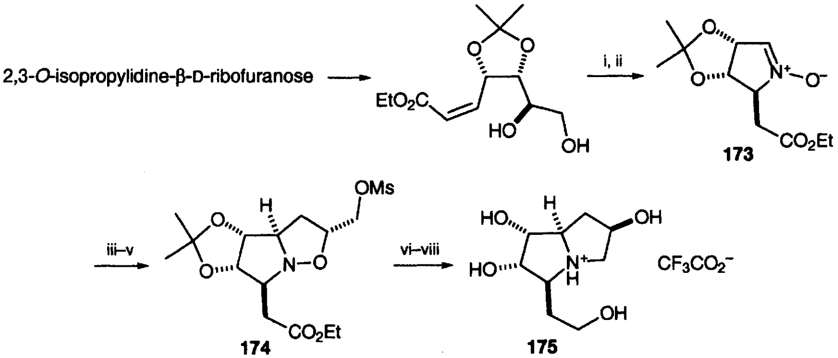


Reagents: i, Te, $NaBH_4$; ii, CF_3CO_2H.

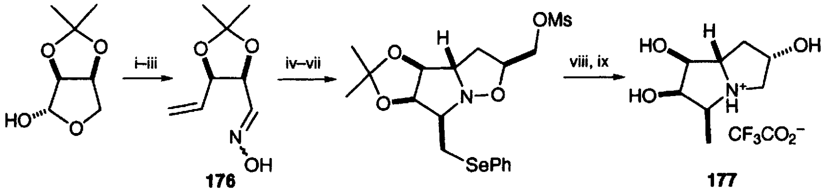
Scheme 34

ine-β-D-ribofuranose, which was converted to nitrone **173** and underwent cycloaddition with allyl Tbdms ether to give (after desilylation and mesylation) **174**. Further elaboration led to the target (**175**) (Scheme 35). The oxime **176** was prepared analogously from carbohydrate material and elaborated into **177** (Scheme 36). Phenylselenyl activation of the olefin was in this case a key early step, the selenide being ultimately reduced concomitantly during the late-stage reductive cyclization.[63]



Reagents: i, $NaIO_4$; ii, NH_2OH; iii, $TbdmsOCH_2CH{=}CH_2$; iv, TBAF; v, MsCl, Et_3N; vi, H_2, Pd/C; vii, LAH; viii, TFA, H_2O.

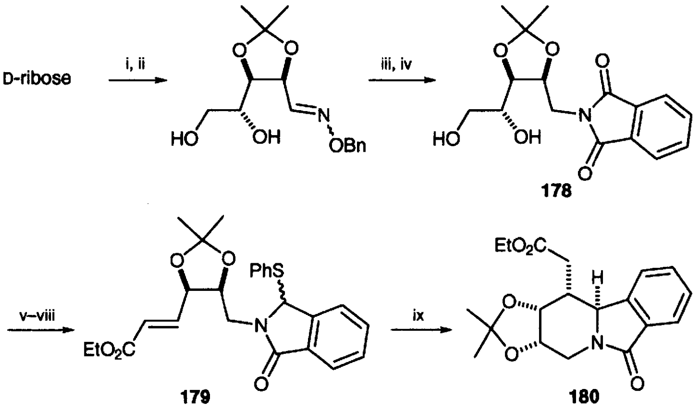
Scheme 35



Reagents: i, $Ph_3P{=}CH_2$; ii, Swern; iii, NH_2OH; iv, PhSeBr; v, $TbdmsOCH_2CH{=}CH_2$, Δ; vi, TBAF; vii, MsCl, Et_3N; viii, H_2, Raney Ni, EtOH; ix, TFA, H_2O.

Scheme 36

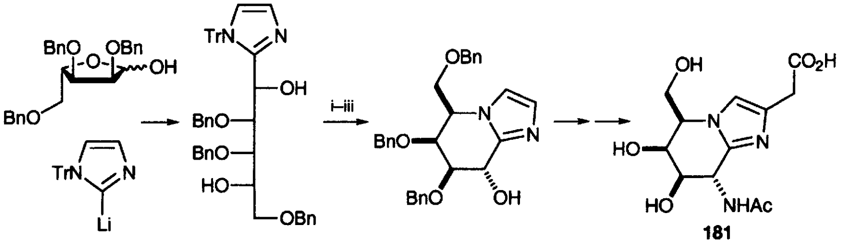
Ribose was the starting material for a synthesis of tacaman indole alkaloid model compound **180**, *via* the derivative **178**. The key step is the intramolecular radical conjugate addition of **179**, affording **180** as the major isomer (Scheme 37).[64]



Reagents: i, H_2SO_4, acetone; ii, $BnONH_2.HCl$, Py; iii, LAH; iv, *N*-CO_2Et phthalimide, Et_3N; v, $NaIO_4$; vi, $Ph_3P{=}CHCO_2Et$; vii, $NaBH_4$; viii, PhSH, $BF_3.OEt_2$, ix, Bu_3SnH, AIBN.

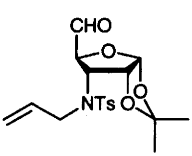
Scheme 37

Nagstatin, **181**, a glycosidase inhibitor, has been prepared from 2,3,5-tri-*O*-benzyl-L-ribofuranose, the imidazole component being introduced by addition of 2-lithio-*N*-trityl imidazole to the starting sugar (Scheme 38).[65]



Reagents: i, $BnSO_2Cl$, Py; ii, Ac_2O, Py; iii, MeONa.

