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Recent Developments in the Synthesis of *C*-Glycosides

Maarten H. D. Postema

Department of Chemistry
University of Alberta
Edmonton, Alberta
Canada T6G 2G2

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Contents

I. INTRODUCTION

Over recent years *C*-glycosides[1] have been the subject of considerable interest in carbohydrate, enzymatic, and metabolic chemistry, as well as in organic synthesis. A *C*-glycoside results when the anomeric oxygen of a glycoside is replaced by a carbon atom. Several physiologically active natural products[2] contain *C*-glycosidic linkages. Two representative examples are showdomycin[3] and vienomycin.[4] When the oxygen linkage in a disaccharide is replaced by a methylene group, a *C*-glycoside, more specifically a *C*-disaccharide is formed. This *C*-disaccharide linkage is no longer cleavable by hydrolysis. As a result, there is now interest in the use of *C*-disaccharides for enzymatic and metabolic studies.[5] From a synthetic point of view, *C*-glycosides serve as a readily accessible source of chiral synthons possessing more carbon functionality than *O*-glycosides.[6]

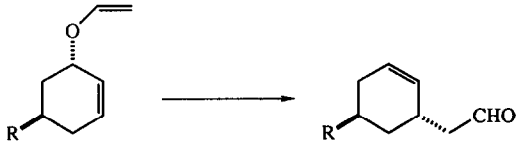
A vast array of methods for *carbon-carbon* bond formation at the anomeric carbon now exist. It is the aim of this review to provide a summary of the available methods and to illustrate their applications in organic synthesis. The most common method for *carbon-carbon* bond formation at the anomeric carbon involves nucleophilic attack on this electrophilic center. A wide variety of electrophilic sugars have been employed, such as glycosyl halides, imidates, glycals, lactones, thioglycosides, as well as *O*-protected glycosides such as *p*-nitrobenzoates. The carbon nucleophiles that have been used include silyl enol ethers, alkenes, allylsilanes, allylstannanes, homoenolates, and organometallics such as Grignard reagents, organolithiums, cuprates, and aluminates.

Quite recently procedures to synthesize *C*-glycosides based on transition metals (palladium, manganese, rhodium, and cobalt) have been developed. Concerted reactions such as [4+2] cycloadditions and sigmatropic rearrangements have also been employed to make *C*-glycosides. Very recently the field of free radical chemistry has been extended to this area; the special merits of free radical methods are mild reaction conditions and tolerance of a wide range of functional groups.The subject of *C*-glycoside synthesis has been reviewed by Hanessian,[7] Suhadoluid,[8] and by Daves and Cheng.[9] The present treatment surveys the literature from 1983 to 1991.

II. CONCERTED REACTIONS

1. Sigmatropic Rearrangements

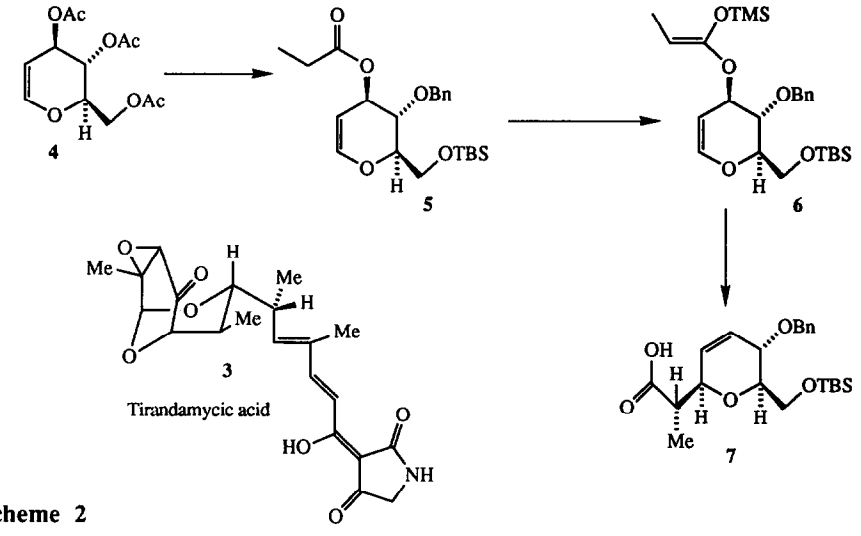
The Claisen and related rearrangements are powerful synthetic tools for stereoselective *carbon-carbon* bond formation. The new carbon-carbon bond is formed syn to the pre-existing oxygen substituent as shown below in Scheme 1. This has been used to advantage in the synthesis of *C*-glycosides.



