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Recent Developments in C-Glycoside Synthesis

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1. INTRODUCTION

C-Glycosides are glycosides in which the carbohydrate unit is linked at position-1 to the aglycon by way of a C-C bond. When the aglycon is a purine or a pyrimidine base these molecules are termed C-nucleosides; most of these C-nucleosides contain D-ribose or 2-deoxy D-ribose as the sugar components. Several reviews have appeared which are concerned with the chemistry and the biochemistry of C-nucleosides (refs. 1-8) but as far as we know no review devoted generally to C-glycosides has been published except a short report in 1989 (ref. 9).

Increased interest in the chemistry of C-glycosides was stimulated by the discovery of diverses biological effects exhibited by a number of them. Moreover the use of C-glycosides as key-intermediates in the synthesis of a variety of naturally occurring products, not all derived from carbohydrates, provides additional impetus for a review article covering this important field of bio-organic chemistry.

The purpose of this article is to objectively review the diverse synthetic strategies for the preparation of C-glycosides. The study of purine and pyrimidine bases as aglycons will be restricted to the methodology permitting the direct introduction of the C-C bond. No attempt will be made to examine systematically all the reported structures but we will consider exclusively those C-glycosides in which the aglycon is introduced by direct formation of the C-C bond at the anomeric center.

The basic presentation is organized according to the chemical type of the precursors. Unsaturated-sugars, glycosides, lactones and free-sugars will constitute the main sections, some of which are subdivided into subsections in order to facilitate comparisons of the exposed techniques.

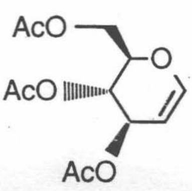
2. UNSATURATED SUGARS

Unsaturated sugars are sugars which possess an endo- or exo-cyclic carbon-carbon double bond. When the double bond is situated between C1 and C2 of the carbohydrate ring, these sugars are termed glycals. Sugar enones will also be studied in this section.

2.1 Glycals

The glycals have proved to be important precursors to prepare, by molecular rearrangement, the biologically interesting 2,3-unsaturated C-glycosides or C-nucleosides.

Before the publication of specific methods leading to unsaturated C-glycosides and C-nucleosides, some C-C-linked compounds have been reported such as the disaccharide (**2**) (ref. 10) which was obtained by treatment of tri-O-acetyl-D-glucal (**1**) with low concentrations of boron trifluoride.



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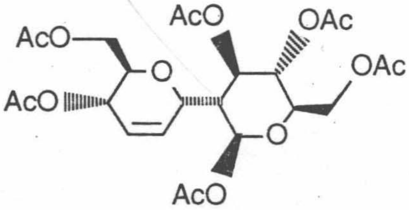

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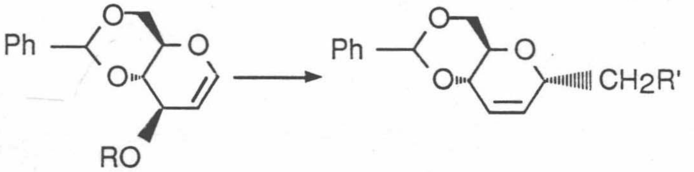
A. *Claisen rearrangement*

The Claisen rearrangement has been applied to glycals (**3**) in specific conditions, to obtain 2,3-unsaturated C-glycosides (**4**), (**7**) (refs. 11, 13) as well as (**8**) from (**6**) (ref. 12). The hydroxymethyl C-glycoside (**7**) could also be obtained from the same substituted glycal (**3**) by treatment with tributyltinmethyliodide and butyl lithium (ref. 13). Moreover the β-C-glycoside (**5**) was prepared from the compound (**4**) using successively Et_3OBF_4 and $LiAlH(OEt)_3$ (ref. 13).