Scheme 38



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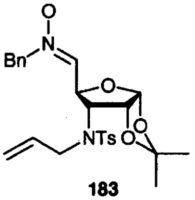

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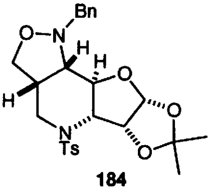

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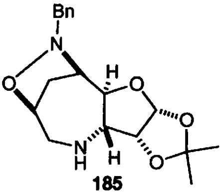
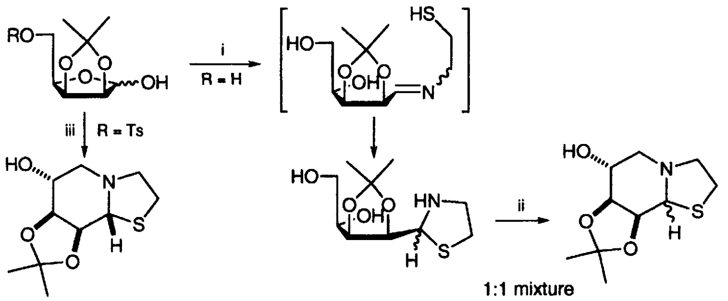


185

Intramolecular nitrone cycloaddition of **183** (from reaction of **182** with benzylhydroxylamine) afforded the tricyclic system **184**. Similar chemistry was also reported for the C-3 epimeric system (D-*xylo*). When the same chemistry was carried out using the nitrogen unprotected starting material, the azepine **185** was formed instead.[66] Seven-membered ring formation predominates with analogous allyl ethers (Vol. 27, pp. 203–204 and Vol. 29, p. 230).

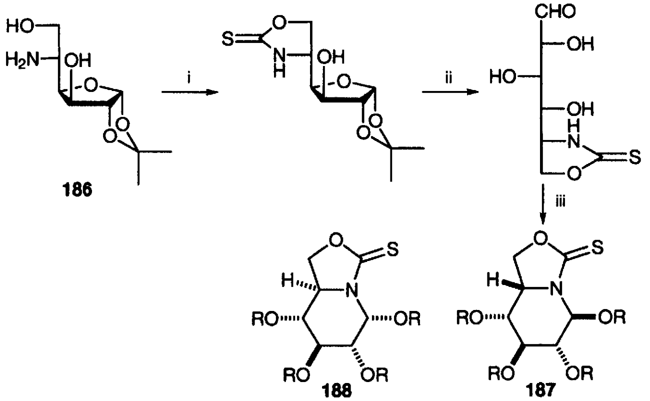
Sulfur-containing indolizidine and pyrrolizidine alkaloid analogues have been prepared starting from pentoses, using either a two-step or a one-step approach. The synthesis is illustrated by the examples in Scheme 39; the two-step approach yielded an equal mixture of diastereomers, whereas the one-step method afforded only the *R*-ring junction configuration isomer.[67]

The D-gluco- and L-ido-*N*-thiocarbonylazasugars **188** and **187** (R = H) were prepared from carbohydrate starting material **186** (Scheme 40).[68]



Reagents: i, $HS(CH_2)_2NH_2$, MeOH; ii, *n*BuLi, TsCl; iii, MeONa, $HS(CH_2)_2NH_3^+Cl^-$

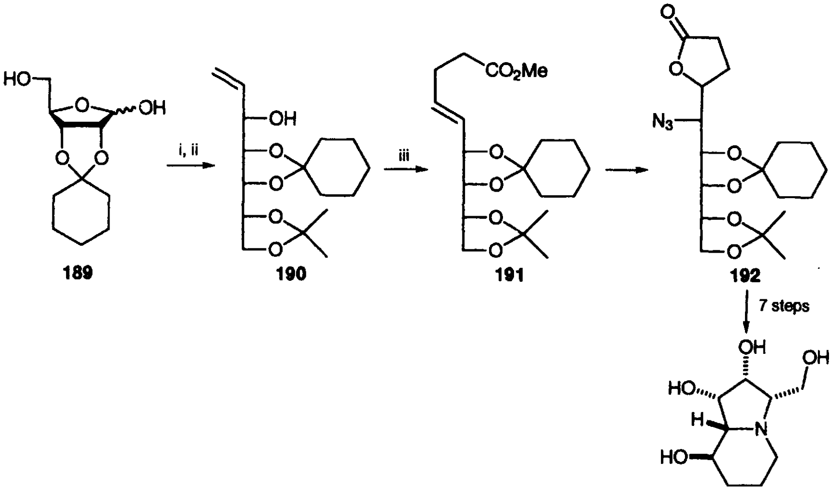
Scheme 39



Reagents: i, CS_2, DCC; ii, 9:1 TFA: H_2O; iii, co-evaporate with H_2O, then IR45 (OH-) resin, GPC.

Scheme 40

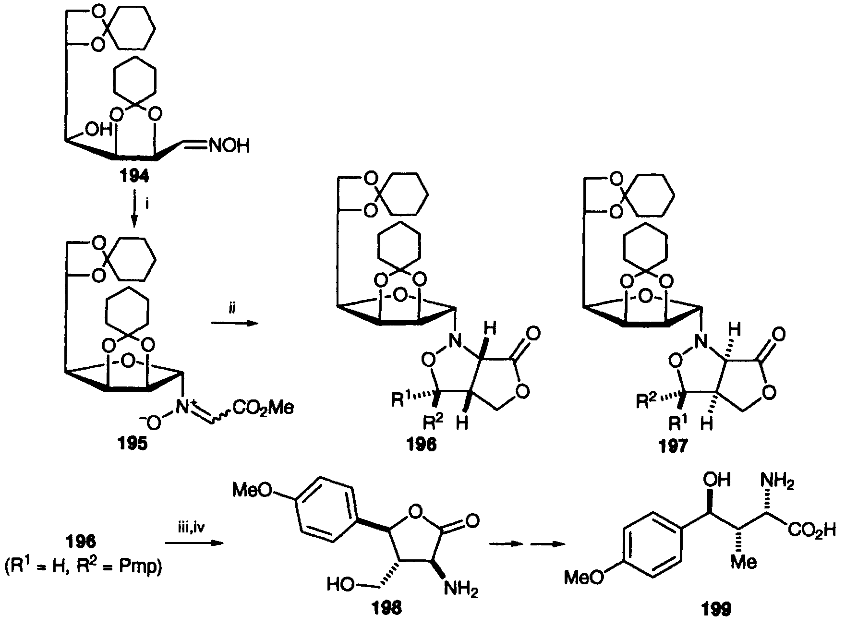
The novel mannosidase inhibitor (3*R*)-3-(hydroxymethyl)swainsonine **193** and its (3*S*)-epimer have been prepared from D-ribose *via* **189** (Scheme 41). Key steps are Grignard addition and cyclohexylidene acetal protection to generate **190**, orthoester Claisen rearrangement to **191**, *cis*-dihydroxylation, lactonization, mesylation and azide displacement yielding **192**, a common intermediate to both **193** (shown) and its 3-epimer.[69]



Reagents: i, $CH_2=CHMgBr$; ii, Me_2CO, H^+; iii, $MeC(OMe)_3$, $EtCO_2H$.

