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Glycals in enantiospecific synthesis

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Abstract. The reactions of 1,2-unsaturated sugars (glycals) are considered in this review in relation to problems of the enantiospecific synthesis of natural products, their fragments, and their analogues. The reactions occurring both with retention of the heterocycle and those carried out with the aim of obtaining open chain chiral units are discussed. It is shown that the use of glycals as a stock of chiral substances which determine the configuration of the asymmetric centres in the target products of multistage synthesis is promising. Schemes for the synthesis of natural products of different types are considered: *O*- and *C*-glycosides, nucleosides, oligosaccharides, pheromones, antibiotics, toxins, glycosphingolipids, etc. The bibliography includes 161 references.

I. Introduction

Glycals — 1,2-unsaturated derivatives of pentoses and hexoses — were first obtained by Fischer and Zach.[1] The factual data on the chemistry of glycals accumulated during several decades have been surveyed in two reviews.[2, 3] Since a detailed description of the results of studies during the last twenty years would have exceeded the available space in the present review, it appears useful to concentrate attention on the most important and interesting aspects of the chemistry of glycals which are of value for fine organic synthesis.

The main principles of the enantiospecific synthesis of natural products using chiral building blocks obtained from carbohydrates were formulated at the beginning of the 1970s. The excellent book by Kochetkov et al.[4] and a number of reviews[5–7] are devoted to this question. On the other hand, a detailed study of the literature enabled us to note that, until the beginning of the 1980s, there were only a few isolated examples of the use of natural sugars such as glycals in the total synthesis of natural products. A notable feature of this decade has been an increasing interest in the chemistry of glycals in connection with problems of enantiospecific synthesis.

At the present time the glycal approach is regarded as one of the promising methods of synthesis of *O*- and *C*-glycosides and oligosaccharides. Reactions involving electrophilic addition to the double bond in glycals are important in this connection. Glycals are completely irreplaceable in the synthesis of natural metabolites incorporating in their structure oxygen-containing heterocycles (ionophoric antibiotics, sea toxins, etc.). The Ferrier reaction,[8] which proceeds as S_N2' substitution accompanied by the allyl rearrangement, has been noted among the reactions which are specially important for the specific modification of glycals. The reactions of alcohols and thiols under the influence of Lewis acids, *C*-glycosylation by cation-active alkenes, allylsilanes, and silyl ethers of enols, the coupling with arenes, malonates, and aryl halides in the presence of metal complex catalysts, and the synthesis of *N*-nucleosides proceed in precisely this way. The reactions of glycals based on the Claisen rearrangement are distinguished by a high enantiospecificity in the formation of new oxygen–carbon bonds. The [2+2]-, [3+2]-, and [4+2]-cycloaddition reactions, which make it possible to obtain cyclic systems and also to achieve the stereospecific introduction of heteroatomic functional groups, are finding applications to an increasing extent. A very promising approach, which has so far been little developed, involves the use of organometallic derivatives of glycals of vinyl type. The products of the oxidation reactions of glycals have acquired great synthetic value. The decyclisation reactions, which make it possible to obtain open chain chiral units, are widely used. Having restricted the present review to the discussion of the methods of synthesis of natural products, we intend at the same time to give a description, which is as detailed and systematic as possible, of the characteristic reactions of glycals and also to include a bibliography, which, although not necessarily referring to the synthesis of natural products and their molecular fragments, is nevertheless of interest to a wide range of readers.

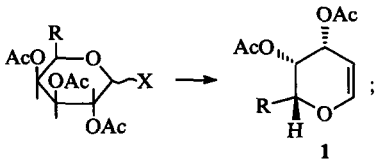
II. Synthesis of glycals

The characteristics of the classical method of synthesis of glycals, which involves treatment of the corresponding acylglycosyl bromides with zinc dust, are given in the paper of Fischer and Zach[1] and in the reviews by Ferrier.[2, 3] The method involves fairly mild conditions, since it makes it possible to obtain in satisfactory yields glycals from disaccharides, for example gentiobial,[9] and modified type **1** glycals from 6-deoxy-6-substituted galactopyranosides (Scheme 1).[10, 11]

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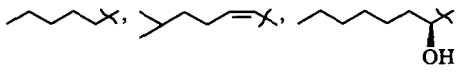
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Uspekhi Khimii **62** (6) 621 – 643 (1993); translated by A K Grzybowski

Scheme 1



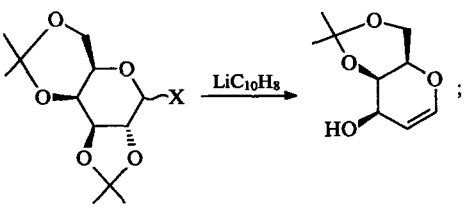
1

X = OAc, Br ;

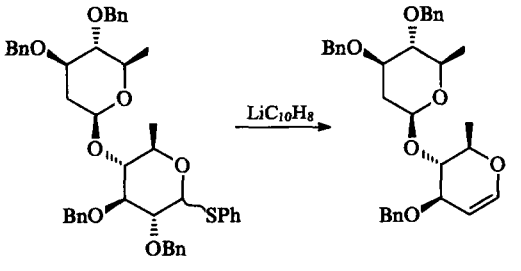
R = 

A number of studies have been devoted to the improvement of the method of synthesis of glycals.[12-14] The possibility of a significant increase in yields when the zinc–silver or the zinc–copper couple,[15, 16] aluminium amalgam,[17] a divalent chromium salt,[18] and lithium in liquid ammonia[19-21] are used was demonstrated. Lithium naphthalide was used successfully in the synthesis of glycals from *S*-glycosides and their oxidised derivatives (Scheme 2).[22, 23]

Scheme 2

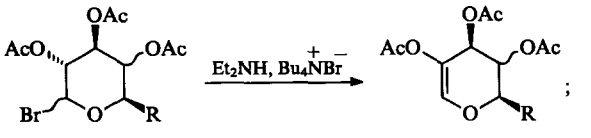


X = PhS, $PhSO_2$.



Derivatives of 2-deoxysugars, containing leaving groups of the type OMs, Cl, and SOPh at the C(1) atom are used in many instances.[24-26] 2-Acyloxyglycals, obtained by treating the corresponding acylglycosyl bromides with diethylamine in the presence of quaternary ammonium salts, have been acquiring increasing importance in the synthesis of natural products (Scheme 3).[27]

Scheme 3

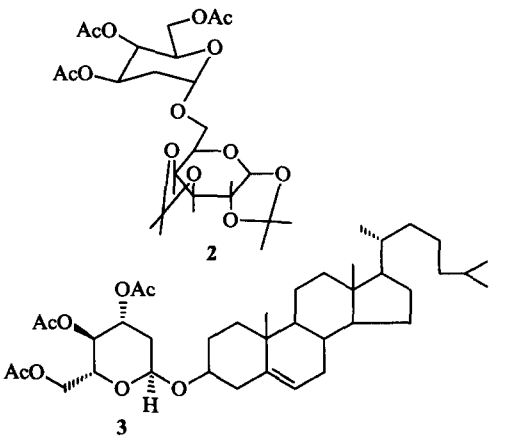


R = H, Me, CH_2OAc .

III. A brief description of the reactions of glycals which have found applications in the synthesis of natural products

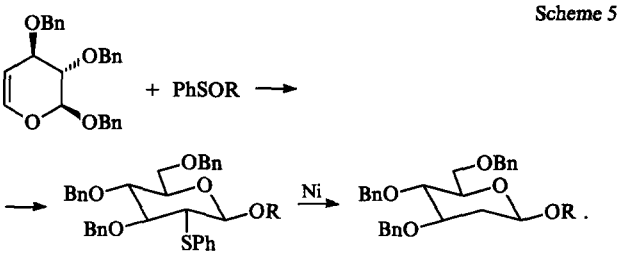
The addition of electrophiles to the double bond of glycals is used in the synthesis of *O*- and *C*-glycosides and oligosaccharides. According to Sabegam and Neira,[28] the very simple reaction involving the addition of water and alcohols is best catalysed by an acid cation exchanger and LiBr. The reactions in the presence of the complex $PPh_3 \cdot HBr$ take place with a high α-stereoselectivity.[29] The α-*O*-glycosides **2** and **3** were synthesised in this way from tri-*O*-acetyl-D-glucal, diisopropylgalactopyranose, and cholesterol (Scheme 4).[2, 3]

Scheme 4



The addition to glycals of benzenesulfenic acid esters, synthesised from PhSCl and the corresponding alcohols, is resorted to in order to obtain the β-*O*-glycosides of 2-deoxysugars (Scheme 5).[30]

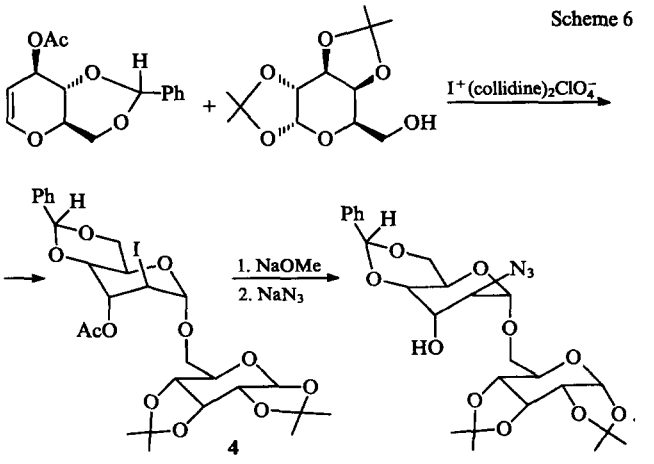
Scheme 5



Phenyl selenyl chloride[31, 32] and phosphorodithioic acid esters[33] can also be used for such purposes.

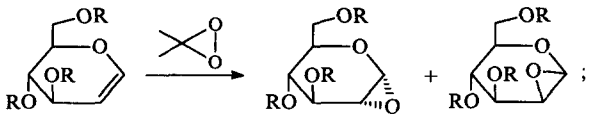
The method based on the addition of alcohols to glycals in the presence of donors of iodonium ions proved to be extremely promising. The complex $I^+(collidine)_2ClO_4^-$ or iodosuccinimide is used as a donor of this kind.[34, 35] The presence of the iodine atom in the adduct **4** makes it possible to introduce nucleophilic groups, in particular the azido-group (Scheme 6).[36]

Scheme 6



The use of 1,2-epoxysugars, obtained by epoxidising glycals with dimethyldioxiran (Scheme 7), has led to extensive prospects.[37, 38]

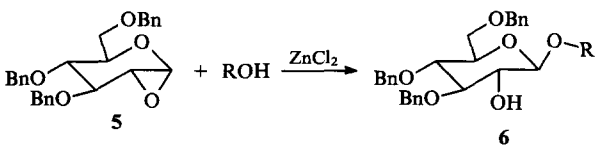
Scheme 7



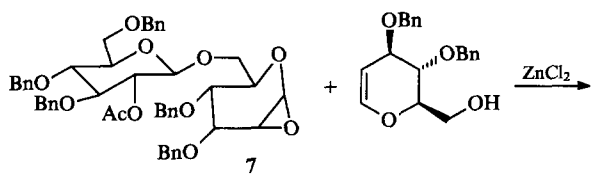
R = Ac, Bn, Bu^{t}Me$_2$Si (TBS).

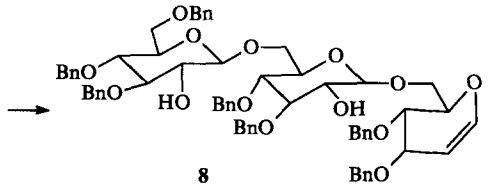
The great synthetic possibilities of this method are demonstrated in Scheme 8. Here the opening of the epoxide ring in compounds **5** and **7** by alcohols in the presence of $ZnCl_2$ proceeds regiospecifically with formation of the individual *O*-glycosides **6** and **8**. The configuration of the latter is determined by the stereochemistry of the initial epoxides.

Scheme 8



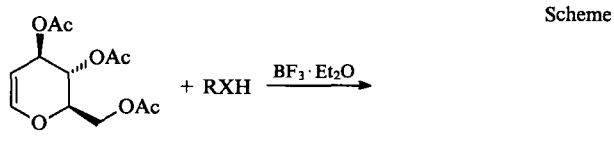
R = cholesteryl.





The reactions of glycals accompanied by the allyl rearrangement have found wide scale application. The first of these, the so called Ferrier rearrangement, takes place with participation of alcohols and thiols in the presence of Lewis acids (Scheme 9).[2, 3, 8]

Scheme 9

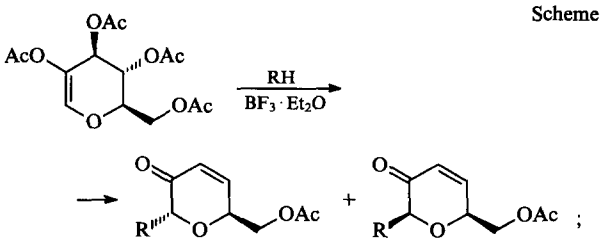


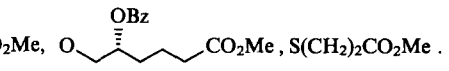
X = O, S.

This reaction is used to synthesise substituted 3-oxo-2*H*-pyrans from 2-acetoxyglycals (Scheme 10).[39, 40]

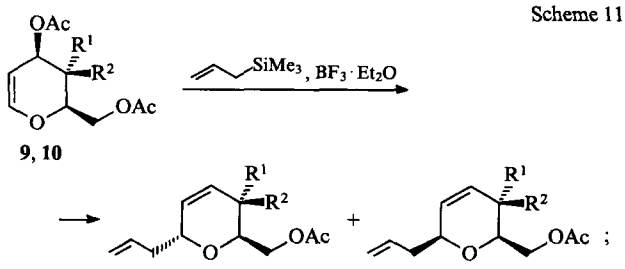
The synthesis of *C*-glycosides is of considerable interest because of the possibility of obtaining 2,6-disubstituted dihydropyrans — important building blocks in the total synthesis of many heterocyclic natural products. The reaction of allyltrimethylsilane with glycals is sensitive to steric factors, which follows from the greater α-stereoselectivity of the interaction of tri-*O*-acetyl-D-galactal **9** compared with tri-*O*-acetyl-D-glucal **10** (Scheme 11).[41]

Scheme 10



R = OCH_2CO_2Me, , $S(CH_2)_2CO_2Me$.

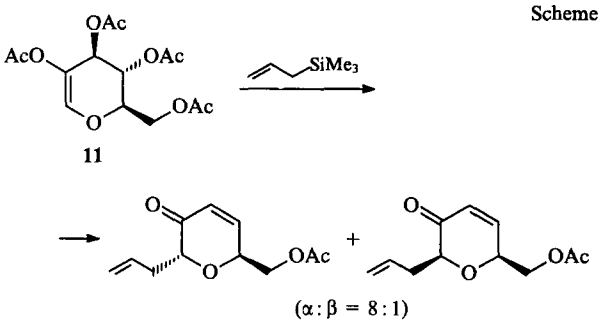
Scheme 11



R^1 = H, R^2 = OAc (**9**) (α:β = 30:1);
R^1 = OAc, R^2 = H (**10**) (α:β = 16:1).

It has been shown that the 2-acetoxyglucal **11** reacts with allyltrimethylsilane in the presence of $BF_2 \cdot OEt_2$ as the catalyst with formation of a mixture of anomeric 3-oxo-*C*-glycosides (Scheme 12).[39]

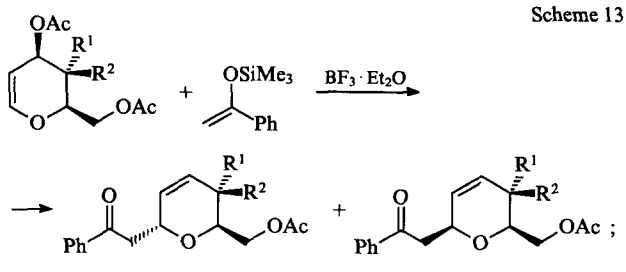
Scheme 12



(α:β = 8:1)

1-Trimethylsiloxystyrene interacts with glycal acetates in the presence of Lewis acids, affording a mixture of isomeric ketones (Scheme 13).[42]

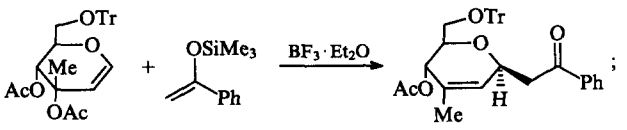
Scheme 13



R^1 = H, R^2 = OAc (α:β = 7:1);
R^1 = OAc, R^2 = H (α:β = 4:1).

This reaction can be carried out α-stereospecifically if a bulky substituent, screening the β-position, can be introduced into the molecule of the initial glycal at the C(6) atom (Scheme 14).[43]

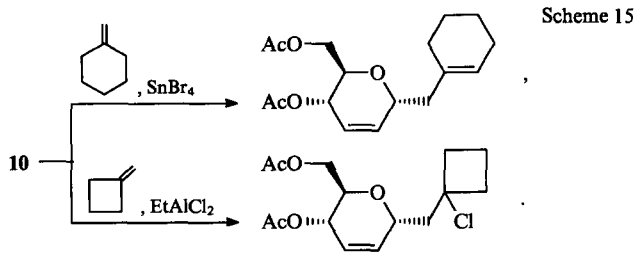
Scheme 14



Tr = Ph_3C .

