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FORMATION OF CONVENIENT CHIRAL INTERMEDIATES FROM CARBOHYDRATES AND THEIR USE IN SYNTHESIS

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1. INTRODUCTION

In 1972 when the subject of carbohydrates in the synthesis of optically active non-carbohydrate compounds was first reviewed[1] there were relatively few examples, even although the potential of carbohydrates for such purposes had been recognised for many years. Over the last 10 years or so the situation has changed dramatically to the point where studies with monosaccharides are no longer the preserve of the carbohydrate chemist but are very much part of mainstream organic chemistry. A number of review articles[2-7] since 1972 have discussed the general philosophy of use of carbohydrates and given examples of their successful application in the synthesis of natural products and other chiral molecules. This review will also present illustrative examples of the use of carbohydrates in chiral synthesis. However, since the convenient application of carbohydrates in chiral synthesis requires that the natural monosaccharides as well as being inexpensive, should be easily converted into a key intermediate, the emphasis of this review will be more on the description of such intermediates which may have wide potential applications, rather than on the subsequent manipulation of those intermediates. For this reason the review will be organised in terms of the sugar precursor rather than in terms of target molecules or reactions employed. (To emphasise that carbohydrates are now mainstream organic chemistry not all the formulae are according to the tradition of carbohydrate chemists—the format is that of the original papers.) In some Schemes all the reagents are listed, in others where each step shown is a multistage sequence or where the procedures are obvious from the text, reagents are omitted.

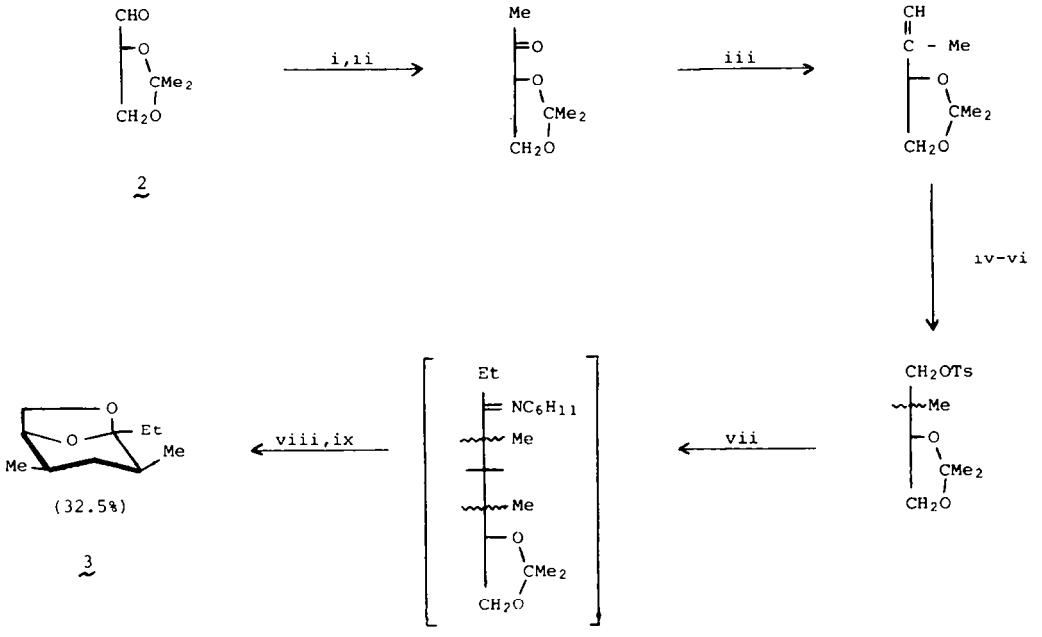
A number of review articles on carbohydrate chemistry concerned with relative reactivities of hydroxyl groups,[8] selective removal of protecting groups,[9] unsaturated sugars,[10] formation[11] and reactions[12] of cyclic acetals are of particular interest to manipulators of carbohydrates for chiral synthesis. Other information is to be found throughout the series Advances in Carbohydrate

Chemistry and Biochemistry and in the Chemical Society Series Specialist Reports on Carbohydrate Chemistry.

2. D-MANNITOL

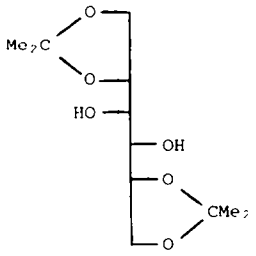
D-Mannitol, an inexpensive hexitol obtained from a variety of natural sources or produced by electrochemical reduction of D-glucose under alkaline (i.e. epimerising) conditions, is readily converted into a number of derivatives which are convenient for subsequent synthesis. The derivatisation depends primarily on the possibilities for selective acetalisation of pairs of OH groups. Thus by control of the conditions of acetonation or by selective hydrolysis it is possible to form 1,2:5,6 or 1,2:3,4-di-isopropylidene derivatives. For example, glycol cleavage of 1,2:5,6-di-O-isopropylidene-D-mannitol[13] **1** with sodium periodate or lead tetraacetate affords 2,3-O-isopropylidene-D-glyceraldehyde **2**. There are many descriptions of convenient routes to **2** but recent papers make it clear that the reaction conditions must be controlled to avoid racemisation.[14-16] The aldehyde **2** has been used[17] for the synthesis (Scheme 1) of (−)-α-multistratin **3** the pheromone from the smaller European elm-bark beetle. Other compounds prepared from **2** include *R*(−) ipsdienol[18] **4** (Scheme 2) an enantiomer of another bark beetle pheromone and prosymal[19] **5** and piperoxan[17] **6** which are competitive antagonists of adrenalin at α-adrenergic receptors. Both the (*R*) and (*S*)-enantiomers of 1-alkylamino-3-aryloxy-2-propanols which are used in medicine as β-blockers have also been prepared[20] from **2** as has prostaglandin F2α.[21] The two enantiomers of isopropylidene glyceraldehyde have been used to show that double stereodifferentiation can be used to alter Crams rule selectivity in addition to chiral aldehydes.[22] This procedure should have considerable application in chiral synthesis.

Following conversion of **2** into *S*(−)benzyl 2,3-epoxypropylether **7** and condensation of the latter with 3,4-dimethoxybenzylcyanide a synthesis of (−)mesembrine **8** has been elaborated.[23] The epoxypropyl ether was also an intermediate for *R*(−) - gamma - benzyloxymethyl - gamma - butyrolactone[24] **9** which has been used for the synthesis of (+)quebrachamine[25] (−)eburraminone[26] and nuciferal.[27] (+)-Brefeldin A **10** has also been prepared[28] from **2** via the iodide **11** and malonate condensation product **12** which was converted into **10** in a multistage sequence. The formation of (+)-Brefeldin **10** from D-mannitol provides an interesting example of



Reagents: i, MeMgI-Et_2O; ii, CrO_3-Me_2CO; iii, $Ph_3P = CH_2$; iv, B_2H_6-THF; v, H_2O_2-NaOH; vi, TsCl-py; vii, $[C_6H_{11}N = CEtCHMe]^-$; viii, dil. HCl; ix, g.l.c.

Scheme 1.



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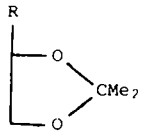
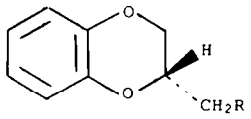
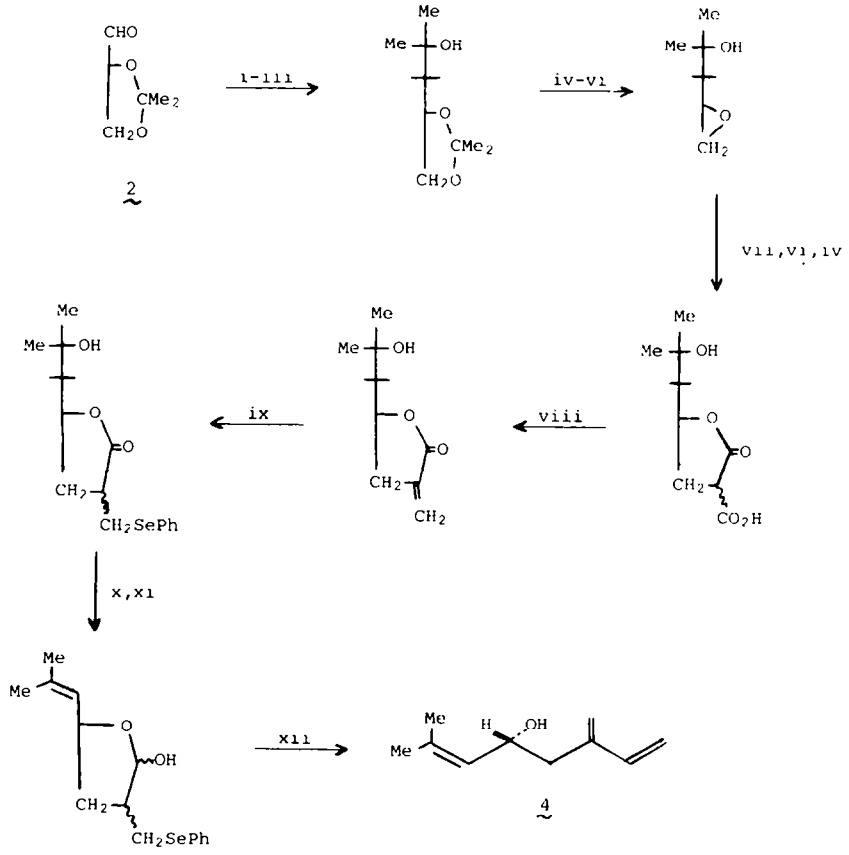


2 R = CHO
11 R = CH_2I
12 R = $CH(CO_2Et)_2$

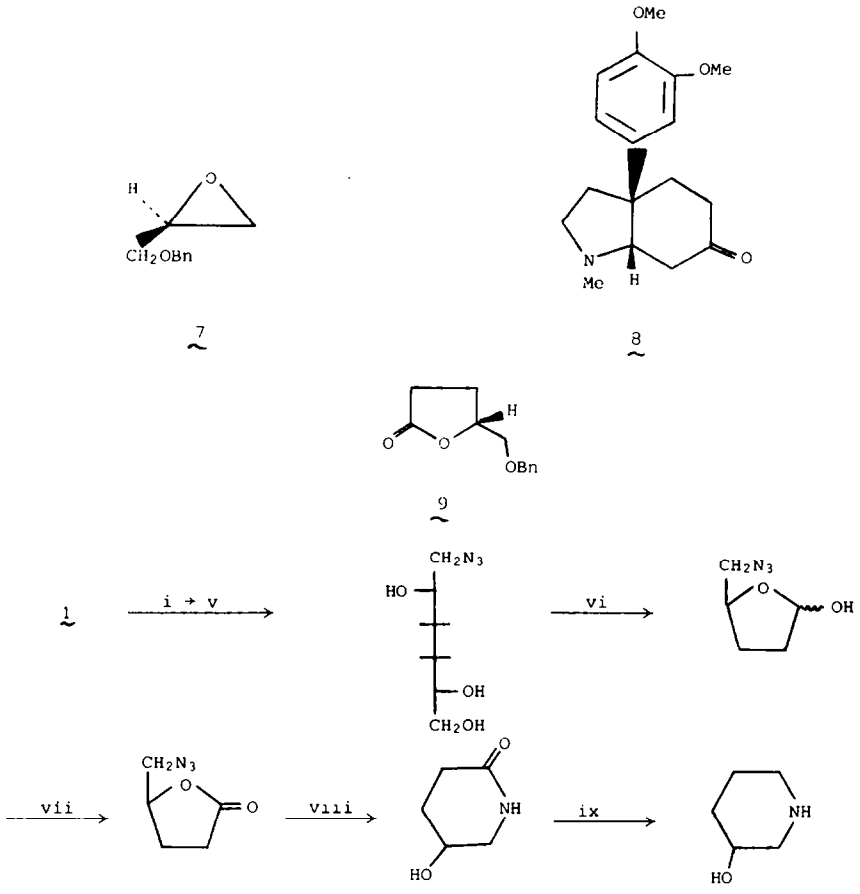


5 R = NEt_2 (prosymal)
6 R = piperidinyl (piperoxan)



Reagents: i, $Ph_3P - CMe_2$; ii, $Hg(OAc)_2$; iii, $NaBH_4$; iv, H_3O^+; v, TsCl (1 mol) - py; vi, aq. KOH; vii, $CH_2(CO_2Et)_2$-EtONa; viii, $HCHO-Et_2NH$; ix, PhSeH; x, $POCl_3$-py; xi, Bu^i_2AlH-

Scheme 2.



Reagents: i, MsCl; ii, Zn/NaI/DMF; iii, H^+; iv, TsCl; v, NaN_3; vi, $NaIO_4$; vii, CrO_3/py; viii, H_2/Pd; ix, $LiAlH_4$.

Scheme 3.

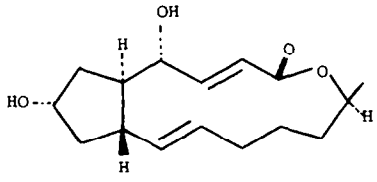
the formation of a chiral cyclopentane derivative from a carbohydrate, the cyclisation step being the transformation **13** to **14** in the presence of $NaN(TMS)_2$.[29]

As well as providing a source of **2** the D-mannitol derivative **1** has been used in procedures which depend on the ease of elimination or substitution of the OH groups at C-3 and C-4. Thus the streptolidine lactone[30] **15** and S(−)piperidinol[31] (Scheme 3) have been prepared conveniently.

1,2:3,4-Di-O-isopropylidene-D-mannitol[32,33] **16** provides an oxidation with lead tetraacetate or sodium periodate a convenient source of the acyclic aldehydo-D-arabinose derivative **17**.[33] This derivative has been used as a starting point for the synthesis of enantiomeric pairs of glycollic acid esters which have been incorporated into anticholinergic drugs.[1] Additions to such aldehydo sugars (or keto sugars) are usually highly stereoselective[1] as are 1,4-addition reactions to some $\alpha\beta$-unsaturated esters such as **18** which are also obtainable from **17** and which provide a route via products such as **19** to optically active butyrolactones[34] **20**. It is not unusual to find that the products from reactions of different Grignard reagents with carbohydrates have opposite stereochemistry or that Grignard reagents and alkyl(aryl) lithiums give configurationally different products.[35,36]

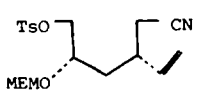
The D-mannitol derivatives **2** and **17** have been used to make a variety of D-pentitols, 2-amino-2-deoxy-D-pentitols and 2-deoxy-D-pentitols which have other synthetic applications.[37]

D-Mannitol is also a convenient precursor for tetrahydrofuran derivatives since on treatment



(+)-Brefeldin A

10



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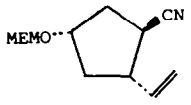

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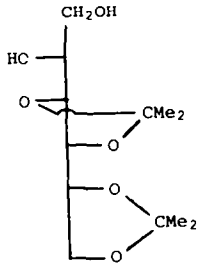

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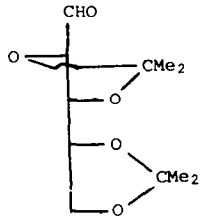

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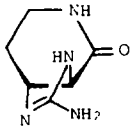

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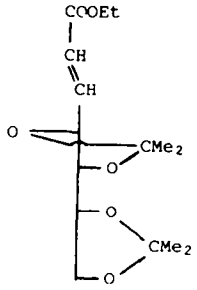

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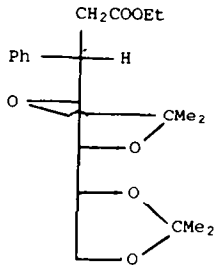

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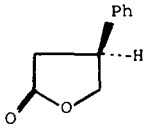

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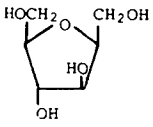

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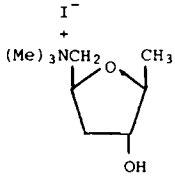


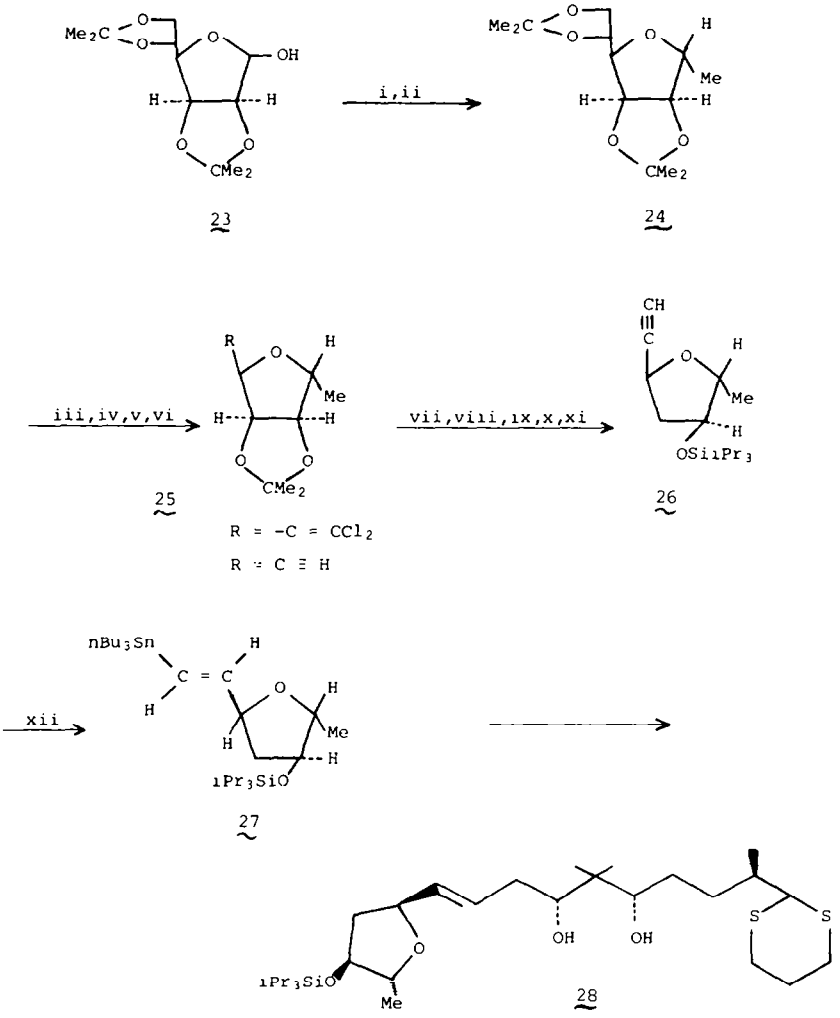
22

with acid it is readily converted into 2,5-anhydro-D-glucitol[38] **21** which is readily isolated and purified as its 1,3-O-isopropylidene derivative. 2,5-Anhydro-D-glucitol has been used for the synthesis of (+)muscarine **22**.[39,40]

3. D-MANNOSE

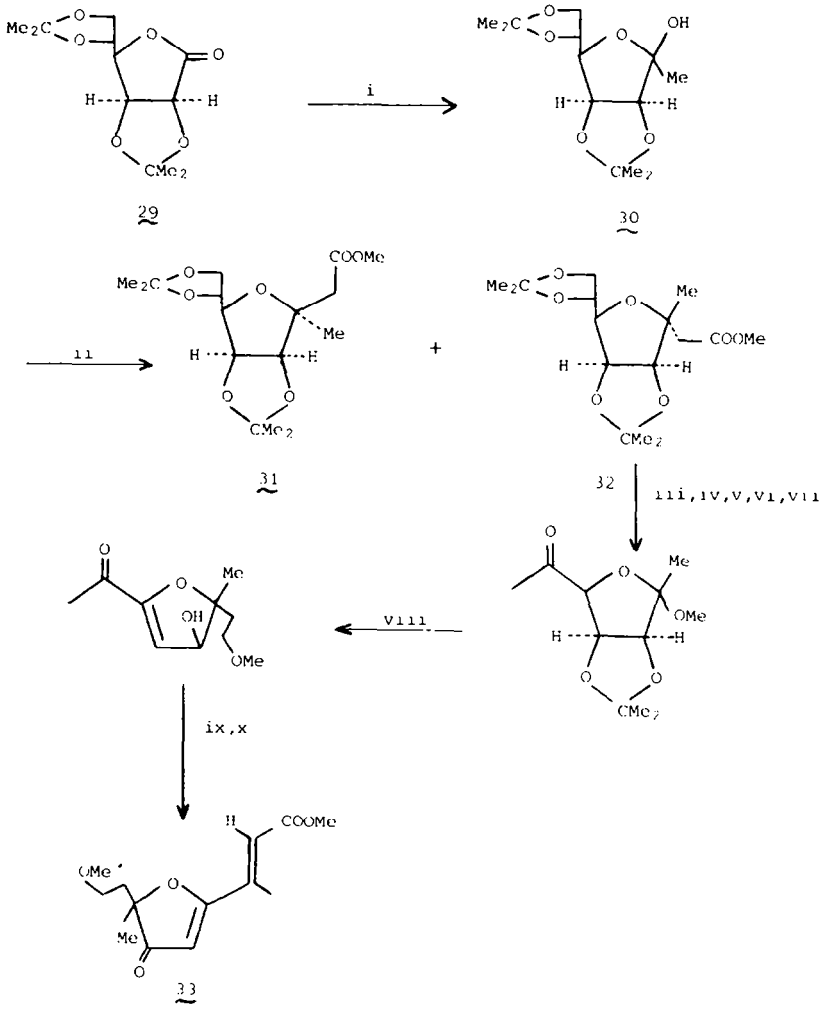
Of the readily available D-mannose derivatives, it is the 2,3:5,6-di-O-isopropylidene-D-manno-furanose[41] **23** that has found most application because it provides one stage access to a sugar with the OH groups except that at C-1 masked and also because selective hydrolysis of the 5,6-isopropylidene derivative is straightforward.

For example **23** has been used[42] for the stereocontrolled construction of the C-3–C-17 fragment **28** of the boron containing antibiotic aplasmomycin. The bisacetonide **23** was converted (Scheme 4) into the tetrahydrofuran **24**, the C-5–C-6 sugar fragment was replaced by an acetylenic group **25**, C-2 was protected and C-3 converted into a deoxy group. The compound **26** was coupled via



Reagents: i, MeLi; ii, TsCl/py; iii, H_3O^+; iv, $NaIO_4$; v, $BrCl_3C/(Me_2N)_3P$; vi, BuLi; vii, H_3O^+; viii, Pr_3SiCl; ix, **Triflic anhydride**; x, Bu_4NI; xi, $NaBH_4/Bu_3SnCl$; xii, Bu_3SnH.

Scheme 4.



Reagents: i, MeLi; ii, Ph_3P = CHCOOMe/MeCN/125 psi/160°; iii, $LiAlH_4$; iv, MeI; v, E^+ then $NaIO_4$; vi, MeLi; vii, CrO_3; viii, NaOMe/MeOH; ix, Ph_3P CHCOOMe/MeCN; x, $AgCO_3$/celite.

Scheme 5.

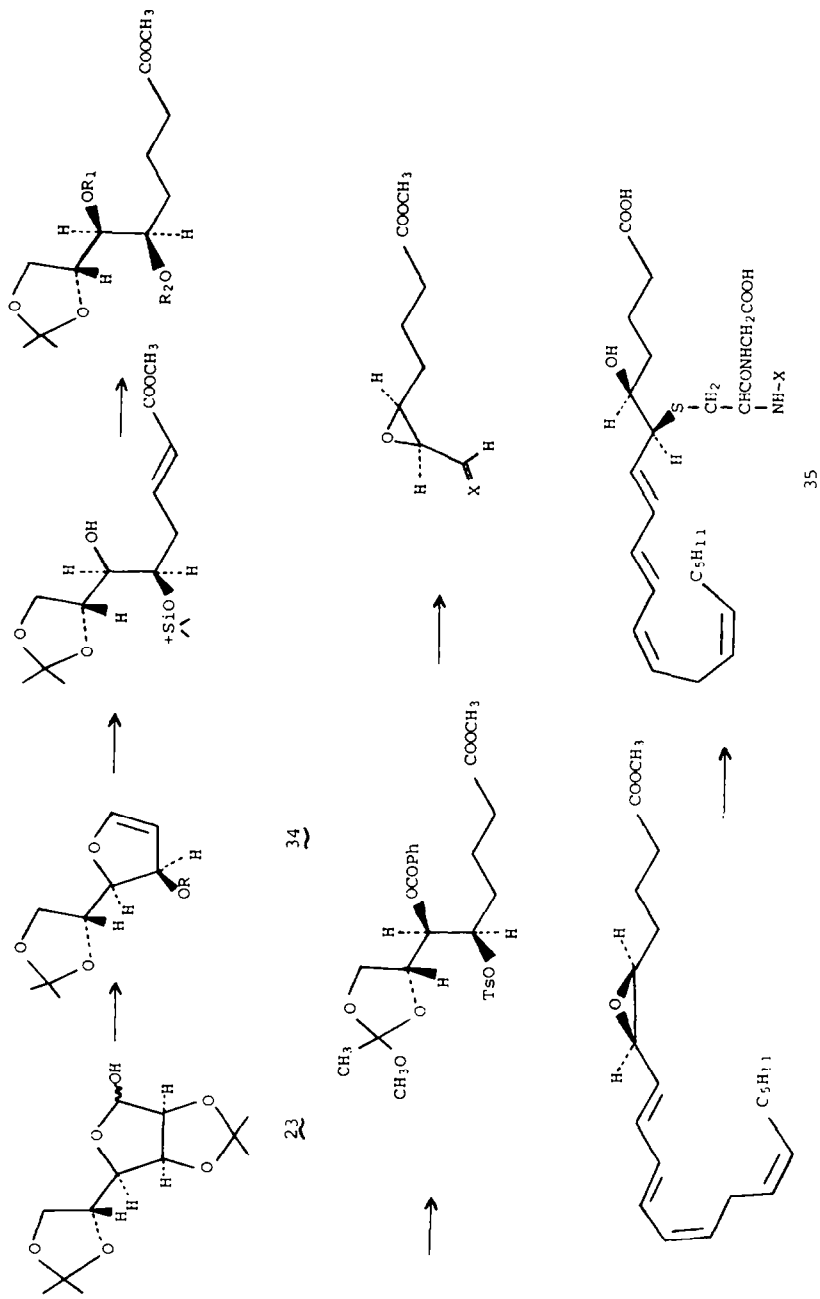
its tributyltin derivative **27** with another optically active fragment derived from (+)pulegone to give **28**.