Scheme 41

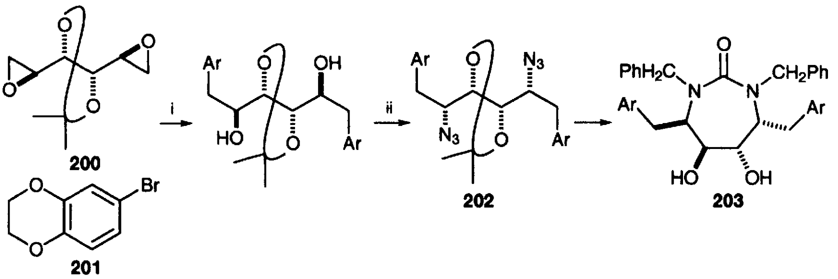
The terminal amino acid of nikkomycin B2 has been prepared from the L-gulose-derived oxime **194**, *via* allylation of **195**, generating isomers **196** and **197**. Elaboration of isomer **196** (R^2 = 4-methoxyphenyl) provided the target **199** (Scheme 42).[70]



Reagents: i, $MeOCH(OH)CO_2Me$; ii, $R^1C(R^2)=CHCH_2OH$, $TiCl_4$; iii, $Mo(CO)_6$; iv, HCl.

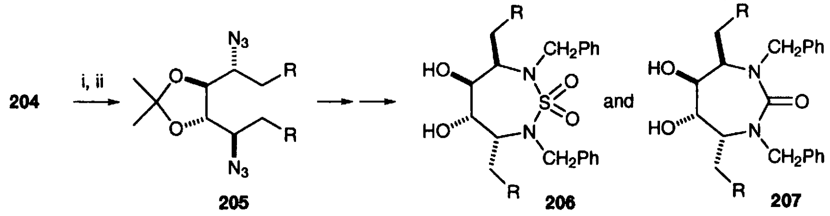
Scheme 42

The C_2-symmetric cyclic ureas **203** (R = phenyl, other aryls), targeted as HIV-1 protease inhibitors, has been prepared *via* a bidirectional synthetic approach from the L-mannonolactone-derived bis-epoxide **200**. The epoxide rings are opened using aryl cuprate derived from **201**, followed by Mitsunobu double azide substitution to yield **202** (Scheme 43).[71] A very similar sort of approach has been employed in the synthesis of both cyclic sulfamides and ureas **206** and **207** *via* the bis-azide **205**, which was also derived from **204** (Scheme 44).[72] This latter method differs from the former in using either phenoxide or Grignard nucleophiles to ring open the starting epoxides.



Reagents: i, *n*-BuLi, CuCN, THF; ii, Ph_3P, DEAD, $(PhO)_2PON_3$.

Scheme 43



R = OPh, $(CH_2)_nPh$ [n = 1,2]

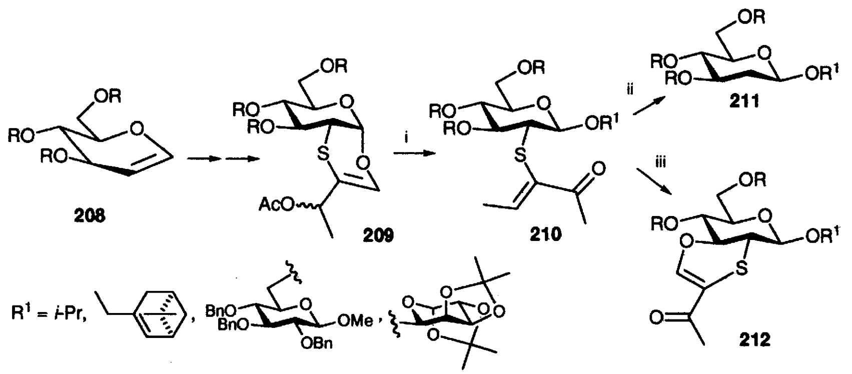
Reagents: i, PhO^- or Grignard; ii, Ph_3P, DEAD, $(PhO)_2PON_3$.

Scheme 44

Syntheses of two diastereomers of 3-methoxy-2-oxa-6-thiabicyclo[3.2.0]-heptan-4-ol from D-xylose and of two diastereomers of 3-methoxy-2-oxa-5-thiabicyclo[2.2.1]heptan-7-ol from methyl 5-acetylthio-2-*O*-mesyl-D-xylofuranoside have been reported.[73]

Glycal **208** was the starting material for a synthesis of sulfur-containing heterocycles **209**, reaction of which with alcohols generating β-glycosides **210**. Further reaction with methyl triflate in nitromethane yielded the new heterocycle **212**, whilst treatment with Raney Ni yielded 2-deoxyglycosides **211** (Scheme 45).[74]

A review on synthesis of both acyclic and heterocyclic natural products from cyclitols [36 refs.] has appeared,[75] and a review of free radical cyclizations involving nitrogen includes examples of preparation of aminocyclitols and polycyclic systems.[76]