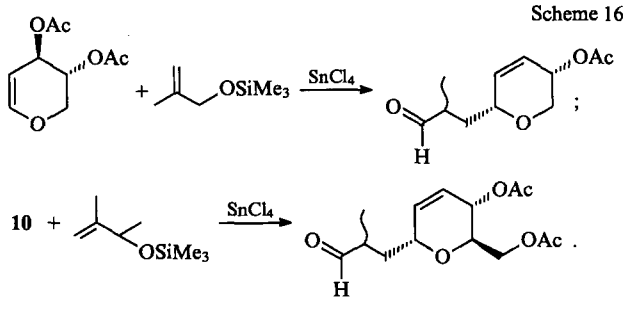
The reactions of cation-active alkenes with various glycals, which occur in the presence of $SnBr_4$ or $BF_3 \cdot OEt_2$, are surprisingly α-stereospecific. If they are carried out in the presence of $EtAlCl_2$ or $TiCl_4$ as catalysts, their products are chloro-substituted *C*-glycosides which also have exclusively the α-configuration (Scheme 15).[44]

Scheme 15



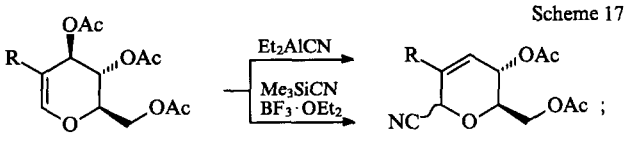
The reactions of glycal acetates with the silyl ethers of methylallyl alcohol and 2-methyl-3-siloxybut-1-ene lead with a high overall yield (77%–96%) to aldehydes in the form of a mixture of (*R*, *S*)-stereoisomers in relation to the side chain (Scheme 16).[45]

Scheme 16



The direct introduction of the cyano-group into glycal ethers by treatment with Et_2AlCN–[46] or Me_3SiCN–$BF_3 \cdot OEt_2$[47] also leads to the allyl rearrangement, affording the corresponding nitriles as a mixture of the α- and β-anomers (Scheme 17).

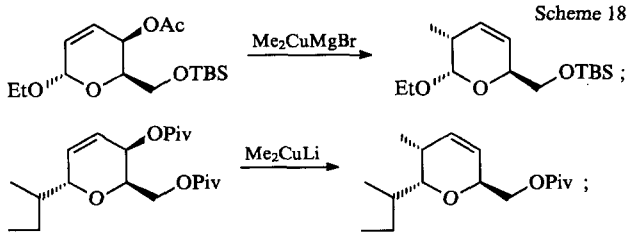
Scheme 17



R = H, OAc .

It is noteworthy that the application of organoelement reagents in the chemistry of glycals does not have particularly distinctive features. Nevertheless the cross-coupling of magnesium and lithium cuprate reagents with derivatives of glycals made it possible to obtain a series of important synthons (Scheme 18).[48, 49]

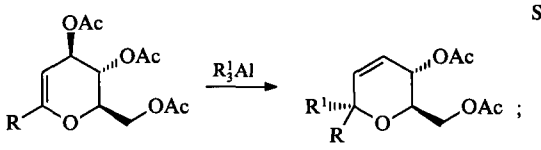
Scheme 18



Piv = C(O)Bu^t .

According to the data of Nicolaou et al.,[50] the $TiCl_4$-catalysed reaction of 1-substituted glycals with organoaluminium compounds proceeds stereospecifically (Scheme 19).

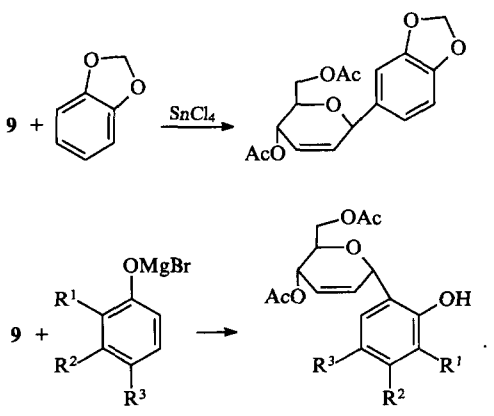
Scheme 19



R = Me, $CH_2CH{=}CH_2$;
R^1 = Me, Et .

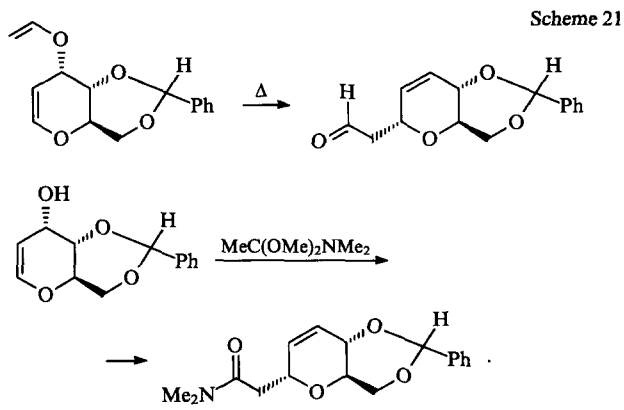
C-Arylglycosides of natural origin can be obtained from glycals. The reaction takes place with the Ferrier rearrangement and the stereochemistry of the product depends on the method selected for this purpose (Scheme 20).[51–56]

Scheme 20



The Claisen rearrangement with participation of glycal derivatives has been extended with the stereocontrolled formation of a new C–C bond. The thermal rearrangement involves the preliminary formation of the vinyl ethers of glycals or the direct reaction of the latter with the dimethyl acetal of *N*,*N*-dimethylacetamide (Scheme 21).[57]

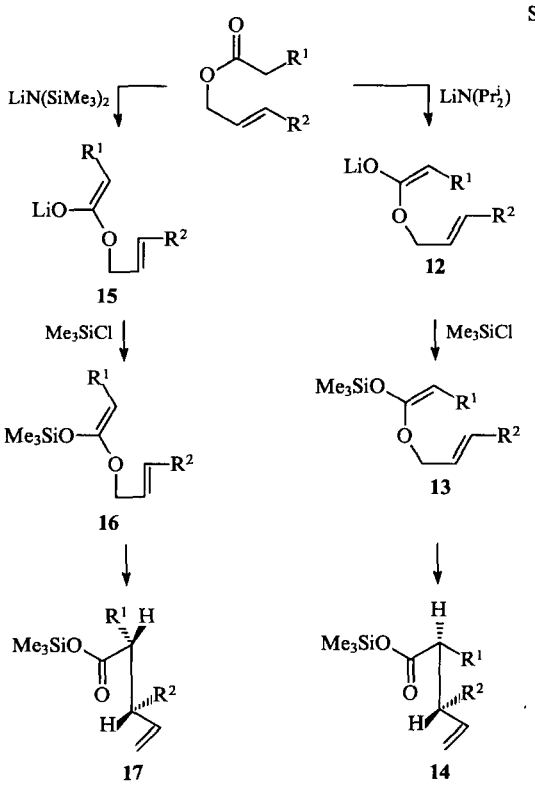
Scheme 21



However, this method is extremely restricted by the choice of the vinyl fragments and one cannot claim that it is widely used. Ireland and coworkers[58–60] found a general approach guaranteeing a high stereoselectivity of the reaction. It is striking that the stereochemistry of the target product can be regulated by altering the nature of the enolisable reagent. Thus the deprotonation of the ethers of allyl alcohols with lithium diisopropylamide in solution in tetrahydrofuran affords the (*Z*)-lithium enolate **12**, the treatment of which with Me_3SiCl leads to the (*E*)-ketene silyl acetal **13**. If the reaction is carried out in hexamethylphosphoramide or lithium bis-(trimethylsilyl)amide is used, then (*E*)-lithium enolate **15** and afterwards the (*Z*)-ketene silyl acetal **16** are formed.

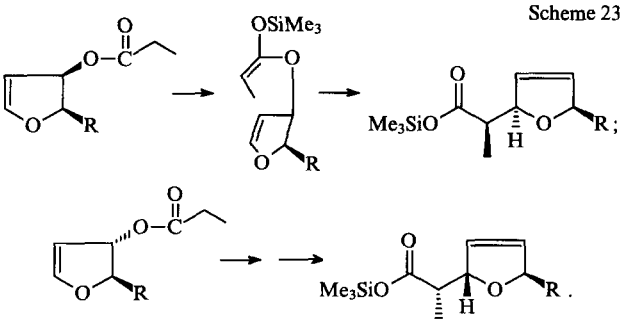
The [3,3]-sigmatropic rearrangement of silyl acetal takes place at −78 °C, the (*E*)-silyl acetal **13** and the (*Z*)-acetal **16** affording respectively the *erythro*-isomer **14** and the *threo*-isomer **17** (Scheme 22).

Scheme 22



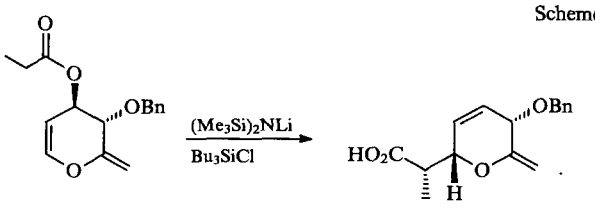
These principles have been clearly demonstrated in relation to the rearrangement of the silyl acetals prepared from the corresponding propionates of furanoglycals (Scheme 23).[60]

Scheme 23



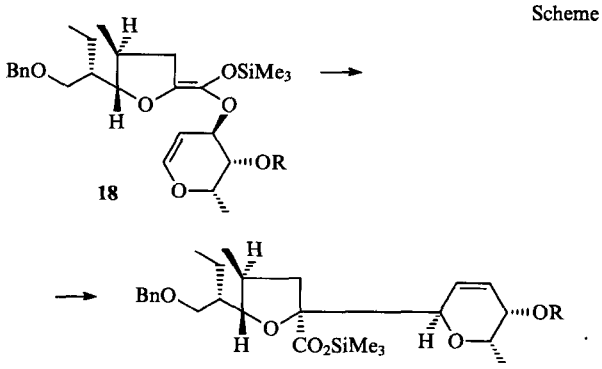
Unfortunately the stereospecificity of the formation of the chiral centre in the side chain breaks down for the propionates of pyranoglycals. For example, a mixture of *C*-glycosides enriched in the α-epimer (up to 86%) was obtained in one of the stages of the synthesis of streptolic acid (Scheme 24).[61]

Scheme 24



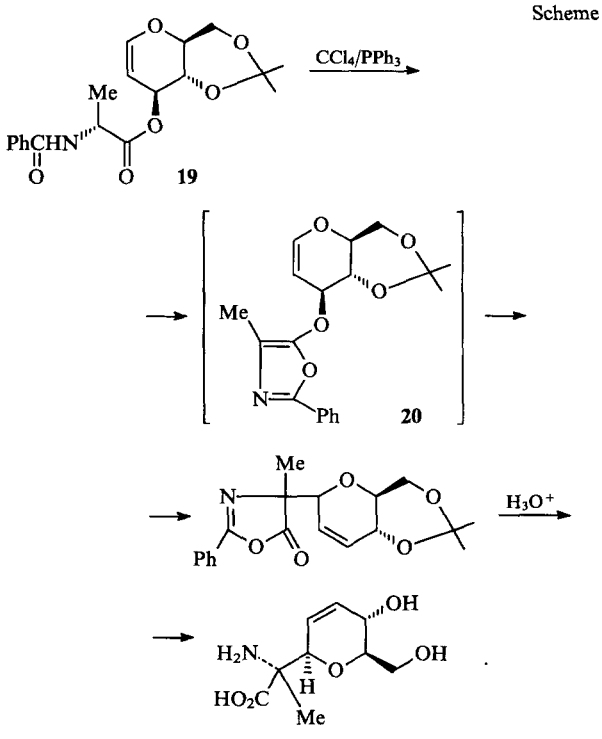
The synthetic possibilities of Ireland's method can be inferred in relation to the rearrangements of the silyl acetal **18**, which has a complex structure (Scheme 25).[62]

Scheme 25



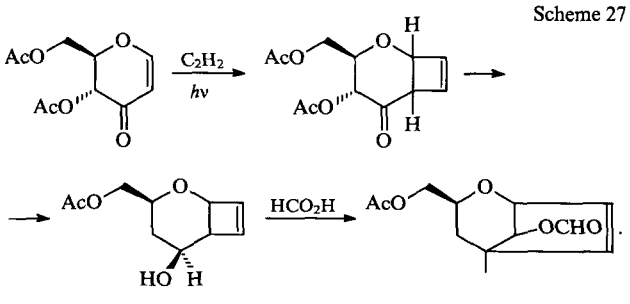
The enolisation of the esters of *N*-benzamidoacids of type **19** makes it possible to achieve an extremely interesting reaction via the oxazole intermediate **20** (Scheme 26).[63]

Scheme 26



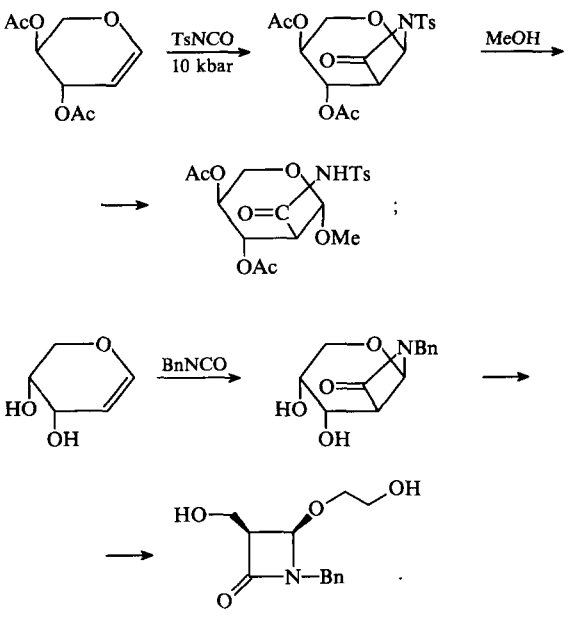
The cycloaddition reactions of glycals and their derivatives have found their place in the stereoselective synthesis of a series of useful bicyclic synthons. Thus the photocycloaddition of acetylene to glycal derivatives via the [2 + 2]-mechanism is regarded as a promising method of constructing the skeleton of trichothecene (Scheme 27).[64, 65]

Scheme 27



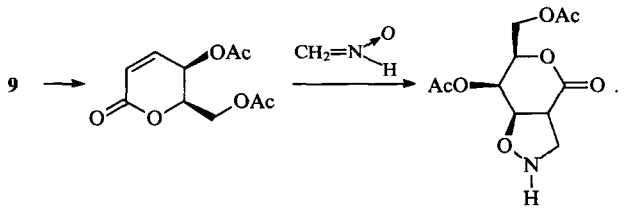
Acyl and sulfonyl isocyanates add to glycals at a pressure of several kilobars, affording [2 + 2]-adducts. The latter have been used in the synthesis of 2-carboxysugars[66, 67] and optically active β-lactams (Scheme 28).[68]

Scheme 28



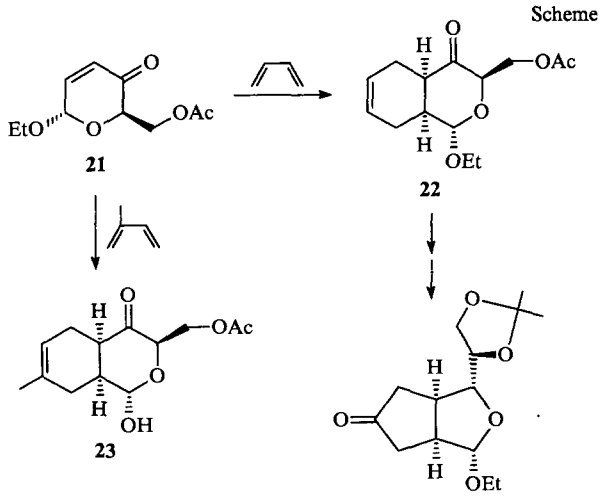
Glycals and their derivatives, which are active 1,3-dipolarophiles, combine with nitrile oxides,[69] nitrones,[70] and formaldoxime (Scheme 29).[71]

Scheme 29



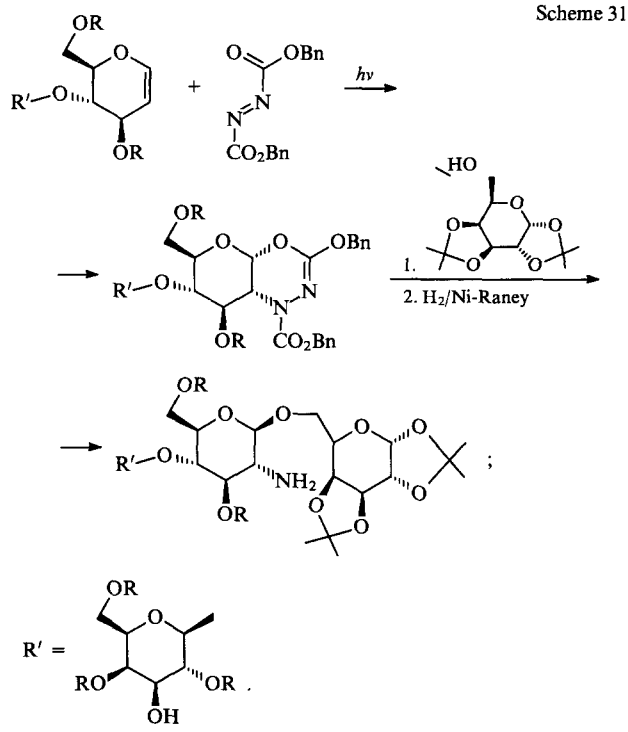
Chiral synthons have been obtained by the [4+2]-cycloaddition reactions of glycals and their derivatives with dienes. Thus the interaction of the enone **21** with butadiene results in the formation of the product **22**, which is used as the starting compound for the synthesis of cyclopentanoid compounds of the type of brefeldin.[72] The Lewis acid-controlled condensation of the enone **21** with isoprene makes it possible to obtain fairly readily compound **23** (Scheme 30).[73]

Scheme 30



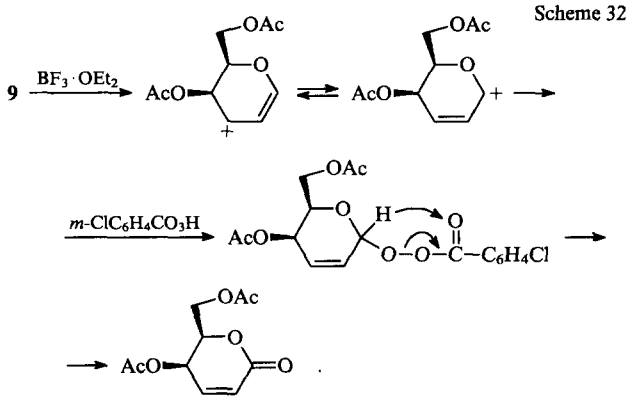
The approach to the synthesis of 2-amino-2-deoxysugars developed by Leblanc and Rokach is of great preparative value.[74-76] The photoinitiated reaction of glycals with dibenzyl azodicarboxylate proceeds as a [4+2]-addition. Treatment of the adducts with alcohols in the presence of toluene-*p*-sulfonic acid affords *O*-glycosides, which are converted after hydrogenolysis into 2-aminosugars (Scheme 31).