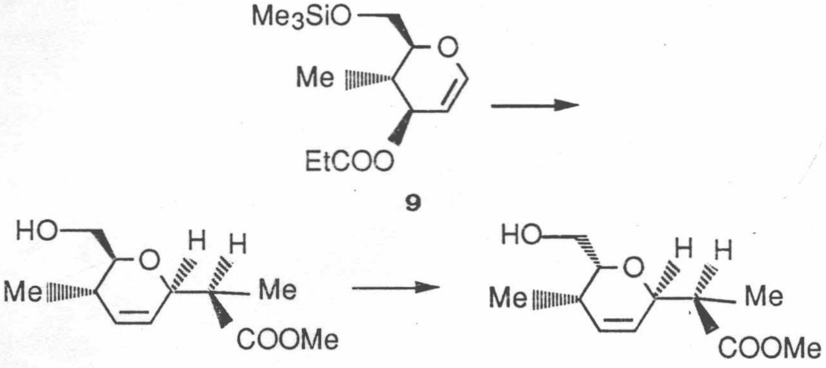


3 R = H
6 R = OAc

4 R' = CONMe$_2$
7 R' = OH
8 R' = COOH

5

The tetrahydropyran fragment (**11**) of an ionophore antibiotic (X-14547A) was obtained also by a Claisen ester enolate rearrangement (**9**) -> (**10**) (ref. 14), followed by epimerization of the C-5 hydroxymethyl group.



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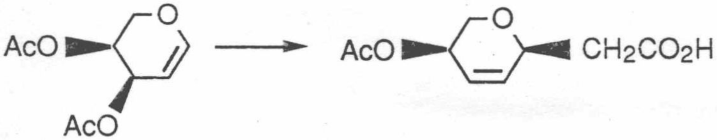
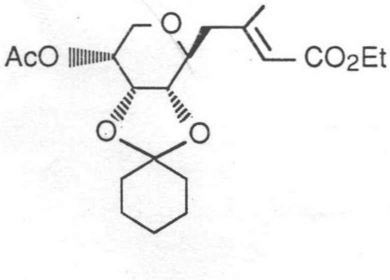
10 **11**

The intermediate (**14**) of pseudomonic acid A was synthesized utilizing a Claisen rearrangement of the arabinal derivative (**12** -> **13**) (ref. 15).



12 **13**



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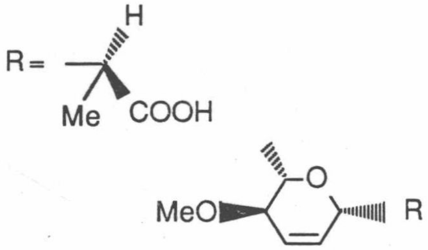
The enol silylether approach has been used to prepare the C-glycoside derivatives (**15**), (**6**) and (**16**) which were employed in polyether antibiotic syntheses (ref. 16).



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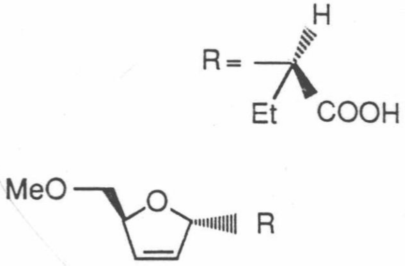

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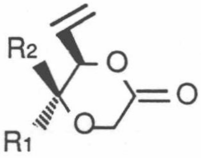
Enolate Claisen rearrangement involving (3,3)-sigmatropic reorganizations of 6-alkenyl-4-oxapyran-2-ones (**17**) permitted the synthesis of polysubstituted dihydropyrans which constitutes a route to C-pyranosides (**18**) (ref. 17). Fragments of erythronolides (**20**) could also be obtained by the dioxanone-to-dihydropyrane enolate Claisen rearrangement (refs. 18, 19) and reductive fragmentation of the intermediate (**19**).



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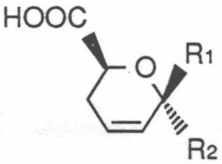

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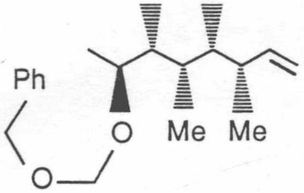

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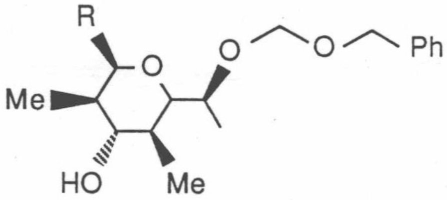

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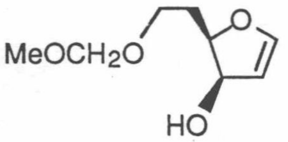
A synthesis of (-)-nonacetic acid (**23**) from 2,3-unsaturated C-glycofuranosyl derivative (**22**) obtained from the corresponding glycal (**21**) also by a Claisen reaction was reported (ref. 20).