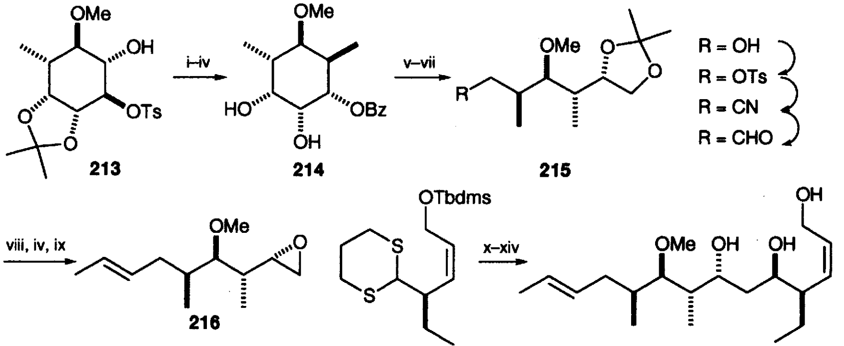


Reagents: i, R^1OH, MeOTf, $MeNO_2$; ii, Raney Ni, wet THF; iii, MeOTf, $MeNO_2$.

Scheme 45

6 Acyclic Compounds

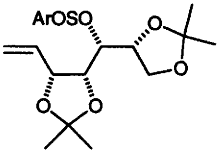
A convergent total synthesis of (−)-PA-48153C (**218**) has been reported starting from L-quebrachitol derivative **213**, elaboration of which afforded intermediate **214**, which was converted into **215** by periodate cleavage, reduction and diol protection. The terminal functionality was then modified by standard means to facilitate a $CrCl_2$-mediated homologation, which, after diol release and Mitsunobu-type conversion of the diol to epoxide, gave **216**. L-Malic acid was the starting material for the other arm of the convergent synthesis, its completion proceeding *via* alkylation of the malic acid-derived dithiane **217** with **216**. Four more steps completed the synthesis of **218** (Scheme 46).[77]



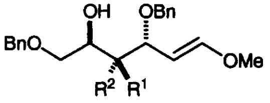
Reagents: i, NaOH, NaOMe; ii, Me_3Al; iii, RBzCl, DMAP, Py; iv, CSA, MeOH; v, $NaIO_4$; vi, $NaBH_4$; vii, CSA, acetone; viii, $MeCHI_2$, $CrCl_2$, THF; ix, Ph_3P, DEAD; x, t-BuLi, HMPA then add **216**; xi, NCS, $AgNO_3$, 2,4,6-collidine, MeCN, H_2O; xii, $NaBH(OAc)_3$; xiii, TBAF; xiv, MnO_2

Scheme 46

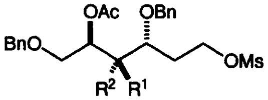
The vinyl ethers **220**, derived respectively from D-glucal and D-galactal, have been converted *via* mesylates **221** into the phytosphingosines **222**.[78]



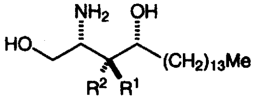
219 Ar = 2,4,-$(NO_2)_2C_6H_3$



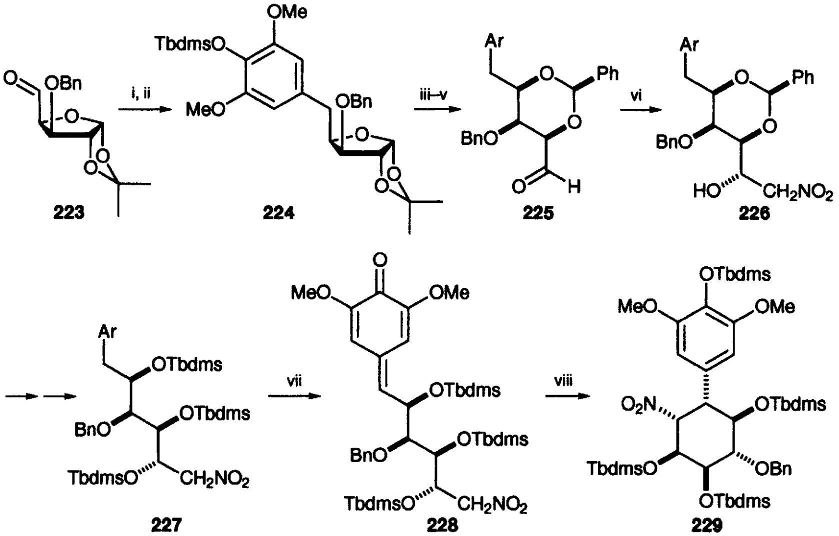
220 R^1 = H; R^2 = OBn
R^1 = OBn; R^2 = H



221



222 R^1 = OH; R^2 = H
R^1 = H; R^2 = OH



Reagents: i, ArZnCl; ii, Et_3N, MsCl, then LAH; iii, Et_3SH, $MgBr_2$; iv, CSA, $PhCH(OMe)_2$; v, HgO, $HgCl_2$; vi, *t*-BuOK, $MeNO_2$; vii, Ag_2O, ultrasound; viii, DMAP, CH_2Cl_2.

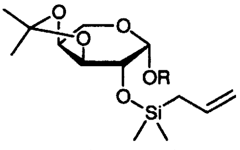
Scheme 47

An approach to the narciclasine alkaloids, such as pancratastatin, starts from D-glucose derived **223**, which underwent arylzinc addition and then mesylation and hydride substitution of the mesylate to give **224**. A key step was the Henry reaction of **225** to give **226** as a single diastereomer, which after deprotection and silylation gave **227** (note that Henry reaction on a silylated analogue of **226** lacked stereocontrol). Ultrasound and silver(I) oxide oxidation generated the key *acyclic* intermediate quinonemethide **228** (hence coverage in this section – see Section 1, Scheme 8 for other pancratistatin work) which on treatment with base underwent cyclization with the anion derived from the methylene carbon α to nitro adding to the quinonemethide to give **229**, which has all the stereochemistry of the pancratistatin cyclohexane, except at the aryl bonded centre (Scheme 47).[79]

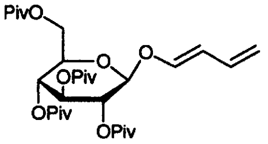
7 Carbohydrates as Chiral Auxiliaries, Reagents and Catalysts

This year has again seen considerable expansion in the application of carbohydrates as chiral auxiliaries, reagents and catalysts and some notable consequential developments.