Scheme 31



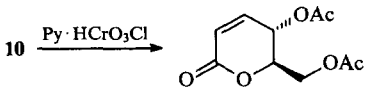
Among the oxidation reactions of glycals, their single-stage conversion into unsaturated lactones on treatment with *m*-chloroperbenzoic acid in the presence of $BF_3 \cdot OEt_2$ is striking.[77, 78] The proposed mechanism of the oxidation reaction is illustrated in Scheme 32.

Scheme 32



Glycals are oxidised similarly by the complex $Py \cdot HCrO_3Cl$. It has been pointed out[79, 80] that the yields of the lactones are higher than in oxidation with peracids (Scheme 33).

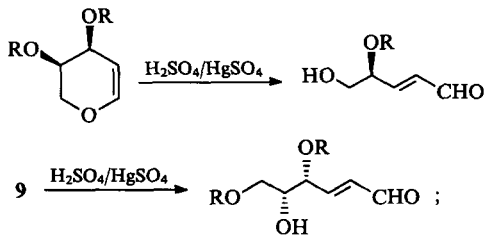
Scheme 33



The decyclisation reaction of glycals has been recently used with increasing frequency in enantiospecific synthesis. Several methods of synthesis of open chain synthons from glycals are known. One of these has been developed by Perlin and coworkers.[81, 82] On treatment with Hg^{2+} salts in an acid

medium, glycal acetates are converted into partial acetates of α,β-unsaturated hydroxyaldehydes. According to Tolstikov et al.[83] and Hirata et al.,[84] the ring is opened similarly to benzyl ethers of glycals based on pentoses and hexoses (Scheme 34).

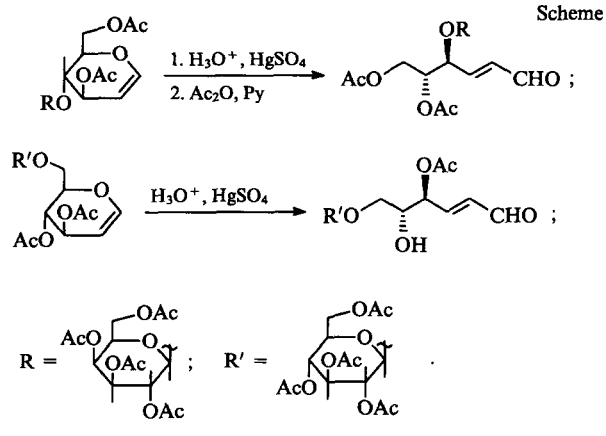
Scheme 34



R = Ac, Bn .

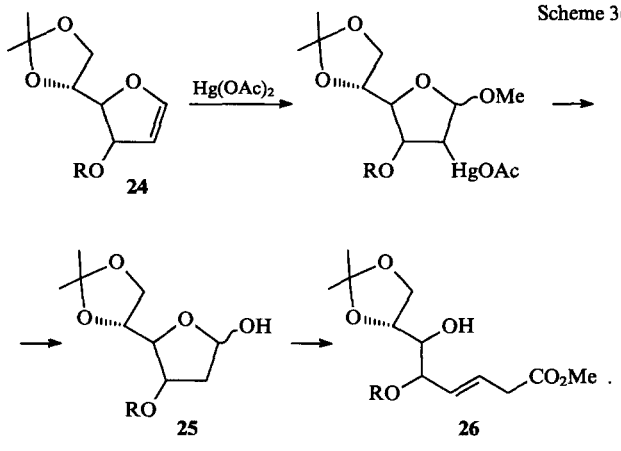
The acid $HgSO_4$-catalysed decyclisation of the full acetates of glycals derived from disaccharides leads to *O*-glycosylated α,β-unsaturated acetoxyaldehydes (Scheme 35).[85–88]

Scheme 35



A convenient method of decyclisation is based on the conversion of glycals into 2-deoxysugars with their subsequent conversion into olefins. Thus the 2-deoxysugar **25** was obtained from the furanoglycal **24** via a methoxymercuration stage, after which the unsaturated ester **26** was prepared (Scheme 36).[89]

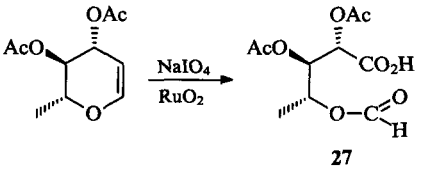
Scheme 36



This approach will probably be used in a specific synthesis, because the method proposed recently for the direct hydration of glycals[90] obviates the need for mercury salts.

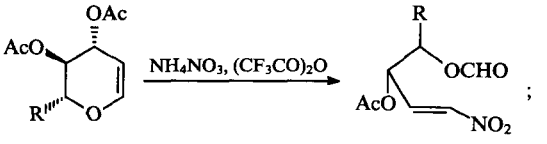
Oxidative degradation involving the double bond of glycals makes it possible to obtain nor-derivatives. For example, the RuO_2-catalysed oxidation of di-*O*-acetyl-D-rhamnal with $NaIO_4$ led to a 5-deoxyarabinonic acid ester **27** (Scheme 37).[91]

Scheme 37



An interesting oxidation reaction takes place when glycals are treated with ammonium nitrate in trifluoroacetic anhydride (Scheme 38).[92]

Scheme 38



R = CH_2OAc, Me .

As can be seen from the data presented, the reactions of glycals are distinguished by high stereoselectivity and in many cases conditions have been found for a stereospecific course of the reaction. Naturally, this characteristic of glycols cannot fail to draw attention to them in the selection of synthons used in the enantiospecific synthesis of natural products.

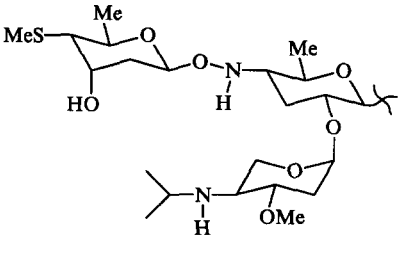
IV. Glycals in the synthesis of natural products with a cyclic structure and their fragments

1. Derivatives of monosaccharides. *O*- and *C*-glycosides

Glycals are being used to an increasing extent in the synthesis of rare mono-, di-, and oligo-saccharides and also *O*-glycosides with aglycones of different structural types. The examples described below convincingly demonstrate the extensive possibilities of the glycal approach.

The recently discovered carcinostatic enediyne antibiotics are distinguished by an abundance of functional groups and an unusual structure of the glycoside fragments. Thus esperamicin contains the trisaccharide fragment **28** incorporating thio- and amino-sugars (Scheme 39).

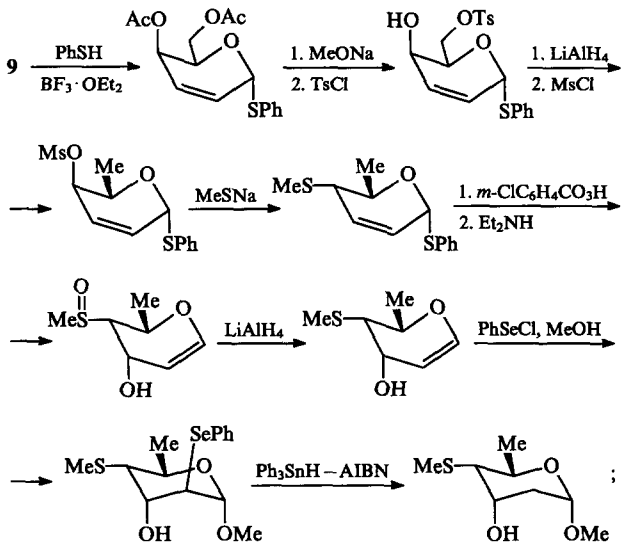
Scheme 39



The scheme for the synthesis of the thiosugar **29**, which forms part of the composition of the trisaccharide fragment of the antibiotic, based on the tri-*O*-acetyl-D-galactal **9**, is attractive because of the stereospecificity of all the stages and the twofold use of the reagent by virtue of the presence of a double bond of the glycal type (Scheme 40).[93]

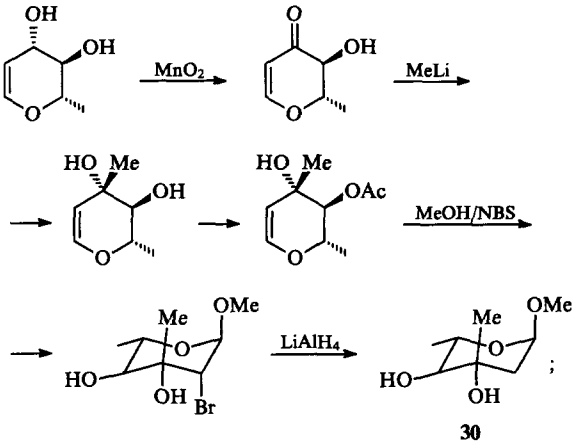
The antibiotics olivomycin and chromomycin contain L-olivomycose **30** as part of the composition of the trisaccharide fragment. Its synthesis from L-rhamnal consists of only a few stages (Scheme 41).[94]

Scheme 40



AIBN = azoisobutyronitrile.

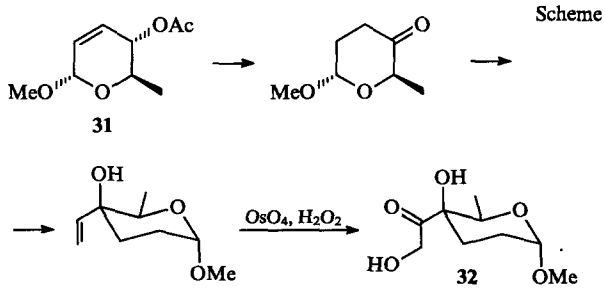
Scheme 41



NBS = *N*-bromosuccinimide.

Pillaromycin A—an antibiotic with anticancer activity—contains a deoxysugar—pillarose **32**, which has been synthesised from the Ferrier glycoside **31** (Scheme 42).[95]

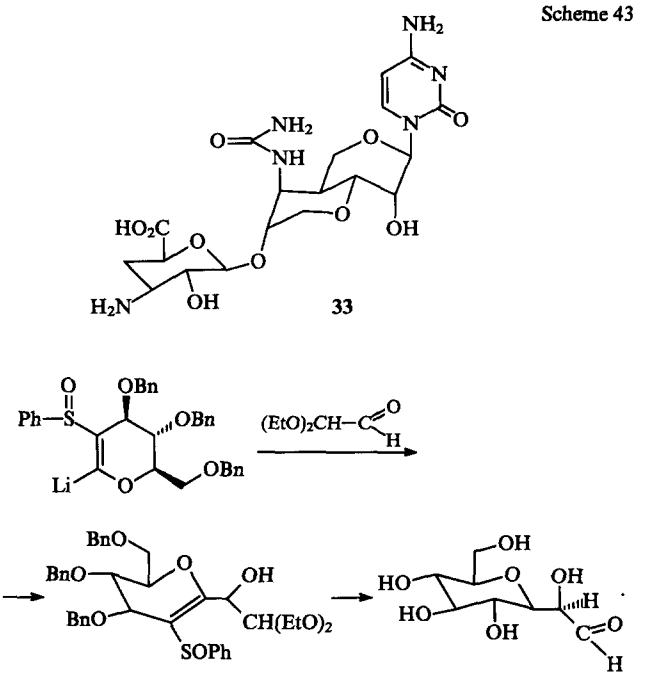
Scheme 42



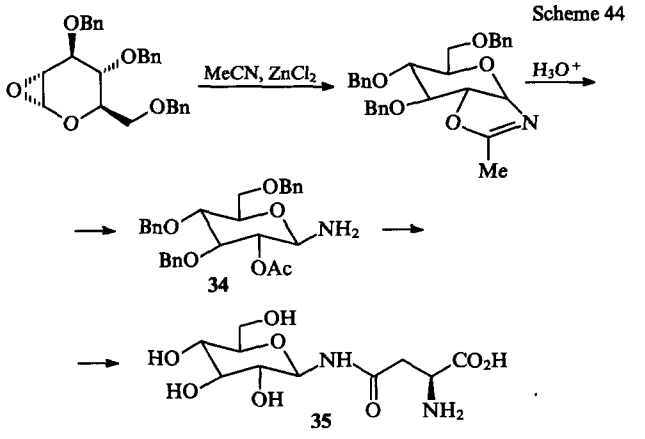
A derivative of vinyllithium, obtained by the direct introduction of lithium into tri-*O*-benzyl-2-benzenesulfoxygalactal, was used in the synthesis of the antibiotic ezomycin **33** from tri-*O*-benzyl-D-glycal. The reaction with the diethyl acetal of glyoxal took place smoothly with subsequent formation of the D-glucose *C*-glycoside as the key synthon (Scheme 43).[96]

Glucosylasparagine **35** was synthesised with the use of the epoxide of tri-*O*-benzyl-D-glucal (Scheme 44).[97] The formation of the indi-vidual β-glucosylamine **34** is striking.

Scheme 43

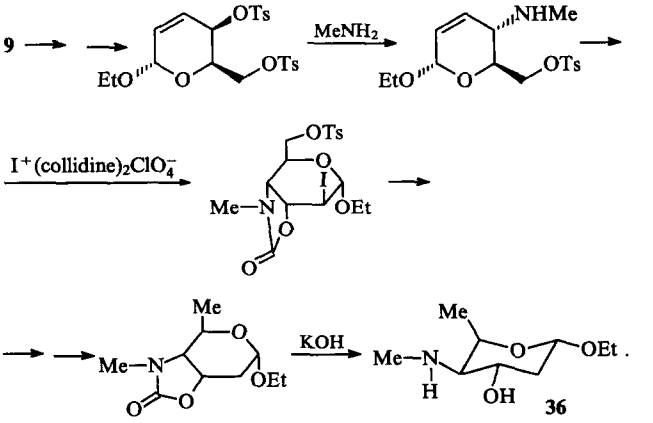


Scheme 44



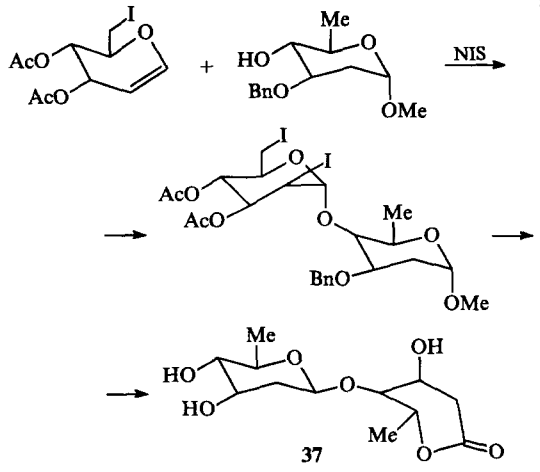
The aminosugar holacosamine **36**, which forms part of the composition of the steroid glycosides holacurtine and holarosine, has been synthesised from tri-*O*-acetyl-D-galactal **9** (Scheme 45).[98]

Scheme 45



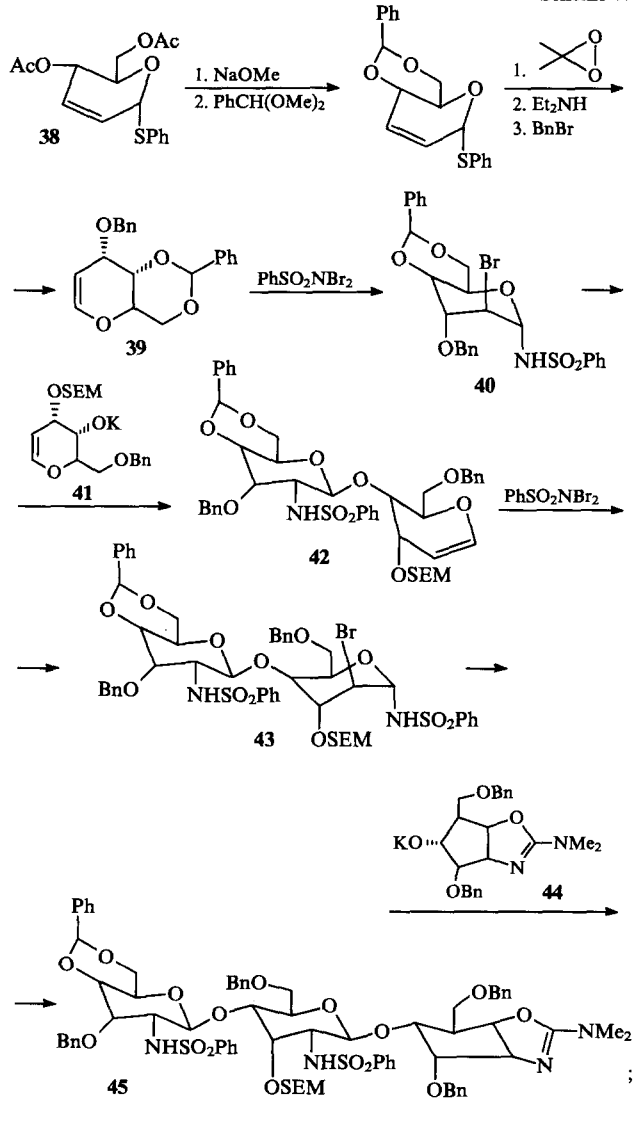
The formation of the glycosidic linkage with the aid of *N*-iodosuccinimide (NIS) has been used successfully in the synthesis of bamflalactone **37** (Scheme 46).[99]

Scheme 46



The glycoside allosamidin (compound **45** is its derivative), isolated the from *Streptomyces* mycelium, is a selective inhibitor of chitinase. Its synthesis represents a very characteristic example of the application of the varied reactivity of glycals. The phenylthioglycoside **38** was converted into the key synthon **39** via a stage involving oxidation to the sulfoxide and the subsequent sulfoxide rearrangement. The reaction of the synthon with *N*-dibromobenzenesulfonamide affords the bromosulfonamide **40**, which readily condenses with the potassium alkoxide derived from the glycal **41**.