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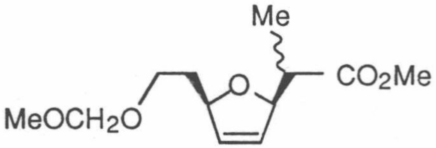

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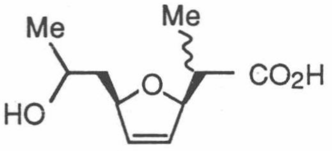

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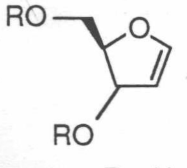
B. *Palladium assisted reactions*

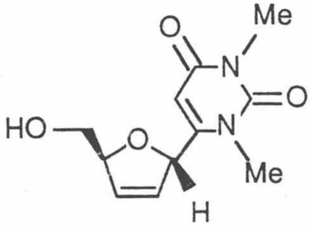
The palladium-mediated coupling reaction constitutes a useful method to link glycals with aglycons in a regio- and stereo-specific manner (ref. 21).

The synthesis of the 2,3-unsaturated C-nucleosides (**26**) and (**27**) was reported by the reaction of furanose-glycals with pyrimidine-mercury/ palladium acetate complexes.

The *erythro*-glycal (**24**) gave the α-anomer (**26**) whereas the corresponding *threo*-O-acetyl (**25**) led to the β-isomer (**27**). This stereospecificity could be explained by the bulky substituent of the glycal (**25**) (ref. 22).



24 R = H
25 R = Ac



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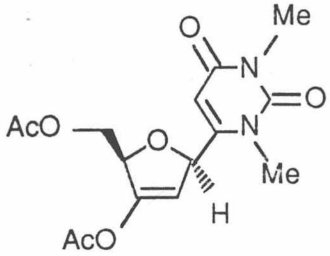
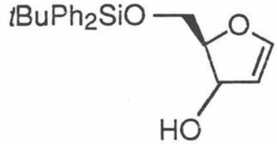


27

In the same fashion the condensation of pyrimidine mercury derivatives with the partially substituded glycal (**28**) afforded the enol silyl C-glycoside (**29**) (ref. 23).



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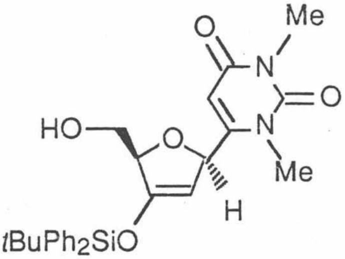
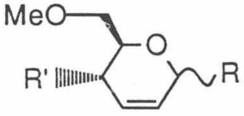


29

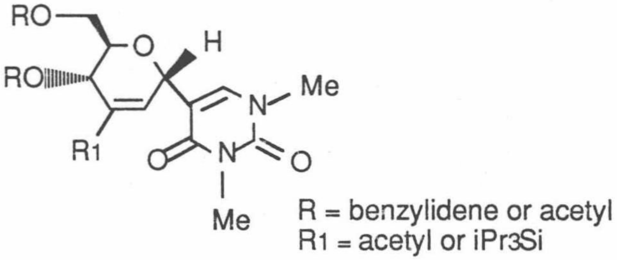
Tetrakis (triphenyl phosphine) palladium(0) effects the regio- and stereoselective alkylation of 2-acetoxy-5,6-dihydro-2H-pyrans and 1-5-acetyl-1-thiohex-2-enopyranosides. Stabilized carbanions led to alkylated dihydropyrans with net retention at the oxygen-bearing carbon atom whereas non-stabilized carbanions such as aryl zinc chlorides gave alkylated dihydropyrans and C-glycosyl derivatives with net inversion (**30**) (ref. 24).



R = Ph, naphthyl
R' = H or OMe

30

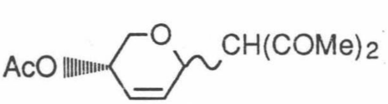
The stereochemistry of the formation of intermediate organopalladium adducts during the palladium-mediated reactions of pyranoid glycals leading to C-glycosides (**31**) has been studied. 3-O-Substituted glycals with (1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)mercuric acetate form regio- and stereo-specifically single organopalladium adducts by attack of the organopalladium reagent on the glycal double bond from the face of the glycal opposite the allylic 3-O-substituent. Factors affecting the stability of the organopalladium adducts were studied (ref. 25).