7.1 Carbohydrate-derived Reagents and Auxiliaries – A review on carbohydrate derivatives as chiral auxiliaries has appeared.[80]



230 R = Me
231 R = Bn



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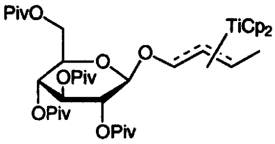

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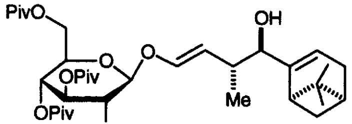

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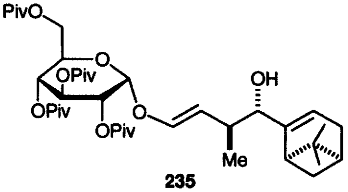
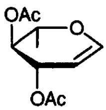


235

This year two examples of chiral allylations with carbohydrate systems have been reported. The first involves a Lewis acid catalysed allylation of aldehydes using carbohydrate allylsilyl ethers **230** or **231**. The best examples involved boron trifluoride as catalyst and heptanal as substrates, but enantioselectivity was modest even in this case, affording products of only 25% and 33% e.e. respectively (*S* enantiomers predominating).[81] The second report features the application of allyl titanium complex **233** (derived from β-glucosyloxy-butadiene **232**) to *diastereoselective* allylations of the (chiral) aldehyde myrtenal and gave exclusively diastereomeric product **234**. The use of the α-anomer of **233** led to complementary diastereoselectivity, with **235** predominating.[82]

An example of a traditional separation of enantiomers by forming separable covalent carbohydrate-linked diastereomeric mixtures involves iodoetherification of **236** with racemic azetidinone, followed by elimination, yielding the azetidinone glycoside **237** as a mixture of separable (*trans*) diastereomers. Glycoside cleavage then led to resolved optically active azetidinones **238** and **239**.[83]



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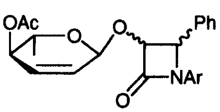

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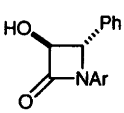

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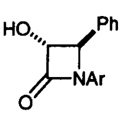

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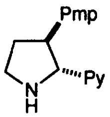
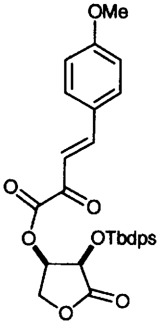


240

Although not an example of a sugar acting as an auxiliary in the traditional sense, a resolution of the chiral pyrrolidine **240** was achieved by co-crystallization with di-*O*-isopropylidene-L-xylo-hex-2-ulosonic acid (diacetone-2-keto-L-gulonic acid).[84]

This year has again seen a range of effective examples of cycloaddition reactions involving one component bearing a sugar auxiliary. The natural lignan *O*-dimethyl-sugiresinol (**244**) was prepared *via* the hetero Diels-Alder reaction of carbohydrate enone **241** and styrene **242** using Eu(fod)$_3$ catalysis, which gave intermediate cycloadduct **243**. This was elaborated to the natural product in a further five steps.[85]



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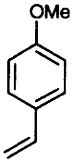

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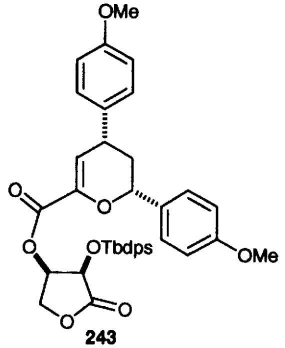

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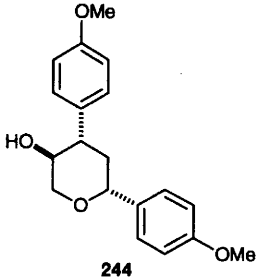
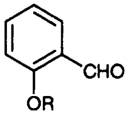


244

Stoodley's group have again reported further examples of applications of their use of glucose-derived auxiliaries. A further example of cycloaddition chemistry was provided by an investigation of the effect of lanthanide catalysts on the diastereomeric outcome of cycloadditions of sugar-derived aryl aldehyde **245**, with diene **246**. This work demonstrated a dependence of diastereomeric outcome on the ionic radius of the lanthanide involved. High selectivity (>90% d.e.) for **248** was seen using Ln(fod)$_3$ where Ln = La, Ce, Pr or Nd. The selectivity in favour of **248** decreased with increasing ionic radius, switching to a 55:45 selectivity in favour of diastereomer **247** at Dy (Table 1).[86]



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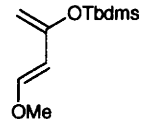

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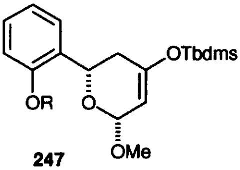

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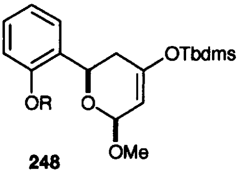

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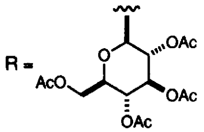
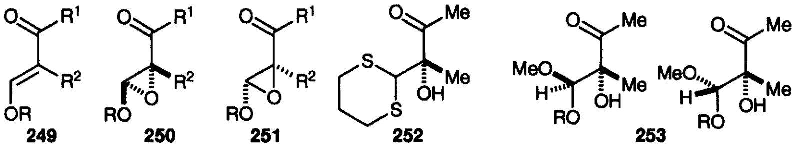
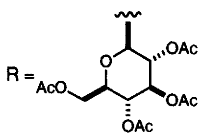


	247	248
La, Ce, Pr, Nd	<5	>95
Eu	18	82
Gd	26	74
Dy	55	45
Ho	61	39
Er	69	31
Yb	66	34