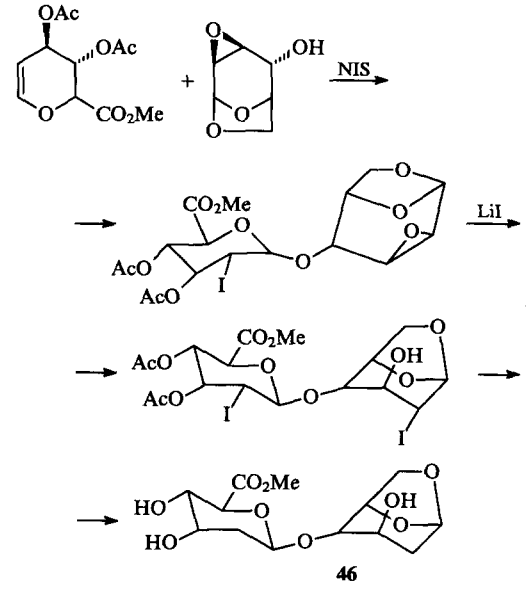
Scheme 47



The repeated reaction of compound **42** with the dibromosulfonamide and the condensation of the product **43** with the potassium alkoxide derived from the aglycone **44** made it possible to obtain the target glycoside **45** (Scheme 47).[100]

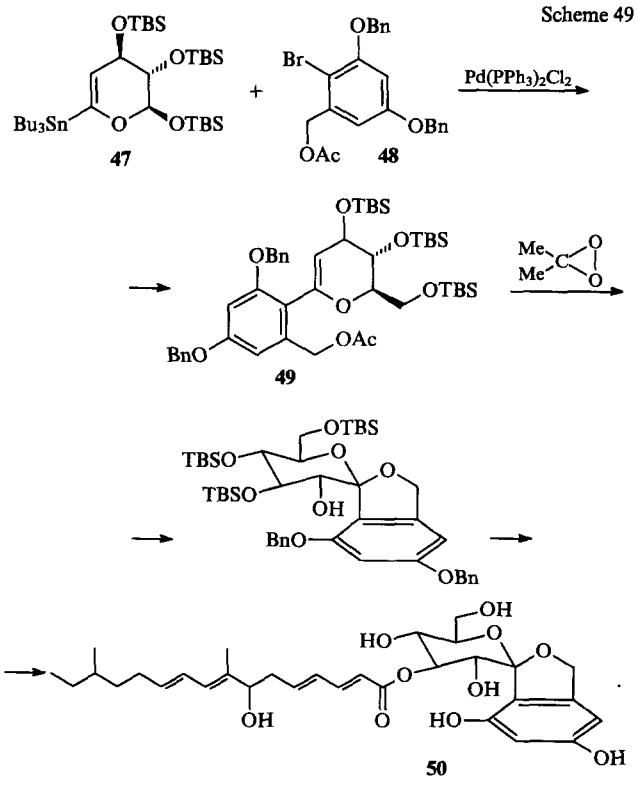
The disaccharide **46**, which forms part of the structure of the heptasaccharide orthosomycin, has been obtained from the glycal of glucuronic acid (Scheme 48).[101]

Scheme 48



Papulacandin **50** is one of the promising fungistatic agents. In the synthesis of the glycoside components of its molecule, the cross-coupling of the organotin glucal derivative **47** with the aryl bromide **48** and the oxidation of the *C*-arylglucal **49** by dimethyldioxiran constitute remarkable stages (Scheme 49).[102]

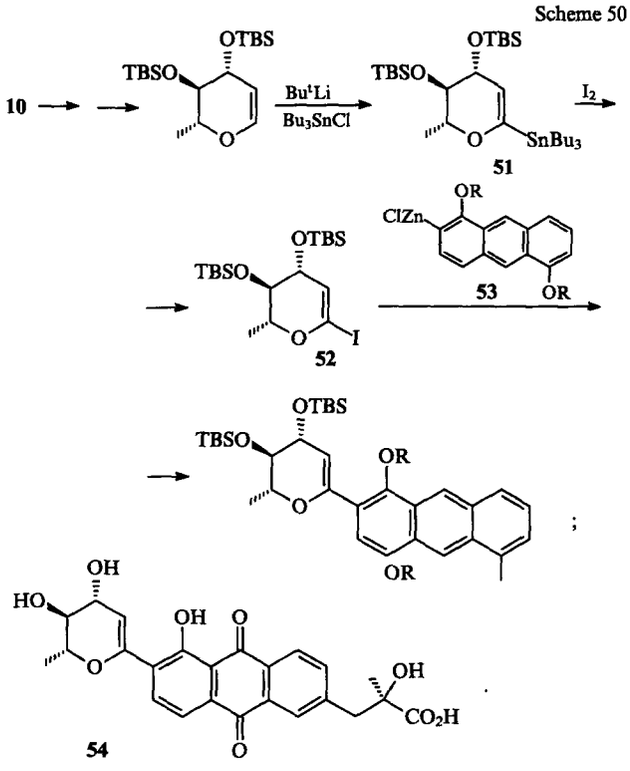
Scheme 49



SEM = β-(trimethylsilyl)ethoxymethyl .

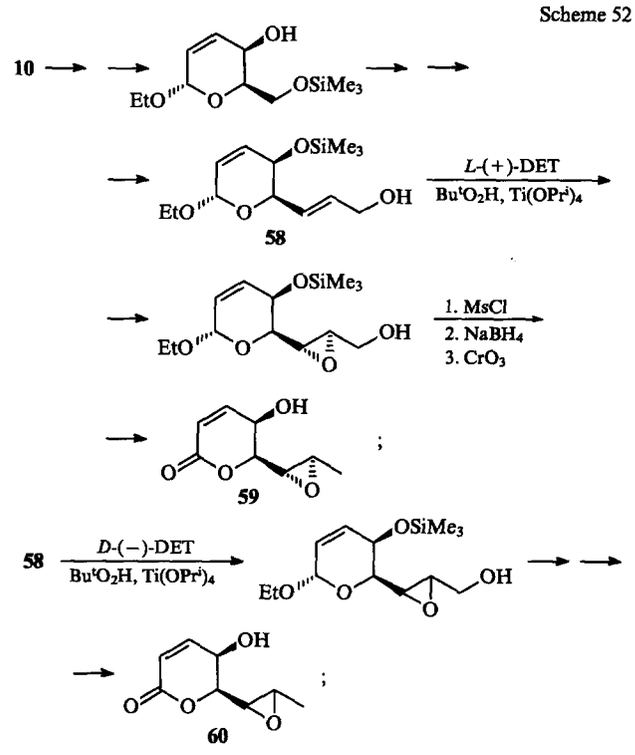
It has been suggested that tri-*O*-acetyl-D-glucal **10** be used for the synthesis of vineomycinone B_2 **54**. Compound **10** was converted in four stages into the organotin derivative **51** and then into the vinyl iodide **52**. The key stage—the coupling of compound **52** with the arylzinc **53**—is catalysed by a palladium complex (Scheme 50).[103]

Scheme 50



The weak point of this scheme is the stage involving the non-stereospecific epoxidation of the precursor **56**. Valverde et al.[104] were able to synthesise the isomers (6*R*, 7*S*)-**59** and (6*S*, 7*R*)-**60** of asperlin with a high optical purity by the asymmetric epoxidation of the allyl alcohol **58** obtained from tri-*O*-acetyl-D-glucal **10** (Scheme 52).

Scheme 52



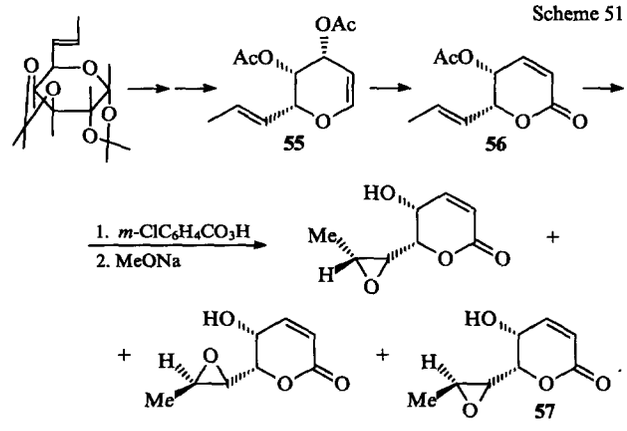
DET = diethyl tartrate .

2. Synthesis of natural products containing a hydropyran fragment

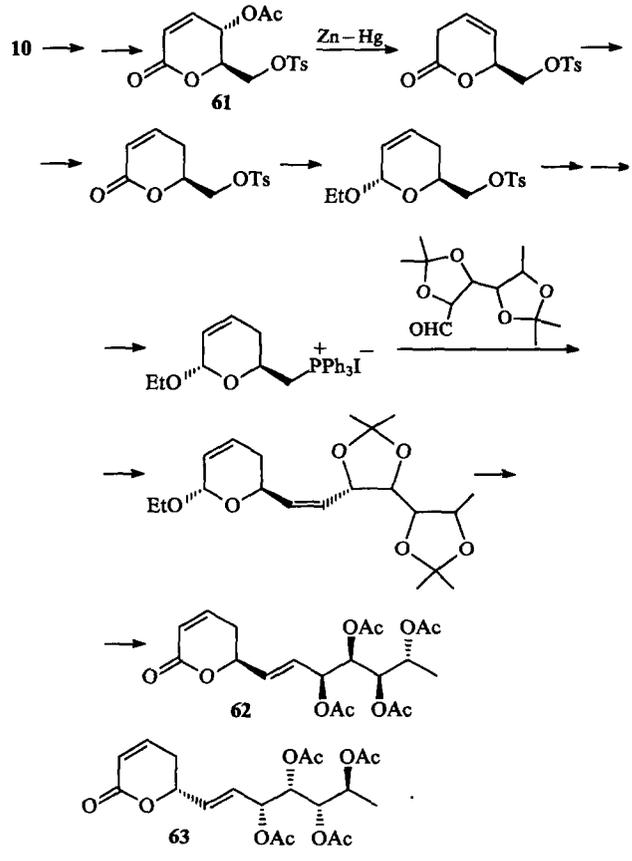
Compounds containing a hydropyran fragment are fairly common in nature. The total synthesis of many of them constitutes a fairly complex problem and is itself of interest as a stage in the development of the enantiospecific synthesis of compounds with a large number of chiral centres. The use of glycals makes it possible to obtain synthons containing up to five chiral centres with a specific configuration. It is noteworthy that compounds combining a high biological activity with a relative simplicity of structure, which renders their synthesis of practical interest, have been found with increasing frequency among natural hydropyrans.

Thus a series of studies have been devoted to the synthesis of the dihydropyran antibiotic asperlin, which exhibits carcinostatic activity. The D-enantiomer of asperlin **57** has been obtained from the modified galactal **55** (Scheme 51).[7]

Scheme 51



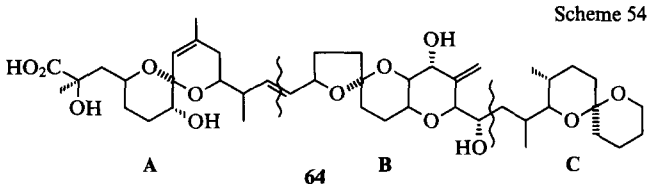
Scheme 53



Anamarin **63**, isolated from a plant of the genus *Hyptis*, has the (*R*)-configuration in the pyranoid ring and an unusual α-gluco-structure of the C(6)-side chain. The enantiomeric (−)-anamarin **62** was synthesised from the unsaturated lactone **61** obtained from tri-*O*-acetyl-D-glucal **10** (Scheme 53).[105]

Okadaic acid **64**, isolated from the sea sponge *Halichondria okadai*, is one of the specially complex compounds whose total synthesis has been undertaken (Scheme 54).

Scheme 54

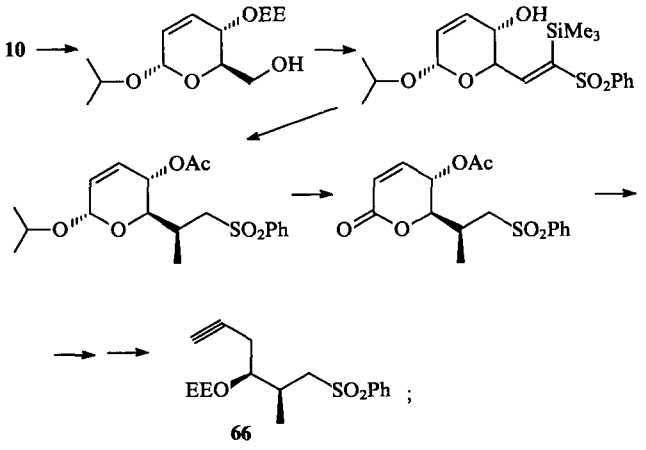


64

Isobe and coworkers described the synthesis of the **A**, **B**, and **C** fragments of the toxin molecule in a series of brilliant studies.[106-109]

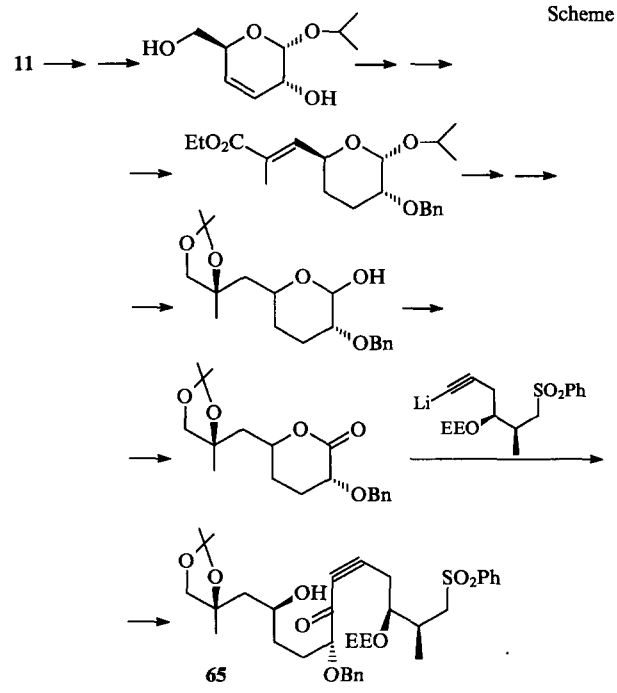
The synthesis of the fragment **A** (compound **65**) involves the preparation of two synthons based on tri-*O*-acetyl-D-glucal **10**

Scheme 55



EE = $EtOC_2H_4$.

Scheme 56

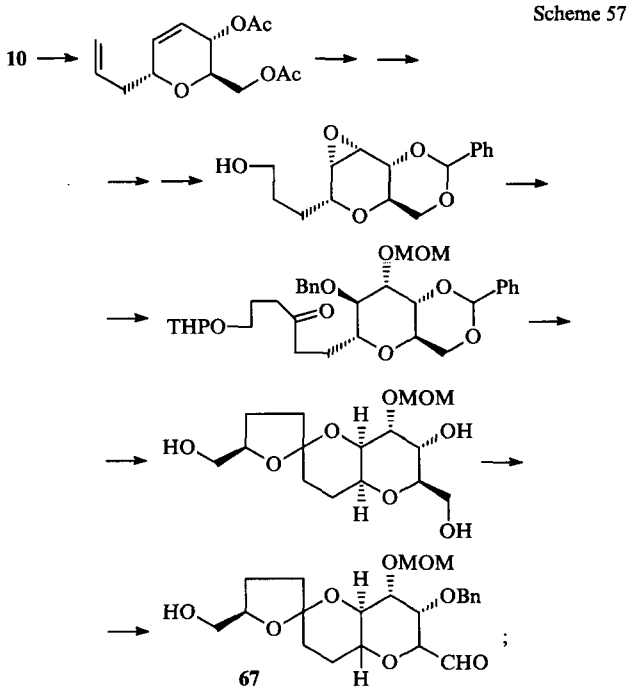


and tetra-*O*-acetyl-2-hydroxy-D-glucal **11**. As can be seen from Scheme 55, the configuration of the carbon atom to which a methyl group is attached in the molecule of the target acetylenic sulfone **66** is specified in conformity with the directing effect of the oxygen-containing functional groups in the 1,4-addition of lithium dimethylcuprate to the silicon-containing unsaturated sulfone.

The key stage in the synthesis of the fragment **A** is the reaction of the lithium derivative of the acetylenic sulfone with the lactone obtained from tetra-*O*-acetyl-2-hydroxy-D-glucal **11** (Scheme 56).[106]

The construction of the segment **B** (compound **67**) begins with the reaction of tri-*O*-acetyl-D-glucal **10** with allyltrimethylsilane. The key stages of this synthesis are presented in Scheme 57.[107]

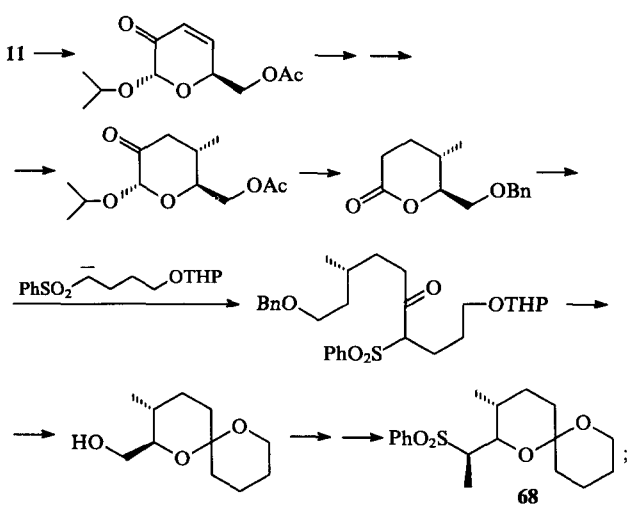
Scheme 57



MOM = $MeOCH_2^-$.