In the study of the synthesis of chiral models of the furanone moiety of germacranolide sesquiterpenes[43] illustrated in Scheme 5 **23** was converted into the lactone **29**, and the lactone treated with methylithium to give **30** which under extremely forcing conditions underwent a Wittig reaction to give **31** and **32**. Further manipulation of the furanoid ring gave the model compound **33**.

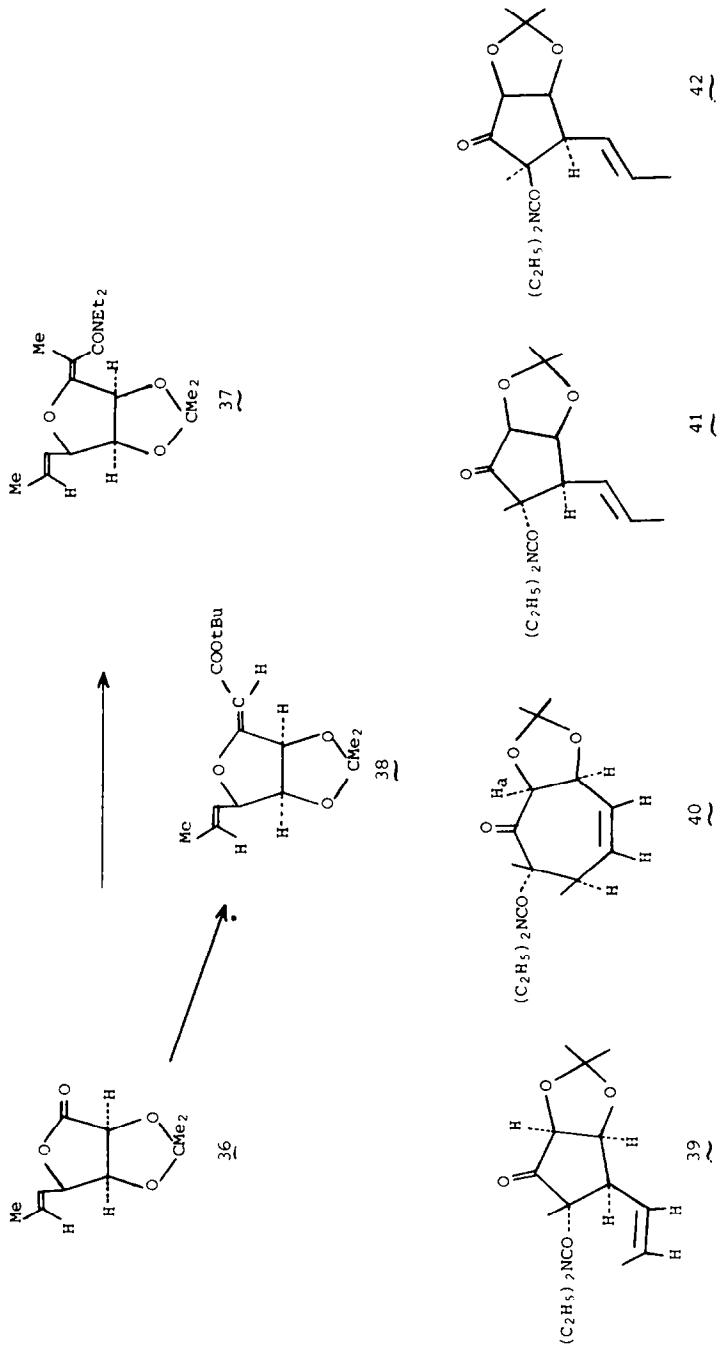
Other applications have been in leukotriene synthesis. The bisacetonide **23** following chlorination and treatment with base gives the furanoid glycal **34**. This glycal (protected at C-3) on hydroxymercuration followed by sequential treatment with potassium iodide and sodium borohydride affords a 2-deoxy hemiacetal which was converted into 6-epi-LTC **35** in a multistage sequence the main intermediates being shown in Scheme 6.[44]

The same 2-deoxyhemiacetal has been used in a similar synthesis[45] of leukotriene B.

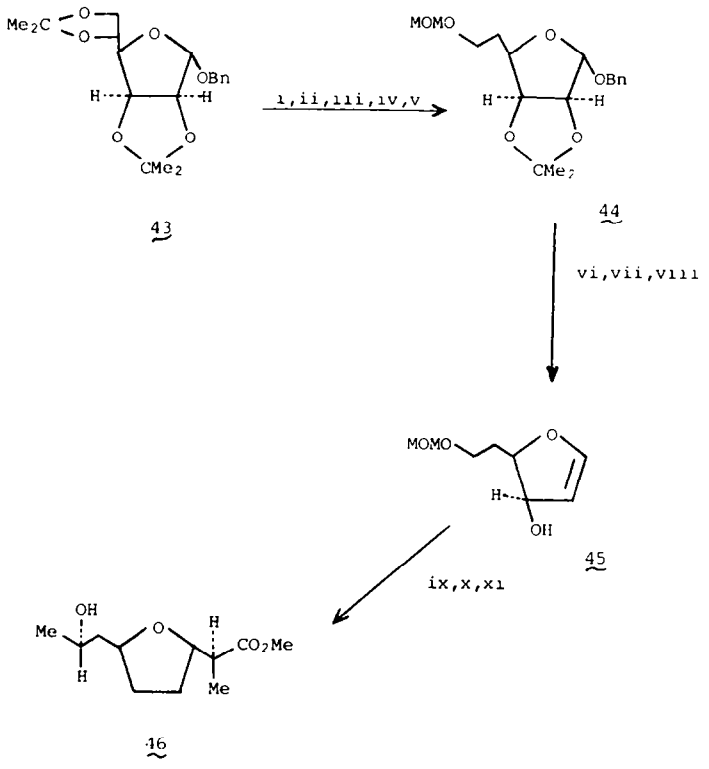
The bisacetonide **23** has also provided convenient entry via the lactone[46] **36** (Scheme 7) to 2-alkylidene-5-vinyltetrahydrofurans required as substrates for Pd-catalysed 1,3-oxygen to



Scheme 6.



Scheme 7.



Reagents: i, H^+/MeOH; ii, $Me_2NCH(OMe)_2$,CH_2Cl_2; iii, Ac_2O/130°; iv, 9BBN;NaOH,H_2O_2; v, KH,$ClCH_2OH$; vi, Li,NH_3,-78°; vii, Ph_3P/CCl_4; viii, Li,NH_3; ix, n-BuLi,C_2H_5COCl; LDA/THF; Me_3SiCl,H_2O,OH^-,CH_3N_2; x, H_2,Rh/C/THF; xi, oxidation-addition reactions.

Scheme 8.

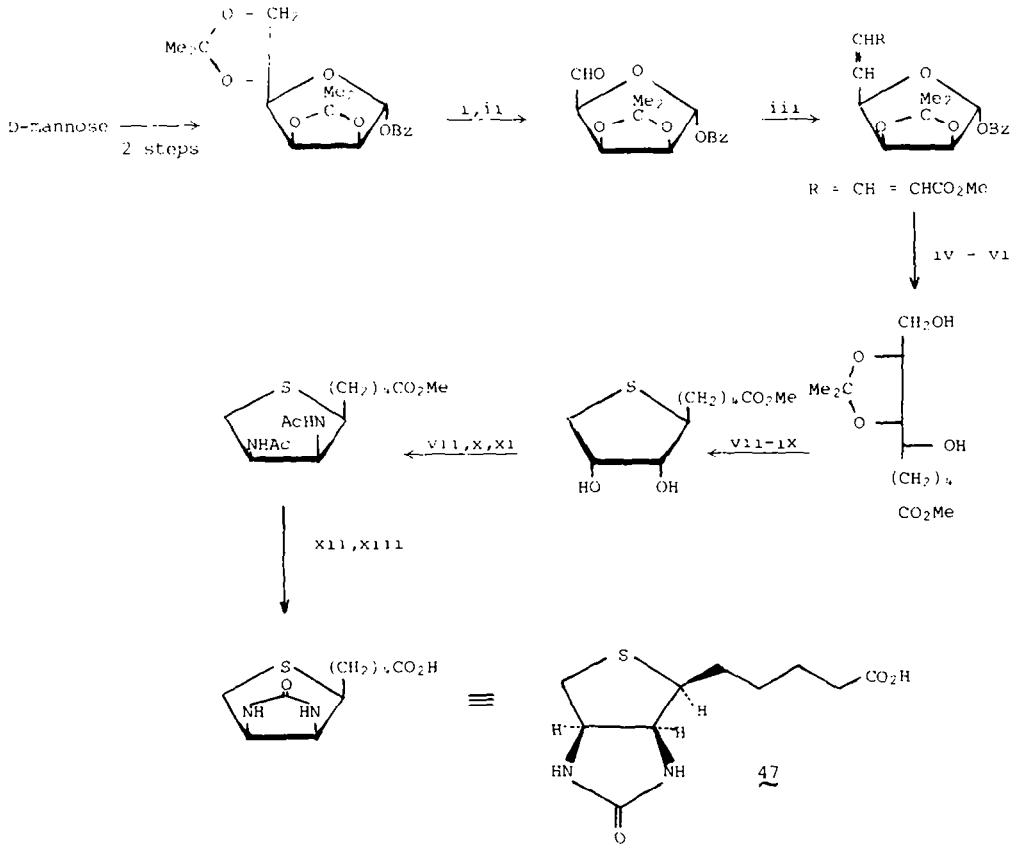
carbon alkyl shifts applied to cyclopentanone synthesis.[47] Thus **36** with 1-(diethyamino)propyne and anhydrous magnesium bromide gave **37** as a single isomer with the *E*-configuration. A two step procedure involving addition of the lithium enolate of t-butylacetate, isolation of the stable β-hydroxy ester and then treatment with mesyl chloride in DBU gave **38** as a mixture of *E* and *Z* isomers. With such products it was possible to study all aspects of the stereochemistry of the Pd-catalysed reactions. For example **37** was converted into a mixture of **39**, **40**, **41** and **42**.

Another interesting use of **23** has been as a precursor for furanoid glycals for studies of the enolate-Claisen rearrangement. The method has been applied[49,50] to the synthesis of optically active nonactic acids as shown in Scheme 8. The glycal **45** is formed by conventional steps, the enolate-Claisen step (**45**–**46**) proceeds in good yield, and the subsequent manipulation is by conventional methods. The total stereospecific synthesis of (+)biotin **47** has been achieved from mannose (Scheme 9) providing an example of both chain extension and then of thiofuran formation by conventional steps.[51]

Methyl α-D-mannopyranoside, forms a 4,6-acetal (similar to methyl α-D-glucopyranoside—see later) and this has been used as a starting material in an approach to the synthesis of maytansinoids.[52]

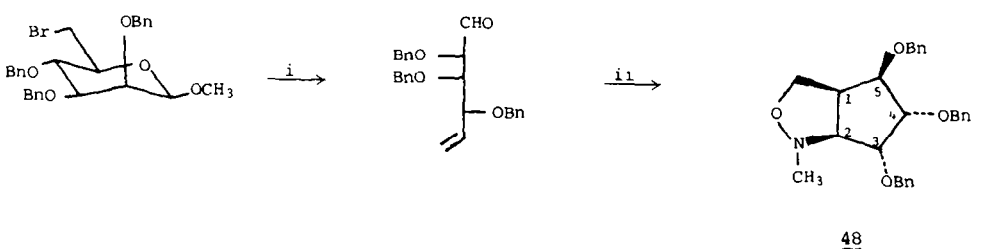
Methods for converting mannose derivatives into cyclopentanes **48** and **49** via intramolecular nitrone–olefine reactions have been reported (Scheme 10).[53]

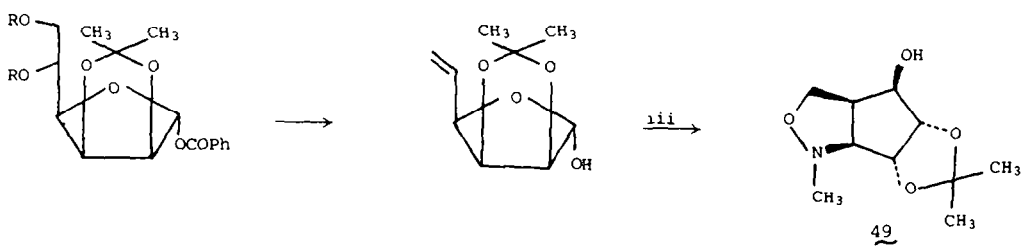
D-Mannose has been converted via methyl α-D-mannopyranoside into D-mannosan which in turn gives 1,6:3,4-anhydro β-D-talopyranose **50** (Scheme 11).[54] Compound **50** was converted via the intermediates shown into methyl N-acetyl-α-D-sibriosaminide (54).



Reagents: i, H_3O^+; ii, $NaIO_4$; iii, Ph_3P = CHR; iv, H_2-Pd; v, MeONa-MeOH; vi, $NaBH_4$; vii, MsCl-py; viii, Na_2S-HMPT; ix, aq. HCO_2H; x, NaN_3-HMPT; xi, H_2-Pt-MeOH-Ac_2O; xii, $Ba(OH)_2$; xiii, $COCl_2$.

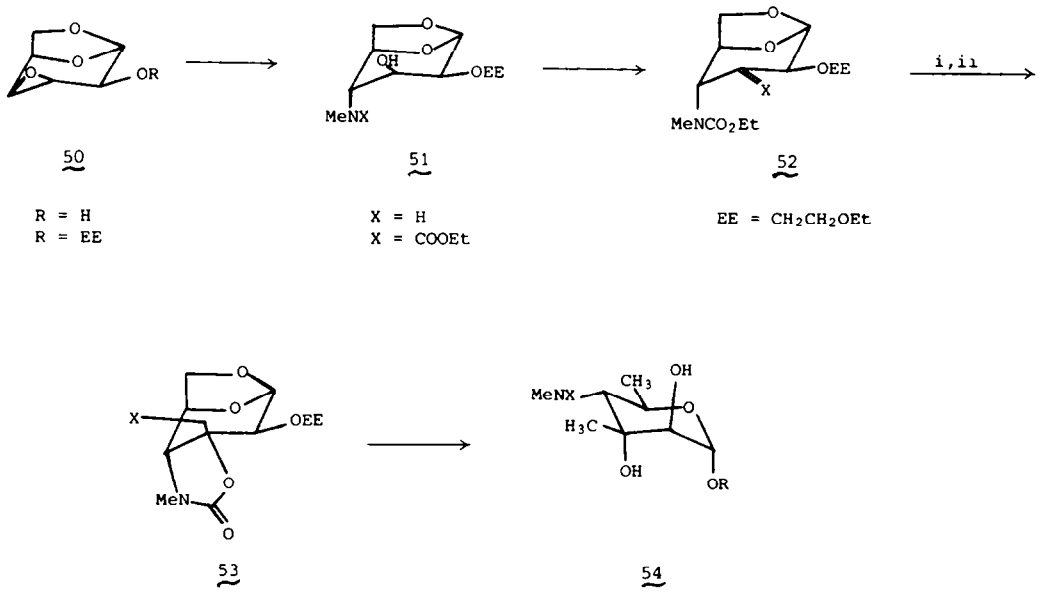
Scheme 9.





Reagents: i, Zn/EtOH; ii, N-methyl hydroxylamine; iii, several steps.

Scheme 10.



Reagents: 52 X = CH_2; i, iodinium dicollidine perchlorate; ii, $LAlH_4$ → 53 X = H.

Scheme 11.

4. L-ARABINOSE

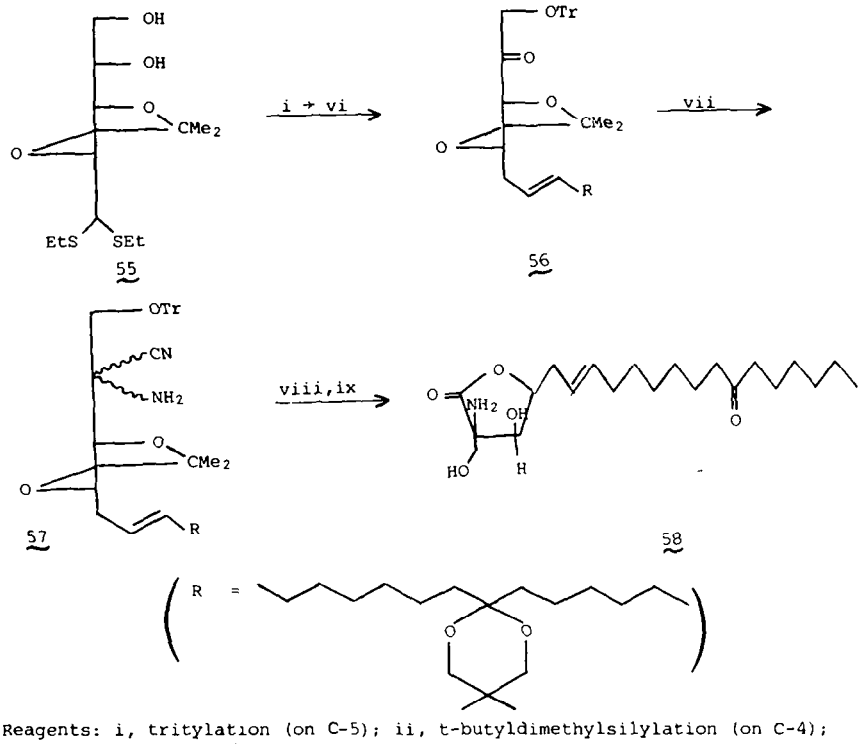
L-Arabinose readily forms a dithioacetal,[55] a 2,3:4,5-di-isopropylidene aldehydo derivative,[56] a 4,5-isopropylidene dithioacetal,[57] methyl β-L-arabinopyranoside[58] and its 3,4-isopropylidene derivative[59,60] and various other derivatives in high yield. Despite this versatility there have to date only been a few examples of chiral syntheses from L-arabinose.

In Scheme 12 is illustrated a synthesis[61,62] of (−)anhydromyrocin (**58**) the enantiomer of the γ-lactone obtained from myriocin. The synthesis, involves diethylthioacetal formation to give **55** protection of the OH groups on C-2 to C-5, de-thioacetalation and chain extension and oxidation to give **56**. Following formation of the cyanomine **57** and hydrolysis the lactone **58** was obtained. From the viewpoint of carbohydrate manipulation it should be noted that de-thioacetalation of **55** (with an isopropylidene group across C-2–C-3, a trityl group on C-5 and a t-butyldimethylsilyl group on C-4) with mercuric chloride–mercuric oxide in acetate gave a high yield of the required aldehyde and there were none of the competing intramolecular reactions or other problems which often cause difficulties in de-thioacetalation reactions.[63]

Another use of L-arabinose, again starting from the diethylthioacetal was the synthesis of ring A of ambruticin[64] **59**. The aldehyde **60** was formed with difficulty from the diethylthioacetal by treatment with iodine in sodium bicarbonate. Compound **60** was converted into **62** as illustrated in Scheme 13. Following formation of the $\alpha\beta$-unsaturated ester **62** ring closure was effected with NaOMe to give **63**. Compound **63** was related to ring A of ambruticin.

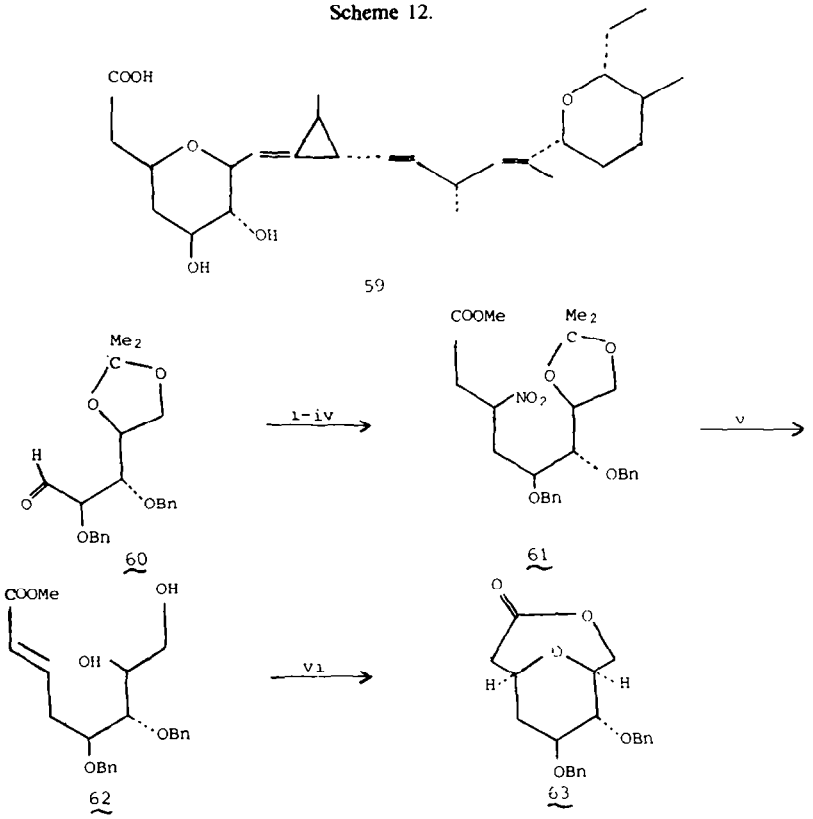
Whereas 2,3-O-isopropylidene-D-glyceraldehyde is readily obtained from D-mannitol, the corresponding L-isomer is obtained from 4,5-O-isopropylidene L-arabinose diethylthioacetal. The L-glyceraldehyde derivative has found use in chiral synthesis.[65]

The aldehydo-tetra-O-acetyl-L-arabinose, obtained via the diethylthioacetal was converted into **64** by treatment with Ph_3PCHCO_2Me (Scheme 14).[56] This dienophile with cyclopentadiene gave the crystalline adduct **65** that was an optically pure single product, one of the four isomers possible in principle from the cycloaddition. Conventional manipulation of **65** gave the tetra-C-substituted cyclopentane[66] having the 1*S*, 2*R*, 4*S*, 5*S* configuration of ring substituents. This approach to chiral cyclopentanes may have some value in the synthesis of prostaglandin analogues and certainly shows the scope of the method for forming cyclopentanes although in some cases mixtures of isomers were obtained.



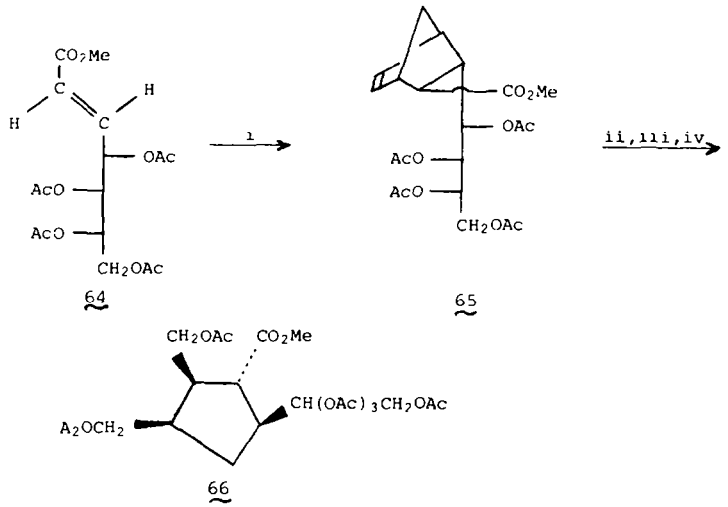
Reagents: i, tritylation (on C-5); ii, t-butyldimethylsilylation (on C-4); iii, $HgCl_2$/HgO/95% aq acetone; iv, chain extension by one carbon then Wittig reaction; v, desilylation ($NBu^{t}_{4}F^{-}$); vi, DMSO/Ac_2O; vii, NaCN/NH_4Cl/NH_3/MeOH; viii, separation of isomers; ix, MeOH/H_2O/HCl.

Scheme 12.



Reagents: i, methyl 3-nitropropionate; ii, Ac_2O/py; iii, Et_3N; iv, $NaBH_4$; v, DBU; vi, NaOMe.