Table 1



249 **250** **251** **252** **253**



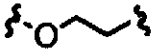
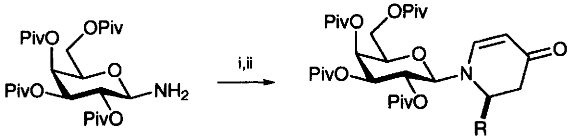
R¹	R²	250	251
Me	Me	90	10
Et	Me	90	10
		91	9
Me	H	69	31
OEt	Me	91	9
		86	14
OEt	H	67	33

Table 2

The same group have reported the diastereoselective epoxidation of a range of enones **249** with dimethyldioxirane, all giving predominantly isomer **250** (over **251**) with diastereomeric ratios of 67:33 to 91:9 (Table 2) The dithiane derivatized building block **252** (released from the auxiliary) was also prepared from **250** ($R^1 = R^2 = Me$); use of dithiane directly led to 82% e.e. product, whereas an indirect route through the mixed acetals **253** (a 9:1 mixture) leads to isolated **252** with 98% e.e.[87]

Kunz and co-workers have reported further applications of hetero cycloadditions of glycosylimines. Glycosylamine **254** was converted to the heterocycle **255** with diastereomeric ratios of at least >20:1 and up to 38:1, through formation of a range of imines and cycloaddition with 1-methoxy-3-trimethylsiloxybuta-1,3-diene under zinc chloride catalysis (Scheme 48). These heterocycles were then elaborated in a number of ways. Hydride reduction and acid catalysed auxiliary release gives **256**, while hydride reduction followed by desulfurization then auxiliary release gives **257**. Diastereoselective conjugate addition of **255** was also employed, giving **258**, which could be further modified by desulfurization to **259**. The disubstituted piperidine **258** ($R = Pr^n$, $R^1 = EEO(CH_2)_3$) was further elaborated to the bicycle **260** and thence to **261**.[88]



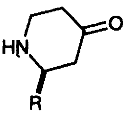
254 **255** R = *n*-Pr, 3-Py, *i*-Pr, 4-CN-Ph

Reagents: i, RCHO; ii, 1-methoxy-3-trimethylsiloxybuta-1,3-diene, $ZnCl_2$.

Scheme 48

Cycloaddition of the nitroso-bearing sugar **262** with the diene **263** provides entry to the bicyclic oxazine **264** after release of the auxiliary. This was then elaborated *via* **265** into the target radiosumin (**266**).[89]

One example of a higher cycloaddition has been reported. The carbohydrate-bearing diene **267** underwent a [6 + 4] cycloaddition reaction with



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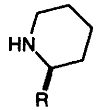

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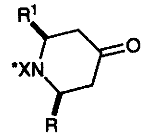

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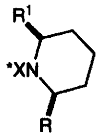

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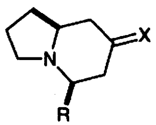
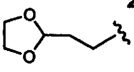
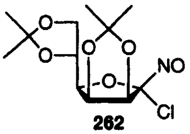


260 X = O
261 X = H_2

R = *n*-Pr, 3-pyridyl; R^1 = Me, EEO$(CH_2)_3$–,





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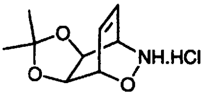

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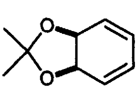

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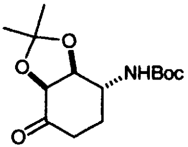

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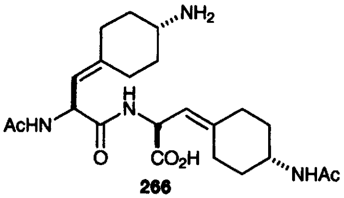

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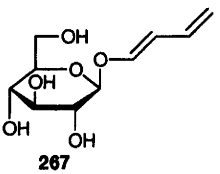
tropone, providing the first example of such a reaction under aqueous conditions. The reaction proceeded under quite mild conditions (50 °C), affording (after acylation) a mixture of the expected *exo*-diastereomers **268** and **269**.[90]



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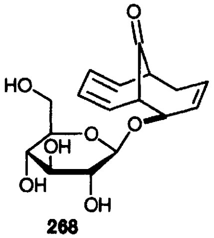

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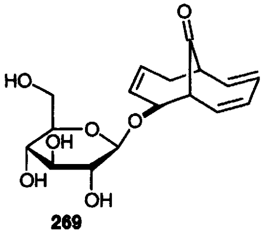

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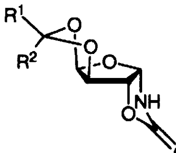
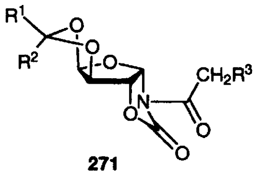
Two examples of the use of sugar-derived chiral oxazolidinones (see the earlier report, Vol. 29, Chapter 24) for controlling asymmetric reactions have been described. The D-xylose derived system **271** was acylated to give **271** the lithium enolate of which (generated using LHMDS) reacted with various aldehydes leading to 'non-Evans' *syn*-aldol products, **272**.[91] The same type of acylated systems **271** ($R^1 = R^2 =$ Me) also underwent diastereoselective acylations and halogenation at the active methine centre, yielding compounds of types **273** and **274**.[92]

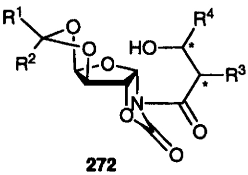
The sugar-fused oxazolidinone **275** has been used to control alkylation/chlorination reactions of α,β-unsaturated systems. Thus, it reacts with ethyl aluminium dichloride and then *N*-chlorosuccinimide to afford adducts **276**, oxidative auxiliary cleavage then providing the chiral α-chloro acids as a 4:1