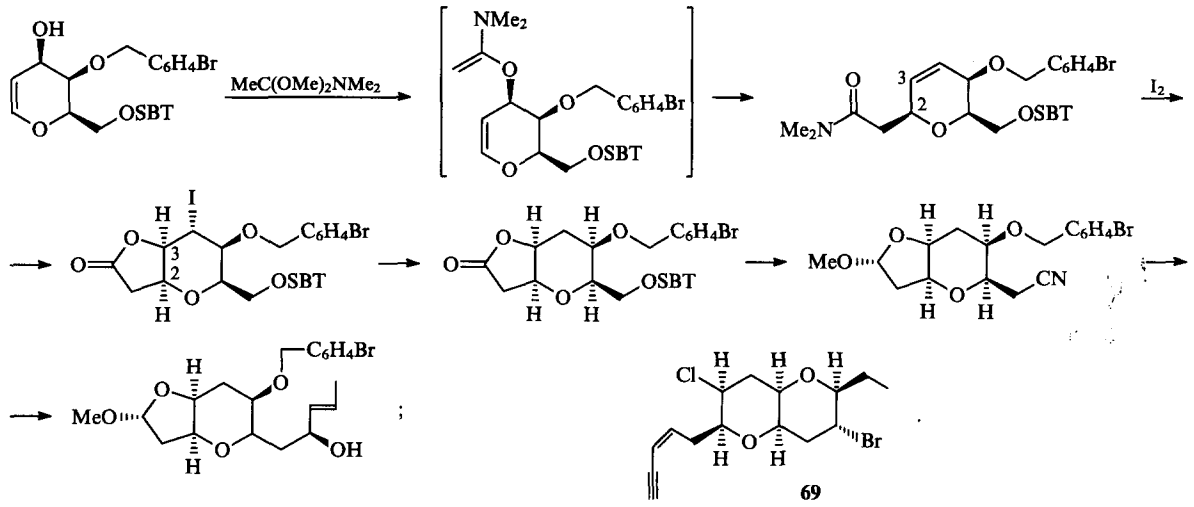
The synthesis of the comparatively simple segment **C** (compound **68**) is also based on the reactions of the 2-acetoxy-glucal **11** (Scheme 58).[108, 109]

Scheme 58



THP = tetrahydropyran-2-yl.

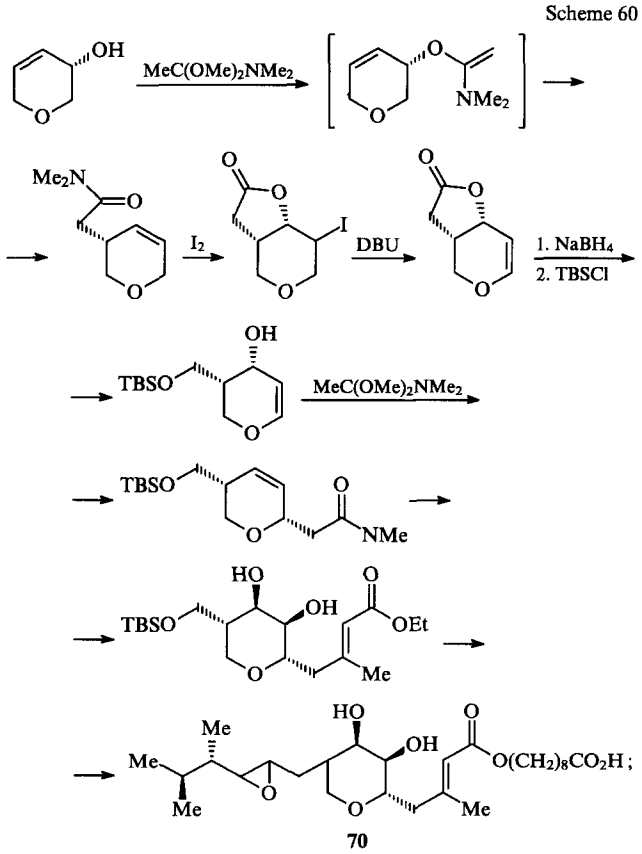
Scheme 59



(3*E*)- and (3*Z*)-Dactomelynes **69**, pyranopyran derivatives isolated from the sea hare *Aplysia daktylomela*, exhibit a valuable biological activity. The chiral centres at C(2) and C(3) are formed by the enantiospecific stages of the Claisen rearrangement involving the dimethyl acetal of *N*,*N*-dimethylacetamide and conversion into an iodolactone. These steps have been incorporated into the synthesis of dactomelynes (Scheme 59).[110]

The Claisen rearrangement of natural glycals is used twice in the scheme for the synthesis of pseudomonic acid **70** (Scheme 60).[111]

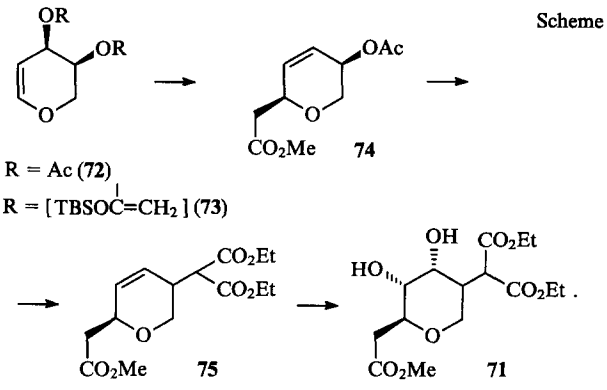
Scheme 60



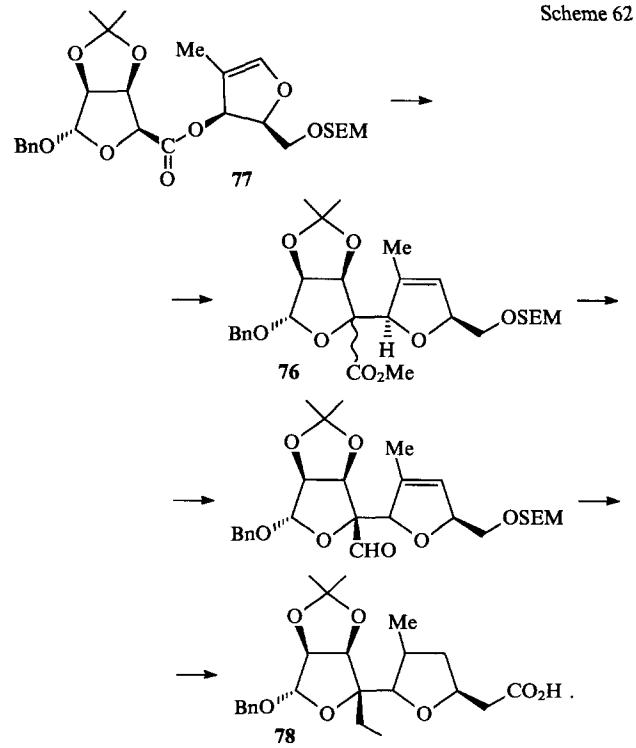
DBU = 1,5-diazabicyclo[5.4.0]undec-5-ene.

A short pathway to the key chiral intermediate **71**, essential for the synthesis of pseudomonic acid, has been proposed.[112] Di-*O*-acetyl-L-arabinal **72** was proposed as the initial chiral compound. It was converted via the rearrangement of the bisketene silyl acetal **73** into compound **74** and further into the ester **75** (Scheme 61).

Scheme 61



Scheme 62

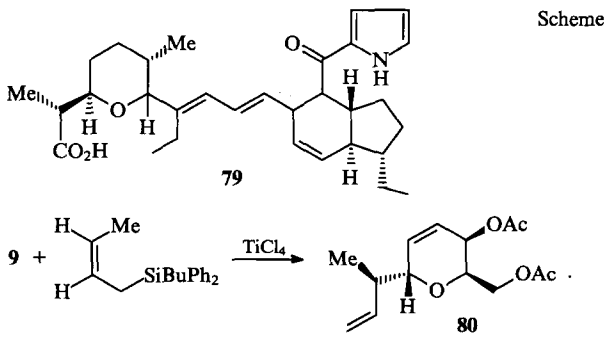


The use of the Claisen rearrangement in the synthesis of antibiotics of the hydropyran type, namely lasalocid, tirandamycin,[7] and monensin,[113] has been described. A strikingly high yield of compound **76** in the rearrangement of the ester **77**, constructed from two furanoid fragments, was noted in the synthesis of the last

compound.[114] One of the key units (compound **78**) necessary for the construction of the monensin molecule was obtained as a result of this reaction (Scheme 62).

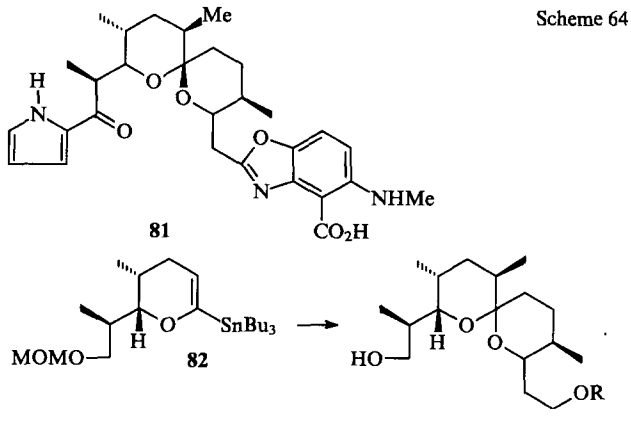
As mentioned above, the stereoselective reaction of glycal acetates with allylsilanes is one of the effective methods of synthesis of chiral building blocks.[41] In the synthesis of the antibiotic indanomycin **79**, the necessary dihydropyran synthon unit **80** was obtained by the reaction of tri-*O*-acetyl-D-galactal **9** with (*Z*)-crotylsilane (Scheme 63).[115]

Scheme 63

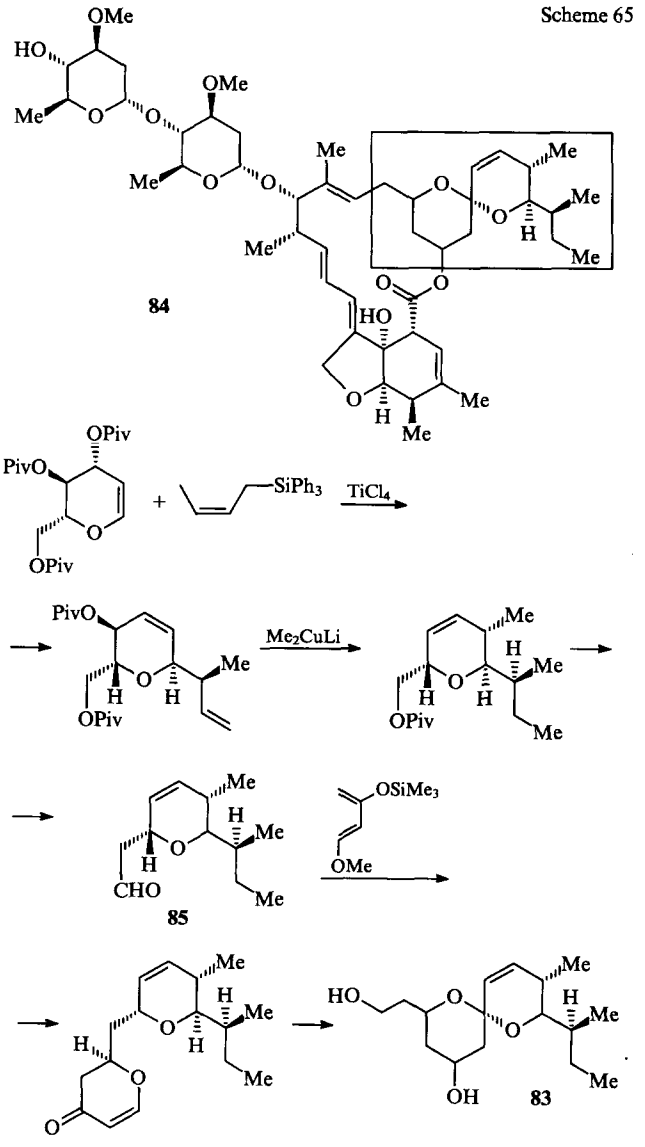


An organotin glycal derivative **82** has been used to synthesise the ionophor calcimycin **81** (Scheme 64).[24]

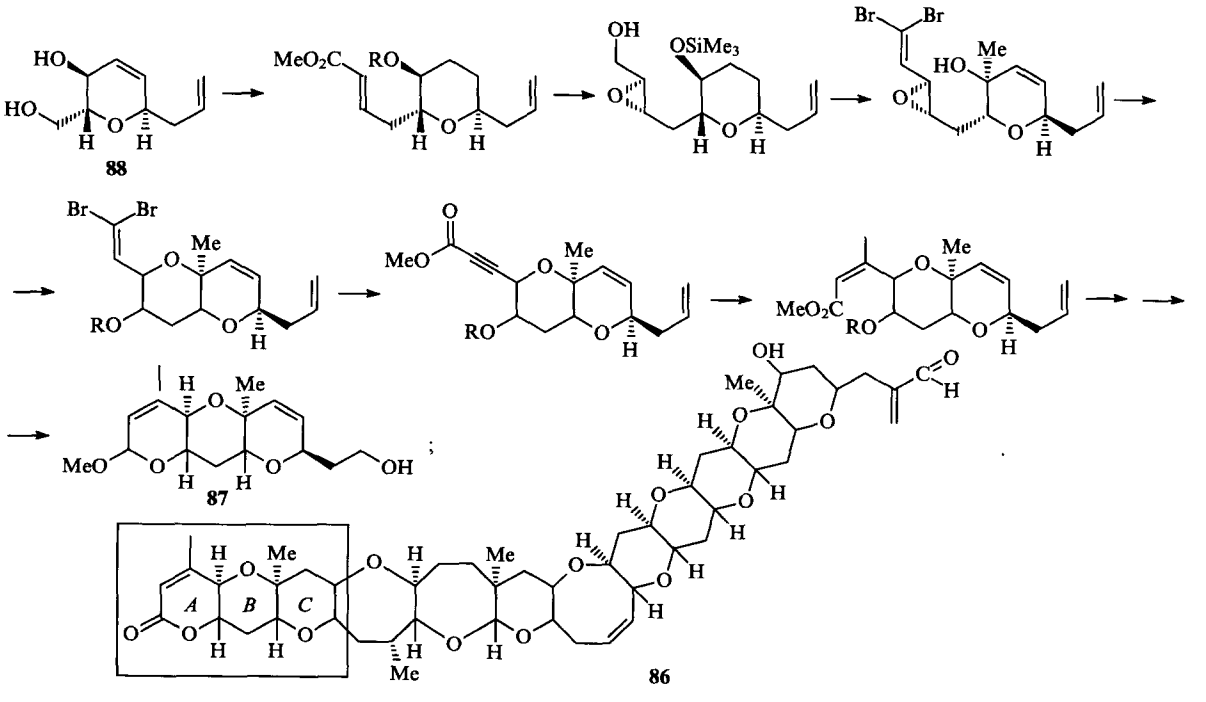
Scheme 64



Scheme 65



Scheme 66

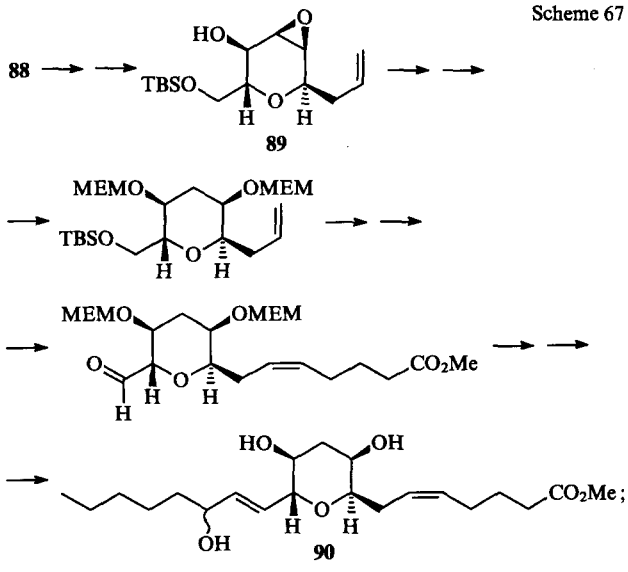


The strategy used in the synthesis of the spiroketal unit **83** of the insecticide avermectin **84** includes the reaction of tri-*O*-pivaloyl-D-glucal with (*Z*)-crotyltriphenylsilane and the [4+2]-addition of the so called Danishevskii's diene to the aldehyde **85** (Scheme 65).[116-118]

The total synthesis of one of the most powerful of the natural toxins — brevetoxin **86** — is extremely complex. The **ABC** fragment **87** of its structure was synthesised from (2*R*, 3*S*, 6*R*)-6-allyl-3,6-dihydro-3-hydroxy-2-hydroxymethyl-2*H*-pyran **88** — the product of the coupling of tri-*O*-acetyl-D-glucal **10** with allyltrimethylsilane (Scheme 66).[119, 120]

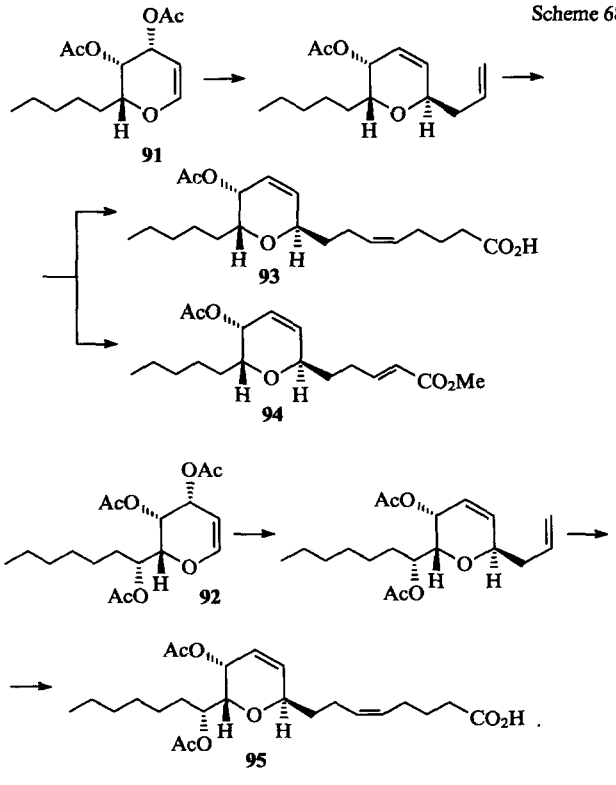
The substituted dihydroxy-2*H*-pyran **88** and its epoxide **89** have also been used as the starting compounds in the synthesis of (8*R*, 9*R*, 11*S*, 12*R*, 15*R*, *S*, 5*Z*, 13*E*)-9,11,15-trihydroxy-8,12-oxy-5,13-eicosadienoic acid **90** — a stereoisomer of the natural metabolite of arachidonic acid (Scheme 67).[121]

Scheme 67



MEM = $MeOC_2H_4OCH_2$.