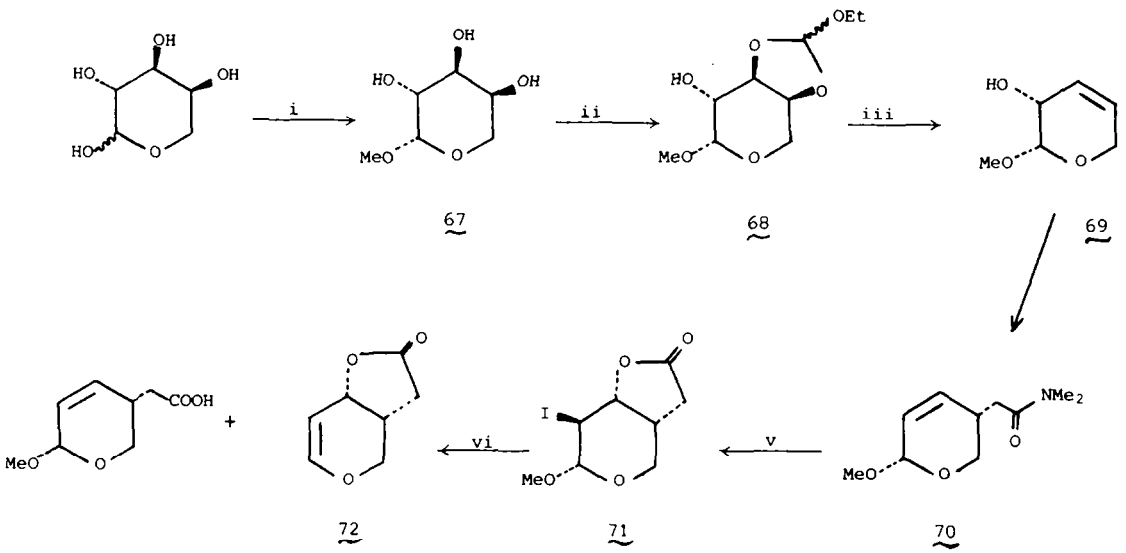
Scheme 13.



Reagents: i, cyclopentodiene; ii, OsO_4-$NaIO_4$; iii, $NaBH_4$; iv, Ac_2O/py.

Scheme 14.

Methyl β-L-arabinopyranoside has been used for the synthesis of the lactone **72**, a key intermediate in the synthesis of pseudomonic acids.[67] The route shown in Scheme 15 involves a Claisen rearrangement of the intermediate ketene aminoacetal to achieve the conversion of the pyran-3-ol **69** into **70** by N,N-dimethylacetamide in hot xylene.

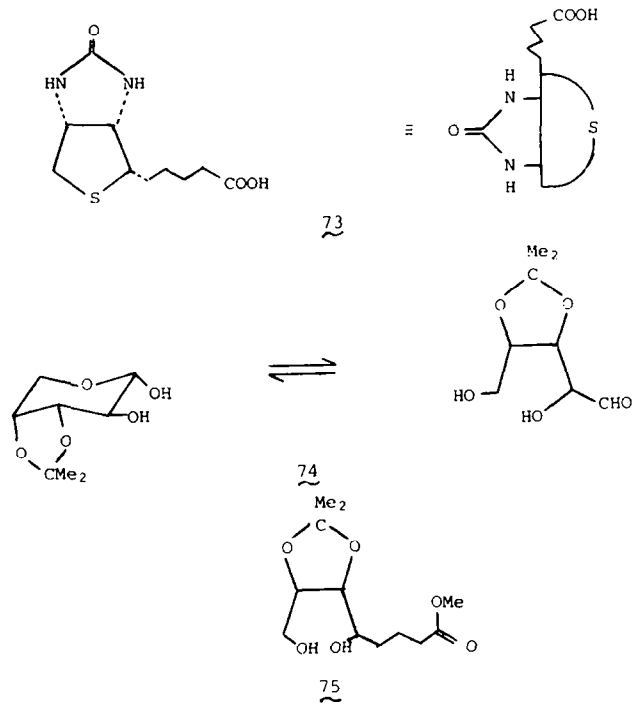


Reagents: i, $MeOH/H^+$; ii, $HC(OEt)_3/H^+$; iii, heat @ 200°; iv, $MeC(OMe)_2NMe_2$; v, iodine in aqueous THF; vi, Zn/NaI in pyridine.

Scheme 15.

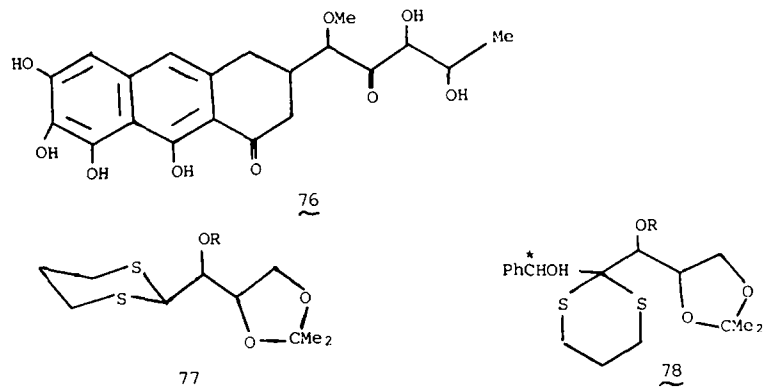
5. D-ARABINOSE

D-Arabinose, although readily available has been used in chiral synthesis even less than the L-isomer. One application has been for the synthesis of (+)biotin **73** for which 3,4-O-isopropylidene-D-arabinose[68] **74** is the key precursor. Wittig chain extension of **74** afforded **75** which can in principle[69,70] be readily converted into biotin.



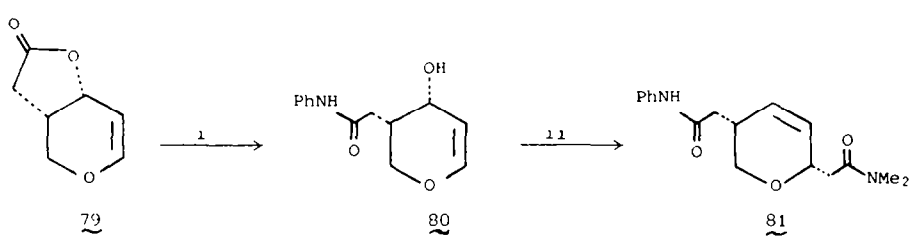
73 74 75

Another use was to prepare the side chain of chromomycinone **76**. The approach here was to convert D-arabinose to D-arabinitol, and to prepare from the latter 2,4-O-benzylidene-D-threose.[71] This route is a convenient entry to 4-carbon sugars. From the threose derivate the thioacetal **77** was prepared which on treatment with butyllithium gave a dianion which with benzaldehyde gave the diastereisomeric mixture **78**.



76 77 78

D-Arabinose has also been used to prepare intermediates for pseudomonic acid syntheses.[67] The enantiomer of **72** (Scheme 15) i.e. **79** (Scheme 16) was converted to **81** using a further Claisen amide acetal rearrangement.



79 80 81

Reagents: i, $PhNHLi$ in THF @ -78°; ii, $MeC(OMe)_2NMe_2$ in refluxing xylene.

Scheme 16.

6. D-RIBOSE

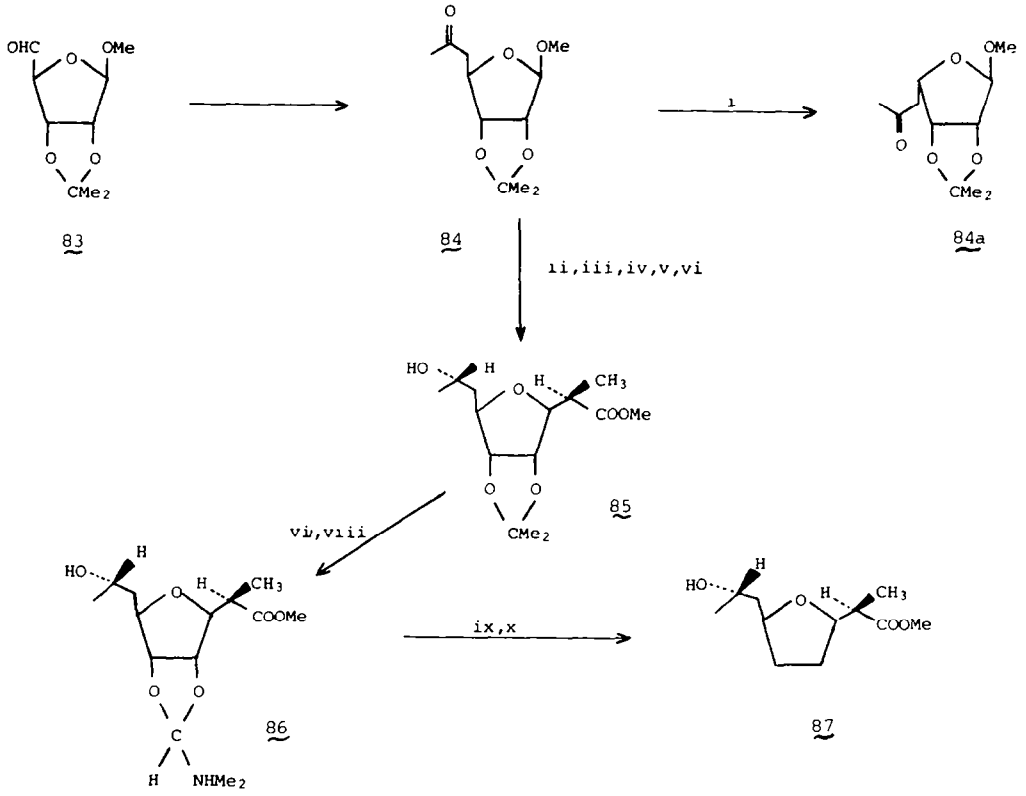
D-Ribose readily forms useful derivatives such as methyl 2,3-O-isopropylidene β-D-ribofuranoside[74] **82** and 3,4-isopropylidene-D-ribopyranose[75] **88**. For example **82** was converted[76] into the aldehyde **83** (Scheme 17) from which a synthesis of (−)methyl nonacetate **87** was developed. The 2,3-deoxy group was introduced (**86** to **87**) by Eastwood deoxygenation.[77] Advantage was taken of the fact that C-glycofuranosides with an activated methylene group at C-1 or C-4 are amenable to epimerisation via a retro-Michael-Michael addition sequence. Thus **84** was converted into **84a** providing the starting material for an analogous synthesis of (+)methyl nonacetate.

3,4-Isopropylidene-D-ribose **88** is an intermediate which allows chain extension and C-glycosidation to give e.g. **89** which may then be equilibrated to a 2,3-isopropylidene derivative **90**. Oxidation and substitution at C-4 gave intermediates **91** and **92** suitable for the synthesis of antimicrobically active pseudomonic acids.[78]

D-(+)-Ribonolactone **93** has provided the starting point for the synthesis of **98** an intermediate required for the synthesis of bis-nor-4,6-maytansinoid[79] (Scheme 18). The acetylenic bond was introduced (**97** to **98**) most conveniently by a bromination–debromination sequence.

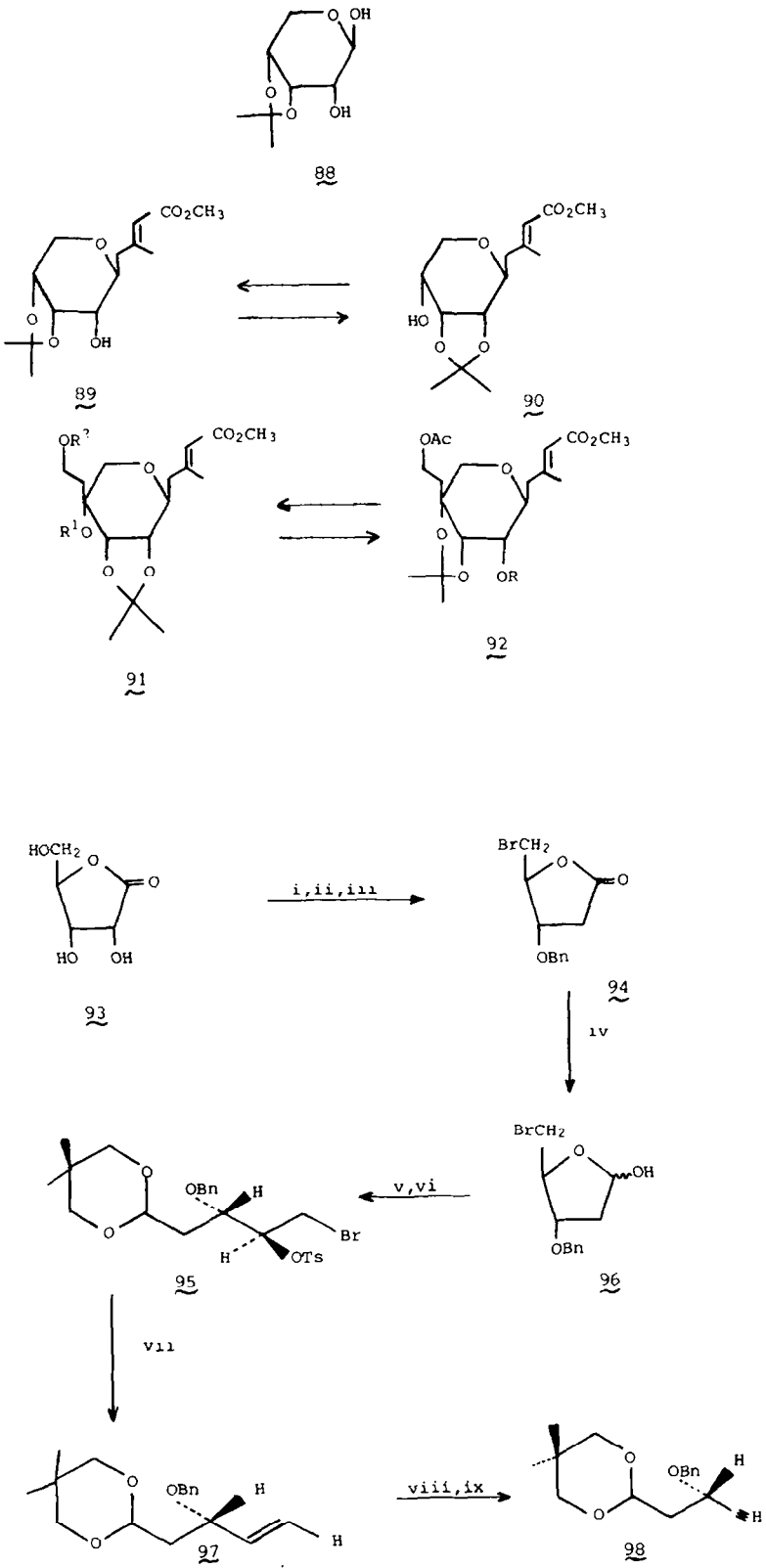
The D-ribose oxime derivative **99** on reaction with glyoxylic esters in the presence of ethylene gave isoxazolidines such as **100** where the diastereoisomers were easily separated, and converted following detachment of the sugar residue to produce chiral proline analogues.[80]

In a synthesis of (−)anisomycin from D-ribose which involves formation of a pyrollidine ring,[81] steric hindrance by an isopropylidene group appeared to prevent displacement of primary sulphonates by ammonia. The amine was introduced by a sequence oxime→cyanide→amine.



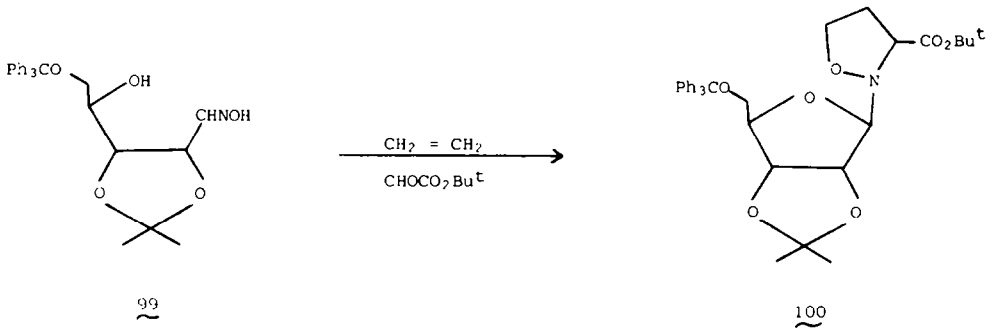
Reagents: i, NaOMe/MeOH; ii, H_2/Ni; iii, H_3O^+; iv, $(CH_3)_2C(OMe)_2$; v, $Ph_3P=C(Me)COOMe$; vi, NaOMe; vii, H_3O^+; viii, $Me_2NCH(OMe)_2$; ix, Ac_2O/reflux; x, H_2/Pd.

Scheme 17.



Reagents: i, TsCl/py (to give 2,5-ditosylate); ii, LiBr/acetone; iii, NaI/TFA/acetone; then BnBr/Ag_2O; iv, diisobutylaluminium hydride; v, 2,2,dimethylpropane 1,3-diol; vi, TsCl/py; vii, NaI/acetone; viii, pyridinium bromide perbromide; ix, NaH/DMSO.

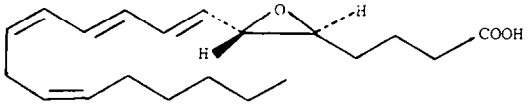
Scheme 18.



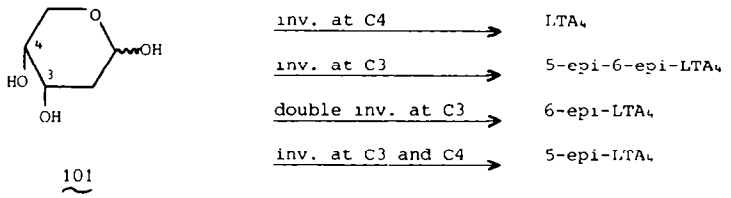
99 100

7. 2-DEOXY-D-RIBOSE

Deoxy sugars are usually quite expensive and are not commercially available in quantities and at prices which make then attractive starting materials for multistage synthesis. They usually have to be made as part of the chiral synthesis. One exception is 2-deoxy-D-ribose **101** which although not as cheap as most non-deoxy sugars is readily available. Most uses of 2-deoxy-D-ribose have involved C–C bond formation at C-1 to form an acyclic molecule of C-glycofuranosides. Such reactions are presumably facilitated because in solution at equilibrium there are significantly higher amounts of the acyclic and furanoid forms of 2-deoxy-D-ribose than with many other sugars.



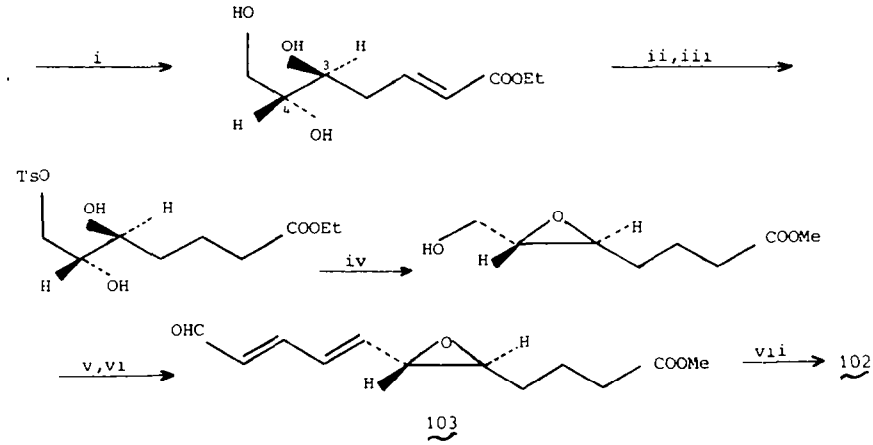
LTA_4 102



101

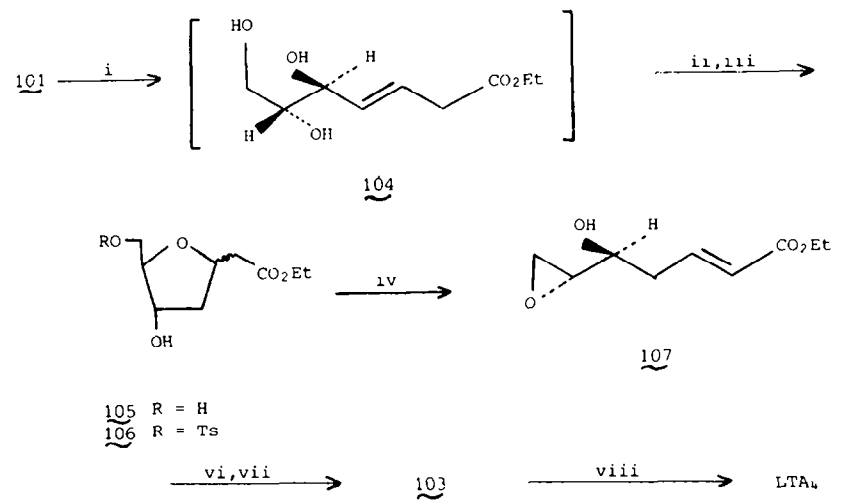
2-Deoxy-D-ribose **101** has found elegant application in the synthesis of leukotrienes. Thus leukotriene A_4 **102** and its three unnatural isomers 5-epi-LTA_4, 6-epi-LTA_4 and 5-epi, 6-epi-LTA_4 have been prepared[82] from **101** using appropriate manipulations of the chiral centres at C-3 and C-4 in **101**. The route to LTA_4 uses very conventional reactions to form and control the stereochemistry of the epoxide ring and liberal use of Wittig reactions to elaborate the unsaturated chains as shown in the Scheme 19. The other isomers are formed similarly after appropriate manipulation of C-3 and C-4.

A more interesting approach to the preparation of **102** and its isomers termed the C-glycoside approach has also been described.[83] As shown in Scheme 20 the initial Wittig product **104** is cyclised (**105**), tosylated (**106**) and then the ring oxygen is β-eliminated to form **107** which is transformed to LTA_4 as before. The other isomers were also prepared by this approach. Other syntheses of **102** from **101** have been reported.[85]



Reagents: i, (carbethoxymethylene)triphenylphosphorane; ii, H_2/Pd/C;
iii, mesitylene sulphonylchloride; iv, NaOMe/MeOH;
v, Collins oxidation; vi, formylmethylenetriphenylphosphorane;
vii, triphenyl[(Z)-non-3-en-1-yl] phosphonium chloride.

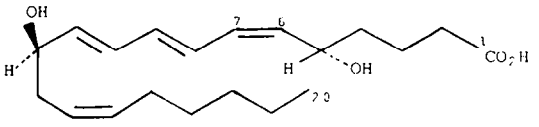
Scheme 19.



Reagents: i, (carbethoxymethylene)triphenylphosphorate; ii, NaOEt/EtOH;
iii, TsCl/py; iv, LDA/THF; v, H_2/Pd/C; vi, NaOMe;
viii, triphenyl [(2)-non-3en-1yl] phosphoniumchloride.

Scheme 20.

Another C-glycoside approach[84] was used to make the leukotriene LTB_4 **108**. The key step in the synthesis is based on the fact that some C-glycosides which possess a leaving group on the tetrahydrofuran ring are masked dienic precursors as illustrated in the conversion of **109** to **111**. **111** was found following addition of the heterocuprate reagent **112** to **113** in the presence of CuBr Me_2S then deprotection and base treatment. Chain extension gave the C-7–C-20 fragment of LTB_4. The C-1–C-6 fragment was also obtained from 2-deoxy-D-ribose via intermediates such as **104**, which after protection of the original C-3 was chain shortened by periodate and then coupled to a modified **111** by Wittig methodology. Other workers have generated the C-1–C-6 fragment similarly.[86] D-(−)muscarine iodide and L-(+)allomuscarine iodide have been synthesised from 2-deoxy-D-ribose.[87]



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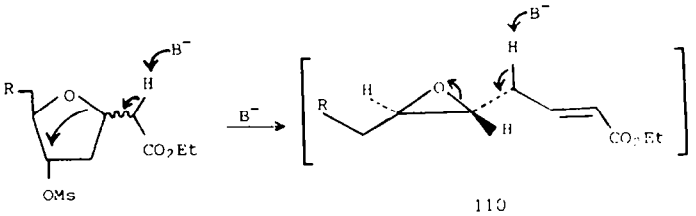
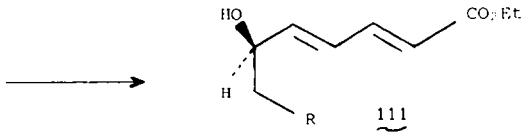
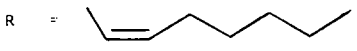
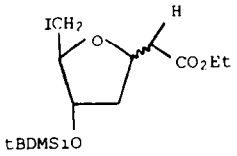


109 110

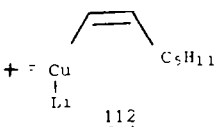


111





113

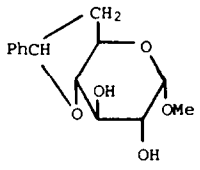


112

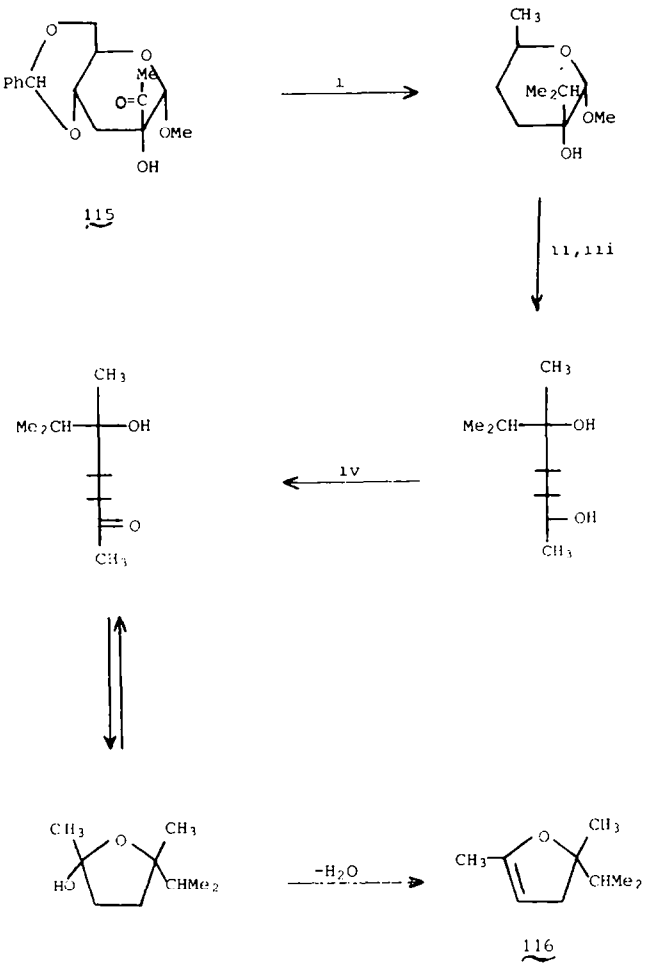
8. D-GLUCOSE

Since D-glucose has been used so extensively its main derivatives will be treated separately.