270
R^1,R^2 = Me or H, Ph



271
R^3 = H, Me, Et, Ph



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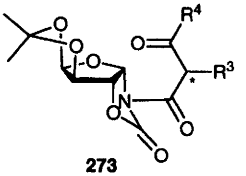
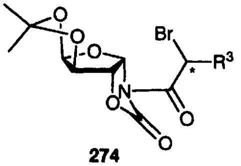


273
R^4 = Me, Et, Ph, *t*-Bu
R^3 = Me, Et, *i*-Pr, Ph



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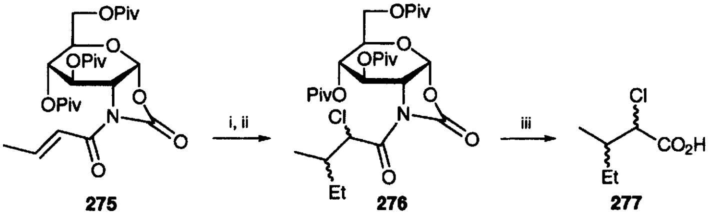
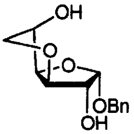
mixture of (2*R*:3*R*) and (2*S*:3*S*) enantiomers **277** (Scheme 49).[93] Benzyl 3,6-anhydro-α-D-glucofuranoside (**278**) has been used as an auxiliary to control a hydride reduction, as a methodology for synthesis of optically active lactones. Thus, **278** was acylated to give **279**, which underwent diastereoselective reduction with zinc borohydride. Hydrolytic removal of the auxiliary then led to concomitant cyclization to the lactones **280**, with e.e. of 82–91%.[94]



Reagents: i, Et_2AlCl; ii, NCS; iii, LiOH, H_2O_2.

Scheme 49

L-Selectride and lithium aluminium hydride reductions of ketone **281** give >98% diastereoselectivity.[95] Reaction of **282** (*S* configuration at sulfur) with methylmagnesium Grignard led to the chiral sulfoxide **283** (*R* configuration at sulfur). In this sense the carbohydrate is not functioning truly as an auxiliary as it it is not affecting the outcome of generation of new chirality, but is simply a chiral template for an achiral reagent substitution.[96]



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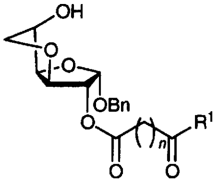

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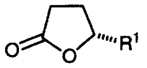
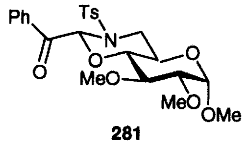


280 R^1 = Ph, Me



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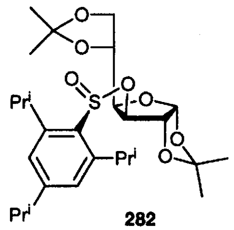

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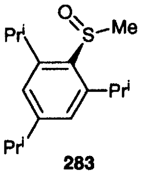

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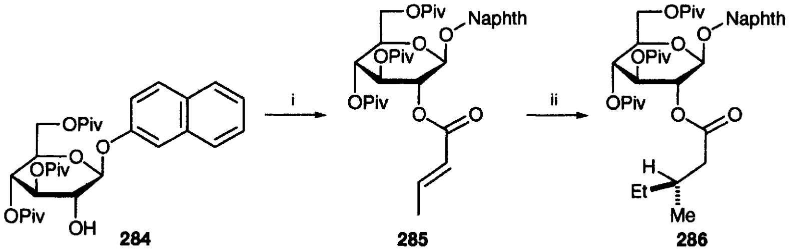
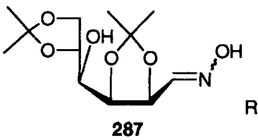
The aryl glycoside **284** (from reaction of the naphthoxide with the precursor α-*gluco*-epoxide; see Chapter 3) was acylated to give enonate **285**. Addition of a cuprate to this led to conjugate adduct **286** with the *S*-configuration at the new chiral centre with >95% selectivity (Scheme 50).[97]



Reagents: i, MeCH=CHCOCl; ii, EtMgBr, CuBr, Me_2S.

Scheme 50

A tandem reaction of **287** with aromatic aldehyde **288** followed by dimethylsulfoxonium methylide $[CH_2SO(CH_3)_2]$ generated adduct **289**, by way of nitrone formation between **287** and **288** (concomitant carbohydrate ring closure to activate the N-nucleophile), ylide addition and then phenoxide promoted expulsion of dimethylsulfoxide to yield **289** (Scheme 51; major isomer shown). Hydroxylamine **289** was then elaborated post-release of the auxiliary into urea-based 5-lipooxygenase inhibitors **290**.[98]



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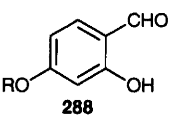

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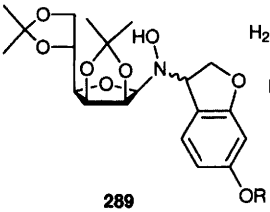

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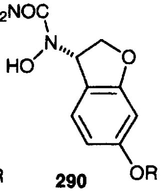
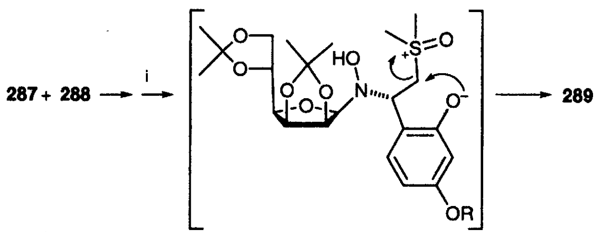


290

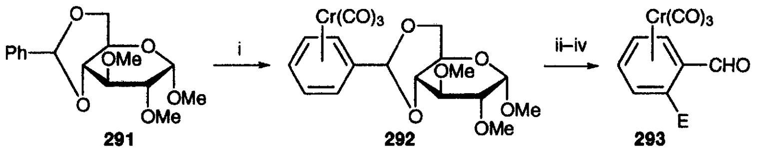
An interesting application of a carbohydrate benzylidene auxiliary has been reported. The benzylidene acetal **291** thus formed an aryl chromium complex (**292**) when treated with chromium hexacarbonyl under standard conditions. Lithiation of this complex then proceeded with high diastereoselectivity and alkylation (with a wide range of electrophiles) and cleavage



Reagents: i, $CH_2SO(Me)_2$.