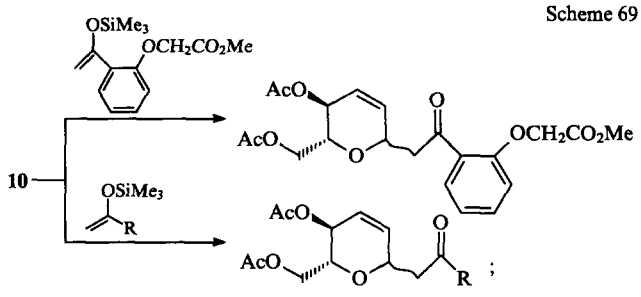
Scheme 68



The stereospecific reaction of the modified glycals **91** and **92** with allyltrimethylsilane served as the key reaction for the synthesis of unsaturated carboxylic hydroxyacids **93**–**95** — structural analogues of arachidonic acid (Scheme 68).[122, 123]

New chiral building blocks, which are promising for the synthesis of the oxo-analogues of the cyclic metabolites of arachidonic acid, have been obtained by coupling silyl ethers of enols with tri-*O*-acetyl-D-glucal **10** (Scheme 69).[124]

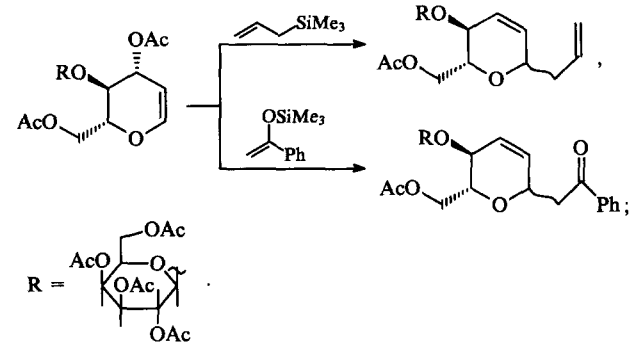
Scheme 69



R = $(CH_2)_nCO_2Me$.

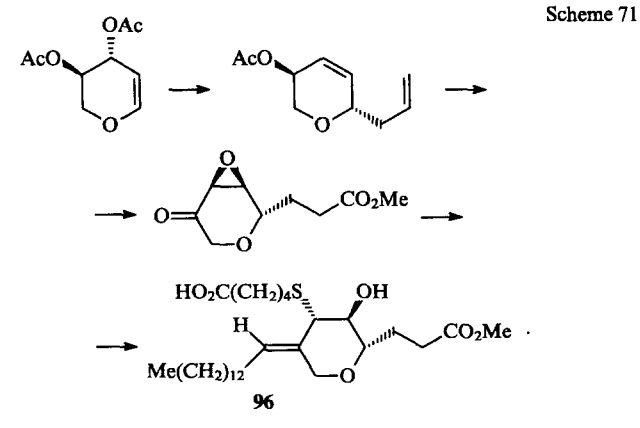
Hexa-*O*-acetyl-D-lactal reacts smoothly on treatment with $BF_3 \cdot OEt_2$ both with allylsilanes and with siloxyethers, affording units suitable for the synthesis of glycosylated derivatives of hydropyran (Scheme 70).[125]

Scheme 70



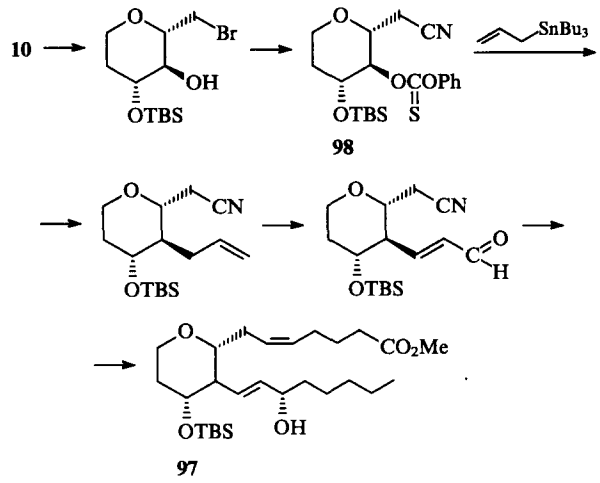
Compound **96**, the synthesis of which from xylal is fairly simple, is able to inhibit the biosynthesis of leucotriene D_4 (Scheme 71).[126]

Scheme 71



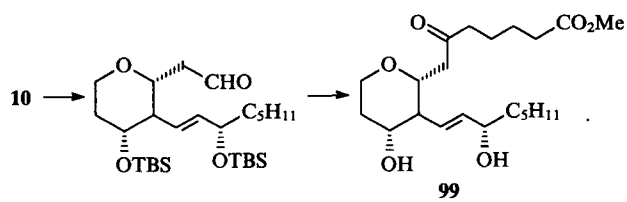
The key stage in the synthesis of the tetrahydropyran analogue of prostaglandin $F_{2\alpha}$ **97** from tri-*O*-acetyl-D-glucal **10** is the free-radical allylation of the intermediate phenyl thiocarbonate **98** by treatment with allyltributyltin (Scheme 72).[127]

Scheme 72



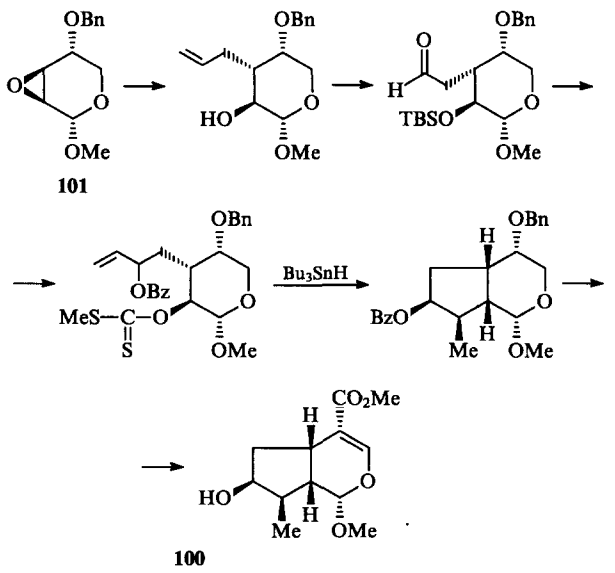
An analogous reaction of tri-*O*-acetyl-D-glucal **10** has been used to synthesise the 6-oxoprostanoid **99** (Scheme 73).[128]

Scheme 73



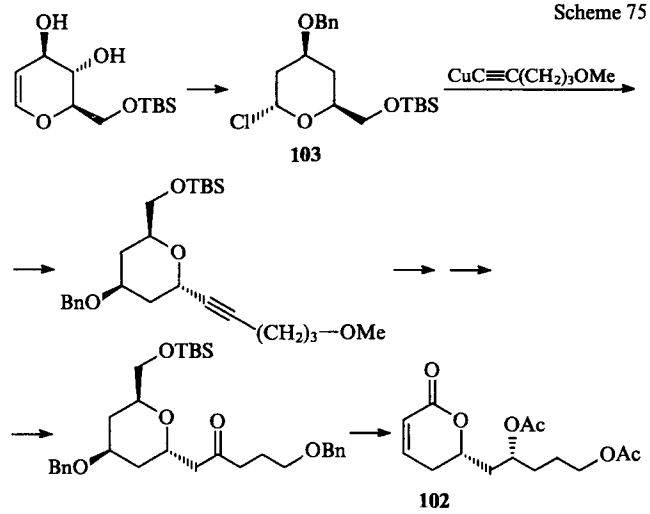
Various approaches have been used in applying the schemes for the synthesis of hydropyran fragments in a series of natural products. Thus in the scheme for the synthesis of α-*O*-methylloganin **100**, in which the starting material is compound **101**, the free-radical cyclisation stage is noteworthy. It affords a cyclopentane fragment with four chiral centres, each having a rigorously defined configuration (Scheme 74).[129]

Scheme 74



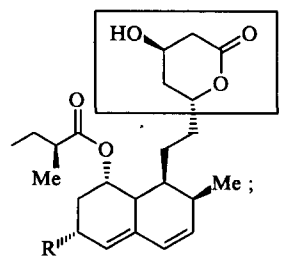
One of the fragments (compound **102**) of the antibiotic nystatin has been obtained by coupling copper acetylide with the chloro-derivative **103** obtained from the monosilyl ether of D-glucal (Scheme 75).[130]

Scheme 75



In the last decade, much attention has been devoted to the synthesis of mevinoids — substances which inhibit the biosynthesis of cholesterol. Analogues of commercial value as medicinal drugs reducing the cholesterol content in the blood have been described. An important element of the structure of compactin **104** and mevinolin **105** as well as their structural analogues is a pyranoid lactone fragment, the synthesis of which has aroused considerable interest (Scheme 76).

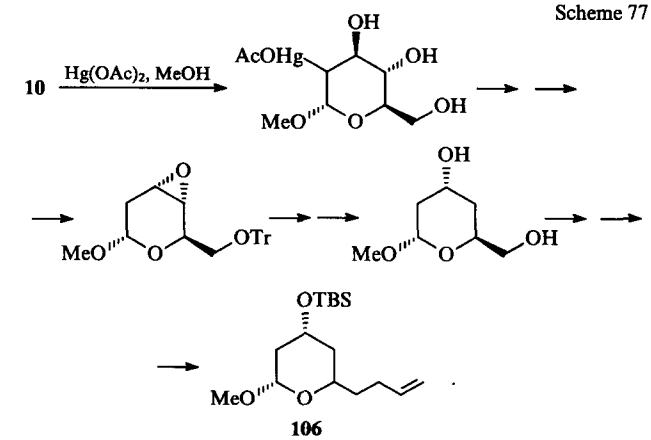
Scheme 76



R = H (**104**), R = Me (**105**).

One of the approaches to the synthesis of the lactone fragment **106** of the (+)-compactin molecule presupposes[131] the methoxymercuration of the initial tri-*O*-acetyl-D-glucal **10** with subsequent transformation of the intermediate epoxide in accordance with Scheme 77.

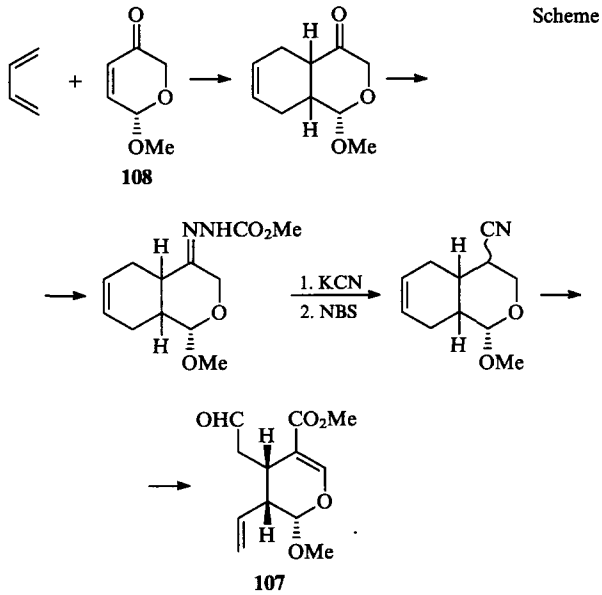
Scheme 77



The [4+2]- and [3+2]-cycloaddition reactions with participation of glycals and their derivatives have served as key reactions in the synthesis of a series of polycyclic natural products containing a hydropyran fragment. Thus the aglycone of the

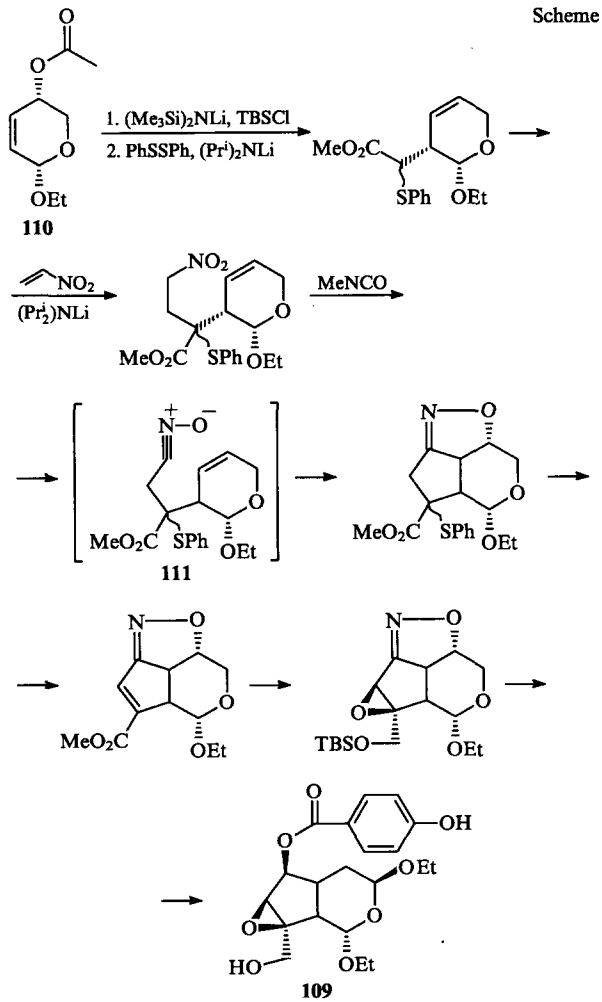
iridoid secologanin **107** has been obtained by the reaction of the methoxyenone **108** with butadiene (Scheme 78).[132]

Scheme 78



Bicyclic iridoids are a group of natural products of interest from the practical point of view. Substances with antileukemic and antimicrobial activities have been found among them. The characteristic cyclopentanopyran skeleton of iridoids determines the approaches to the synthesis based on the use of carbohydrates.

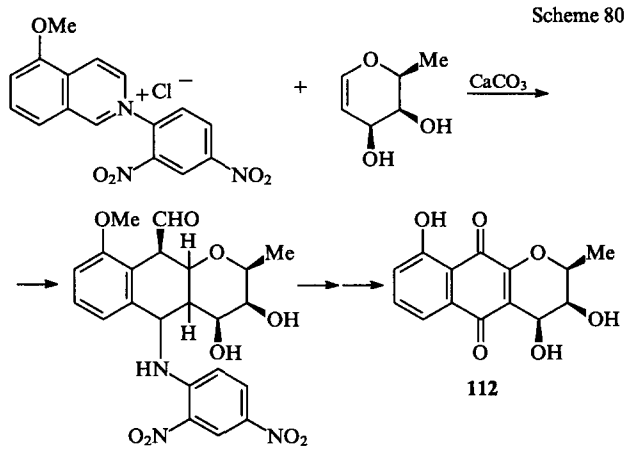
Scheme 79



Specionin **109** is regarded as a promising antifeedant. The multistage scheme for its synthesis includes reaction such as the Ireland–Claisen rearrangement of (*E*)-ketene silyl acetal derived from the D-xylal **110** and the dipolar [3 + 2]-addition of the nitrile oxide **111**, which ensures the stereospecific synthesis of the polyfunctional cyclopentane ring (Scheme 79).[133, 134]

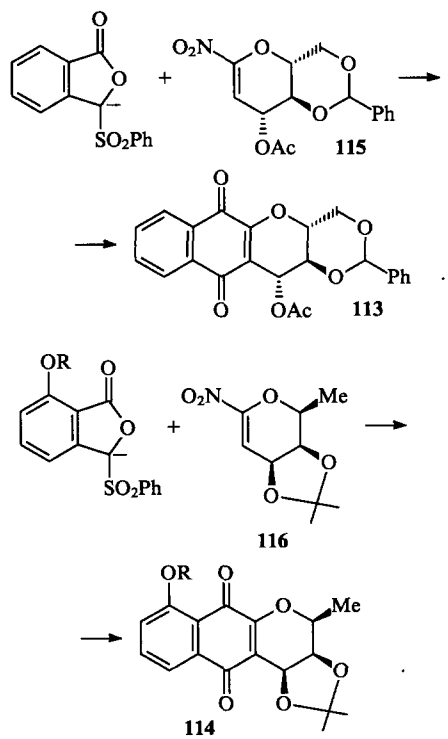
The generation of quinodimethanes from isoquinoline salts has led to extensive possibilities for the synthesis of polycyclic structures based on the [4 + 2]-cyclo-addition reaction. In Scheme 80 for the synthesis of the fungal metabolite cryptosporin **112**, which is active against gram-positive bacteria, the above reaction constitutes the key stage.[135]

Scheme 80



The reaction of glycals with the anions of arenesulfonyl- or cyano-phthalides, which formally constitutes [4 + 2]-addition, has found an application in the synthesis of natural metabolites of the quinone type. In particular, the derivatives **113** and **114** of the cryptosporin mentioned above have been obtained by reaction with the nitroglycals **115** and **116** (Scheme 81).[136]