1 2

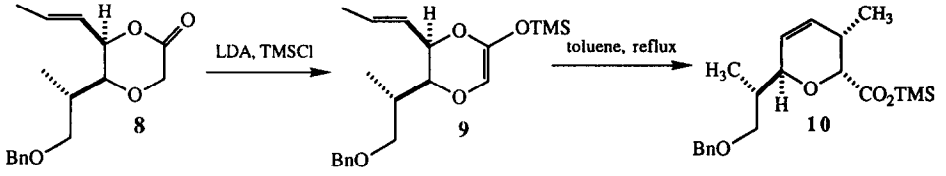
Scheme 1

The high degree of stereochemical control involved in the Ireland ester rearrangement has been applied to the synthesis of tirandamycic acid (**3**), an antibiotic[10] that belongs to a small group of 3-acyltetramic acids.[11] Tirandamycic acid is of particular importance due to its powerful inhibition of bacterial DNA-directed RNA polymerase.[12] A key intermediate in the synthesis of tirandamycic acid was made as shown in Scheme 2. The glycal **4** afforded **5** by application of standard methods, and the ester was then converted into the silyl enol ether **6** in good yield. Ireland ester enolate rearrangement occurred smoothly in refluxing benzene to give *C*-glycoside **7** with the desired stereochemistry.



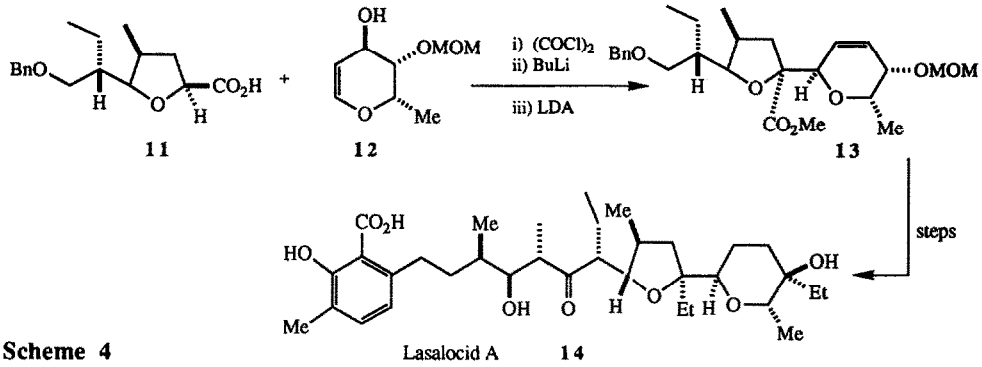
Scheme 2

The enol ether may also be formed inside the ring as shown below. Treatment of the ether lactone **8** (Scheme 3) with LDA and trapping of the enolate with trimethylsilyl chloride gave compound **9**. The enol ether **9** then rearranged in refluxing toluene to furnish **10**.[13]



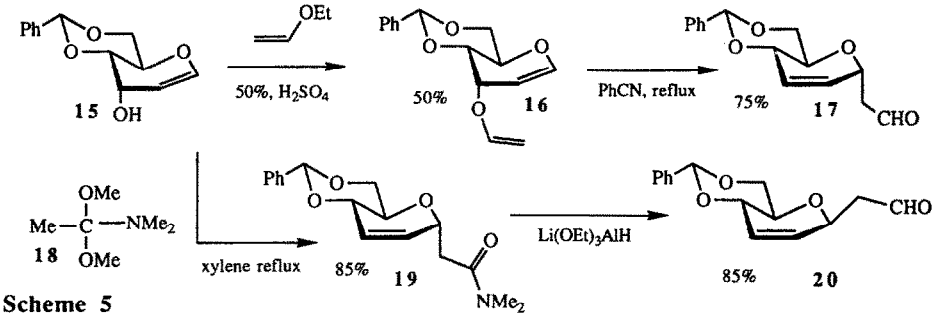
Scheme 3

Ireland and co-workers[14] have also employed the ester enolate rearrangement as the key step in a synthesis, again via a *C*-glycoside, of lasalocid A (**14**). Coupling of acid **11** (Scheme 4) with the protected glycal **12**, followed by rearrangement, gave two products, **13** being the major component. This *C*-glycoside was then elaborated into lasalocid A (**14**).