Scheme 51

of the acetal yielded the chiral complex **283** with >98% e.e. (Scheme 52).[99]

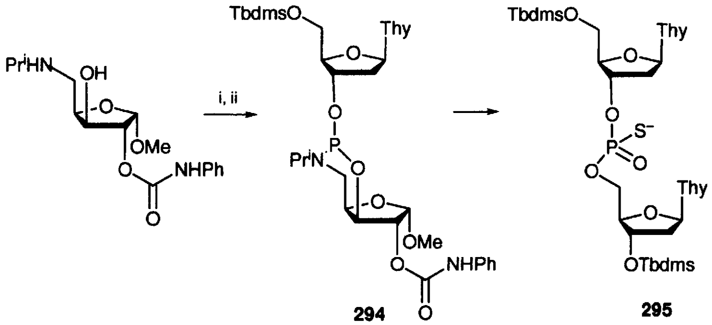


E = Tms, Me, Bu_3Sn, Ph_2COH, SPh, PPh_2, allyl

Reagents: i, $Cr(CO)_6$; ii, BuLi; iii, E^+; iv, H_2SO_4, H_2O.

Scheme 52

An unusual use of a 5-amino-5-deoxy-D-xyloside auxiliary to control the construction of a P-chiral dinucleotide is illustrated in Scheme 53. The auxiliary-bearing derivative **294** thus controls the outcome of the synthesis of **295** from this intermediate.[100] Similar work has been reported previously by these workers (Vol. 30, Chapter 20, ref. 202).

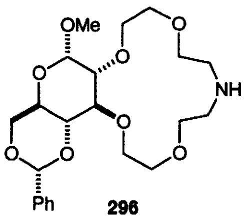


Reagents: i, PCl_3, Et_3N; ii, 5'-O-Tbdms thymidine, Et_3N.

Scheme 53

A review has appeared on the preparation of monodeuterated glycerol, chiral deuterated glycines, chiral amino acids and (2*R*,3*S*)-3-alkylmalic acids using diacetone-D-glucose as a chiral template.[101]

7.2 Carbohydrate-derived Catalysts – A review on the applications of phase transfer catalysts in carbohydrate chemistry has appeared, covering anomeric transformations, glycosylations (see Chapter 3) and the use of sugar derivatives as phase transfer catalysts.[102]



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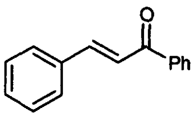

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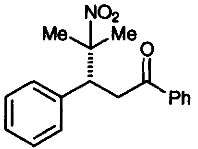
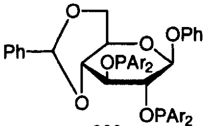


298

The carbohydrate aza-crown **296** (see Section 4 for synthesis) has been employed as a phase transfer catalyst for asymmetric conjugate addition of nitroalkyl anions. The α-anion of nitroisopropane (generated using sodium *tert*-butoxide), reacts with chalcone **297** in toluene with 7 mol% of catalyst, to give the chiral adduct **298** with 90% e.e, with the *S*-configuation at the new centre. Other conjugate systems were evaluated but this is the most selective example.[47]

A study of the electronic tuning in sugar-derived bis-phosphinite ligands (**299** and **300**) used as catalysts for asymmetric hydrogenations of dehydroamino acids established that electron-releasing substitutents in the aryl phosphorus substituents leads to higher e.e.s. By use of the information gained enantiomeric purity in excess of 99% was obtained for the reaction shown in Scheme 54. It is notable that ligands **299** led to *S* amino acids, while the ligand **300** led to *R*-amino acids (both sugars having the D-configuration).[103]



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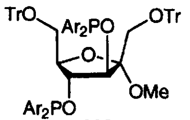

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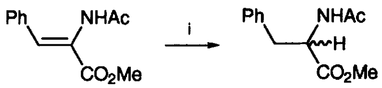
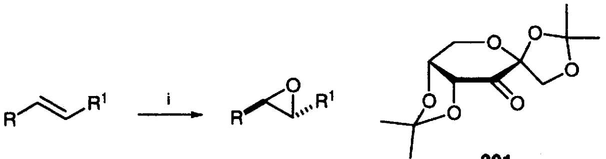


(Ligand = **299**, **300**)

Reagents: i, H_2, Rh(ligand)$^+X^-$

Scheme 54

A significant development reported in full this year is the use of a sugar-derived ketone as a catalyst ligand to effect dioxirane-based asymmetric alkene epoxidation. Although a number of groups have proposed and/or evaluated various C_2- or *pseudo*-C_2 symmetric ketones (including carbohydrate-based compounds) for this process, this provides the first practically successful example which proceeds with high selectivity. Thus, fructose-derived ketone **301** is an effective agent for the epoxidation of a number of alkenes, using Oxone® ($KHSO_5$) as primary oxidizing agent (Scheme 55) (see also a preliminary report: *J. Am. Chem. Soc*, 1997, **62**, 2326). As had been proposed by other workers, *E*-alkenes (or trisubstituted) would be the favoured substrate types from transition state models, to provide a complement to Jacobsen-Katsuki type technology. Styrene was epoxidized to (*R,R*)-styrene epoxide using 30 mol% catalyst in 75% yield and 97% e.e. (Scheme 55). An evaluation of the pH-dependence and optimization of the catalytic system was reported.[104,105]



301

Reagents: i, Oxone, **301**.

Scheme 55

These authors subsequently reported further details and more examples, including some which widened the range of substitution patterns (Scheme 56). They also made the enantiomer of **301** (from L-sorbose) and showed that this gives the same degree of (opposite sense) enantioselectivity as **301**.[106]

Reagents: i, Oxone, **301**.

Scheme 56

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