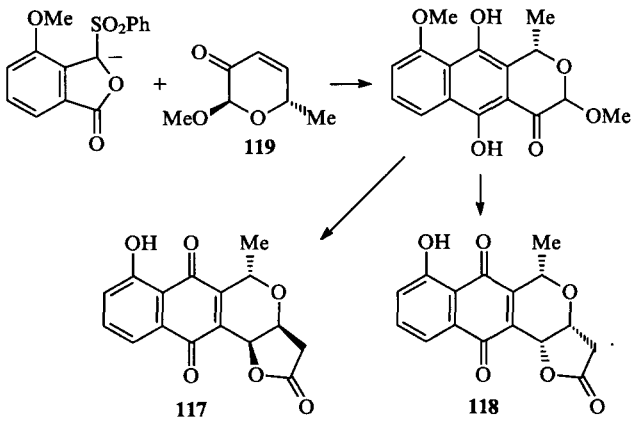
Scheme 81



Nanaomycine **117** and its natural stereoisomer kalafungin **118** have attracted attention by their high antimicrobial and anticancer activities. Japanese investigators developed a synthesis based

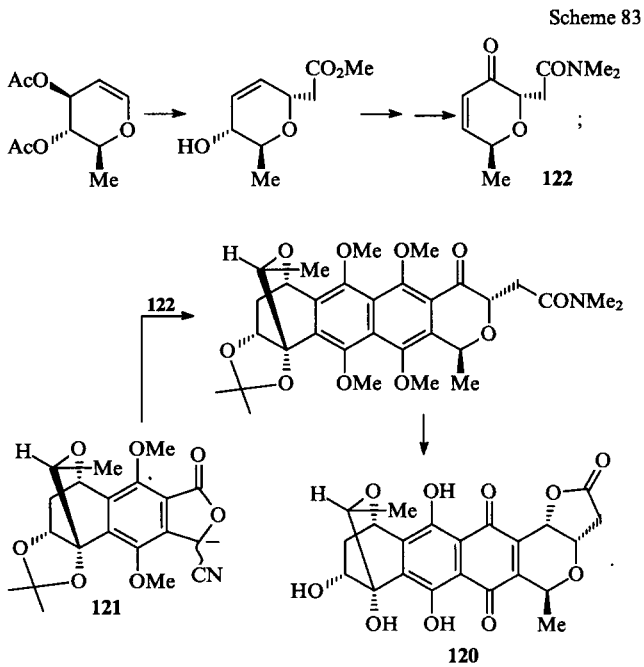
on the reaction of benzenesulfonylmethoxyphthalide with the methoxyenone **119** obtained from L-rhamnal (Scheme 82).[137]

Scheme 82



Scheme 83 for the synthesis of the antibiotic granaticin **120** includes a stage involving the condensation of the cyanophthalide **121** with the ketoamide **122** obtained from di-*O*-acetyl-D-rhamnal.[138]

Scheme 83



3. Synthesis of nitrogen-containing compounds

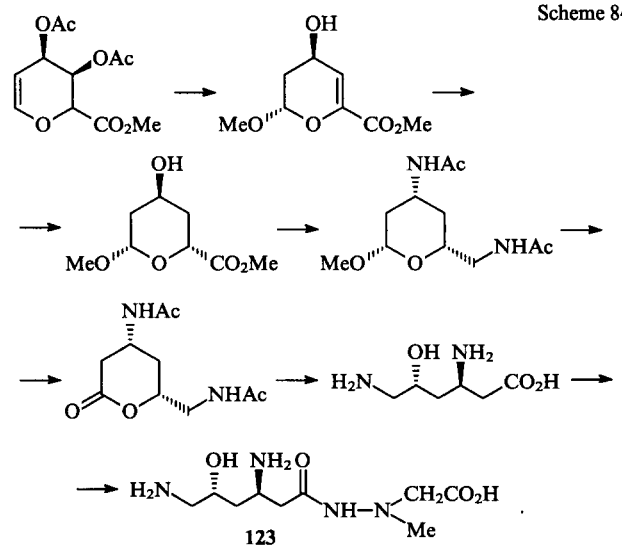
The use of glycals in the synthesis of nitrogen-containing natural products so far covers only a small number of examples. However, the schemes described in the literature are fairly interesting and demonstrate new possibilities in the chemistry of glycals.

The antibiotic negamycin **123** belongs to the class of hydrazine derivatives which are rarely encountered in nature. Its synthesis from the glycal of D-galacturonic acid includes more than ten stages,[139] some of which are presented in Scheme 84.

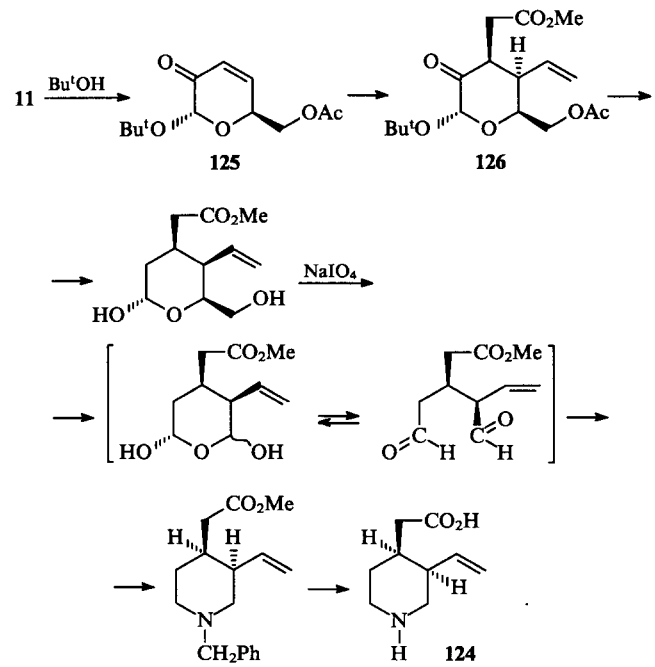
In Scheme 85 for the synthesis of meroquinene **124** from tetra-*O*-acetyl-2-hydroxy-D-glucal **11**, there is a stereospecific stage including the conversion of the enone **125** into the ketoester **126**, which involves the 1,4-addition of the vinylcuprate reagent and the alkylation of the enolate with methyl bromoacetate.[140]

The quinuclidine fragment enters into the structures of a whole series of important alkaloids. One of the approaches to the synthesis of optically active quinuclidines is based on the use of the natural D-glucal **127** (Scheme 86).

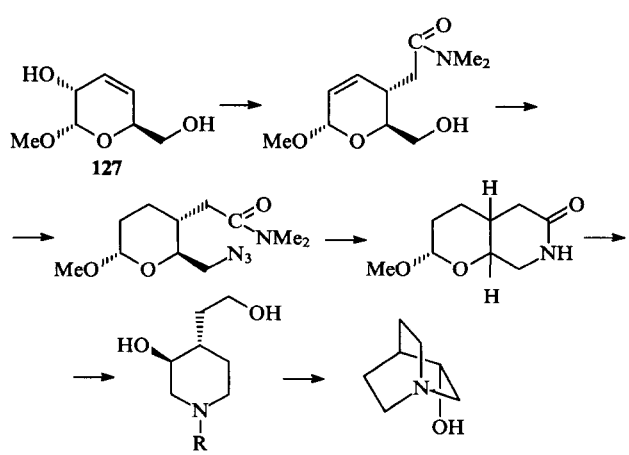
Scheme 84



Scheme 85

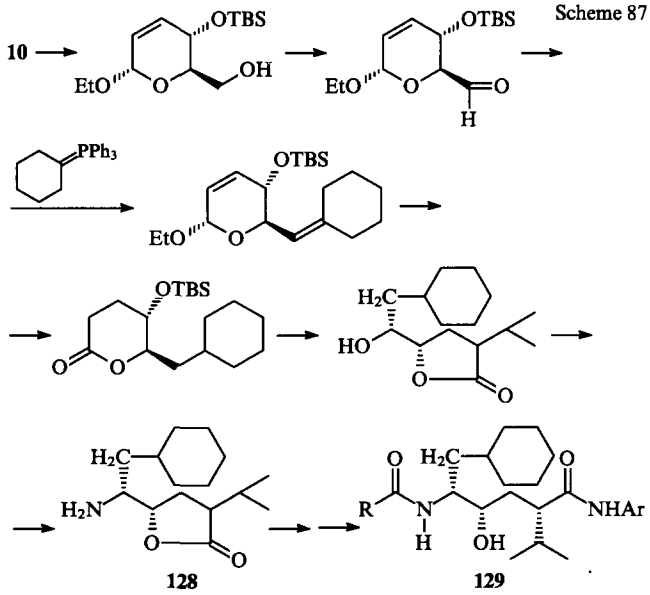


Scheme 86



The inhibitors of renin belonging to the group of low molecular mass peptides are regarded as highly effective antihypertensive agents. The aminolactone **128**, which is a key synthon unit for the construction of peptides of type **129**, was synthesised from tri-*O*-acetyl-D-glucal **10** (Scheme 87).[142]

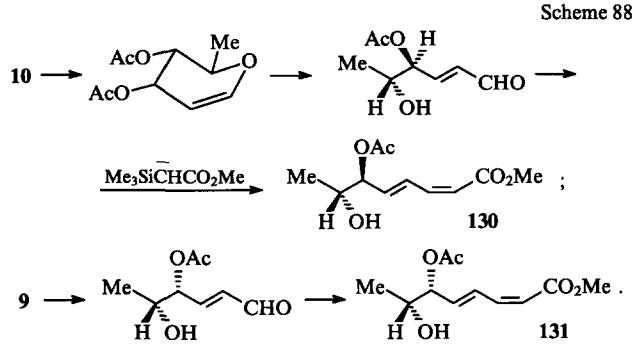
Scheme 87



V. Decyclisation of glycals as a basis for synthesis of natural products and their structural analogues

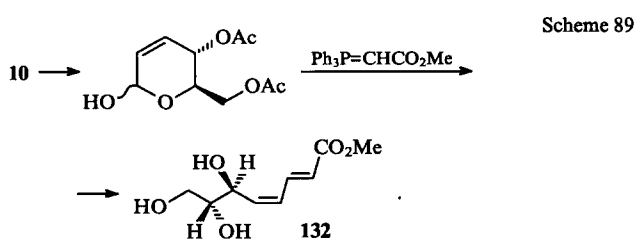
The products of the decyclisation of glycals were not considered for a long time as objects meriting attention in designing schemes for enantiospecific synthesis. The situation began to change after the publication of a study[143] devoted to the synthesis of 6,7-dihydroxyocta-2,4-dienoic acids, which form part of the structures of a series of toxins of the trichothecane series. Thus (6*R*, 7*R*)- and (6*S*, 7*R*)-dihydroxyacids **130** and **131** with the (2*Z*, 4*E*)-configuration of the double bonds have been synthesised from tri-*O*-acetyl-D-glucal **10** and tri-*O*-acetyl-D-galactal **9** (Scheme 88).[143, 144]

Scheme 88



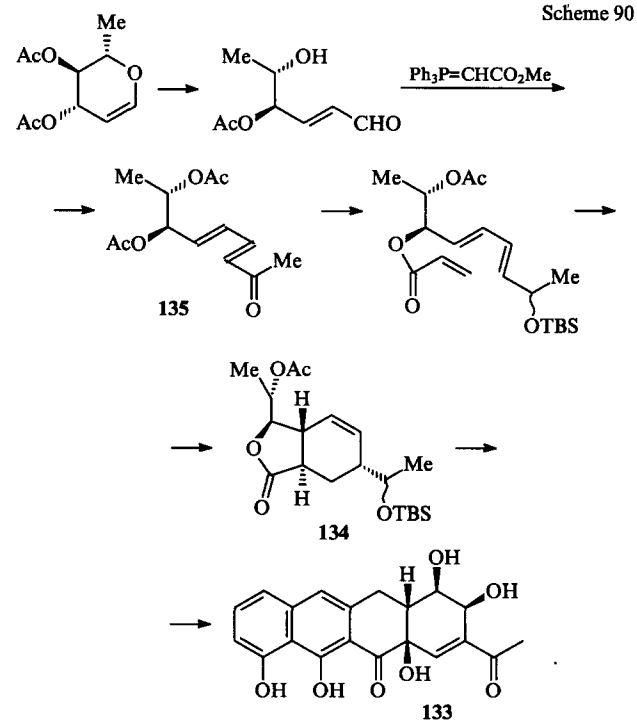
The method of synthesis of the (2*E*, 4*Z*)-isomer **132** is based on the two-stage conversion of tri-*O*-acetyl-D-glucal **10**. Derivatives of compound **132** have been used in the synthesis of trichoverrol B and trichoverrin B (Scheme 89).[144]

Scheme 89



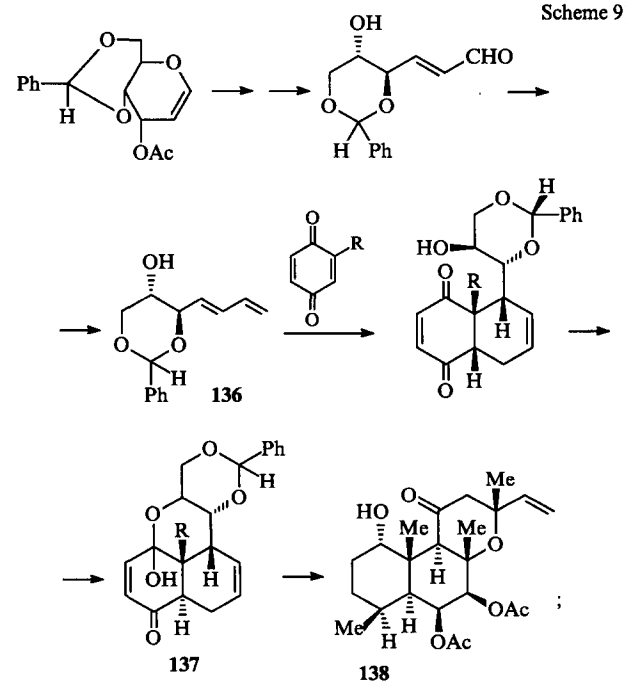
The synthesis of (+)-pillaromycinone **133** includes a stage involving the intramolecular Diels–Alder reaction, which leads to the key cyclic adduct **134**. The diene component **135** was obtained from di-*O*-acetyl-L-rhamnal (Scheme 90).[145]

Scheme 90



The reaction of 2-methoxycarbonylquinone with the diene **136**, synthesised from 3-*O*-acetyl-4,6-*O*-benzylidene-D-allal, has been proposed as a convenient method of synthesis of compound **137**—an intermediate for the construction of the molecule of the diterpenoid forskolin **138** with an exceptionally valuable biological activity (Scheme 91).[146]

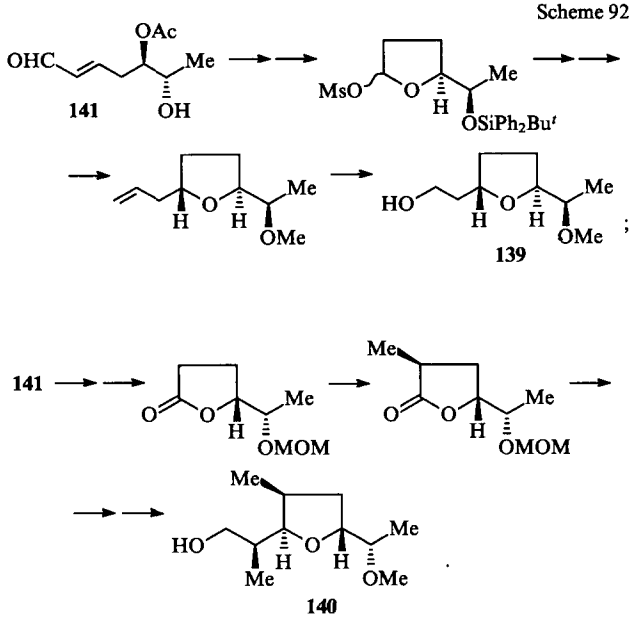
Scheme 91



R = CO_2Me.

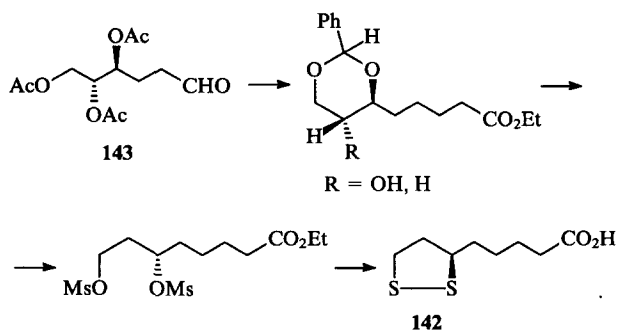
The tetrahydrofuran fragments **139** and **140** of the antibiotics tetronasin and tetronomycin have been synthesised from the heptenal **141** — a product of the decyclisation of di-*O*-acetyl-L-rhamnal (Scheme 92).[147]

Scheme 92



The syntheses of (*R*)-(+)-α-lipoic acid and its (*S*)-(−)-enantiomer from the products of the opening of the dihydropyran ring in glycals based on hexoses and pentoses have been described. The scheme for the synthesis of (*R*)-(+)-α-lipoic acid **142**, in which the triacetoxyhexenal **143**, obtained from tri-*O*-acetyl-D-glucal, was used, has been realised in practice (Scheme 93).[148]

Scheme 93



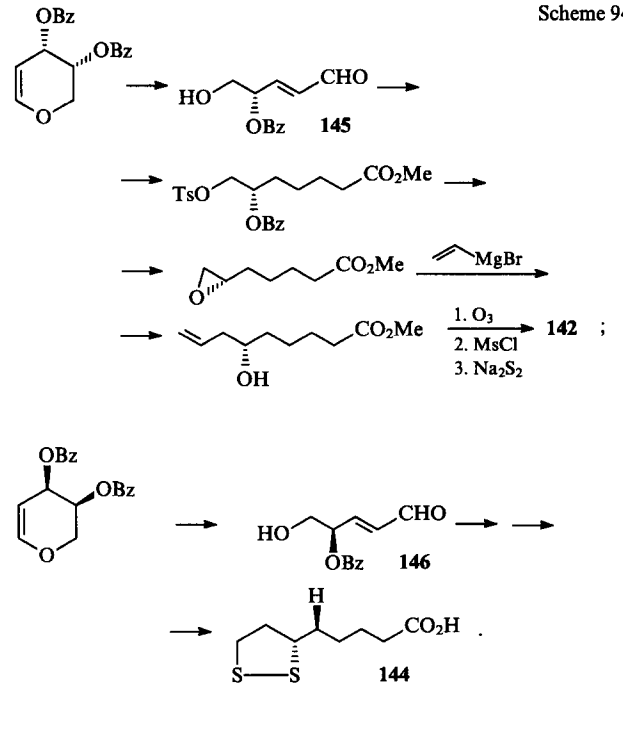
According to Tolstikov et al.,[149] (R)-(+)-α-lipoic acid and its (*S*)-(−)-enantiomer **144** can be obtained from the pentenals **145** and **146** synthesised from di-*O*-benzoyl-D-arabinal and di-*O*-benzoyl-L-arabinal (Scheme 94).