R = benzylidene or acetyl
R1 = acetyl or iPr3Si

31

β-Dicarbonyl compounds reacted with peracetylated glycals in the presence of palladium (0) to yield the unsaturated C-glycoside (**32**) (ref. 26).



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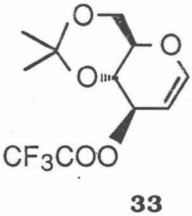
This alkylation was improved by using trifluoroacetate ester (**33**) in the presence of dibenzylidene acetal bis(diphenyiphosphino)ethane (ref. 27).



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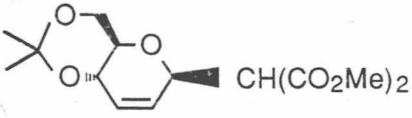
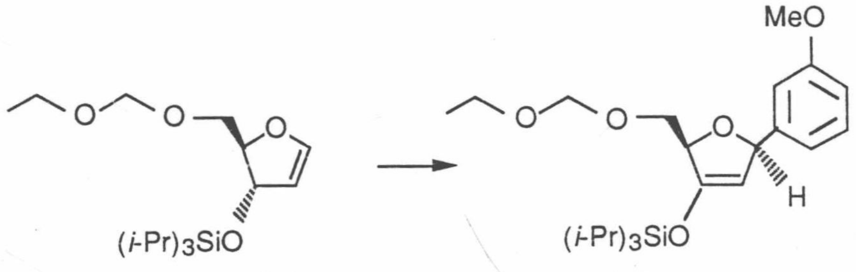
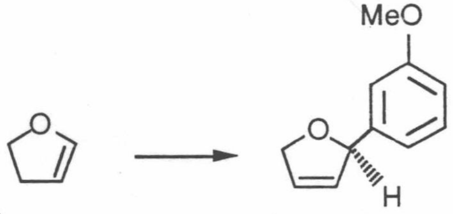


34

The furanoid C-glycosides (**36**) and (**38**) related to the gilvocarcin, ravidomycin and chrysomycin class of antibiotics, have been obtained by the regio- and stereo-specific coupling of furanoid glycals (**35**) (**37**) with tri-nbutylstannyl derivatives of benzo[d]naphto[1,2-b]pyran-6-ones in the presence of stoïchiometric palladium (II) acetate (ref. 28).

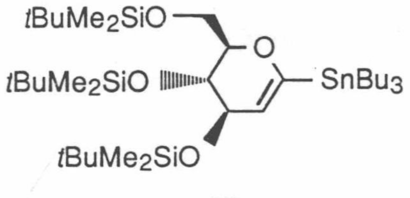


35 **36**



37 **38**

C-Arylglycals (**40**) have also been prepared by palladium catalyzed coupling of protected 1-(terbutylstannyl)-D-glycal (**39**) and substituted aryl bromides (ref. 29).



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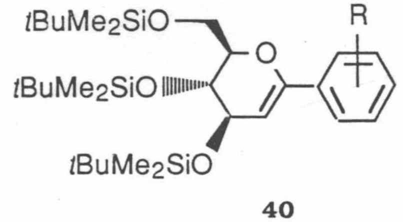

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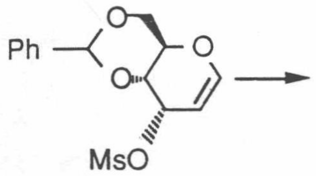
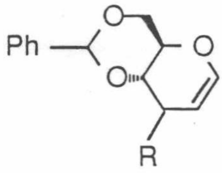
R = NO_2, CN, Cl,
Me, CH_2OAc
BnO, OMe

C. *Various organometallic reagents*

Reaction of benzylidene glycal (**41**) with various allyl magnesium bromides gave the corresponding 1-C-glycopyranosides (**42**) and 3-C-alkyl-enitols (**43**), whereas the use of methyl magnesium chloride led to a mixture of α and β-1-C-methyl glycosides (ref. 30).