(a) *Methyl 4,6-O-benzylidene-α-D-glucopyranoside.* Methyl 4,6-O-benzylidene α-D-glucopyranoside **114** which is readily prepared from methyl α-D-glucopyranoside and benzaldehyde/zinc chloride[88] (or with benzaldehyde dimethylacetal[89]) has been used in a variety of ways. The utility of **114** is that the diol can be converted into the *manno* or *allo* epoxides[90] which can be converted into 2- and 3-deoxy sugars by $LiAlH_4$ reduction or may be substituted by reaction with Grignard reagents[91] or alkyllithiums.[92] The mono-OH derivatives may be oxidised to keto sugars which undergo ready reaction with Wittig reagents,[93] cyanide, Grignard reagents,[94] diazoalkanes[95] etc. 2,3-Enes or 2,3-dideoxy derivatives may be formed.[96] The benzylidene group may be removed by hydrolysis or catalytic hydrogenolysis or may be removed selectively to give 4-O-benzyl[97] or 4-O-benzoyl derivatives.[98] The glycoside is readily hydrolysed. In summary it is probably true that no sugar derivative has been manipulated as successfully as **114** and with such a comprehensive store of "carbohydrate" information it is not surprising that it has been so widely employed in chiral synthesis.



114



Reagents: i, multistage; ii, $HS(CH_2)_3SH/H^+$;
iii, Raney Ni; iv, CrO_3/py.

Scheme 21.

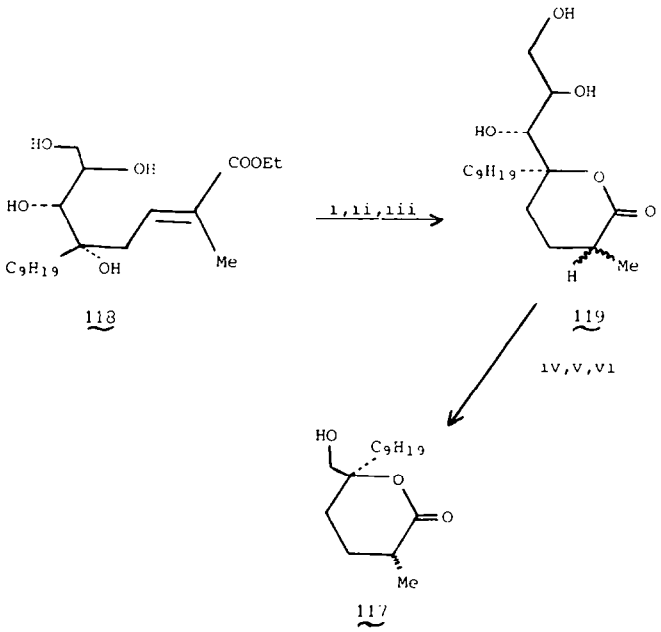
In Scheme 21[99] is illustrated the synthesis of (*S*)-2,5-dimethyl-2-isopropyl-2,3-dihydrofuran a constituent of the Wharf beetle, *hylecoetus dermestoides L.* The derivative **115** was obtained by addition of an appropriate dithian to the corresponding 2-keto sugar; the transformation of **115** to **116** was by conventional methods.

Scheme 22[100] shows the synthesis of the marine antibiotic (−)malyngolide **117**. Grignard addition to the 2-deoxy 3-keto sugar from **114** followed by deprotection and Wittig addition gave **118** which was converted via **119** into **117** as shown.

Various methods have been used for converting **114** into 2,3,4-tri-deoxy 2,4-dimethyl-hexose derivatives. One such approach (Scheme 23)[101] has provided a highly stereoselective route to (−)α-multistratin **120**. Another approach gave an intermediate for the synthesis of the antibiotic A23189.[102] A 2,3,6-trideoxy hexose prepared from **114** has been converted into (+)azimic and (**123**) (+)carpamic acids **124** (Scheme 24)[103] with the reductive cyclisation **121** to **122** a key step.

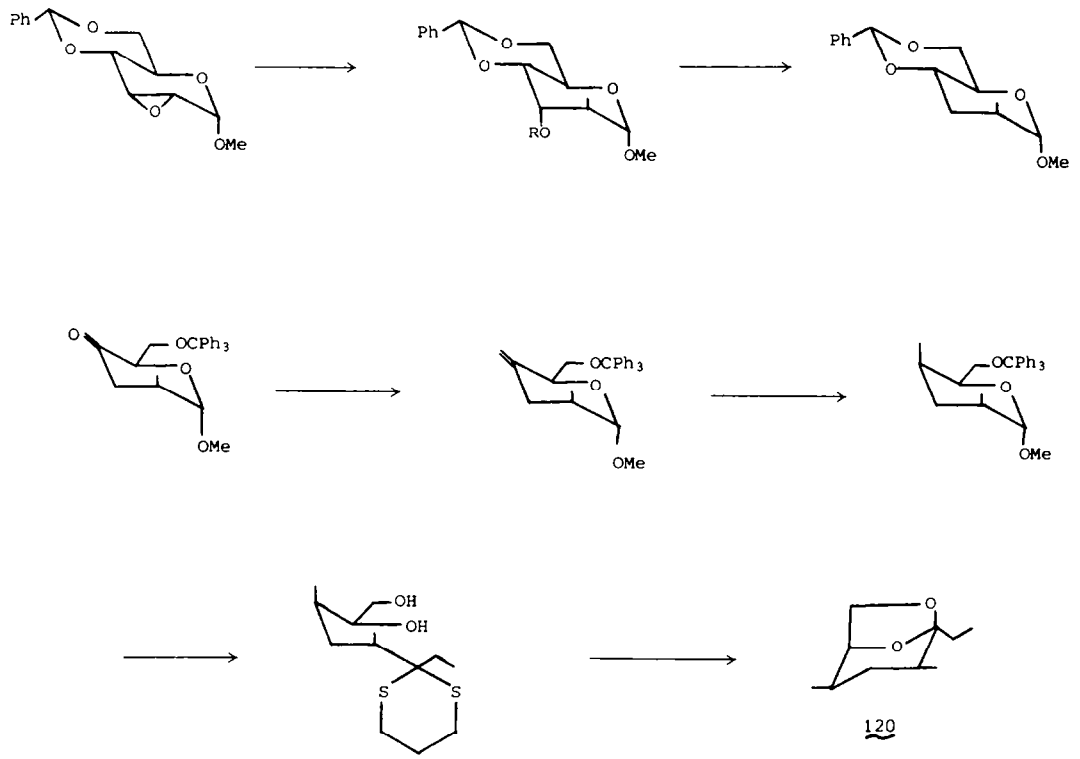
Other uses of **114** to provide an appropriately substituted derivative for subsequent modification include the preparation of the 3-azido-4-cyano derivative **125** for conversion via **126** to thienamycin[104] **127**. A similar synthesis has been reported.[105] The thiazole-4-carboxylic **128** a fragment of the antibiotic nosiheptide[106] was prepared from **114** via **129** and **130**.

Of the more unusual applications of **114**, the route in Scheme 25[107] to prostaglandins is of particular interest. The cyclopentane forming step was achieved by treatment of **132**, prepared from

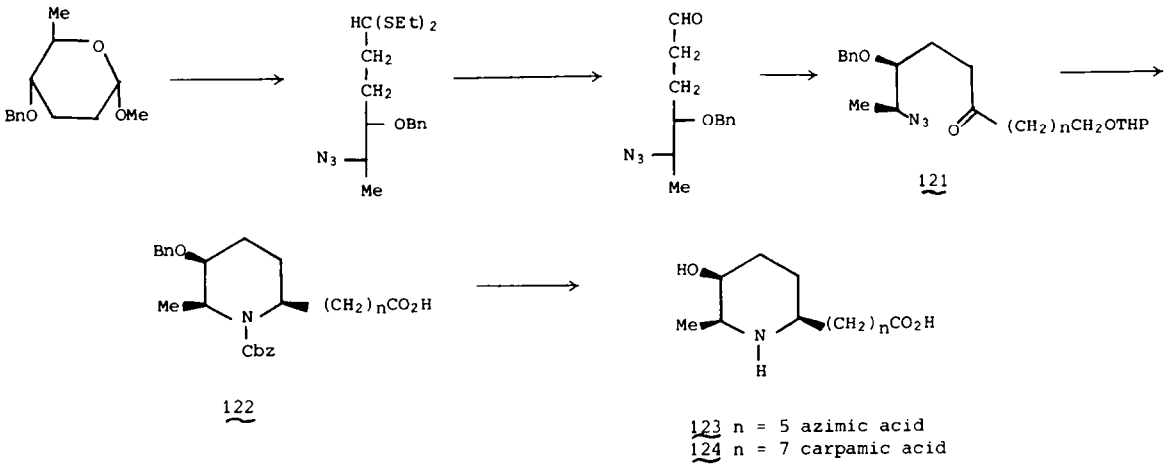


Reagents: i, H_2/Pd; ii, NaOH; iii, $[pyr\text{-}S\text{-}]_2$/Ph_3P; iv, $Pb(OAc)_4$; v, Ph_2SnH_2; vi, t.BuOK/DMSO.

Scheme 22.



Scheme 23.



Scheme 24.

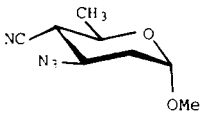
131 with Zn in boiling ethanol and used without purification, with N-methylhydroxylamine hydrochloride in ethanol–pyridine. The isoxazolidine **133** was reductively opened with Raney nickel and the resulting aziridine **134** converted into an alkene **135** with chloroperbenzoic acid. Subsequent transformations gave the products **136**, **137**, **138**, **139** shown.

Another application is that shown in Scheme 26[108] for the synthesis of detoxinolactone derivatives where pyrollidine ring formation is accomplished before the pyranose ring is destroyed. The ring forming step **140** to **141** by $NaBH_4$ reduction of the cyanomesylate in the presence of $COCl_2$ followed by alkaline treatment did not take place with $LiAlH_4$. The product **142** contains reversed configurations to detoxinine **143**.

A total synthesis[109] of (+)methylpseudomonate **144** has been achieved using D-xylose (see later) and D-glucose. Scheme 27 shows the involvement of **114** to produce **145** which was made into a Grignard reagent to couple with **232** (Scheme 52).

Scheme 28[110] illustrates a synthesis of (−)chrysanthemumdicarboxylic acids, **146** the key step being the formation of the cyclopropane **148** from the epoxide **147**.

Methyl 4,6-O-benzylidene α-D-glucopyranoside **114** and 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (see later) have been used to make the C_{17}–C_{29} fragment **155** of rifamycin.[111] One key



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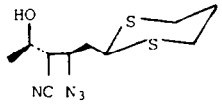

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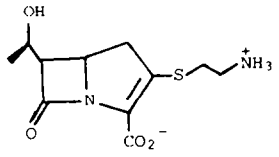

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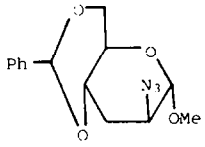

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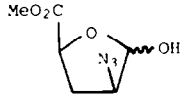

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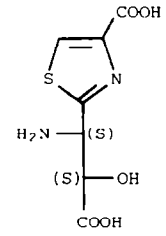

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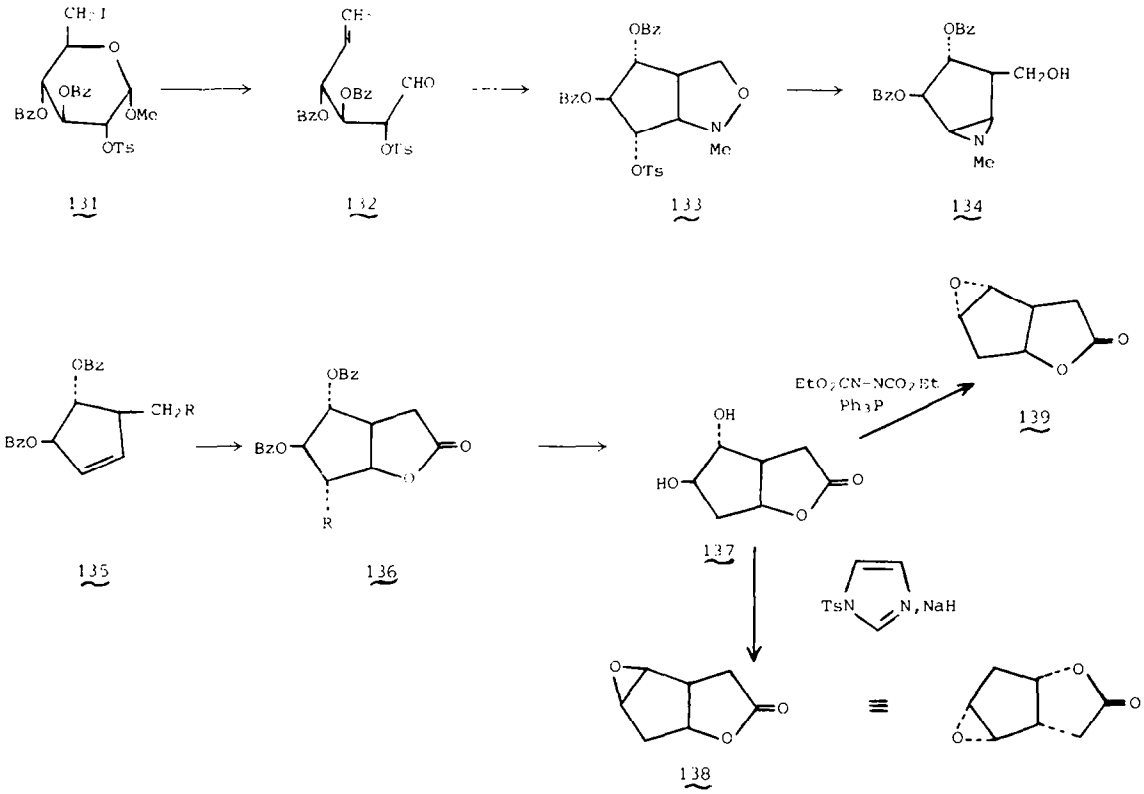
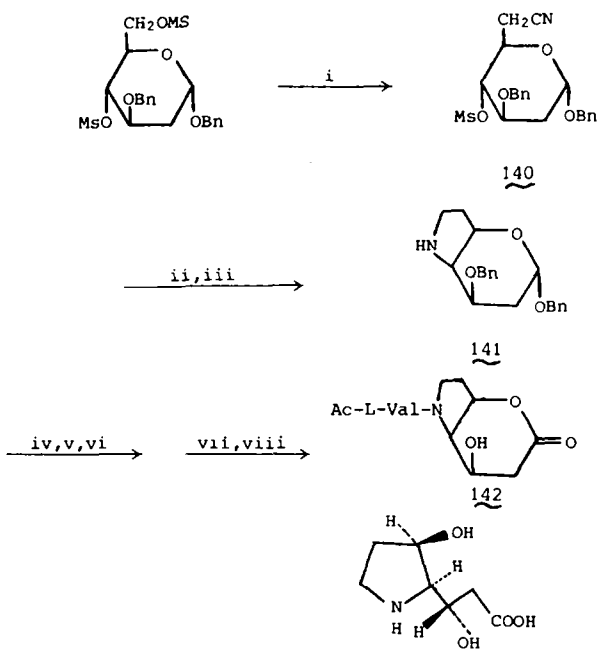
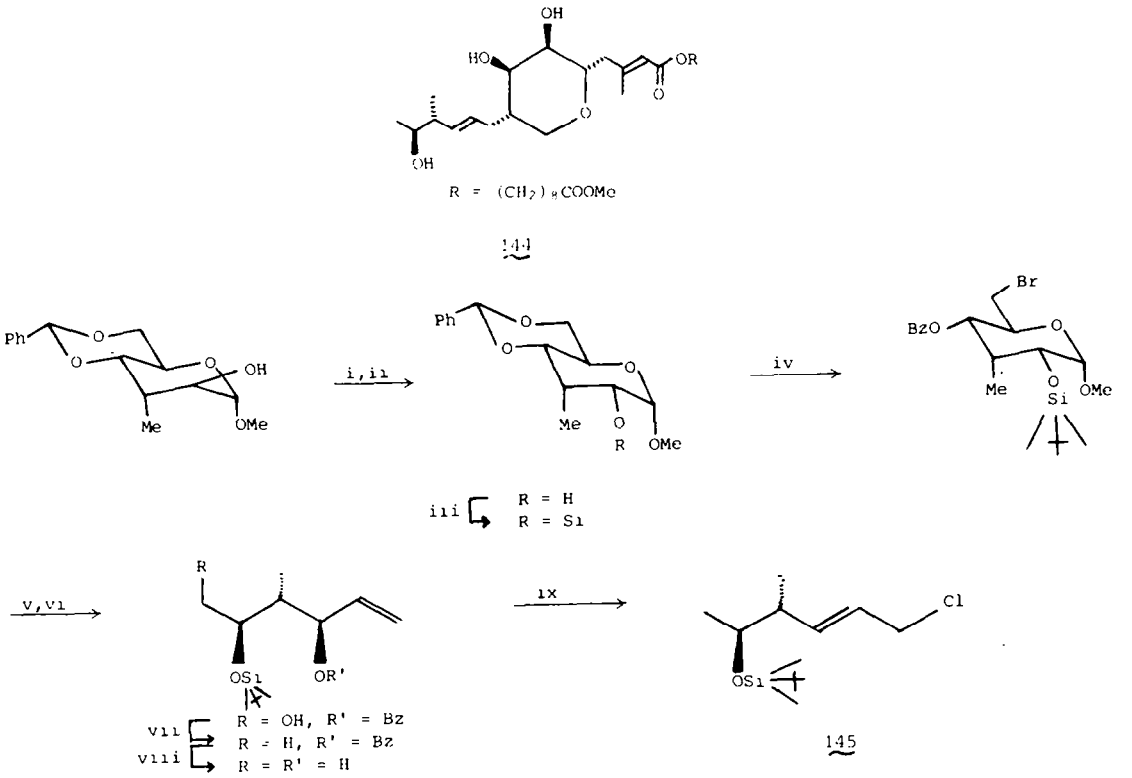


Scheme 25.



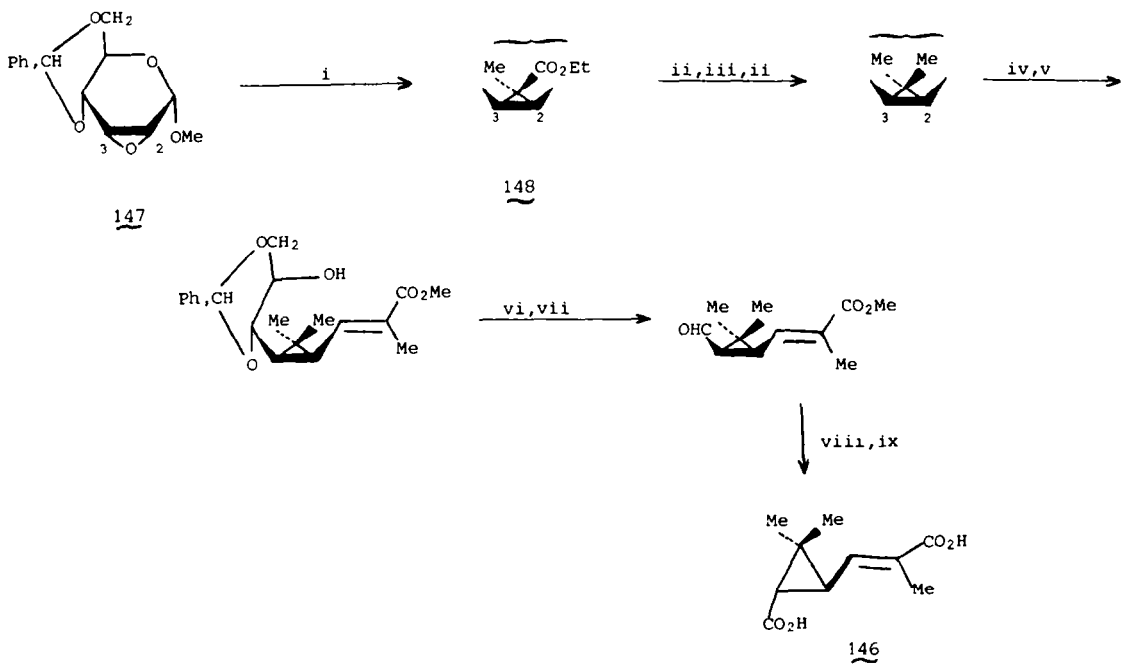
Reagents: i, NaCN.DMSO; ii, $NaBH_4/COCl_2/MeOH$; iii, KOH/MeOH; iv, L-ValOH; v, HCl; vi, PCC/CH_2Cl_2; vii, H_2/Pd; viii, Ac_2O/Me.

Scheme 26.



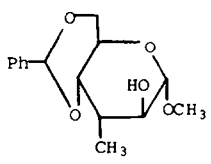
Reagents: i, DCCI-DMSO-TFA-pyridine, room temperature, 2 h; ii, $LiAlH_4$, Et_2O, 0°C, 30 min, 95% from 7; iii, TBDMSCl, imidazole, DMF, room temperature, 12 h, 83%; iv, NBS, $BaCO_3$, CCl_4, 80°C, 1.5 h, 75%; v, acid washed Zn (100 equiv) 9:1 propanol-water (v/v), 80°C, 30 min; vi, $NaBH_4$, EtOH, -35°C, 30 min, 50% from 10; vii, (1) TsCl, pyridine, room temperature, 12 h, (2) NaI, $H_3CC(O)C_2H_5$, 80°C, 10 h, (3) $NaBH_4$, Me_2SO, room temperature, 12 h, 60%; viii, MeONa, MeOH, room temperature, quantitative; ix, $SOCl_2$, pyridine, 0°C, 1.5 h, 88%.

Scheme 27.



Reagents: i, $(EtO)_2POCH(Me)CO_2Et$; ii, LAH; iii, MsCl-DMF; iv, H_3O^+; v, $Ph_3P = C(Me)CO_2Et$; vi, H^+; vii, IO_4^-; viii, MeO^-; ix, Ag_2O-NaOH.

Scheme 28.