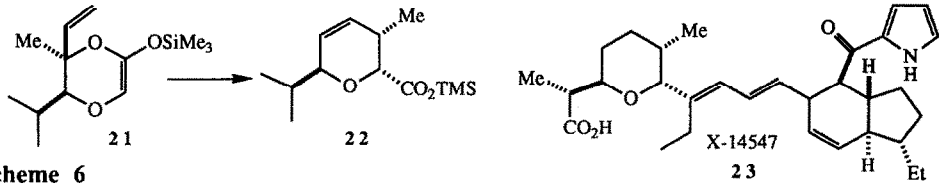
Scheme 4

In an analogous procedure, Fraser-Reid,[15] using the Claisen rearrangement, has made functionalized *C*-glycosides suitable for further elaboration. Formation of **16** (Scheme 5), via treatment of the protected glycal **15** with ethyl vinyl ether in 50% sulfuric acid, proceeded in 50% yield. The condensation product **16** then easily underwent sigmatropic rearrangement in refluxing benzonitrile to give the α-*C*-glycoside **17** in 75% yield. Alternatively, reaction of **15** with *N*,*N*-dimethylacetamide dimethyl acetal (**18**) in refluxing xylene gave the amide **19** in 85% yield. Reduction with lithium triethoxyaluminohydride furnished the epimeric aldehydic *C*-glycoside **20**.



Scheme 5

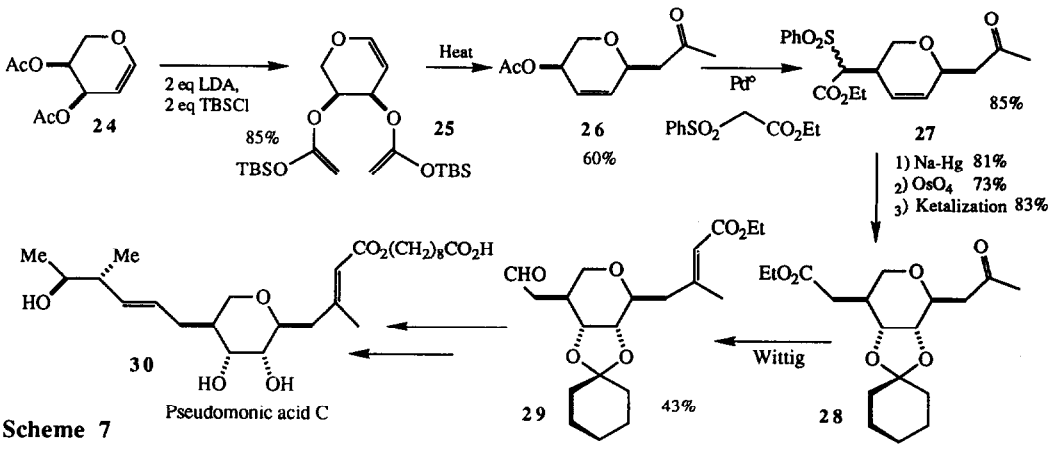
During model studies directed at the antibiotic X-14547 (**23**), Burke and co-workers[16] also used Claisen methodology to stereospecifically synthesize a *C*-glycoside (Scheme 6). Silyl enol ether **21** was converted to **22** which is a model of the *C*-pyranoside system of X-14547.



Scheme 6

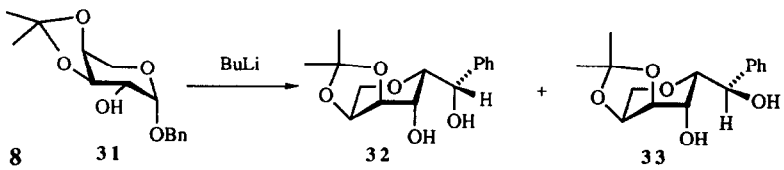
The synthesis of pseudomonic acid C (**30**), by Curran and Suh,[17] represents another application of the Ireland ester enolate-Claisen rearrangement leading to a *C*-glycoside (Scheme 7). The bis(ketenesilyl)acetal **25** was prepared by adding the glycal **24** to a solution of LDA, followed by silylation of the resulting bis enolate with two equivalents of *t*-butylchlorodimethylsilane. Heating of **25** brought about rearrangement and this was followed by desilylation and conversion to the acid chloride. The latter was treated with lithium dimethylcuprate to produce ketone **26**. Palladium catalyzed coupling of **26** with ethyl phenylsulfonyl acetate then furnished **27**

as a 1:1 mixture of isomers. The sulfonyl group was removed by the action of sodium amalgam and this step was then followed by osmylation and diol protection to afford **28**. Wittig reaction of the ketone followed by conversion of the original ester group to an aldehyde then provided **29**.