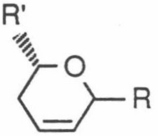




R = Et, iPr, Et(Me)CH, PhCC

41 **42** **43**

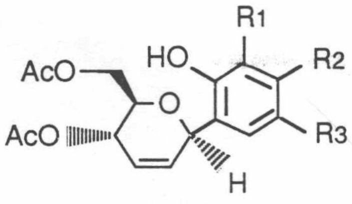
The stereoselective C-glycosidation of substituted glycals (**44**) based on the use of organoaluminium reagents permitted the synthesis of a series of C-glycosides (**45**) (ref. 31).



R = Me, Pr, iBu, alkynyl
R' = Phenyl, cyclohexyl, cinnamyl

44 **45**

A stereoselective arylation of pyranoid glycals has also been proposed for the synthesis of unsaturated C-glycopyranosides. Bromomagnesium phenolates provided a highly stereoselective route to 2,3-unsaturated α-C-glycopyranosylarenes (**46**) (**47**) (refs. 32, 33, 34).



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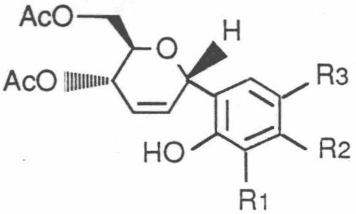

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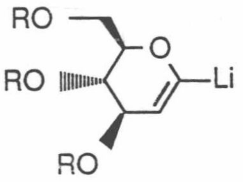
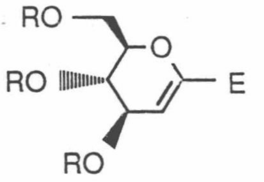
1-Lithio glycals (**48**) (**50**) prepared either by direct lithiation or from a tributyltin derivative reacted with various electophiles to yield the C-glycosides (**49**) (**51**) (ref. 35) whereas methyl-β-C-glycosides (**52**) were obtained by similar procedures (ref. 36).

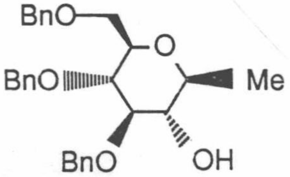




E = All, Me or COOH

48 R = *t*Bu(Me)2Si
50 R = Bn

49 R = *t*Bu(Me)2Si
51 R = Bn



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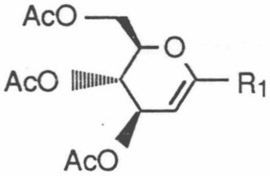
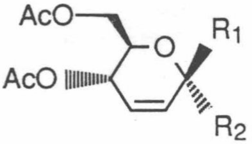
The lithioglycal (**48**) reacted with electrophilic agents in the presence of copper halides to yield, after deprotection and acetylation, the glycal acetate (**53**) which permitted the synthesis of 2,3-unsaturated C-glycosides (**54**) carrying geminal substituents at the anomeric center (ref. 37).





R_1 = Me, All
R_2 = Me, Et, CN, All

53

54

Direct lithiation of substituted 2-benzyloxy and 2-phenylthio glucals (**55**) at the anomeric center leads to intermediates which react with various electrophiles (**56**), thus providing a convenient entry into functionalized C-glucopyranosides (ref. 38).

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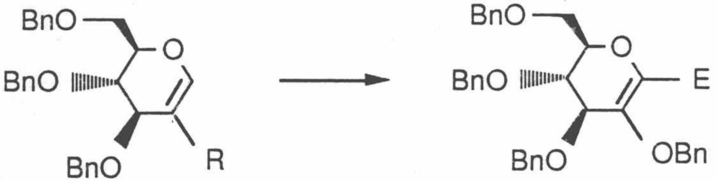
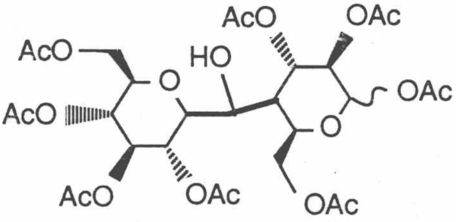


R = SPh, OBn

E = Me, COOMe

55 **56**

A C-disaccharide (**57**) was also obtained by a diastereocontrolled reaction of 1-C-lithiated species with a 4-deoxy-4-formyl-D-glucose derivative. This compound could be transformed into the carbon bridged cellobiose derivative (ref. 39).