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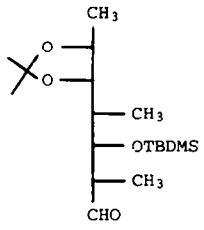

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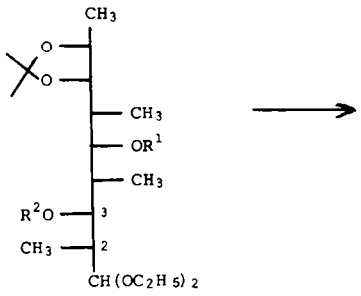

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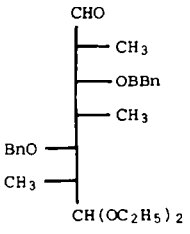

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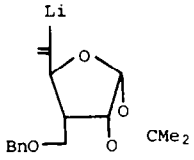
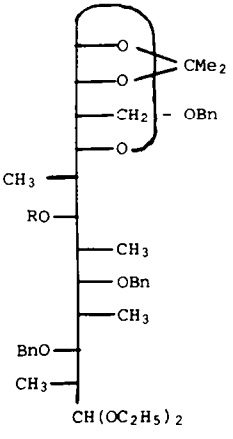
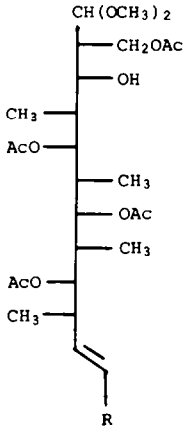


153



154



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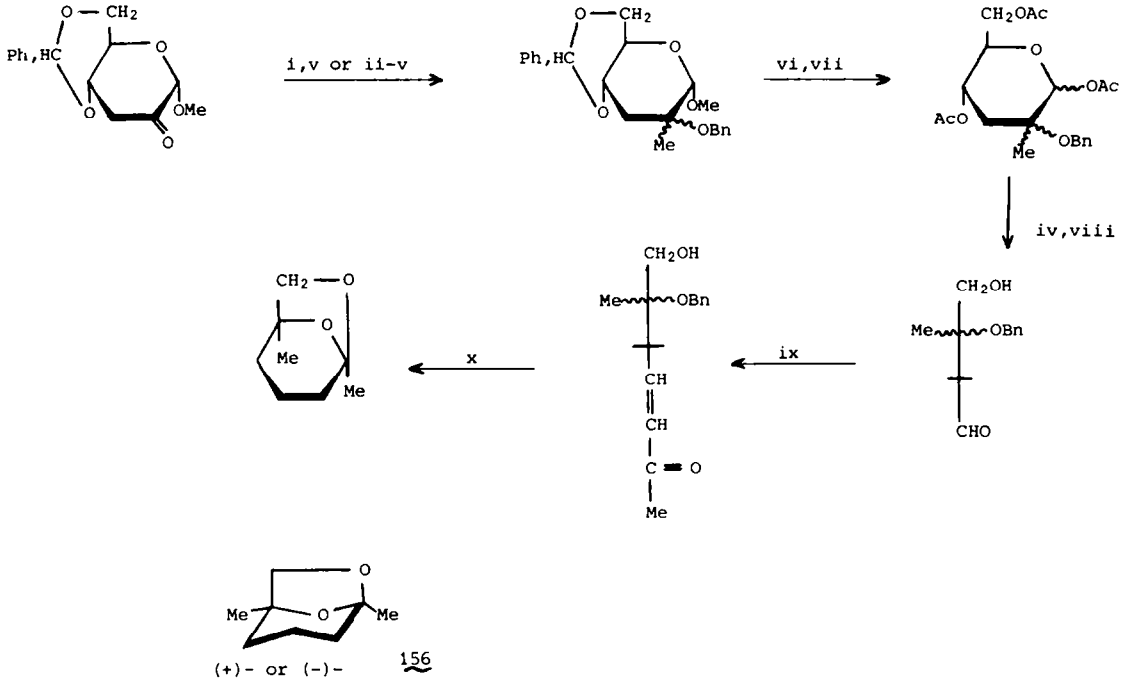
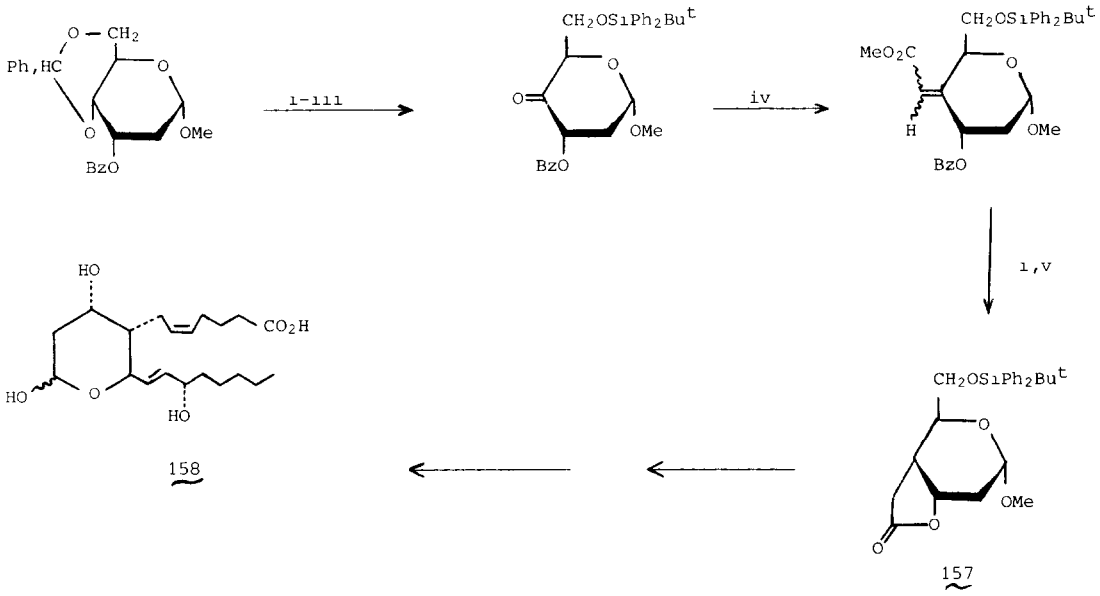


Reagents: i, MeMgI; ii, $Ph_3P = CH_2$; iii, $Hg(OAc)_2$; iv, $NaBH_4$; v, BnCl-NaH-DMF; vi, H^+; vii, Ac_2O-BF_3, Et_2O; viii, $NaIO_4$; ix, $Ph_3P = CHCOMe$; x, H_2-Pd-C.

Scheme 29.

intermediate **150** was synthesised from **149** in 30% yield in 15 steps. **150** was converted via **151** into **152** and condensed with the lithio reagent **153** to give **154** which was converted into **155**. All the transformations were complex and multistep.

(−)Frontalin **156** has been synthesised from **114** (Scheme 29).[112,113] Intermediates such as **157** have played an important role[114–116] in the synthesis of thromboxane B_2 **158** and related compounds (Scheme 30).



Reagents: i, $Pd(OH)_2$-C-H_2; ii, Bu^tPh_2SiCl-py; iii, DMSO-$Me_2N(CH_2)_3N$ = C = NEt-$pyH^+CF_3CO_2^-$; iv, Me_3P = $CHCO_2Me$; v, K_2CO_3-MeOH.

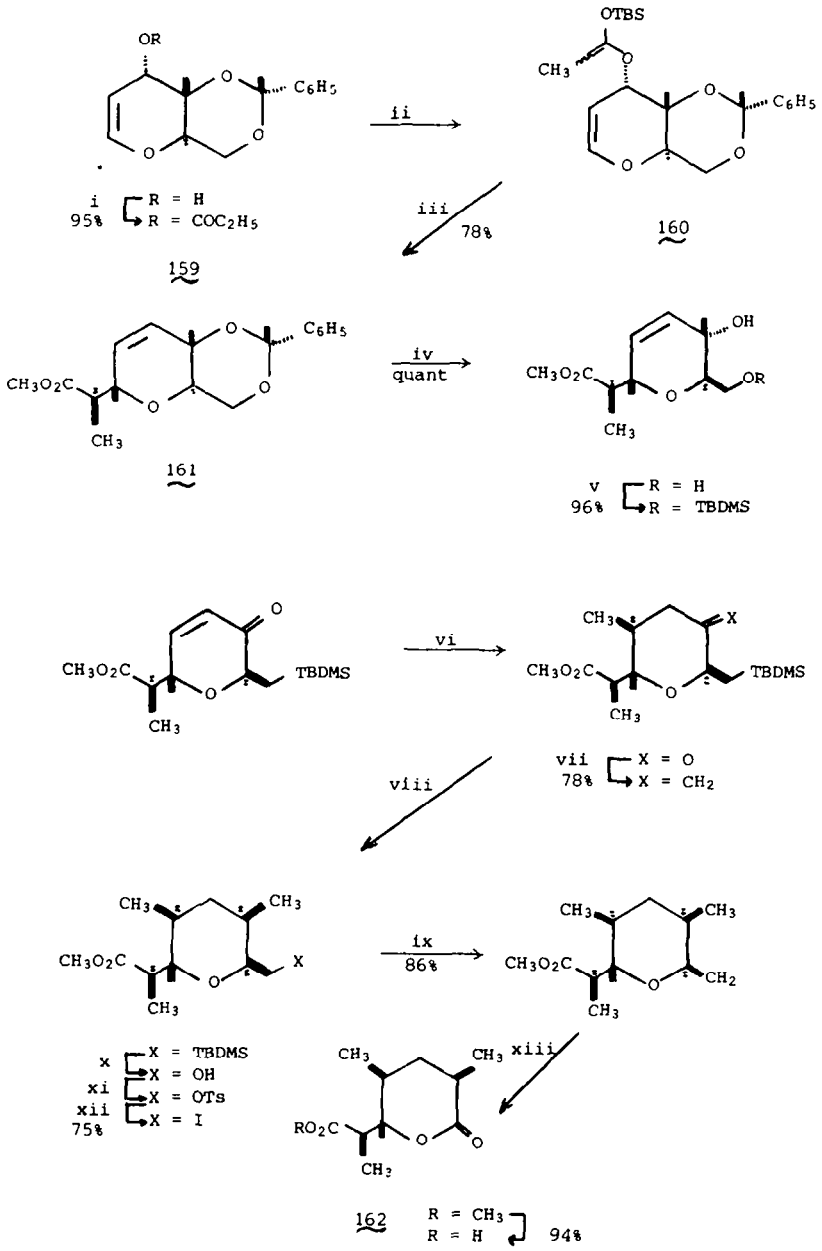
Scheme 30.

Compound **114** has been converted[117] (Scheme 31) into Prelog–Djerrasi lactone **162** via the 2,3-ene **159** the key step being the conversion **160** to **161** in an enolate-Claisen rearrangement. Modifications and use of the lactone for macrolide total synthesis have been described.[118,119] The Prelog–Djerrasi lactone has been prepared from **114** by other procedures.[120]

Starting from **114** the 4,6-dideoxy derivative was prepared and oxidised at C-2 to provide the chiral substrate for the synthesis of (+)spectinomycin (**162a**).[121] Carbons 2,3,4 correspond to carbons 5,4,3 respectively in D-glucose.

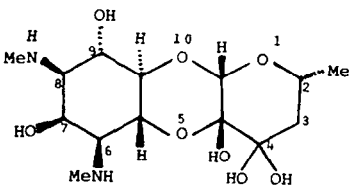
(b) 1,2,:5,6-*Di*-O-*isopropylidene*-α-D-*glucofuranose*. 1,2:5,6-di-O-Isopropylidene α-D-glucofuranose **163**, easily prepared from D-glucose by condensation with acetone[132] has found particularly wide application in chiral synthesis. Compound **163** may be selectively hydrolysed to 1,2-O-isopropylidene-α-D-glucofuranose **164**, before or after protection, inversion (oxidation-reduction)[123] or removal of the 3-OH group.[124] The exocyclic C-5–C-6 chain may be shortened or extended by a variety of methods as illustrated below, and the C-1 aldehydo-function is not difficult to expose for further manipulation. Most of the possibilities for modifying **163** have been used to advantage.

For example (Scheme 32) (−)canadensolide **168a** was obtained[125] from **163** in 7.1% overall yield. **163** with C-3 protected was partially hydrolysed, the C-5–C-6 chain was shortened to $-CH_2OH$ and the primary OH group tosylated and converted into the n-Bu derivative. Hydrolysis, glycosidation and oxidation then gave **165** which on reaction with the appropriate Wittig reagent and deprotection of C-3 gave **166** which via **167** and **168** was converted into **168a**. Compound **163** has been used in a synthesis of (+)-exo-brevicomin[126] similar in concept to that described for frontalin. In another study C-3 and C-4 of **163** provided the chiral centres for a novel platelet activating factor.[127]

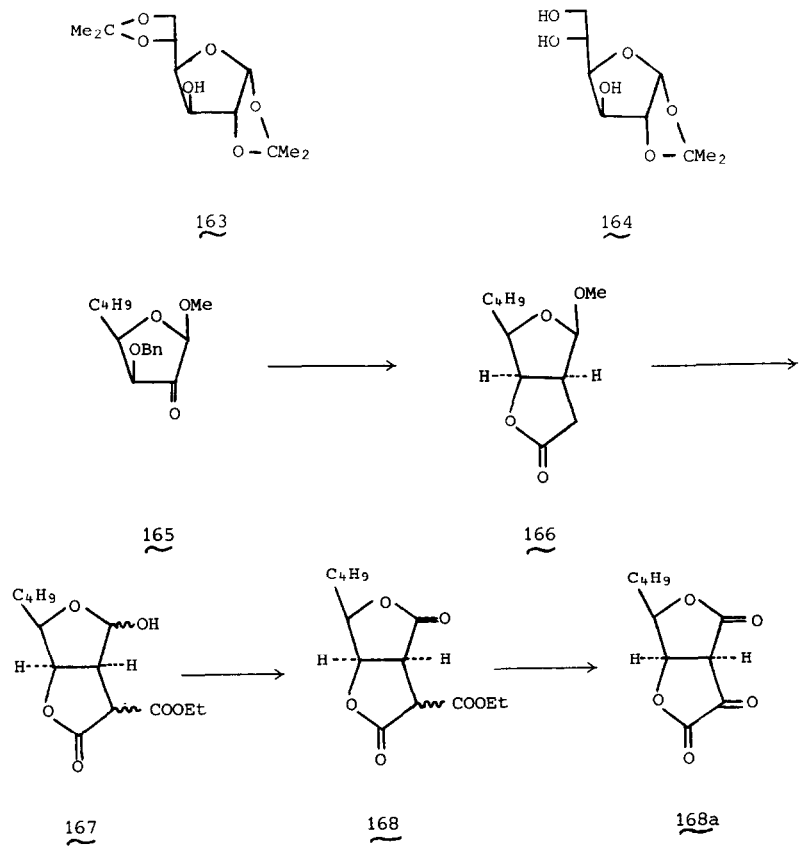


Reagents: i, $(CH_3CH_2CO)_2O$,pyridine,(dimethylamino) pyridine (cat),CH_2Cl_2; ii, LiHMDS,THF,-100°C; t-Bu$(CH_3)_2$SiCl,HMPA,-100°C → room temp; iii, C_6H_6, 80°C,19h; H_3O^+,THF,room temp; CH_2N_2, Et_2O; iv, H_3O^+,THF,60°C; v, t-Bu$(CH_3)_2$SiCl,pyridine,0°C; vi, PDC, CH_2Cl_2; vii, LiCu$(CH_3)_2$, Et_2O, 0°C; viii, $(C_6H_5)_3PCH_2$,THF; ix, PtO_2,H_2,pentane; x, (n-Bu)$_4$NF,THF; xi, p-TsCl,pyridine; xii, NaI,2-butanone,80°C; xiii, AgF,pyridine; xiv, O_3,CH_2Cl_2,-78°C; $(CH_3)_2S$; xv, LiOH,H_2O,MeOH.

Scheme 31.



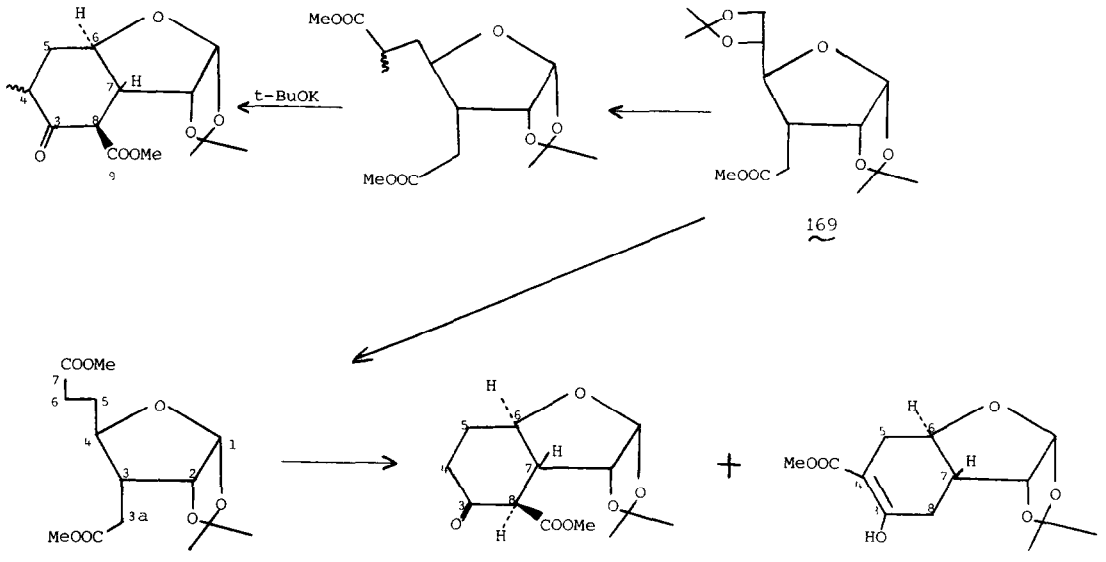
162a



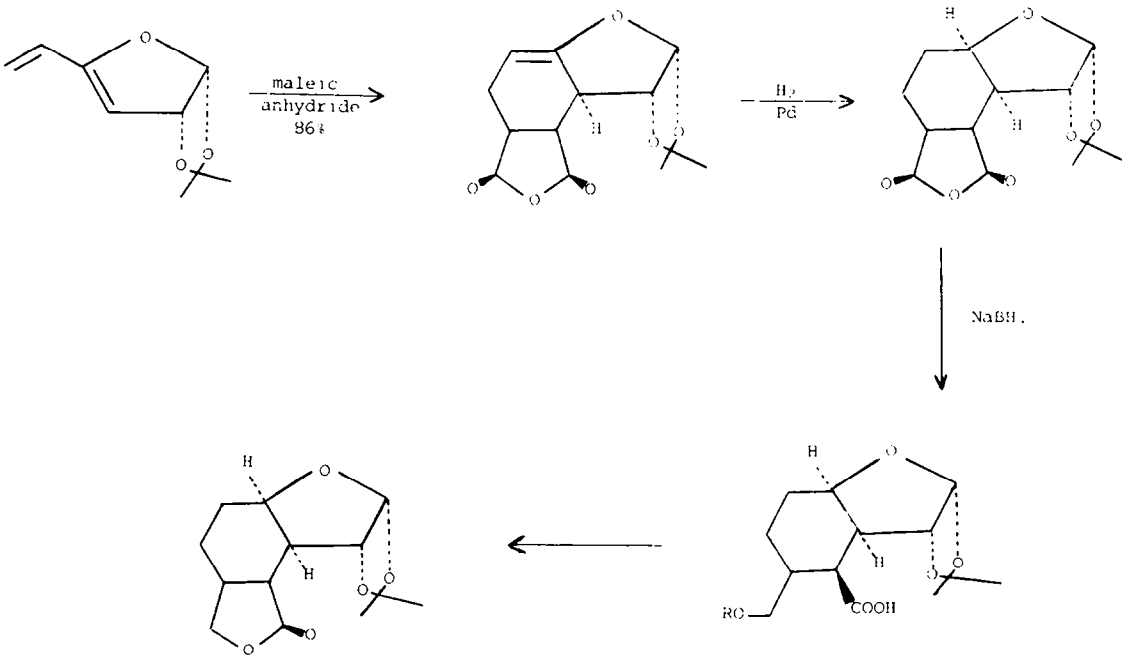
Scheme 32.

Other uses of **163** which involve formation of fused ring systems are illustrated, Scheme 33[128] and Scheme 34.[129] Scheme 33 shows an approach which requires oxidation then Wittig addition at C-3 to give **169** then removal of the 5,6 isopropylidene group and modification of the exocyclic side before cyclisation. Scheme 34 show the potential of unsaturated sugars for Diels–Alder reactions. Similar routes have been used to give chiral α-methylene-γ-lactones.[130]

Compound **163** provides the possibility for structural modifications before forming an acyclic

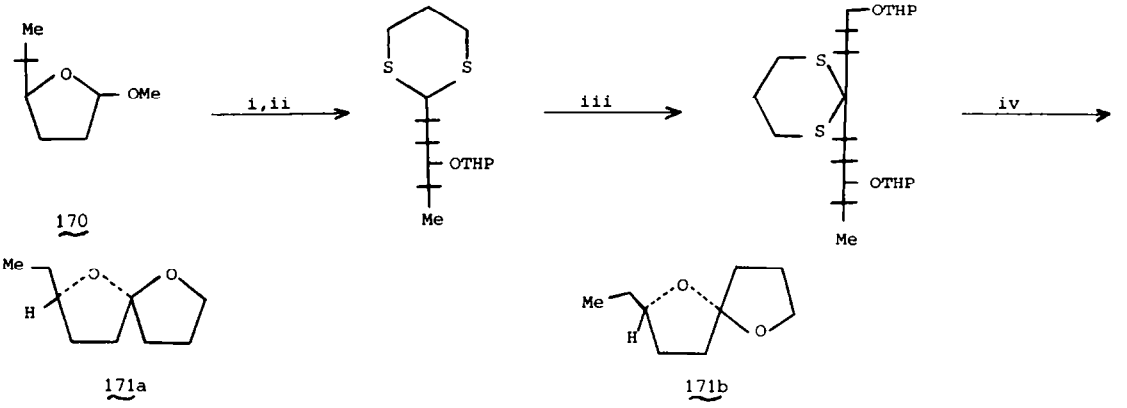


Scheme 33.



Scheme 34.

derivative. For example in Scheme 35[131] compound **170** was prepared from **163**, before being transformed as illustrated into the isomers of chalcogran **171a** and **171b**.



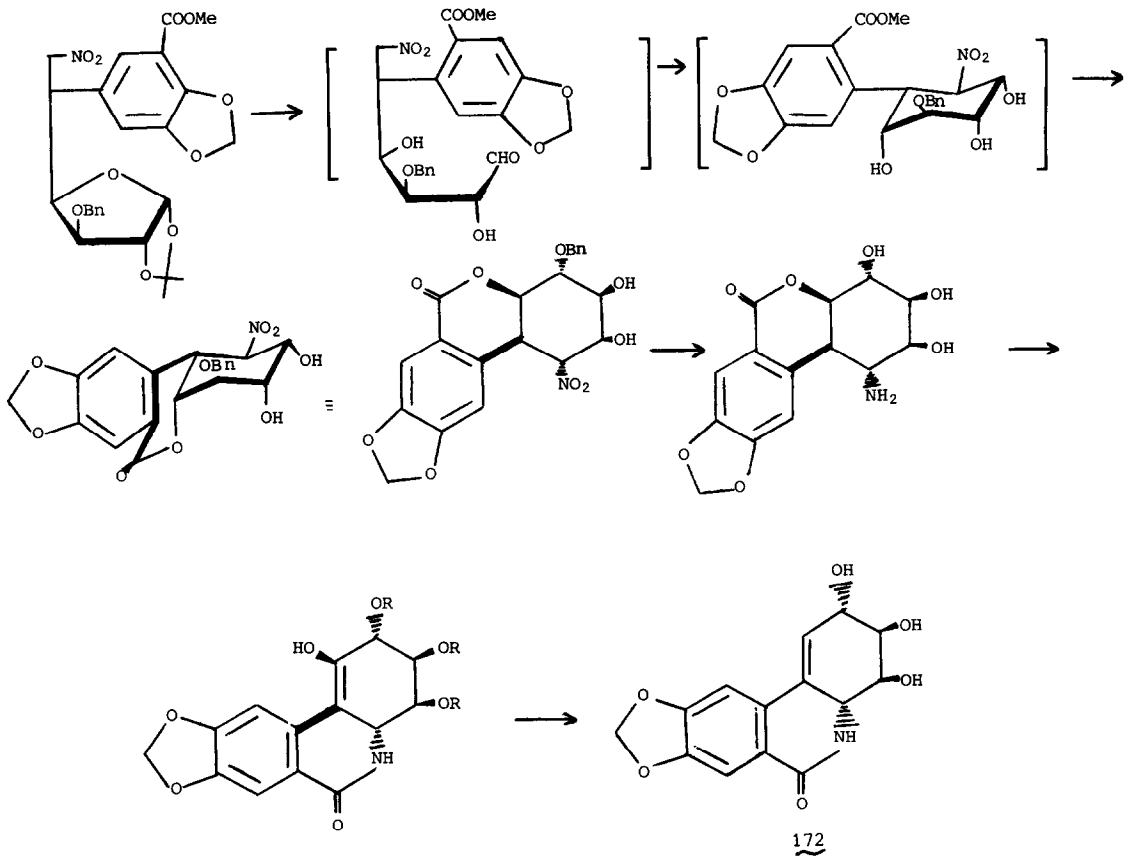
Reagents: i, $HSCH_2CH_2CH_2SH/H^+$; ii, THP/H^+; iii, $BrCH_2CH_2CH_2OTHP$; iv, H^+

Scheme 35.

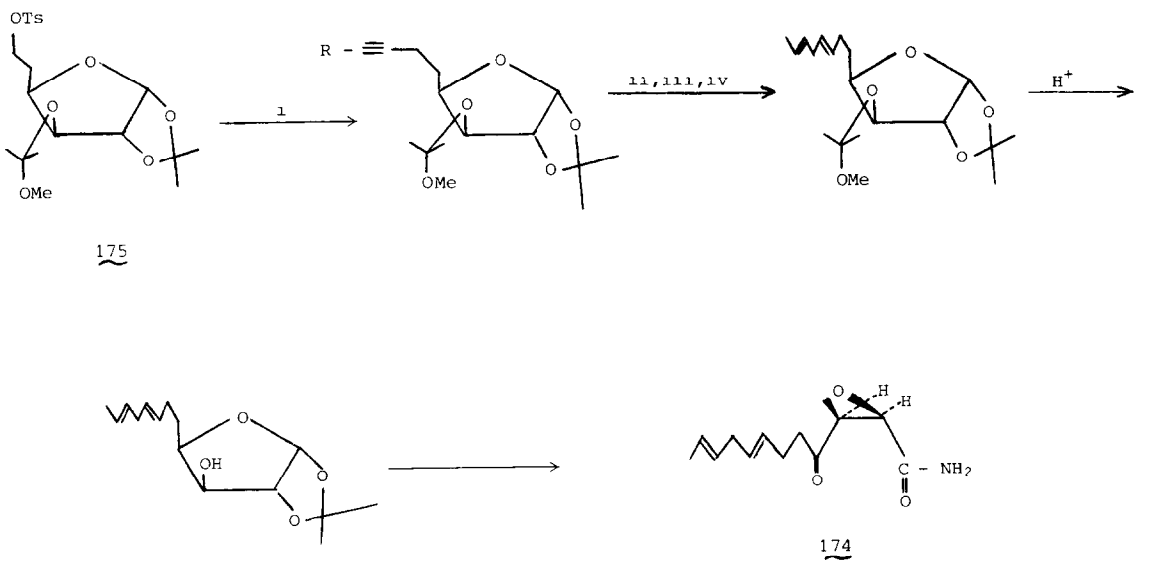
Scheme 36[132] which shows a synthesis of (+)-lycoricidine **172**, involves a nitroalkane chain extension of the 5-aldehydo sugar derived from **163**. Elimination and addition of a substituted aromatic, then deprotection of C-1 to allow a further nitroalkane–aldehyde condensation gave a cyclitol which by appropriate manipulation of protecting groups gave **172**.

A similar route from **163** using a nitroalkane→cyclitol ring closure has been used to provide intermediates for a synthesis of tetrodotoxin.[133] Compound **163** via intermediates such as **173** has been used to give new branched chain cyclitols having *neo*, *myo* and *chiro*-configurations.[133a]

Scheme 37[134] shows a synthesis of the fungal metabolite cerulenin **174** from **163**. **175** formed by routine manipulation was converted into **174** as indicated in a route which well illustrates a variety of chain extension procedures.