Scheme 7

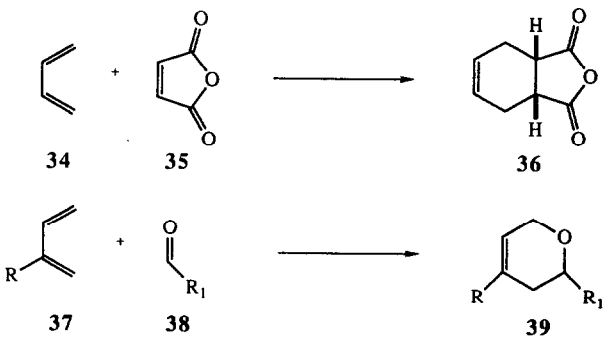
Scheme 8 shows an application of the Wittig rearrangement as applied to *C*-glycoside synthesis. Reaction of compound **31** with butyllithium gave **32** and **33** in fair yield.[18]



Scheme 8

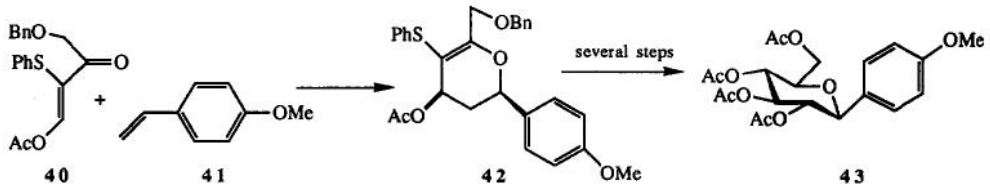
2. Cycloadditions

The Diels-Alder Reaction, which is possibly the most important reaction in organic chemistry, has also found application in *C*-glycoside synthesis. In general terms the reaction can be described as the cycloaddition of a suitable diene **34** with an appropriate dienophile **35** to form a six-membered ring. If one of the carbon atoms participating in the cycloaddition is replaced by a heteroatom, such as oxygen, the reaction is now termed a hetero-Diels-Alder reaction. This type of cycloaddition has been applied to the construction of *C*-glycosides.



Scheme 9

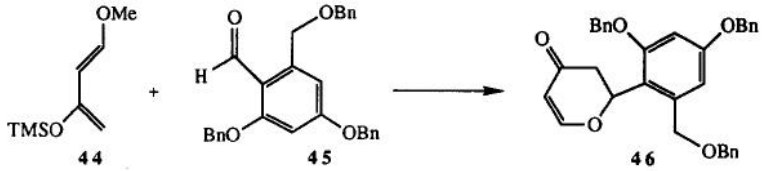
Scheme 10 shows the reaction of hetero diene **40** with the substituted styrene **41**. The cycloadduct **42**[19] is formed in good yield and further steps gave the *C*-glycoside **43**.



40 41 42 43

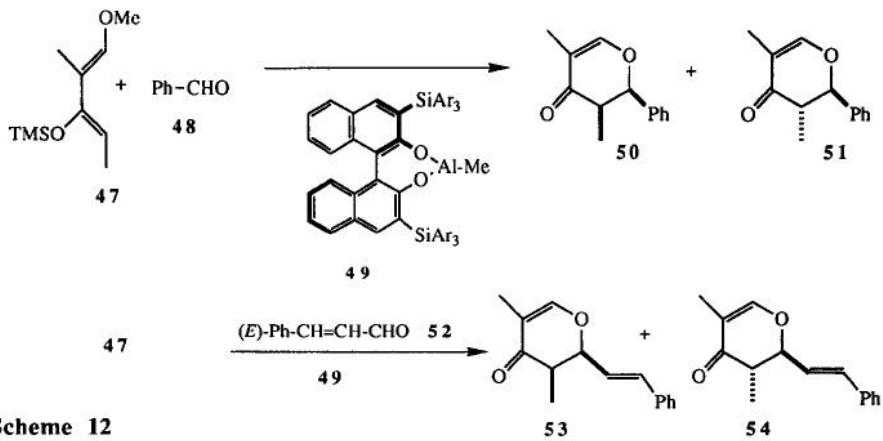
Scheme 10

Reaction of Danishefsky's diene[20] (**44**) with the benzaldehyde derivative **45** (Scheme 11) afforded the cyclic enol ether **46** in good yield.[21] Although seemingly lacking the characteristics of a carbohydrate, this molecule was then transformed into a sugar derivative.