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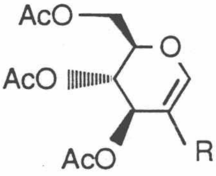
D. *Lewis acid assisted condensations*

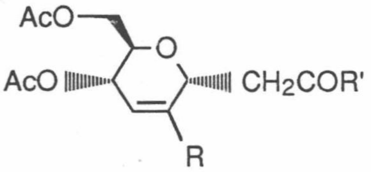
Application of the Ferrier reaction to carbon nucleophiles led to various 2,3-unsaturated C-glycosides, their structure depending on the reagent (refs. 40-50).

The reaction of 1-trimethylsilyl enol ether with oxocarbonium ion generated from peracetyl glucal (**1**) in the presence of Lewis acids led to a mixture of the α- and β-C-glycosides (**60**) and (**61**) in a ratio showing an extremely high dependance upon the various reaction parameters (refs. 40, 41).

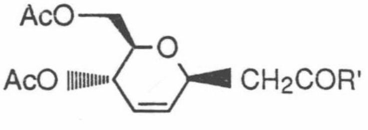


1 R = H
58 R = OAc
59 R = NAc_2

Condensation of (**1**) with enol esters led also to a mixture of C-glycosides (**62-65**) whereas the 2-substituted glycals (**58**) and (**59**) reacted in the presence of boron trifluoride etherate to yield stereoselectively the α-anomers (**64**) and (**65**) (ref 42).

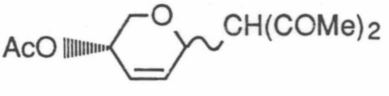


60 R = H R' = Ph
62 R = H R' = Me
64 R = Ac R' = Me
65 R = NAc_2 R' = Me



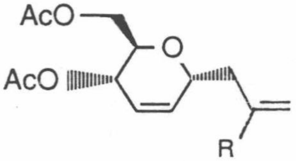
61 R = H R' = Ph
63 R = H R' = Me

In a similar way β-dicarbonyl compounds in the presence of boron trifluoride gave the unsaturated C-glycoside (**32**) (ref. 26).



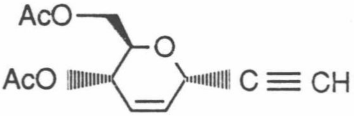
32

Reaction of allyltrimethylsilane with glycals afforded only one regioisomer arising from entry of the nucleophile at C_1 with transposition of the double bond to C_2-C_3. The reaction gave α-allyl glycosides (**66**) by an *anti* $SN_{2'}$ displacement (ref. 43). The reactions of (E) and (Z)-crotylsilanes with acetylated glycal derivatives (**1**) in the presence of BF_3 etherate are regiospecific and permitted the incorporation of 3-methylprop-1-ene-3-yl function at the 1 position of the pyran with formation of a 2,3 double bond (**67**). The stereochemistry at 1' was induced by the stereochemistry of the starting crotylsilane. The application of this process permitted the synthesis of the pyranoid segment of *indanomycin* in optically active form (ref. 44).



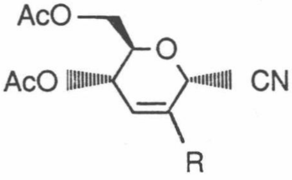
66 R = H
67 R = Me

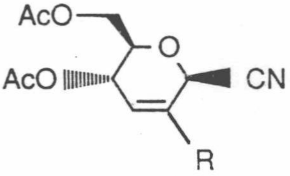
Bis(triethylsilylacetylene) reacted with (**1**) in the presence of titanium(IV) chloride to afford selectively (**68**) in good yield (ref. 45).



68

Treatment of glycal (**1**) with trimethylsilyl cyanide in the presence of boron trifluoride etherate yielded quantitatively the cyano derivative (**69**). On the other hand condensation with the peracetylated 2-hydroxy glycal (**58**) produced an anomeric mixture of nitriles (**71**) and (**72**) (refs. 45, 46). Reaction of glycals with Et_2AlCN which has the double advantage of being a Lewis acid as well as providing a nucleophile, afforded a mixture of nitriles (**69**) and (**70**) at room temperature (ref. 47) but only (**69**) was obtained in refluxing benzene (ref. 13).