The products of the acid decyclisation of glycal esters proved to be convenient starting materials for the synthesis of open-chain insect pheromones. Thus the gypsy moth pheromone (+)-*cis*-disparlure **147** was synthesised from (4*R*, 5*R*)-4,5,6-triacetoxy-(2*E*)-hexenal **148** — a derivative of tri-*O*-acetyl-D-galactal (Scheme 95).[150, 151]

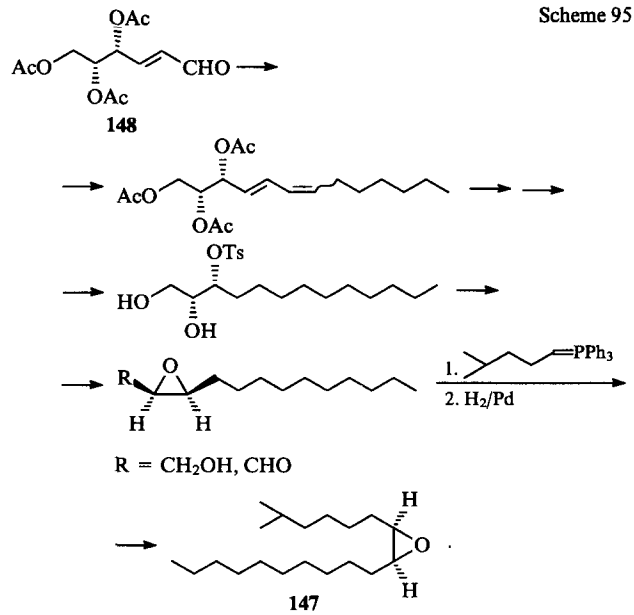
The key synthon **149** for (−)-*cis*-disparlure **150** has been obtained by decyclising a modified D-galactal **151** (Scheme 96).[10]

The α,β-unsaturated aldehyde **148** served as the initial compound in the synthesis of (3*Z*, 6*Z*, 9*S*, 10*R*)-*cis*-9,10-epoxyheneicosa-3,6-diene **152** — the principal component of the sex pheromone of the American white butterfly *Hyphantria cunea drury* (Scheme 97).[152]

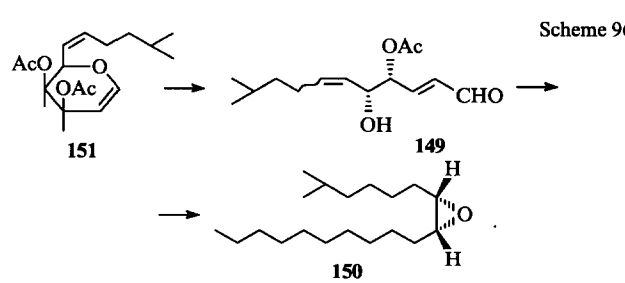
Scheme 94



Scheme 95

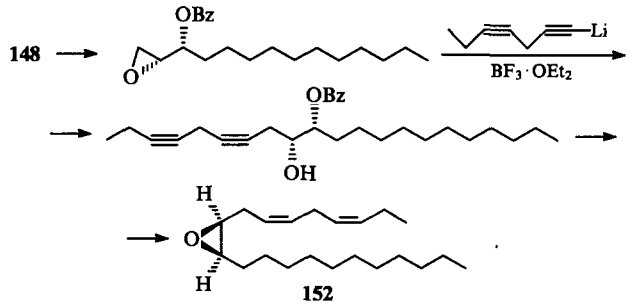


Scheme 96

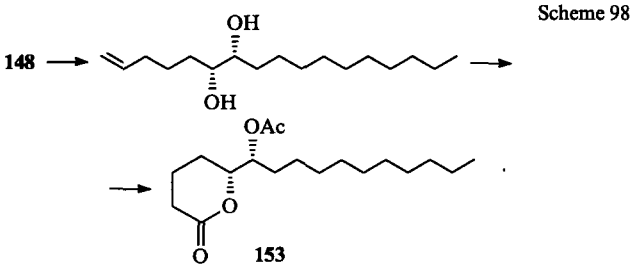


The hexenal **148** has also been used to synthesise (5*R*, 6*R*)-6-acetoxy-5-hexadecanolide **153** — the stereoisomer of the oviposition of pheromone of the gnat *Culexpipiens fatigans* (Scheme 98).[153]

Scheme 97

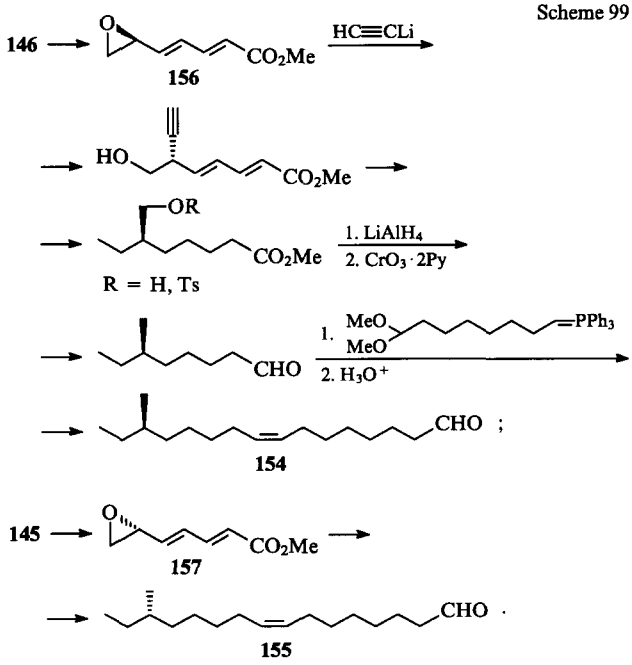


Scheme 98



The key stage in the synthesis of the aggregation pheromone of the leather eating beetles of the genus *Trogoderma*, namely (14*R*, 8*Z*)-trogodermal **154** and its (14*S*, 8*Z*)-enantiomer **155**, from the aldehydes **145** and **146** is the stereospecific reaction of their derivatives, i.e. (6*S*, 2*E*, 4*E*)- and (6*R*, 2*E*, 4*E*)-methyl-6,7-epoxyhepta-2,4-dienoates **156** and **157** respectively, with ethynyllithium. An approach to the synthesis of the enantiomerically pure methyl-branched synthons has been developed in relation to this reaction (Scheme 99).[154]

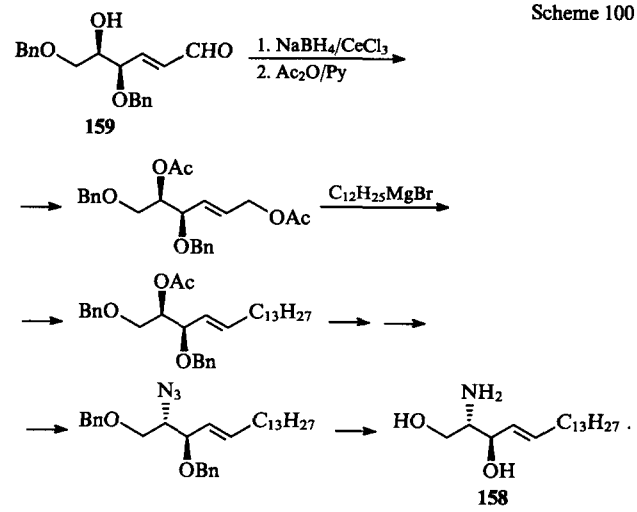
Scheme 99



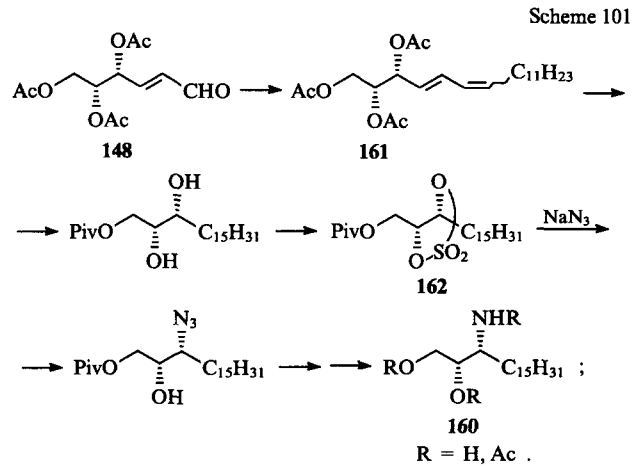
Six-carbon units with two chiral centres, obtained from glycals based on hexoses, have been used in the synthesis of sphingolipids. Thus a highly effective stereocontrolled synthesis of D-*erythro*-C_{18}-sphingosine **158**, based on the transformations of (4*R*, 5*R*, 2*E*)-4,6-di-*O*-benzyl-5-hydroxyhex-2-enal **159**, has been described (Scheme 100).[84]

The synthesis of the regioisomer of dihydrosphingosine **160** presupposes the use of the triacetoxydiene **161** obtained by converting the familiar hexenal **148** into an olefin (Scheme 101).[155]

Scheme 100



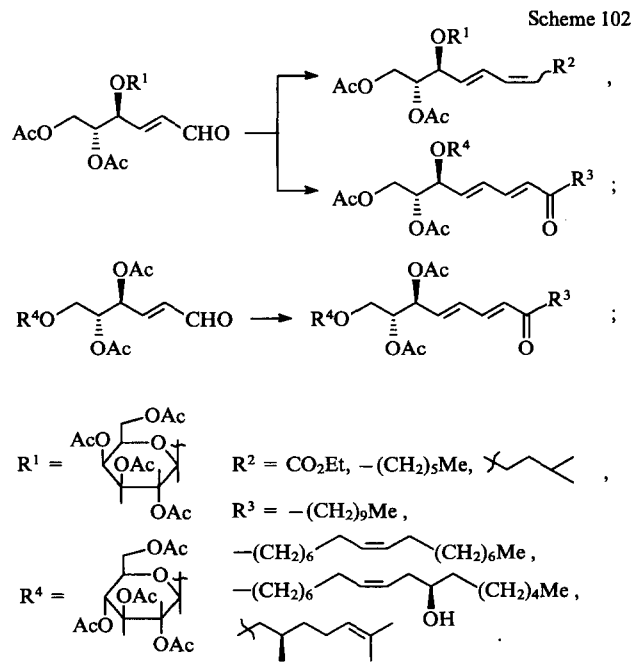
Scheme 101



The stage involving the regiospecific opening of the cyclic sulfate ester **162** on treatment with sodium azide is noteworthy.

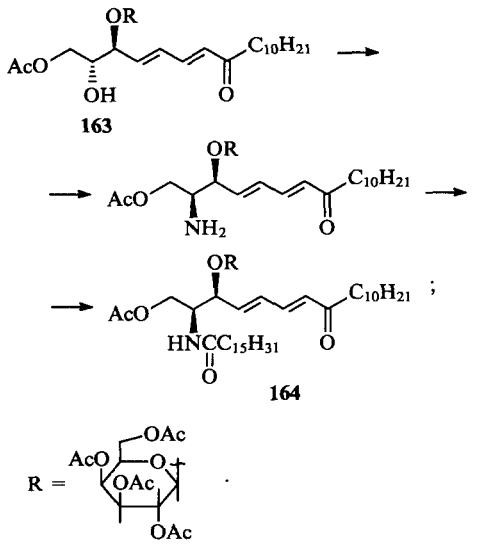
The *O*-glycosylated α,β-unsaturated aldehydes, synthesised by the decyclisation of glycals derived from disaccharides, enter fairly readily into the olefin formation reaction with various phosphoranes and 2-oxophosphonates (Scheme 102).[9, 85–88]

Scheme 102



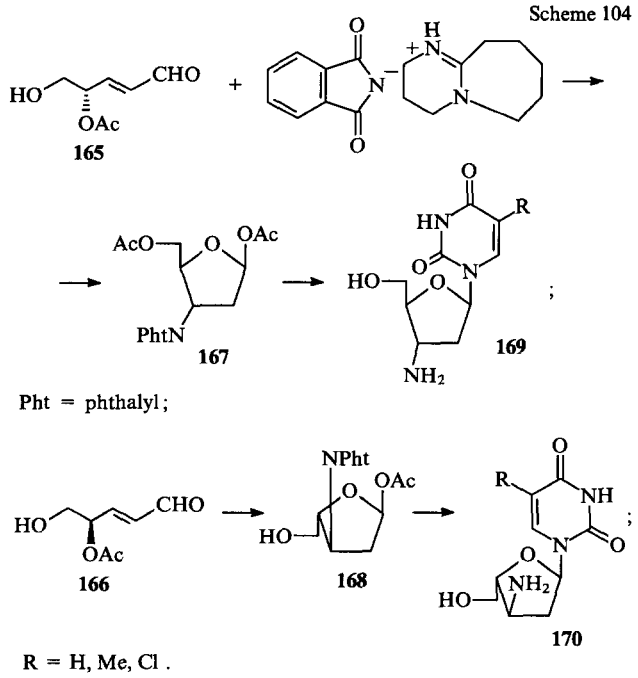
The glycoside **163**, obtained in this way, has been used in the synthesis of the pentaacetate of (2*S*, 3*S*, 4*E*, 6*E*)-3-*O*-(β-D-galactopyranosyl)-2-*N*-hexadecanoyl-8-oxosphinga-4,6-diene **164** — a structural analogue of the membrane galactocenebroside (Scheme 103).[156]

Scheme 103



The monoacetates of the α,β-unsaturated dihydroxypentenals **165** and **166**, obtained by the decyclisation of di-*O*-acetyl-D-xylal and di-*O*-acetyl-L-arabinal, react with phthalimide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene via a recyclisation mechanism, affording the phthalimido-2',3'-dideoxypentoses **167** and **168**. The latter have been used in the synthesis of 3'-amino-3'-deoxythymidine **169**[157] and L-3'-amino-2',3'-dideoxyuridines **170** (Scheme 104).[158]

Scheme 104



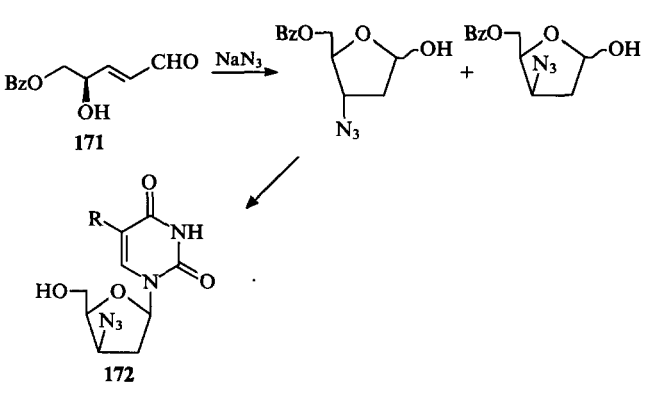
Pht = phthalyl;

R = H, Me, Cl .

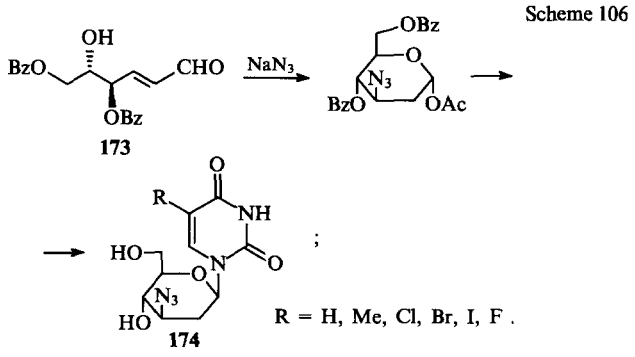
The cyclisation of the benzoyloxypentenal **171** on treatment with NaN_3 leads to stereoisomeric azidopentoses, one of which has been used to synthesise azidothymidine **172**, which possesses a high antiviral activity (Scheme 105).[159]

3'-Azido-2',3'-dideoxyhexosouridines **174** have been synthesised from the aldehyde **173** in accordance with a similar scheme (Scheme 106).[160]

Scheme 105



Scheme 106



R = H, Me, Cl, Br, I, F .

The syntheses of analogues of azidothymidine from the products of the decyclisation of glycal esters derived from hexoses have been described.[161]

As can be seen from the present review, the study of the reactions of glycals has outgrown the framework of the chemistry of carbohydrates proper and has made it possible to discover their extensive possibilities in relation to enantiospecific synthesis. One cannot fail to draw attention to the fact that synthon units of special preparative value by virtue of the enantiomeric purity of the natural and synthesised chiral centres and the presence of the reactive functional groups most suitable for subsequent transformations can be obtained precisely from the glycals. Judging from the rate of growth of the publications during the last five years, glycals are rapidly occupying an honourable place among the series of sources of chiral carbon which are of general importance for the synthesis of complex natural products, their analogues, and their derivatives.

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