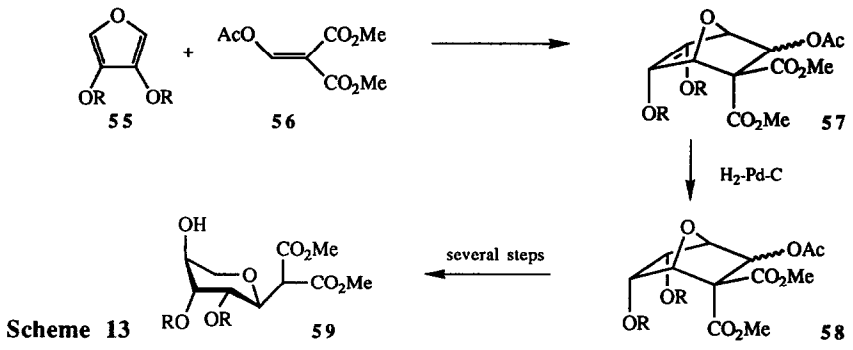
Scheme 11 44 45 46

Yamamoto has developed an asymmetric hetero-Diels-Alder reaction between various dienes and aldehydes using the organoaluminum catalyst **49**.[22] Reaction of diene **47** with benzaldehyde (**48**) in the presence of a catalytic amount of **49**, followed by exposure of the adducts to trifluoroacetic acid, gave the *cis*-dihydropyrone **50** (77%) and its *trans*-isomer **51** (7%). The enantiomeric excess for the *cis*-isomer was found to 97%. A similar example is also shown in Scheme 12, the same diene reacting with cinnamaldehyde (**52**) to give again a mixture of adducts with the *cis*-compound **53** predominating over **54**. Since both enantiomers of the catalyst are available, this route shows promise for the application of Diels-Alder reactions in the synthesis of L-sugars.



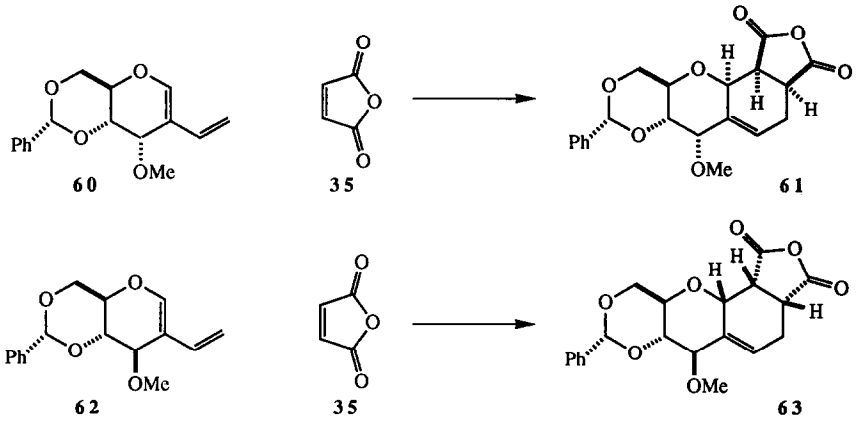
Scheme 12

Scheme 13 summarizes the Diels-Alder reaction of the substituted furan **55** with enol acetate **56** to produce the bicyclic compound **57**. Hydrogenation then yielded **58** which, in turn, was transformed into the *lyxo*pyranosyl *C*-glycoside **59**.[23]