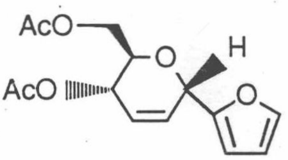




69 R = H
71 R = OAc

70 R = H
72 R = OAc

Furan and thiophene C-glycosides could be prepared from glycals (**1**) and (**58**). With acetylated glycal (**1**), α-C-glycosides (**73**) and (**74**) were recovered with an equal amount of 1,2-unsaturated C-glycosides whereas with 2-hydroxy glycal (**58**) the condensation was more chemoselective leading only to the 2,3-unsaturated C-glycosides as a mixture of α and β-isomers (**75-78**) (ref. 48).



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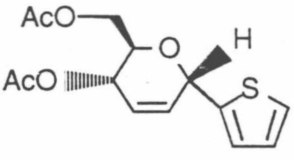

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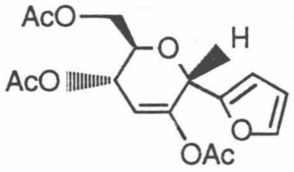

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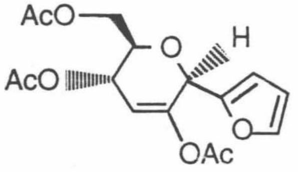

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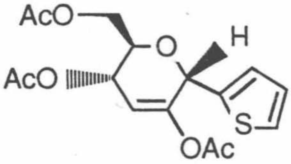

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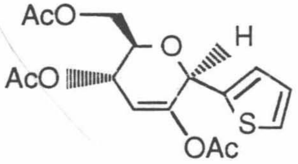
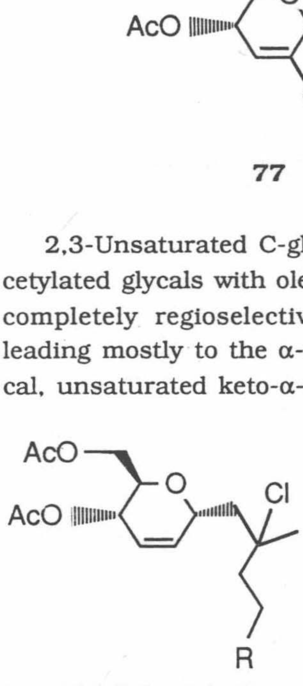


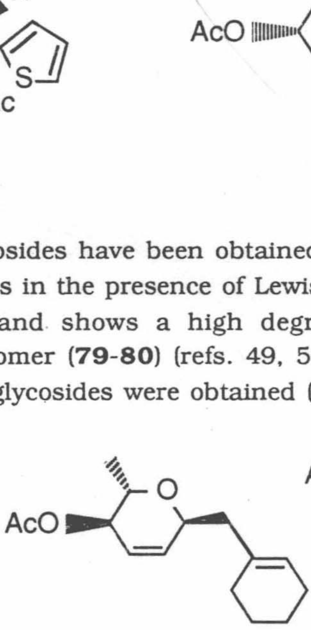
78

2,3-Unsaturated C-glycosides have been obtained by treatment of peracetylated glycals with olefins in the presence of Lewis acids. The reaction is completely regioselective and shows a high degree of stereoselectivity leading mostly to the α-anomer (**79-80**) (refs. 49, 50). With 2-hydroxy glycal, unsaturated keto-α-C-glycosides were obtained (**81**) (ref. 49).



R = OH, OAc, SO_2Ph

79



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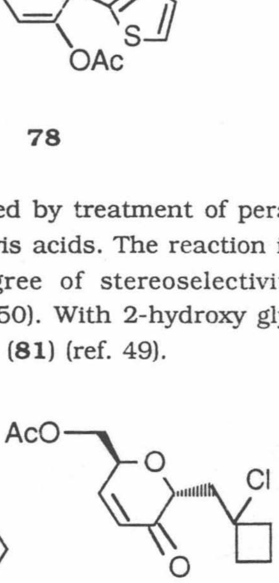
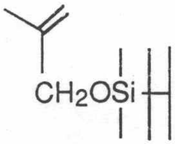


81

A direct and highly steroselective route to 1-aldo (**83**) and 2-keto-C-glycosides (**84**) has been developed by using the first example of Lewis acid induced generation of homoenolate equivalents from allylic silyloxy ethers (**82**) (ref. 51).