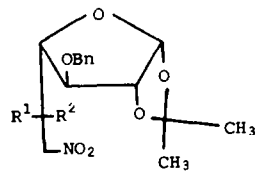


Scheme 36.



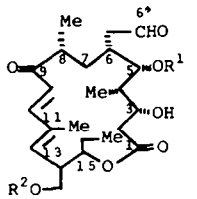
Reagents: i, LiC≡CH/DMSO; ii, PhLi; iii, $CH_3.CH = CH - CHCl$; iv Li/NH_3.

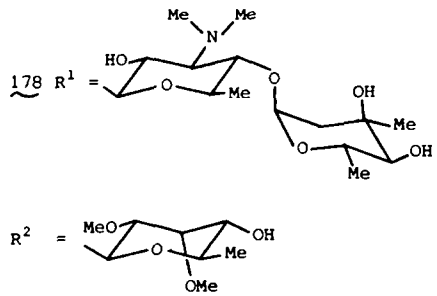
Scheme 37.



173

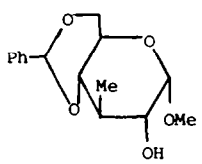
Perhaps of considerable interest are applications of **163** in the synthesis of macrocycles. For example, 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose derivatives have been used[135] for the total synthesis of **176** a precursor of tylonide **177** an aglycone of tylosin **178** (Scheme 38). The 3-methyl glucose derivative **179** was converted into **180** which could also be prepared from **163** and then into **181** by a multistep sequence. Wittig chain extension and acetonation with 2,2-dimethoxy propane then gave **182** into which an aldehyde equivalent was introduced (i.e. **183**). Further



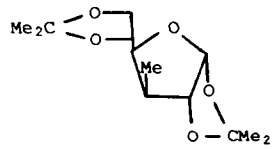


176 R^1 = methylacetal with aldehyde, R^2 = trityl

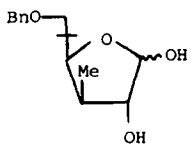
177 R^1 = H, R^2 = H



179



180



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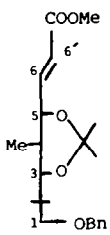

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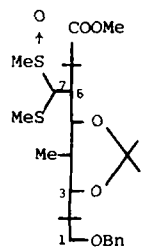
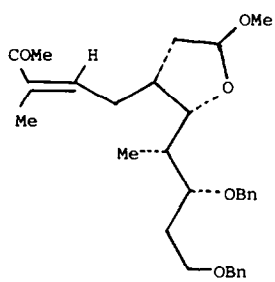
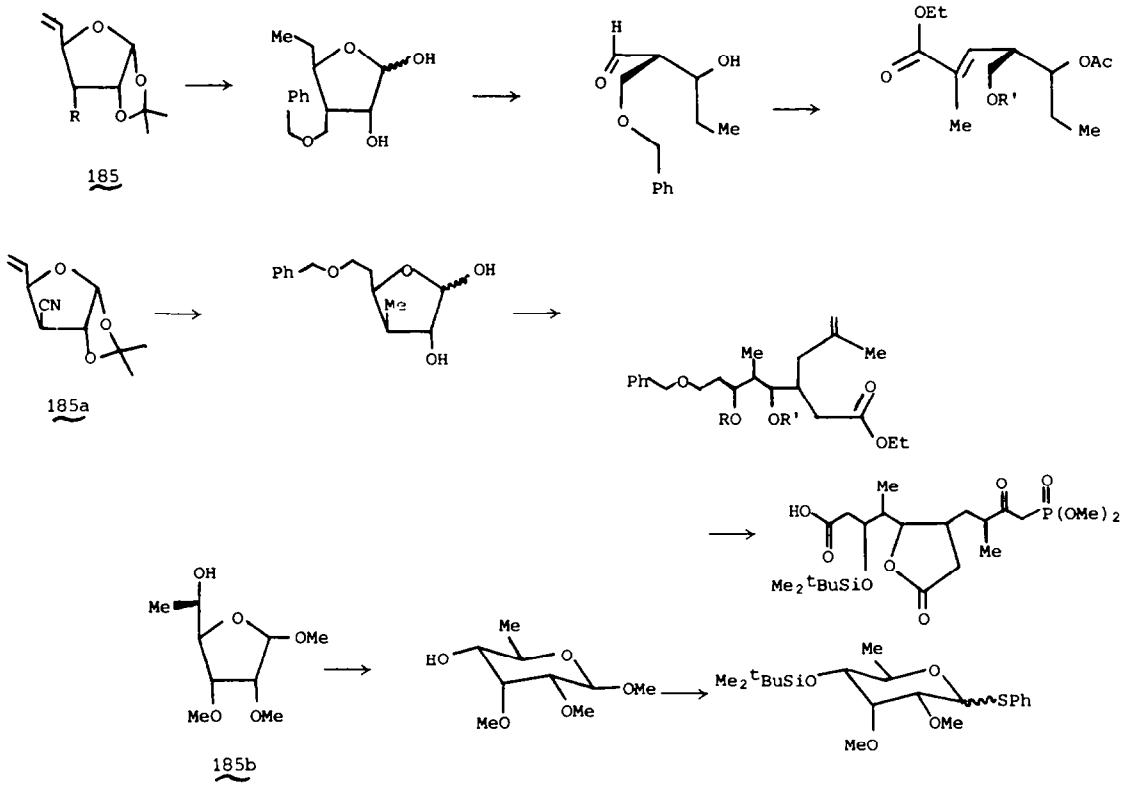


183

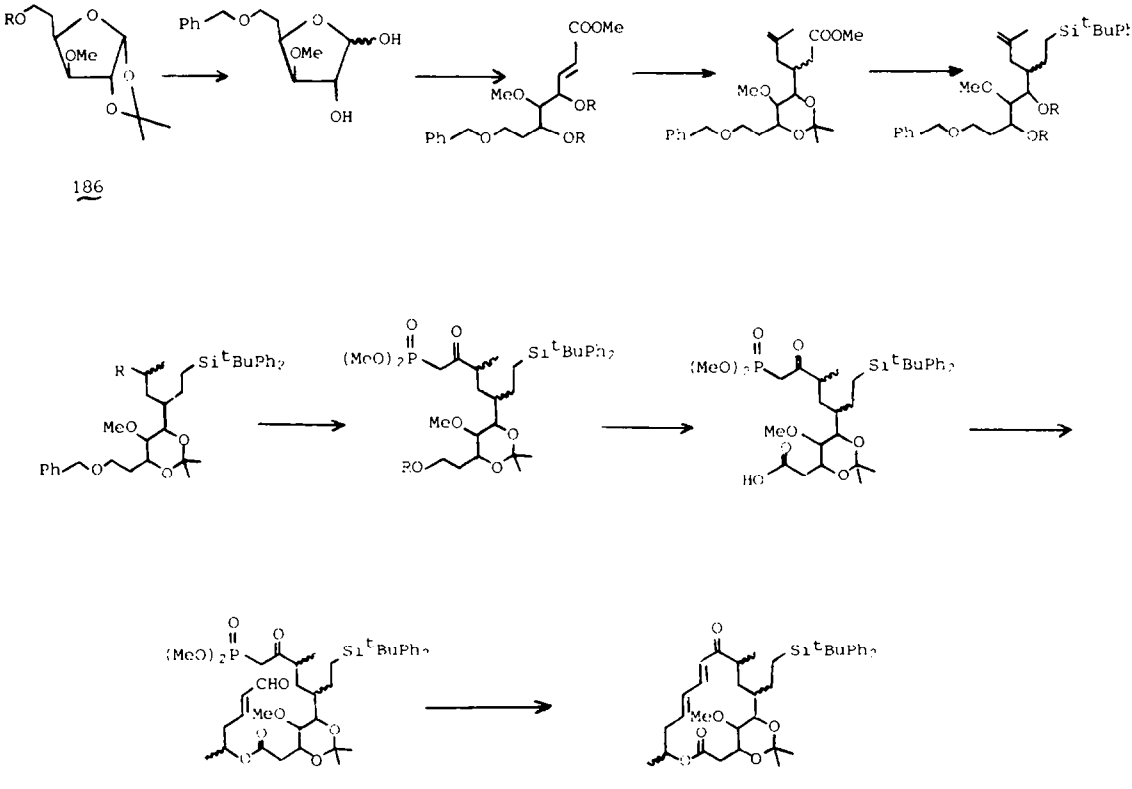


184

Scheme 38.



Scheme 39.



Scheme 40.

multistage reactions converted **183** into **184** to give the C-1–C-10 backbone of tylosin. The C-11–C-17 fragment was also obtained from a branched D-allofuranose derivative for which **163** was again the starting point. The two fragments were combined by aldolcondensation. Other workers have also synthesised O-mycinosyltylonolide.[136] The build up of key intermediates is shown in Scheme 39.[137] One intermediate **185** (R = triflate) was prepared from D-glucose via **163** in 55% yield through the steps i, $RuO_2/NaIO_4$; ii, $NaBH_4$; iii, benzoylation; iv, H^+; v, olefination $(EtO)_3CH/H^+$, heat; vi, $K_2CO_3/MeOH$; vii, $(CF_3SO_2)_2O$/py. The key intermediate cyanides **185** (R = CN) and **185a** were prepared by treating the triflate **185** (R = triflate) with KCN, **185a** is the kinetic product and **185** (R = CN) is the thermodynamic product. Compound **185b** prepared from α-rhamnose was converted to the thioglycoside by sequential treatment with MeOH/HCl, $PhSSiMe_3/CH_2Cl_2$ and t-$BuMe_2SiCl$.

An approach to the synthesis of carbomycin and leucomycin A3 is shown in Scheme 40. Compound **163** was converted conventionally into **186** and then chain extended. The established stereochemistry at C-2, C-3 and C-4 of the glucose moiety was used to control subsequent build up of the macrocycle structure.[138]

Other approaches using **163** to produce key intermediates for macrocycles include the synthesis of **187**[140] and **187a**.[139] **163** has also been used[141] to give the four isomers **188**, **189**, **190** and **191**.

There have been a series of elegant studies of the synthesis of arachidonic acid oxidation products.[142–146] For example Scheme 41[144] shows **163** undergoing elimination of the C-3 OH, and inversion of configuration at C-4 before 5,6-epoxide formation with chain extension by the appropriate lithium acetylide. C-1 deprotected by hydrolysis, thioacetalation, acetonation and dethioacetalation (mercuric chloride/mercuric oxide) gave a free aldehyde which could be further chain extended to give **192**. The other isomers of **192** with different stereochemistry at C-8, C-9 and C-10 were prepared by similar routes.[142,143]

In an approach[147] to th synthesis of the vitamin E side chain **193**, **163** has been converted into **194** (Scheme 42) then to **195**. The critical alkylation of **195** (1.3 equiv of sodiomalonate, 5% Pd $(PPh_3)_4$, THF) proceeded smoothly to yield **196** which was converted into **193** in a number of stages.

Starting from the 3-keto derivative of **163** a method has been developed for preparing glycine (Scheme 43) that is chiral because of D incorporation. High stereoselectivity in the formation of **197** was observed when the precursor acetylene was deuterated by treatment with n-BuLi followed by the hydrolysis with D_2O. The corresponding *Z*-olefin was obtained by direct reduction of the acetylene with $LiAlD_4$.[148] Following epoxidation and amination the glycine moiety was detached from the carbohydrate by periodate oxidation.

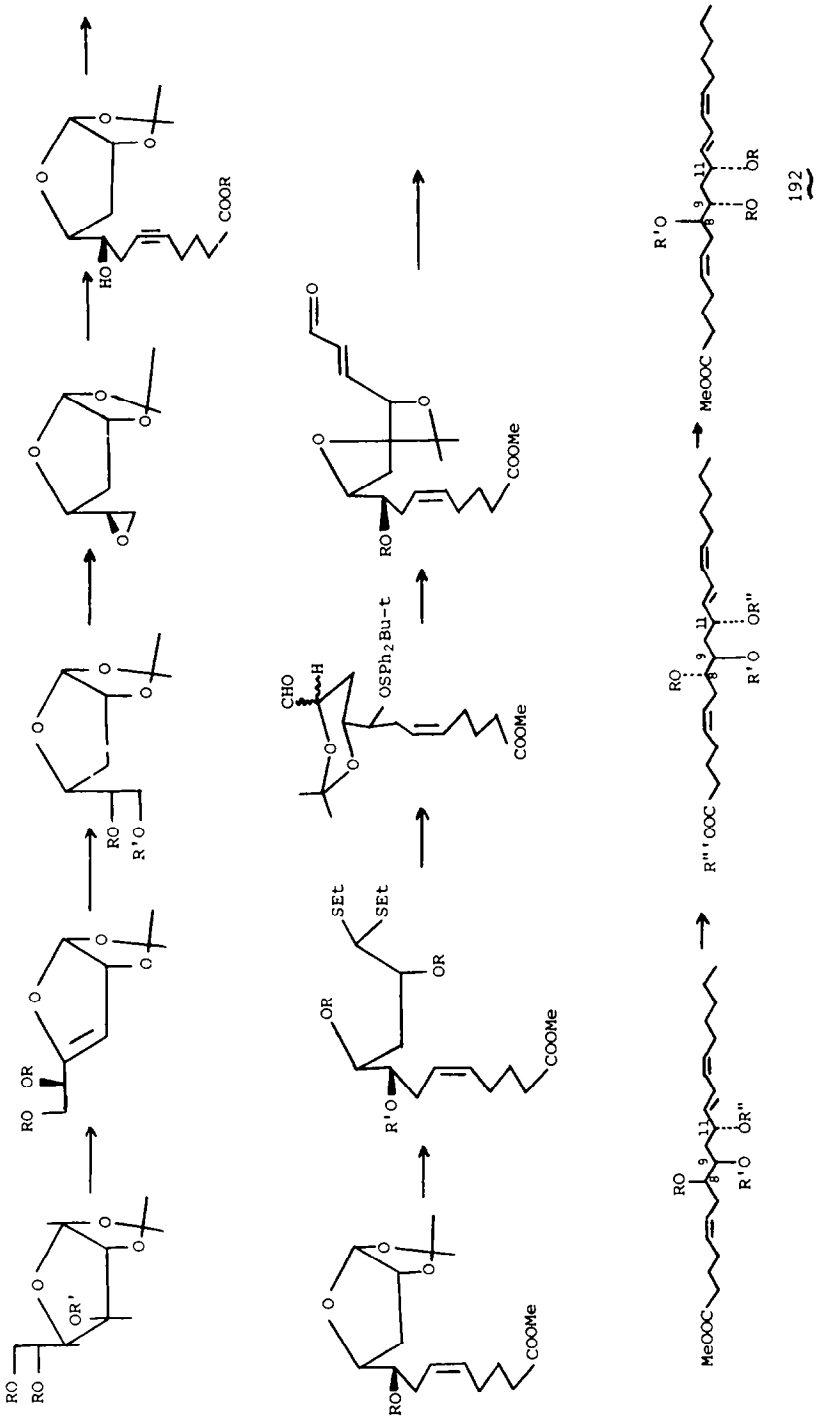
The furan derivative **198** obtained from **163** by partial hydrolysis of the 5,6-isopropylidene grouping, tri-O-tosylation and treatment with 2% methanolic hydrogen chloride, was a key intermediate for the synthesis of (+)-furanomycin **201** as shown in Scheme 44.[149] One particularly interesting step was the conversion of **199** into **200** with a mixture of α-(+)-methylbenzylamine, benzoic acid and t-butylisonitrile. The furan **198** has also been used for the synthesis of various muscarine analogues.[150]

(c) *Tri-O-acetyl-D-glucal.* 3,4,6-Tri-O-acetyl-D-glucal **202** is conveniently prepared from D-glucose by sequential acetylation, bromination and reduction.[151] Since the double bond undergoes a variety of addition and migration reactions[210] **202** provides a useful intermediate to many products.

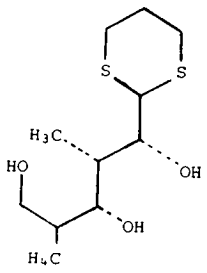
For example in Scheme 45[152] the 2,3-ene-4-one **203** prepared from **202** in 5 steps is first converted into the 2,4-dimethyl derivative **206** before the crucial step of elaboration of the carboxylic group as indicated to give (+) Prelog–Djerassi lactonic acid **207**. An alternative treatment of **202** afforded **208** (Scheme 46[153]) which with lithium dimethyl cuprate gave **209**, which was further transferred to the 2,4-dimethyl derivative **211**.

A benzoate analogue of **208** i.e. **212** undergoes a remarkable Wittig reaction with methylene triphenylphosphorane to give **213** (Scheme 47[154]) which was converted into chiral 5-hydroxy-2-methylhexanoic acid lactones **214a**, **214b** (pheromones of the Carpenter bee). This, possibly unique Wittig reaction presumably involves initial attack on the 2-acyloxy ester leading to an intermediate enone which undergoes the normal reaction with a second equivalent of the reagent.

Similar approaches have been used to make the 2,4-dimethyl structure in (−)multistratin[155,156] **215**. Final chain extension was by sequential reaction with alkyl magnesium bromide, oxidation and reduction as shown (Scheme 48).



Scheme 41.



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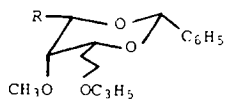

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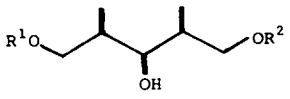

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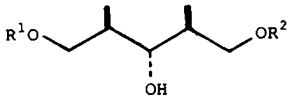

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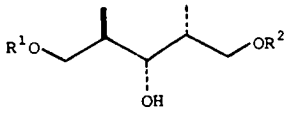

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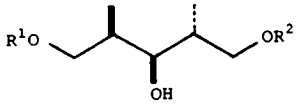

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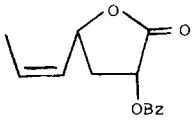

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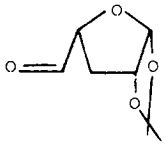

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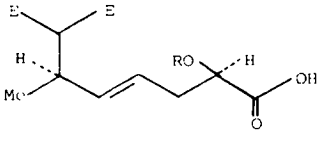

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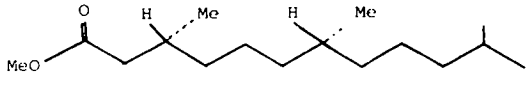

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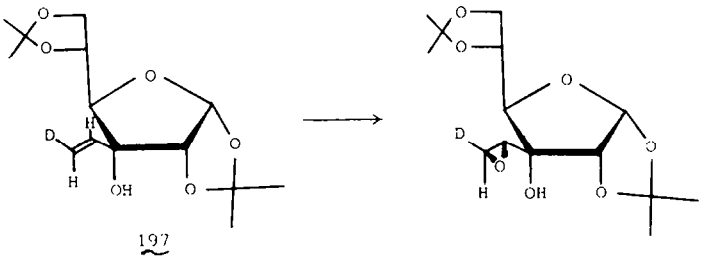
Scheme 42.



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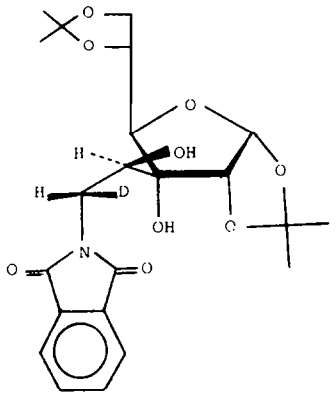
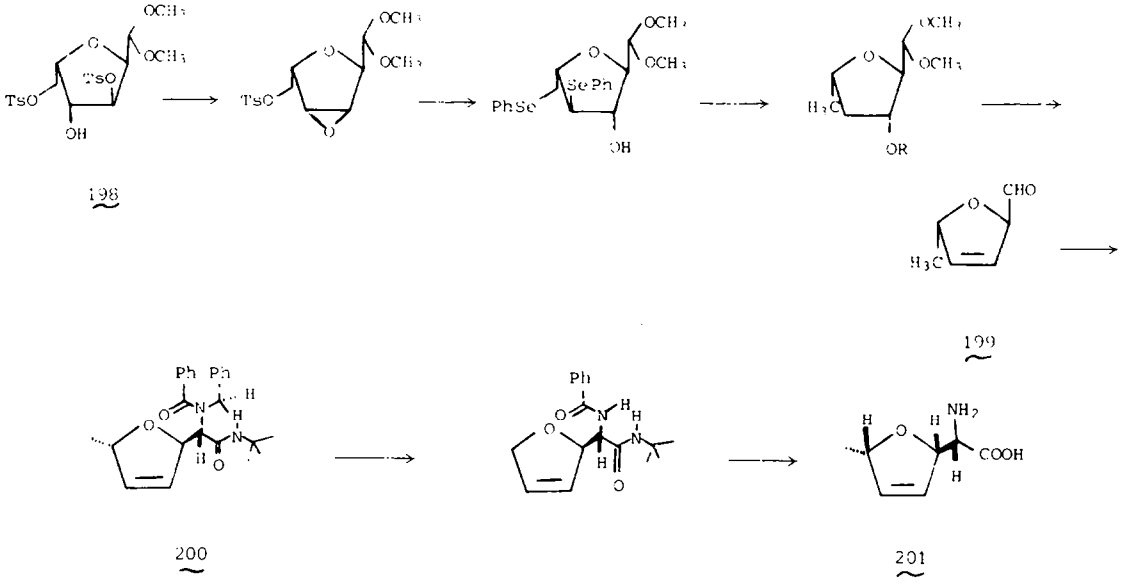


Scheme 43.



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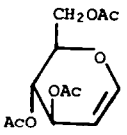
Scheme 44.



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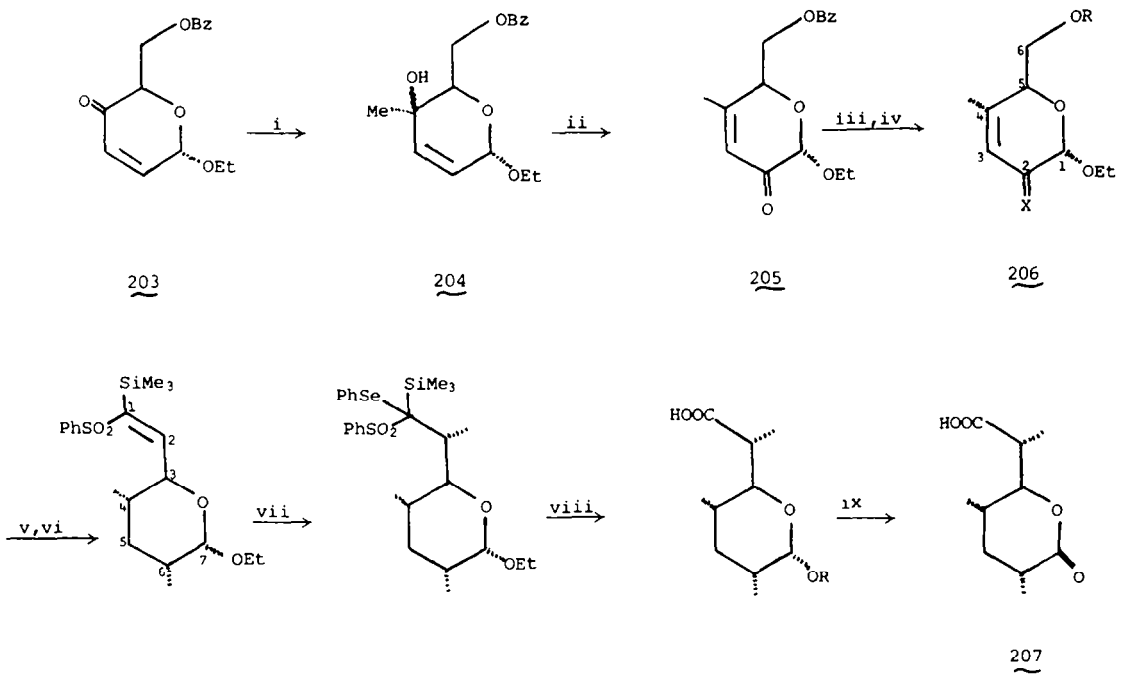
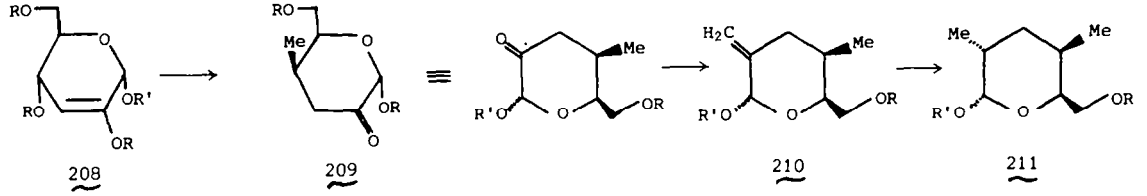
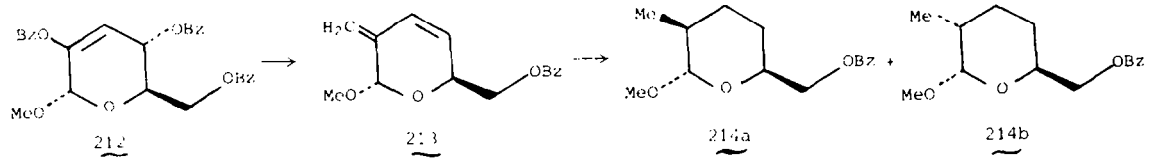


Reagents: i, MeLi/i-Pr_2O; ii, CrO_3; iii, H_2/Pd-C; iv, $Ph_3P{=}CH_2$; v, $(COCl)_2$/DMSO/Et_3N; vi, $PhS(Me_3Si)_2CLi$:mCPBA; vii, MeLi:PhSeCl; viii, H_2O_2/H_3O^+; ix, Br_2/AcONa.