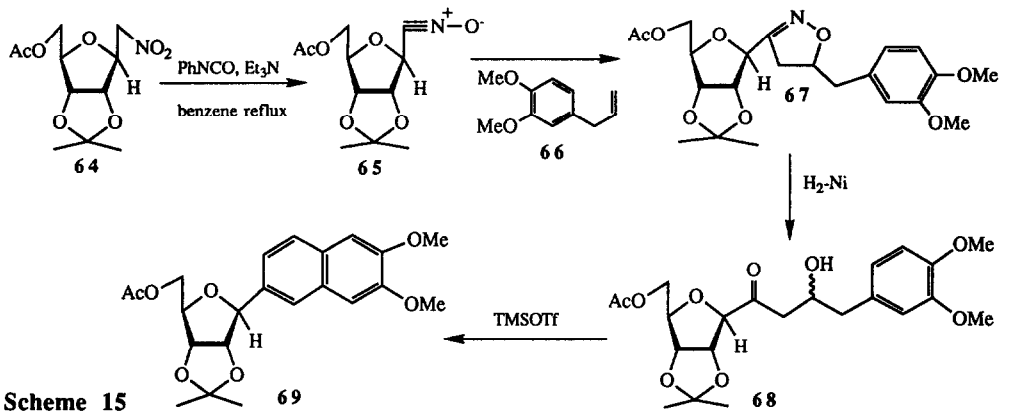
Scheme 13

Lopez and co-workers have studied the Diels-Alder reaction of the carbohydrate derived dienes **60** and **62** with maleic anhydride. Scheme 14 shows the results. The reaction proceeded in an endo fashion to give the annulated *C*-glycopyranosides **61** and **63** respectively.[24]



Scheme 14

Kozikowski[25] has used dipolar addition chemistry to synthesize an aryl *C*-glycoside from a previously prepared *C*-glycoside. Starting with the *C*-glycoside **64**, conversion to the nitrile oxide **65** was achieved as shown, and cycloaddition with the substituted allyl compound **66** afforded the **67**. Reduction with Raney nickel then gave **68**, which was cyclized to the aryl *C*-glycoside **69** by exposure to trimethylsilyl triflate.



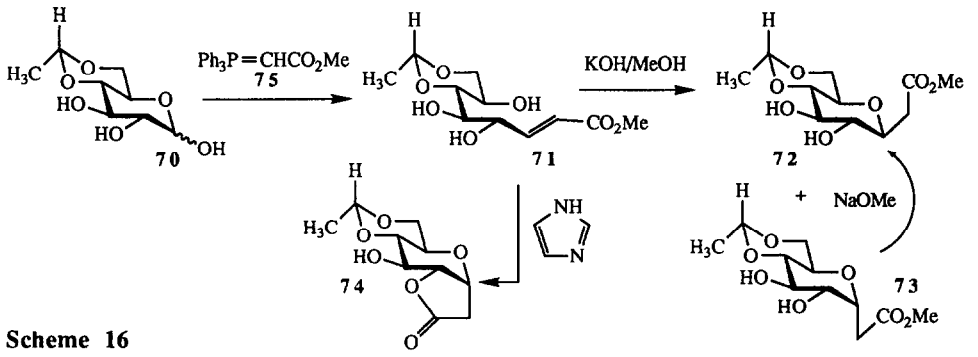
Scheme 15

III. WITTIG APPROACHES

The Wittig reaction has also been extensively applied to *C*-glycoside synthesis. Ylides can react with lactols to yield open chain sugars which either cyclize *in situ* to produce a *C*-glycoside, or can be isolated and cyclized via other means. Both Wittig like reactions on sugar lactones and reactions of anomeric phosphoranes with suitable carbonyl compounds have been used to construct exo-methylenic sugars.

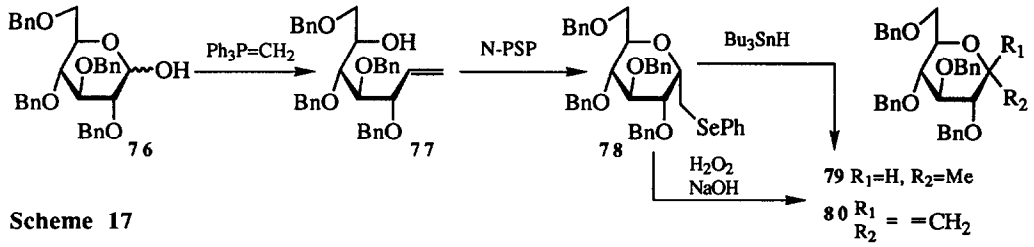
1. Reactions of Hemiacetals followed by Ring Closure

Reaction of compound **70** (Scheme 16) with Wittig reagent **75** gave compound **71** in good yield.[26] Addition of **71** to potassium hydroxide in methanol produced mainly the β-isomer **72**. The small amount of the α-epimer **73** could easily be converted to the β-isomer **72** by treatment with sodium methoxide. Reaction of **71** with imidazole in water provided compound **74**, which is a masked form of **73**.