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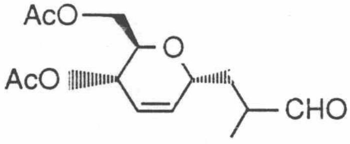
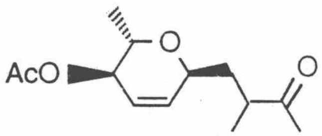
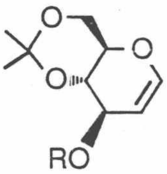


83

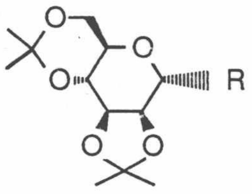


84

The reaction of a bicyclic carbohydrate radical, generated by an intramolecular cyclisation of the mixed acetal (**85**), with various radical traps afforded highly functionalized C-glycosides (**86-88**) (ref. 52).

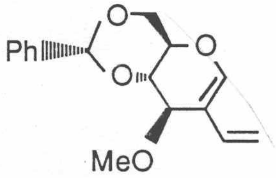


85 R = CH(OEt)CH$_2$Br

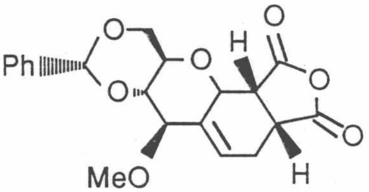


86 R = CH$_2$CH$_2$CN
87 R = CN
88 R = CH$_2$CH = CH$_2$

A study of facial selectivity in Diels-Alder cycloadditions of pyranose diene (**89**) towards maleic anhydride or symmetrical and nonsymmetrical acetylenic dienophiles has been reported. This reaction led to annulated C-glycopyranosides (**90**), a new class of C-glycosides (ref. 53).

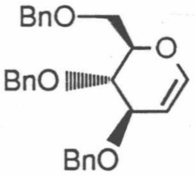


89



90

The ring contracted aldehyde (**93**) was prepared by treatment of tri-O-benzyl D-glucal (**91**) with thallium (III) nitrate trihydrate (ref. 54) whereas the same (**93**) was obtained by an alternative reaction of (**91**) with benzeneselenyl chloride and subsequent oxidation with m-chloroperbenzoic acid of the intermediate 2-phenylseleno sugar (**92**) (ref. 54).



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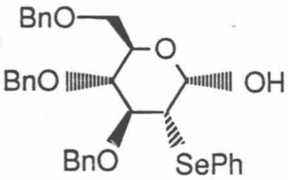

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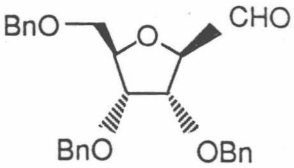
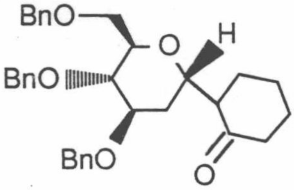


93

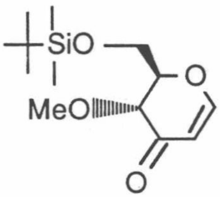
2.2 Enones

Stereospecific synthesis of C-glycosides has been performed by conjugate additions of α-alkoxycopper reagents to sugar enones (ref. 56). (Benzyloxy)methyl- and [((tetrahydropyran-2-yl)oxy)methyl]]lithium reagents have been converted into organocopper reagents which reacted with various sugar enones to give the corresponding C-glycosides (**94**).



94

Also the additions of R(PhS)CuLi to the enone (**95**) led to the α-isomers (**96**) with high selectivity (ref. 57).



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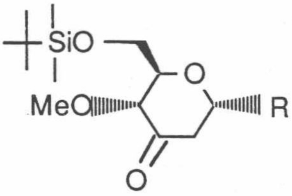

96

Stereospecific conjugate-addition of organocopper reagents to peracetylated hex-1-enopyran-3-uloses (**97**) and (**99**) leads to (2-deoxy-α-D-glyc-2-enopyranosyl) arenes (**98**) and (**100**) respectively. The α-D-anomer was obtained with complete stereocontrol, without epimerization at C-4 (ref. 58).

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