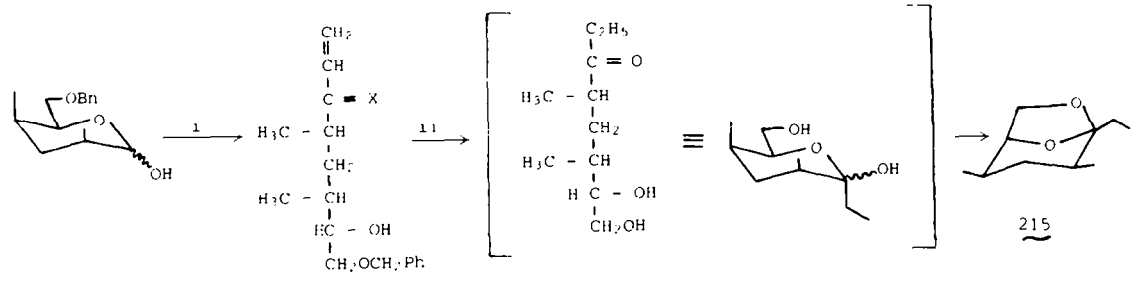
Scheme 45.



Scheme 46.

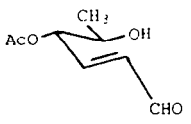


Scheme 47.



Reagents: i, $CH_2{=}CHMgBr$; ii, H_2.

Scheme 48.



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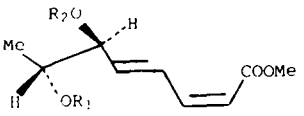

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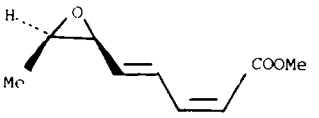

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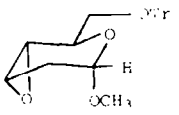

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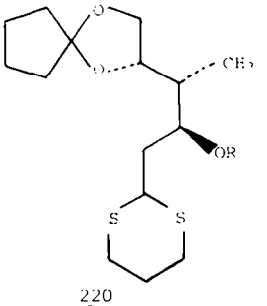

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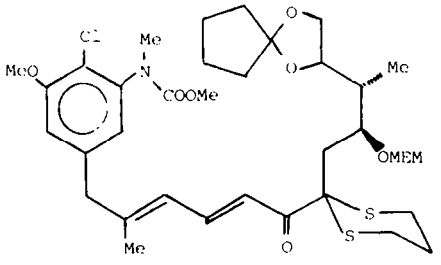

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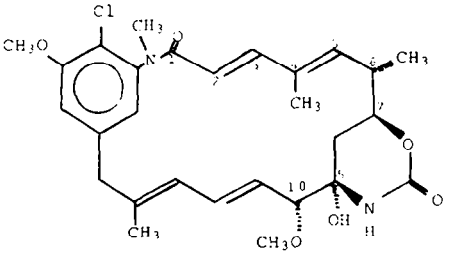

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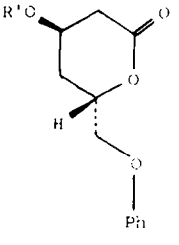
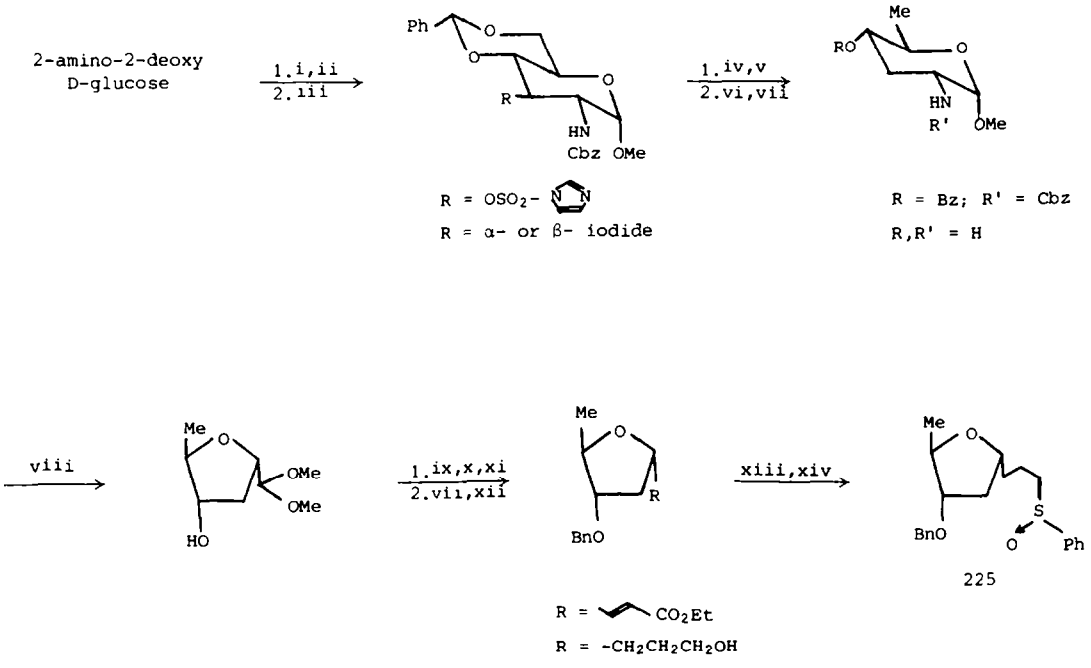


223

An application where tri-O-acetyl-D-glucal is first converted into a 6-deoxy derivative and then to the 2,3-ene is in the synthesis of the C-4 octadienic esters of trichothecenes.[157] Products such as **216** were converted by the procedure of Peterson[158] into the *cis trans* isomer **217** and then into **218**.

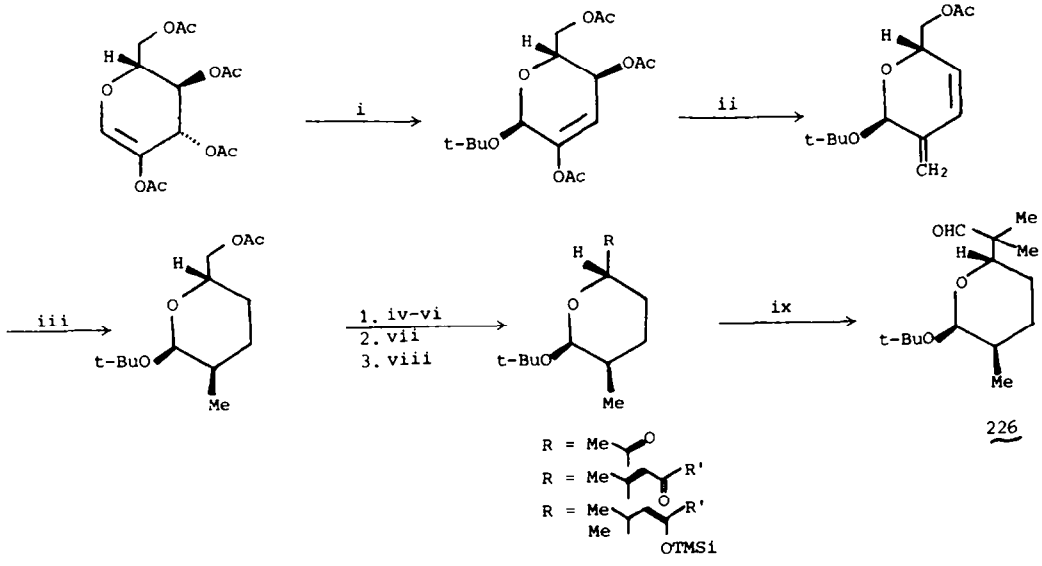
A different use of tri-O-acetal-D-glucal **202** is in the synthesis of (−)-N-methyl-maysenine[159] **223**. Direct use was not made of the double bond in **202** but instead **202** was converted in 3 steps to the epoxide **219** which was then converted into **220** and then through intermediates such as **221** to **222**. The epoxide **219** has also been shown to be of use in the synthesis of mevinic acid derivatives[160] (e.g. **223**).

A total synthesis has been achieved[161] of the $C_{18}H_{32}O_5$ degradation product **224** of the macrolide antibiotic bromycin. One fragment was obtained from tri-O-acetyl-D-glucal (Scheme 49) and the other from D-glucosamine (Scheme 49a) the key coupling step to give **224** being the reaction of the carbanion of **225** with the aldehyde **226** (Scheme 50).



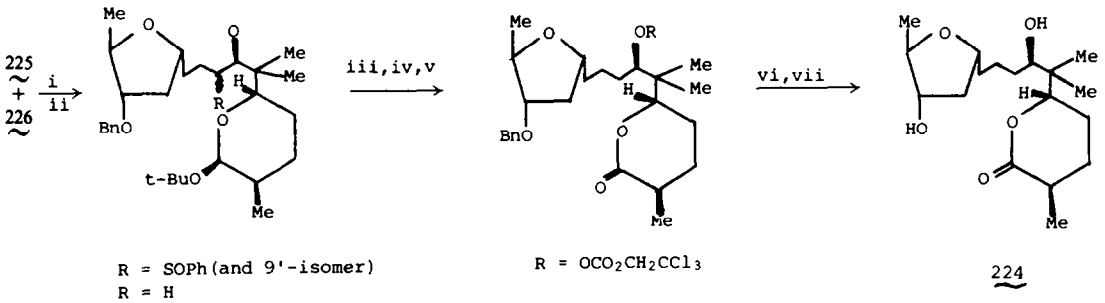
Reagents: i, PhCHO, HCO_2H, 92%; ii, SO_2Cl_2 (2 equiv), DMF, -40°C; imidazole (10 equiv), 25°C, 87%; iii, Bu_4NI, benzene, reflux, 4 h, 85%; iv, NBS, CCl_4, $BaCO_3$, reflux; v, Bu_3SnH, AIBN, toluene, 80-90°C, 50% (overall 3 steps); vi, NaOMe, MeOH; vii, Pd/C, H_2, EtOAc, ∿ quantitative; viii, N_2O_3, H_2O, then MeOH, HCl, reflux, 30 min, 62% overall 4 steps; ix, BnBr, NaH, THF, 83%; x, aqueous AcOH, THF, quantitative; xi, Ph_3P = $COCO_2Et$, THF, 30 min, 92%; xii, LAH, THF; xiii, PhSSPh, Bu_3P, CH_2Cl_2, 25°C, 2 h, 88% (overall 3 steps); xiv, MCPBA, CH_2Cl_2, -40-25°C, 92%.

Scheme 49(a).



Reagents: i, t-BuOH,$BF_3 \cdot Et_2O$, toluene, 25°C, 6 h, 90%. ii, Ph_3P = CH_2 (2.5 equiv), THF, 25°C, 2 h; then acetylation, 90% overall. iii, Pd/C, H_2, EtOAc, 95%, 9:1 mixture. iv, NaOMe, MeOH, 98%. v, Collins, 25°C, 96%. vi, MeMgBr, ether, 25°C, 30 min; then Collins ∿ 90% overall, separate 17 from epimer. vii, $(MeO)_2P(O)CH_2COC_5H_{11}$, NaH, DME, reflux, 24 h, 72% (91% based on recovered ketone). viii, Me_2-CuLi, ether, -40°C, 30 min; then Me_3SiCl, Et_3N, HMPA, -40°C, then 25°C, 1.5 h, ∿ quantitative. ix, O_3, CH_2Cl_2, 1% pyridine, 78°C.

Scheme 49.



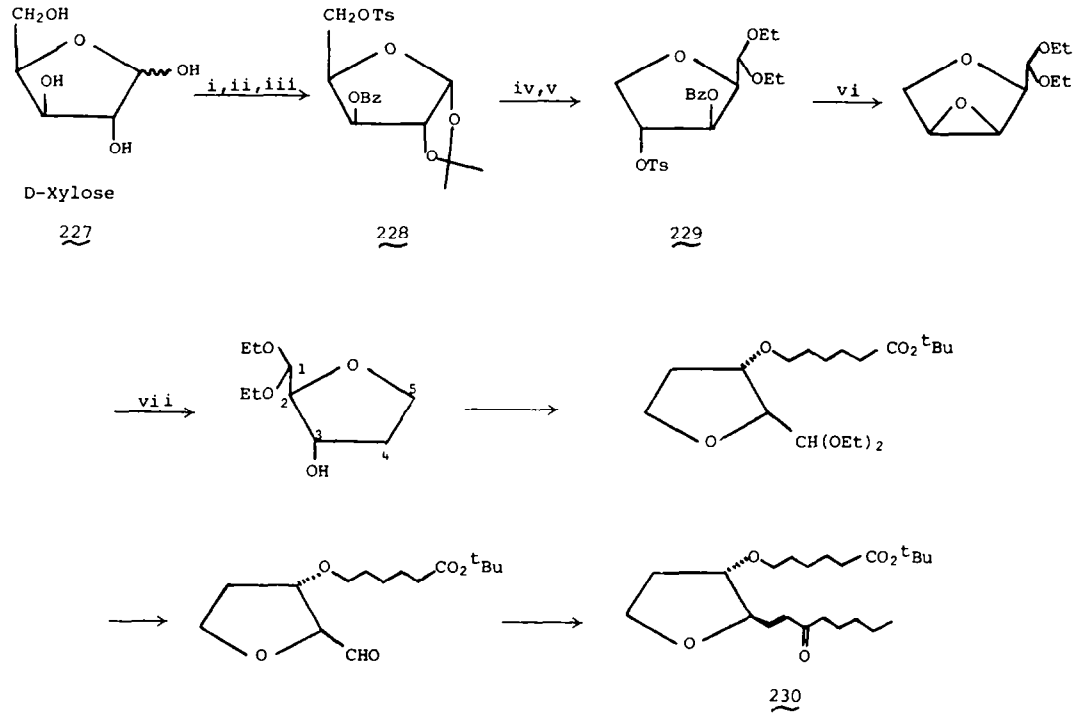
Reagents: i, LDA, THF/10% HMPA, -78°C, 1 h, 87%; ii, Raney Ni (in portions), hexanes, 25°C, 89.5%; then Pd/C, H_2, EtOAc (monitor by TLC); then flash chromatography; iii, Cl_3CCH_2OCOCl, pyridine, 25°C, 18 h; iv, Aqueous HCl, THF, 25°C, 1-2 days; v, PCC, NaOAc, CH_2Cl_2, 25°C, 1 h, 92% (overall, 3 steps); vi, Zn, THF, aqueous KH_2PO_4, 25°C, 30 min; vii, Pd/C, H_2, EtOAc.

Scheme 50.

9. D AND L-XYLOSE

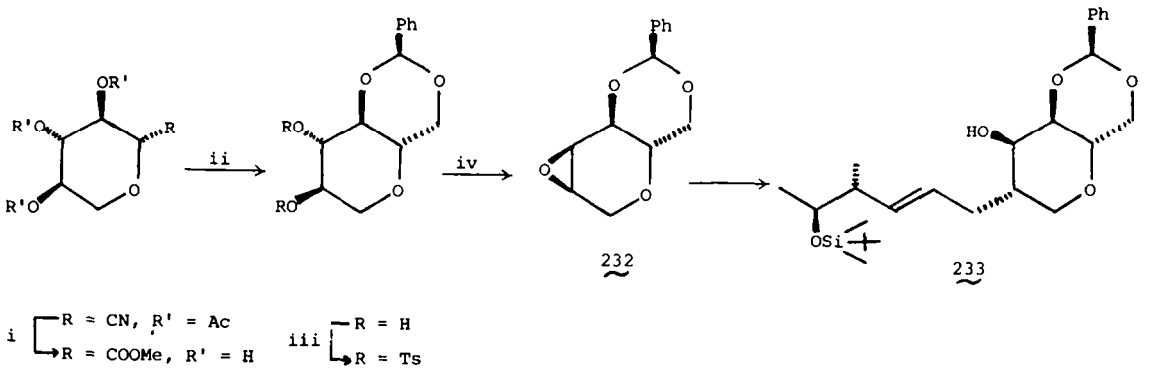
D-Xylose **227** forms a 1,2-O-isopropylidene α-D-furanose[161a] which allows selective substitution of C-3 and C-5 prior to furan ring formation as shown in the Scheme 51.[162] Compound **229** (from L-xylose) has been converted into deoxaprostanoic acid derivatives such as **230**.

D-Xylose gives a crystalline cyanide **231**[163] which may be converted into the epoxide acetal **232**[109] (Scheme 52). This epoxide was the key intermediate used for a synthesis of (+)methyl pseudomonate C **144**. Ring opening of **232** with a Grignard reagent (Scheme 27) prepared from **145** gave **233** which after extensive experimentation was converted into analogues of **144**.



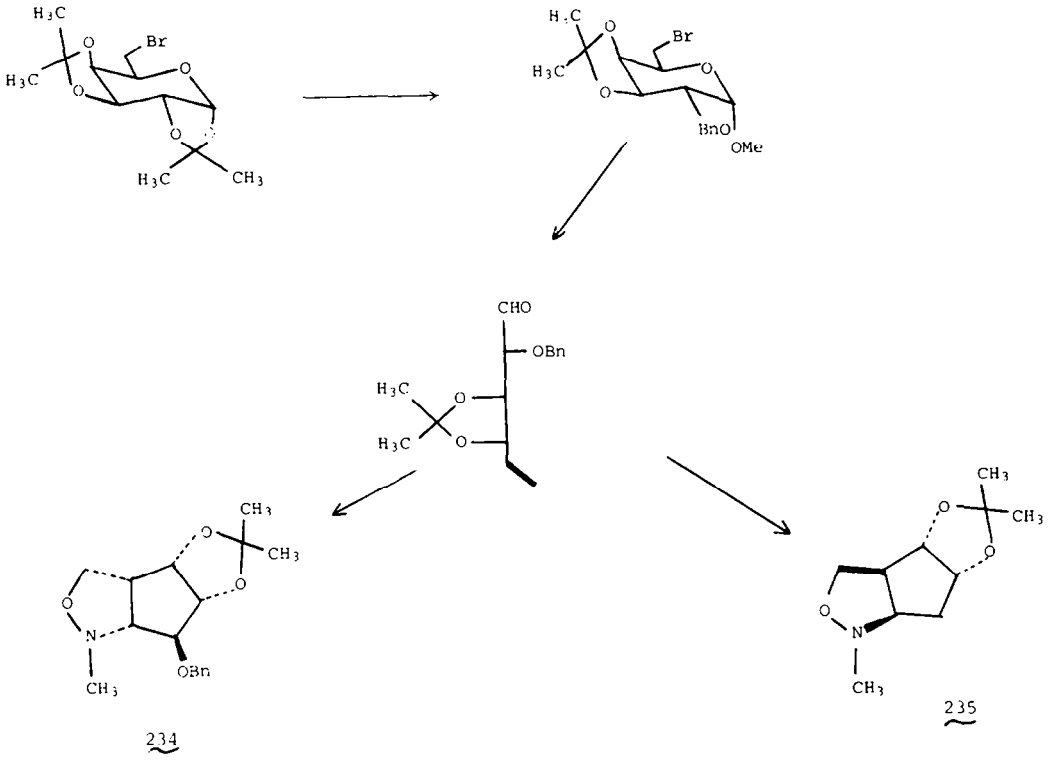
Reagents: i, acetone; ii, TsCl; iii, BzCl; iv, EtOH/H^+; v, TsCl; vi, NaOMe; vii, $LiAlH_4$.

Scheme 51.

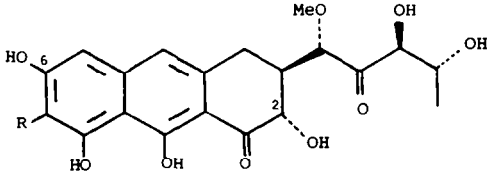


Reagents: i, MeONa, NaOH, MeOH-HCl, 70%; ii, $LiAlH_4$, $PhCH(OMe)_2$, TsOH, 85%; iii, TsCl, pyridine, 70%; iv, MeONa, $CHCl_3$, room temperature, 24 h, quantitative.

Scheme 52.



Scheme 53.

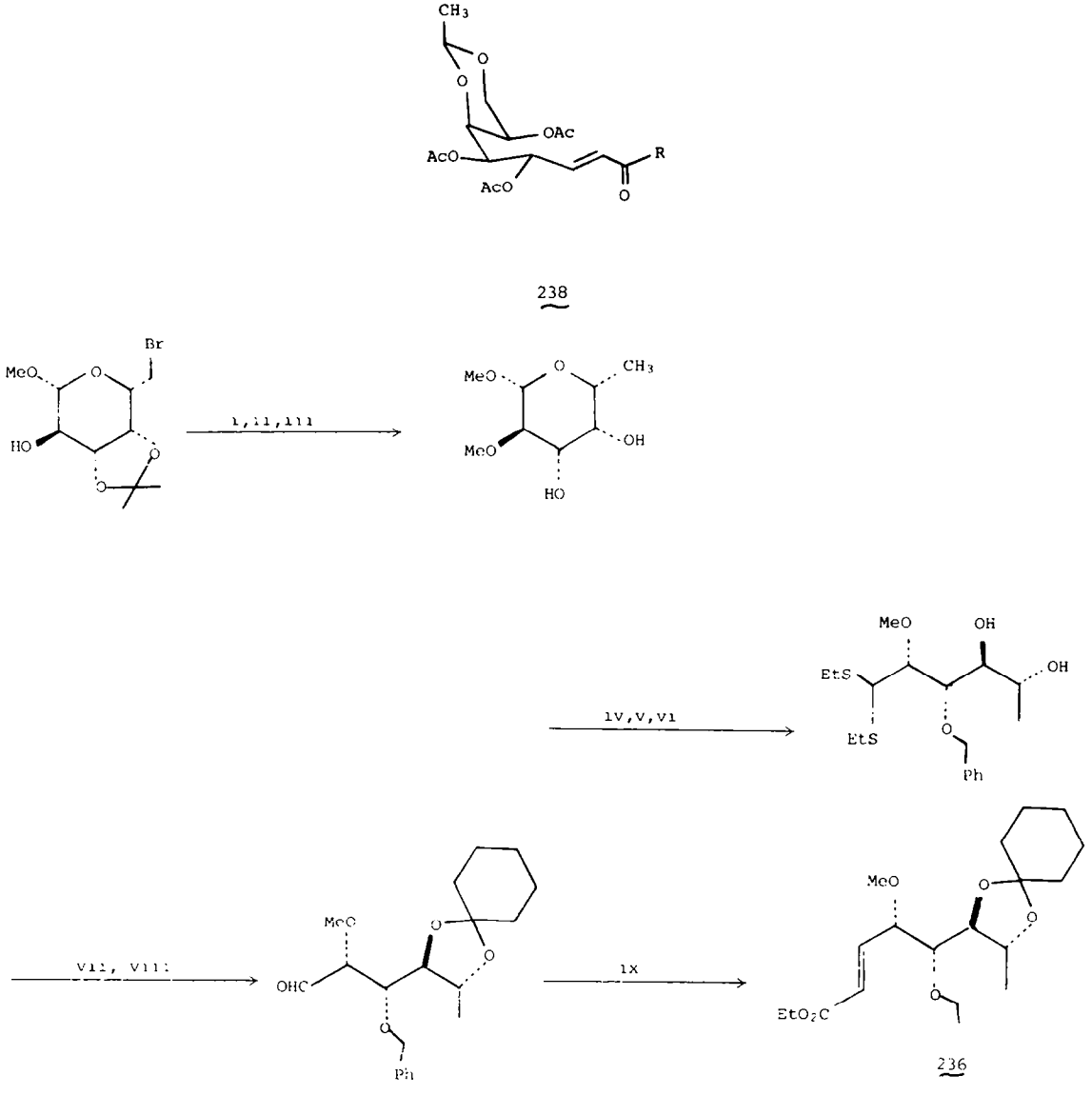


10. D-GALACTOSE

D-Galactose which readily forms a 1,2:3,4-di-O-isopropylidene derivative[164] and methyl 4,6-benzylidene-α-D-galactopyranoside (as for glucose derivatives) has not been used much for chiral synthesis. One use has been in the intramolecular nitrone–olefin cyclo-addition to form cyclopentone derivatives such as **234** and **235** (Scheme 53).[165]

Another use[166] is in the synthesis of **236** (Scheme 54) a key fragment in the synthesis of olivin **237** and like D-arabinose D-galactose has been used as a precursor for the chromomycinone side chain.[72]

The stereochemistry of Diels–Alder reaction between the galactose derivative **238** and diene precursors have been investigated[167] as a continuation of studies of similar reactions[168] with glucal derivatives aimed at a synthesis of a model aureolic acid aglycone.



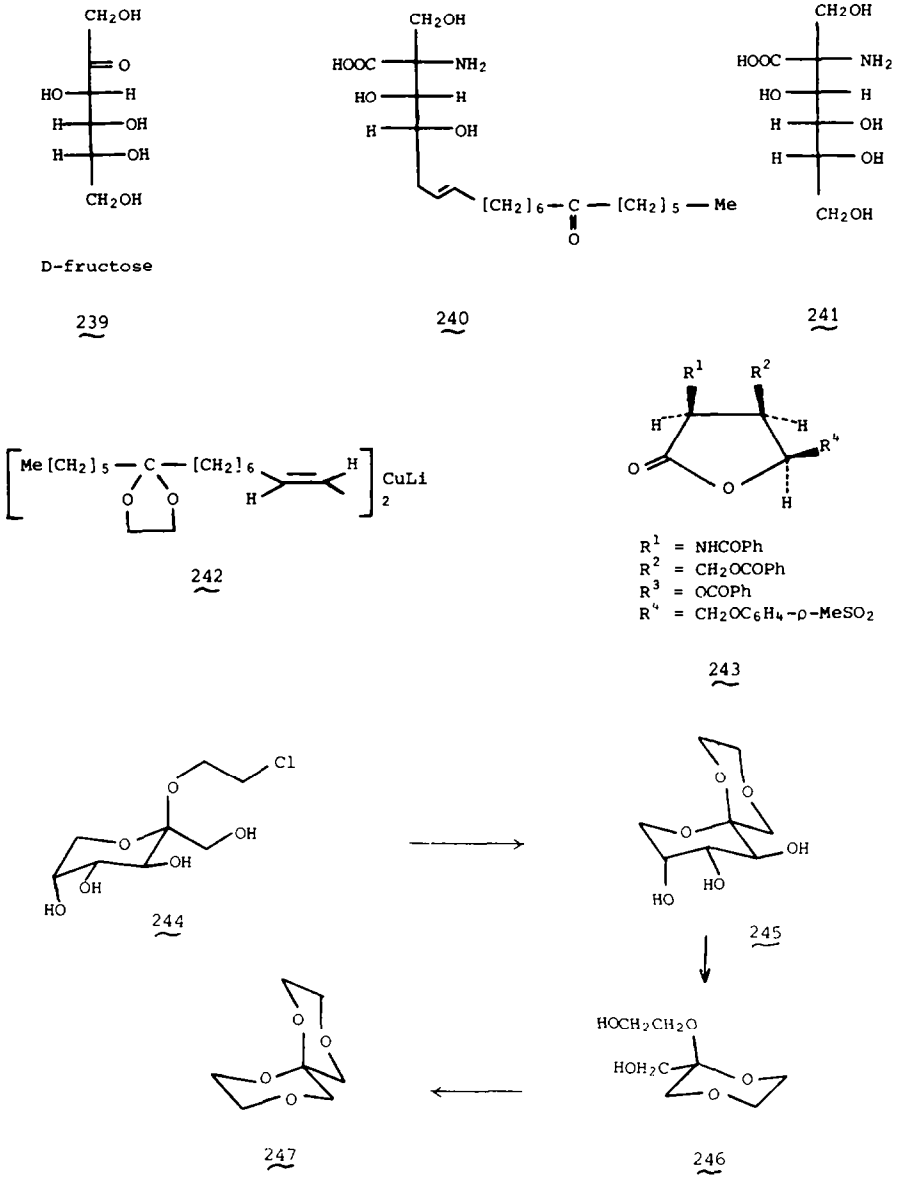
Reagents: i, NaH,CH_3I,DME; ii, $LiAlH_4$,THF,Δ; iii, HOAc,H_2O,55°; iv, Bu_2SnO,C_6H_6; then $C_6H_5CH_2Br$,DMF,130°; v, CF_3CO_2H,H_2O,75°; vi, EtSH, conc. HCl,0°; vii, cyclohexanone, $CuSO_4$,H^+; viii, NBS, collidine, CH_3CN,0°; ix, $(^iPrO)_2POCH_2CO_2Et$/KO^tBu,THF,-78°.

Scheme 54.

11. D-FRUCTOSE

The 2-keto sugar D-fructose **239** has found some application in chiral synthesis. For example a total synthesis of thermozymocidin **240**[169] has been achieved from **239**, the key steps being the transformation of **239** to 2-amino-2-deoxy-2-hydroxymethyl-D-mannoic acid **241** and the stereoselective synthesis of the disubstituted (*E*)-double bond by reaction of the *E*-alkenylcuprate **242** with the tosylate **243**.

Several insect pheromones and other natural products contain an acetal carbon at a spiro-ring junction. One particularly interesting compound is 1,7-dioxaspiro[5,5] undecane (2,2[1]-spirobitetrahydropyran) which functions as a sex pheromone of the olive fruit fly. Analogues have been made starting from D-fructose as shown in Schemes 55[170] the key steps being the formation of the glycoside **244** with 2-chloroethanol, the periodate oxidation **245** and borohydride reduction to give **246** and the ring closure to give **247**.



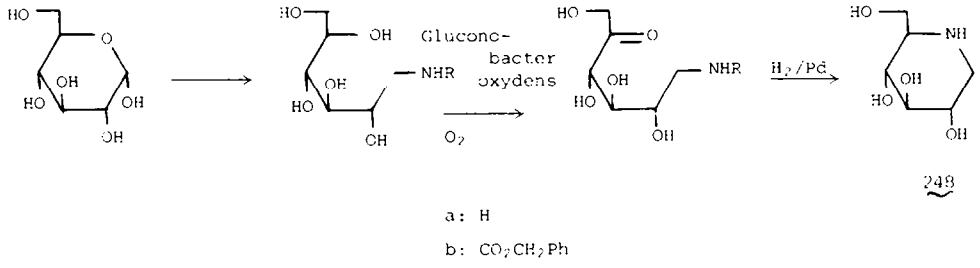
Scheme 55.

12. MISCELLANEOUS SUGAR DERIVATIVES

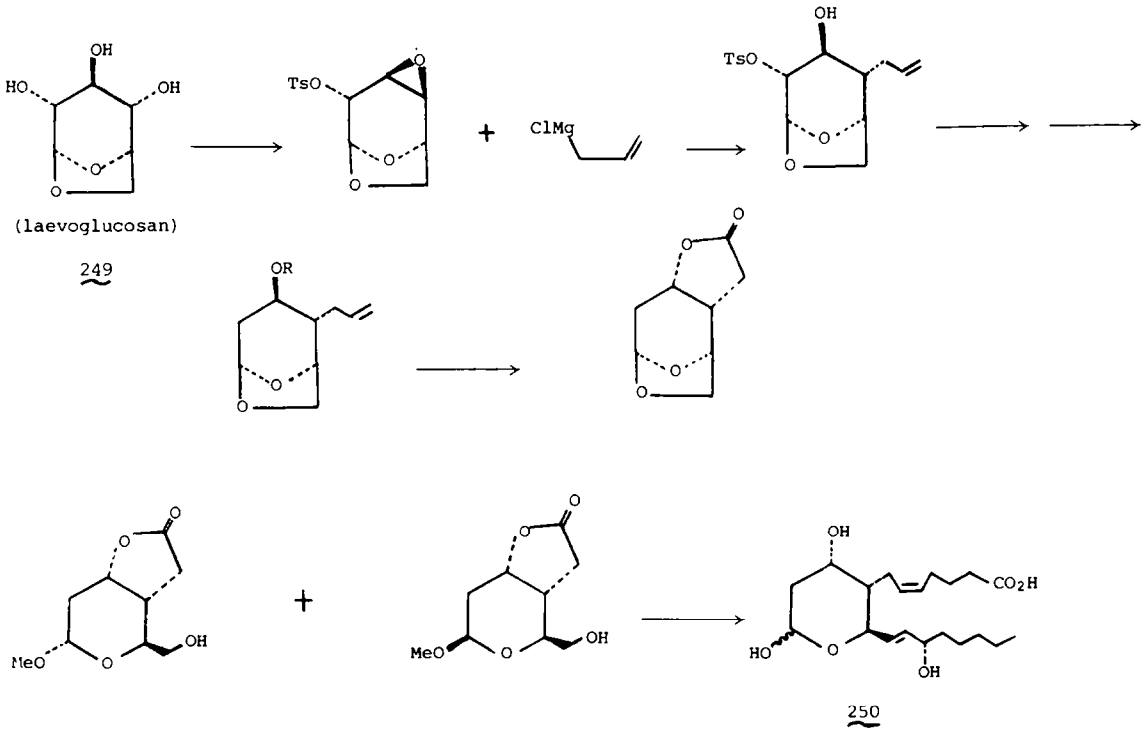
Biotransformations of sugars have been used as in the conversion of D-glucose into 1-deoxynojirimycin[171] (Scheme 56).

1,6-Anhydro-β-D-glucopyranose (laevoglucosan), readily available from a wide variety of carbohydrate sources,[172] for example by the controlled pyrolysis of starch, has been used in a stereocontrolled synthesis[173] of a Thromboxane B2 **249** synthesis as shown in Scheme 57.

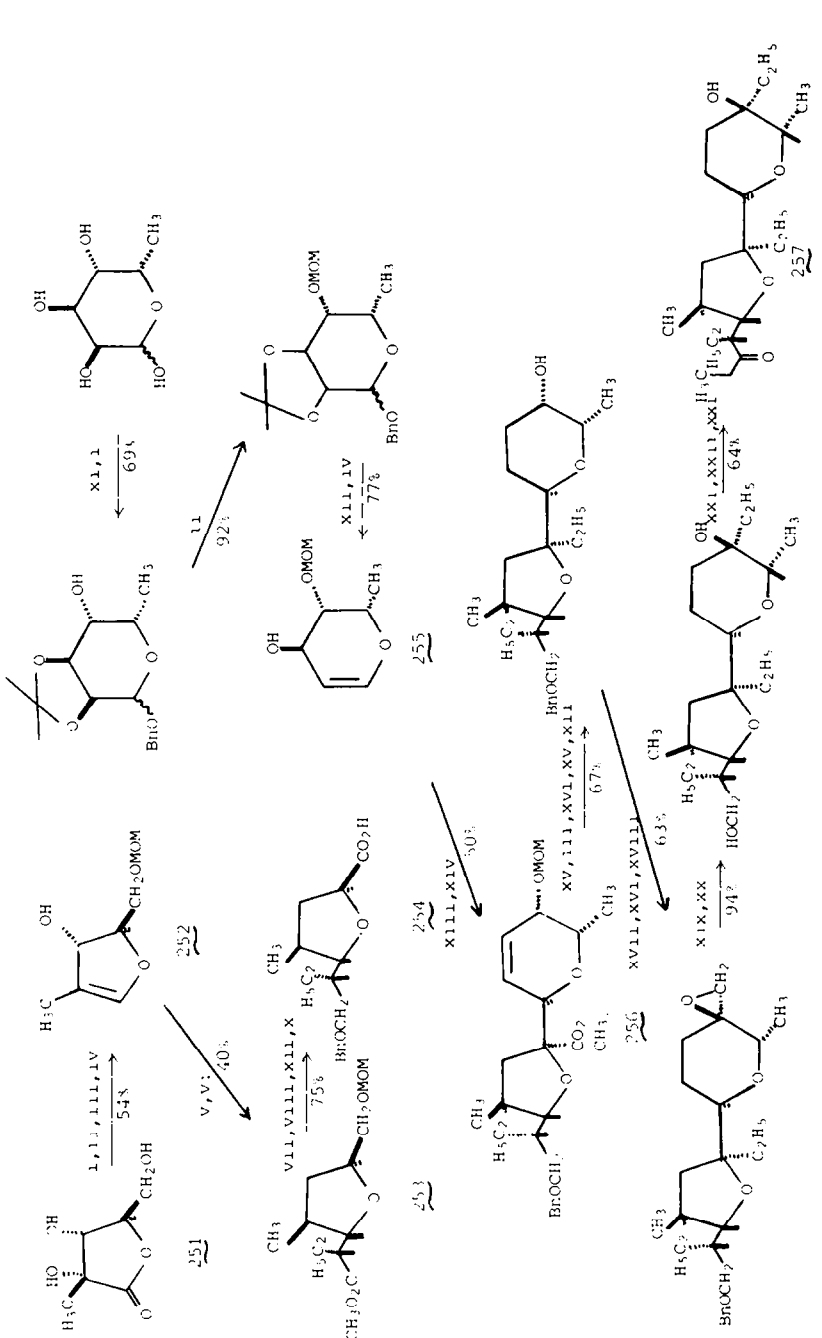
α-D-Glucosaccharino-1,4-lactone[174] **251** has been used to produce a furanoid glycal **252**[175] for enolate-Claisen rearrangement to **253** leading to product **254** for subsequent coupling with a chiral moiety **255** prepared from 6-deoxy L-glucose[176] (Scheme 58). The product **256** was modified to **257** which was used for the total synthesis[177] of the polyether ionophore antibiotic Lasalocid A (X537A). Other enolate-Claisen rearrangements of esters from furanoid and pyranoid glycols of potential use in chiral synthesis have been described.[48]



Scheme 56.

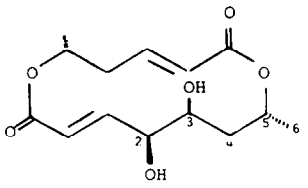


Scheme 57.



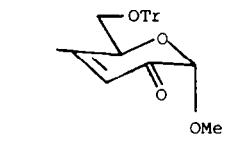
Reagents: i, CH_3COCH_3, H^+; ii, KH, $ClCH_2OCH_3$; iii, Dibal, Et_2O; iv, $P(NMe_2)_3$, CCl_4, Li, NH_3; v, n-BuLi, n-C_3H_7COCl, LDA, 23% HMPA–THF, TMSCl, RT, H_2O, OH^-, CH_2N_2; vi, H_2, Pt/C, EtOAc; vii, LiAlH$_4$, Et_2O; viii, KH, $C_6H_5CH_2Br$; ix, H_3O^+; x, Pt, O_2, aqueous $NaHCO_3$; xi, BnOH, HCl; xii, H_2, Pd/C, EtOAc; xiii, $(COCl)_2$, C_6H_6; xiv, n-BuLi, THF, LDA, THF, TMSCl, RT, H_2O, OH^-, CH_2N_2; xv, H_2, Ni(R), EtOAc; xvi, $(C_6H_5)_3PCH_2$, THF; xvii, Me_2SO, $(COCl)_2$, Et_3N; xviii, MCPBA, CH_2Cl_2; xix, Li, $(CH_3)_2Cu$, pentane; xx, Li, NH_3; xxi, PCC, CH_2Cl_2; xxii, C_2H_5MgBr, THF.

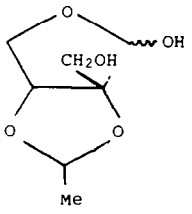
Scheme 58.



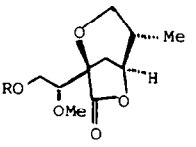
(colletodiol)

258





259



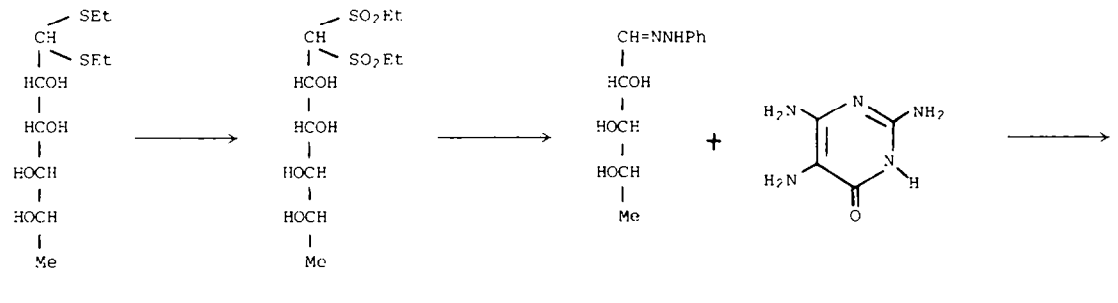
260

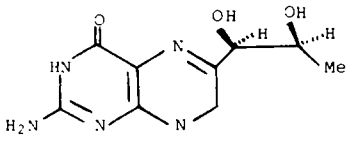
D-Glucose has been used as a source of two of the chiral components required for the synthesis of the marocyclic lactone antibiotic A26771B.[178,179]

6-Deoxy-D-glucose and L-rhamnose (6-deoxy-L-mannose) following conversion into their 4-deoxy derivatives by standard methods have been used to provide the hydrophilic portion of the 14-member-ring macrolide colletodiol **258**.[180]

D-Glucose is a source of 2,3-O-ethylidene-D-erythrofuranose **259** which has been used to prepare[181] in many steps the intermediate **260** required for the construction of maytansine.

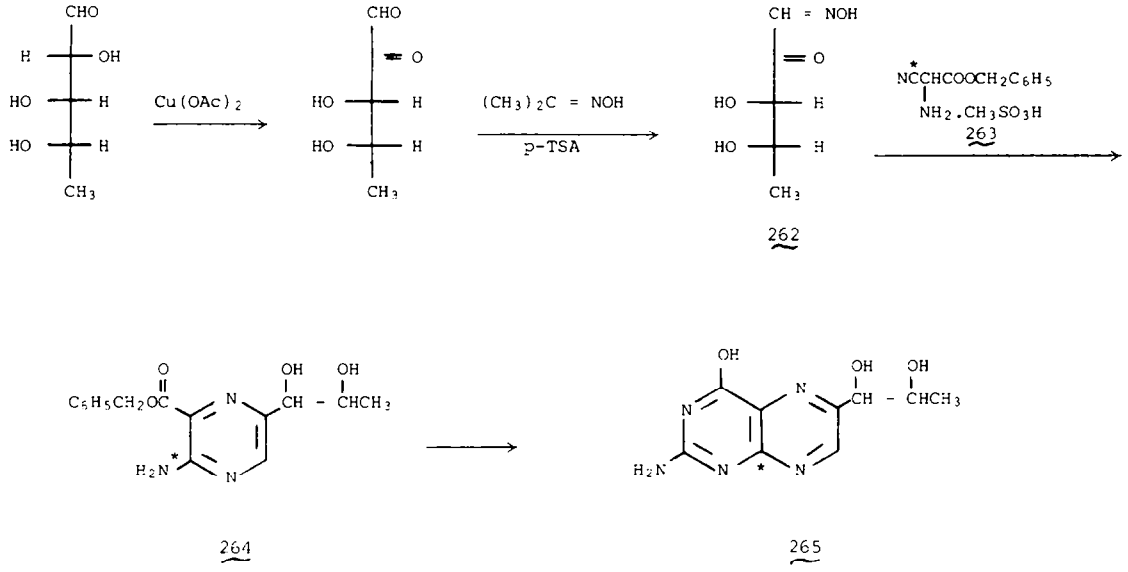
6-Deoxy-L-mannose (L-rhamnose) has been chain shortened and converted into Biopterin **261** as shown in Scheme 59.[182]





261

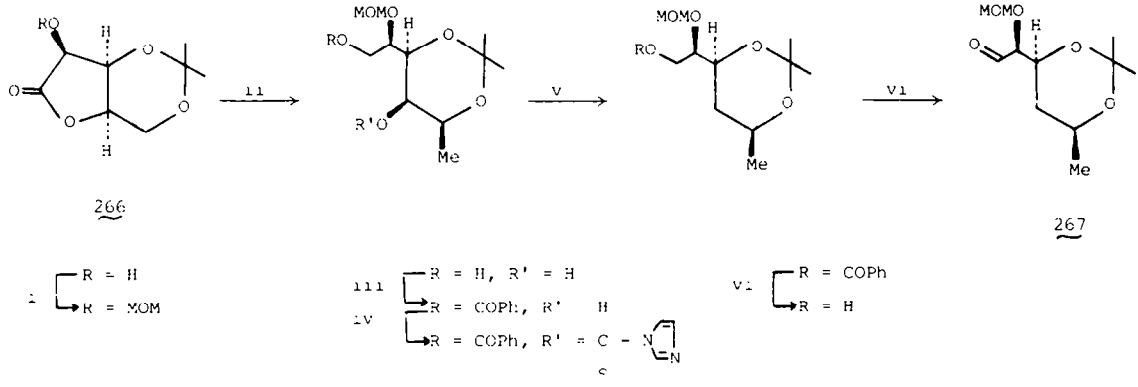
Scheme 59.



Scheme 60.

5-Deoxy-L-arabinose was converted into the monoxime **262** and condensed with the amino-cyanoester **263** to give **264**. Compound **264** was condensed with guanine and appropriately modified to give the labelled biopterin derivatives **265**[183] (Scheme 60). The L-gulono γ-lactone derivative[176] **266** (Scheme 61) has been converted into **267** an intermediate required for the synthesis of (+)-deoxygriseusin.

A series of papers[185–189] have used acyclic sugars (some prepared from 1,2:5,6-di-O-isopropylidene α-D-glucofuranose or methyl 4,6-benzylidene-α-D-glucopyranoside to obtain the correct substituent pattern) have been described as intermediates for bicyclic chiral derivatives.



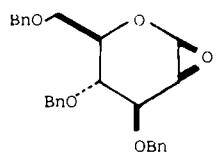
Reagents: i, CH_3OCH_2Cl, $PhNEt_2$, CH_2Cl_2; ii, $LiAlH_4$, THF; iii, PhCOCl, pyr, CH_2Cl_2; iv, Im_2CS, $ClCH_2CH_2Cl$; v, n-Bu_3SnH, toluene; vi, MOH, MeOH; vii, Me_2SO, $(COCl)_2$, CH_2Cl_2.

Scheme 61.

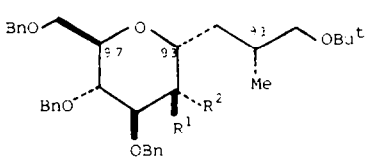
13. PALYTOXIN

Many different carbohydrate derivatives have been used to aid stereochemical assignments and to provide components for the total synthesis of palytoxin **277** the toxic principle from marine soft corals which is the most toxic non-protein material known.

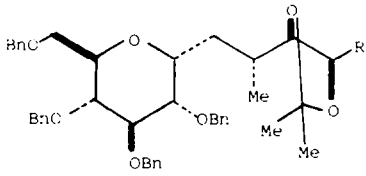
As part of studies of the C-85–C-115 segment, 3,4,6-tribenzyl D-mannose 1,2-epoxide[190] **268** was converted to products such as **269** by treatment with the Grignard reagent prepared from (*S*)-(+)-3-tert-butoxy-2-methyl-bromopropane in the presence of Li_2CuCl_4. **269** was also converted into products such as **270**. 1,2-isopropylidene-D- and L-glyceraldehyde were also employed for studies of the C-85–C-115 fragment.[19]



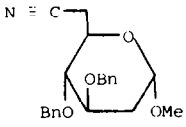
268



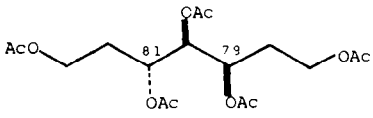
269



270



271



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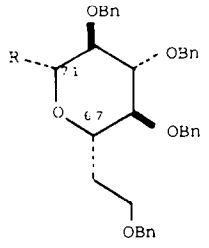
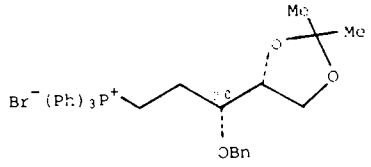
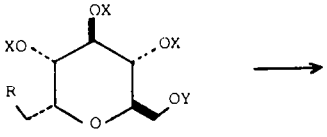


273

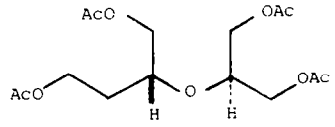


274

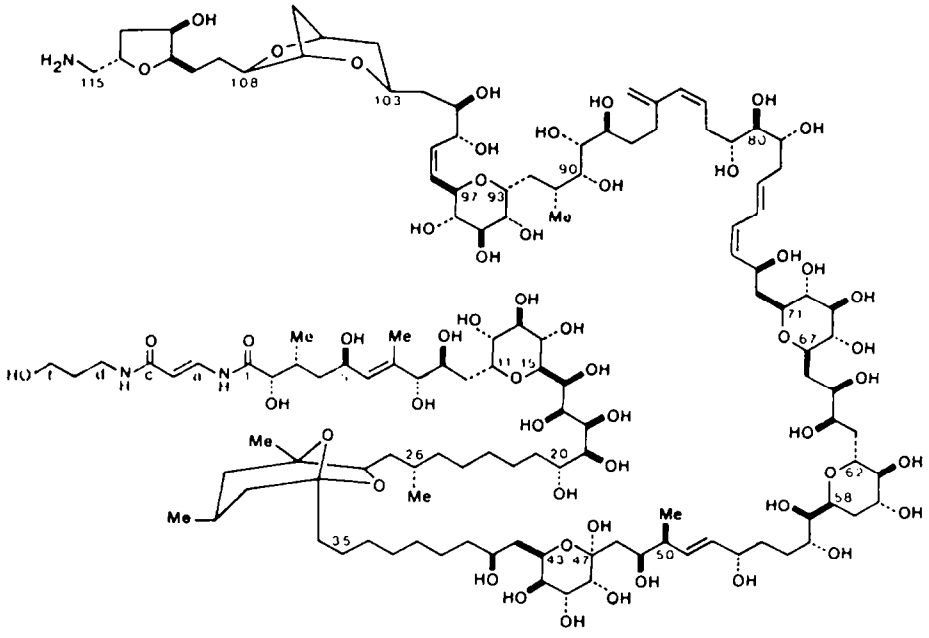


R = CH_2=CH-, X = Bn
Y = H

275



276



277

For the C-77–C-83 fragment[192] the pentaacetate **272** from the 2-deoxy-glucose nitrile **271** was prepared and for the C-52–C-74 carbon backbone the trans-allylic alcohol **273** was utilized. For the C-7–C-51 segment[193] the phosphonium salt from L-xylose **274** the corresponding derivative from L-xylose, and the product **276** derived from **275** prepared from 2,3,4-tribenzyl 1,6-anhydrogluco-pyranose[194] were all used. The complete structure of palytoxin **277** was then determined by synthesis.[195]

CONCLUSIONS

There is now no doubt that the utility of carbohydrates for chiral synthesis is well demonstrated and well recognised. There is also no doubt that many of the initial stages are time consuming and tedious requiring very careful control of reaction conditions to avoid the preponderance of competing and unwanted reactions. What is required are improved and hopefully "one pot" procedures to speed the process from the readily available parent sugar to the functionalised derivatives from which chiral synthesis can be relatively rapid.

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