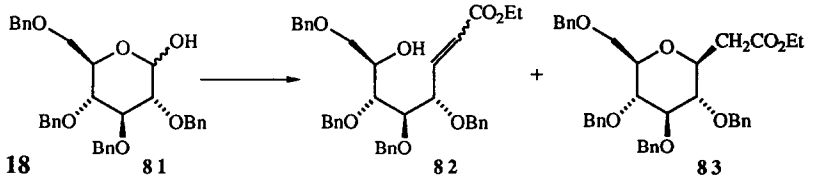
Scheme 16

Conversion of glucose derivative **76** to **77** was accomplished with the conventional Wittig reagent, $Ph_3P{=}CH_2$, and further reaction with *N*-(phenylseleno)phthalimide, in the presence of camphorsulfonic acid, then gave the α-*C*-glycoside **78**. Treatment of **78** with tributyltin hydride afforded the reduced methyl glycoside **79**. Alternatively, the seleno group may be oxidatively eliminated with hot alkaline hydrogen peroxide to give the *exo*-methylene sugar **80**.[27]



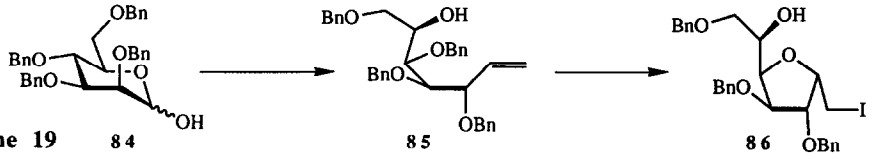
Scheme 17

Reaction of the benzylated glucose **81** (Scheme 18) with triethyl phosphonoacetate and sodium hydride in tetrahydrofuran gave a mixture of **82** and the *C*-glycoside **83**.[28] When the same reaction is carried out in dimethyl sulfoxide the product exists exclusively in the open chain form **82**.



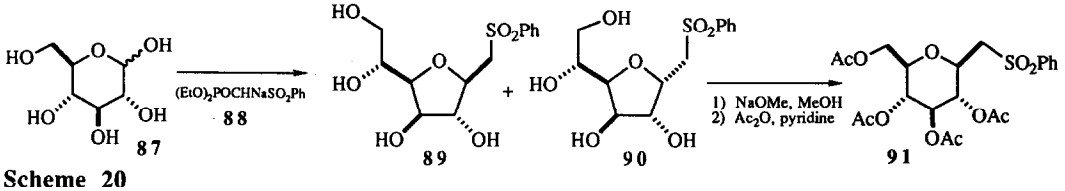
Scheme 18

Russo has recently used[29] Wittig olefination in conjunction with iodocyclization to produce *C*-glycosides. The Wittig product was easily made (Scheme 19) by reaction of **84** with methyltriphenylphosphorane iodide to give 3,4,5,7-tri-*O*-benzyl-1,2-deoxy-D-*gluco*-hept-1-enitol (**85**). This compound was then treated with buffered iodine to produce the functionalized carbon glycoside **86**. Iodocyclization complements mercuriocyclization since the former yields furanoses while the latter tends to afford pyranoses.



Scheme 19

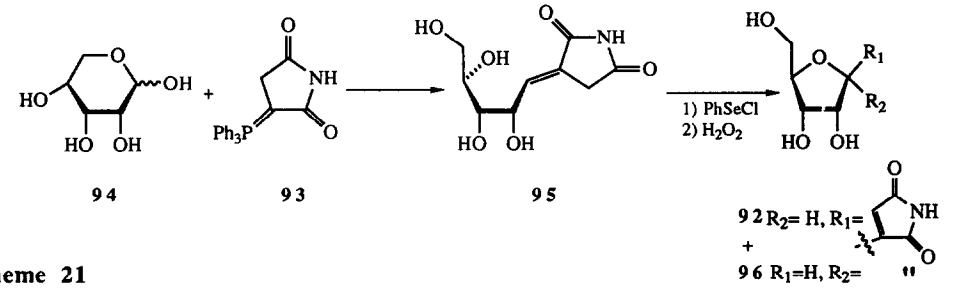
Many of the approaches toward the synthesis of *C*-glycosides from carbohydrates use protected sugar derivatives, but Davidson[30] has devised a method in which a Wittig reagent reacts with an unprotected sugar to yield a *C*-glycoside (Scheme 20). Reaction of glucose (**87**) with the phosphonate sulfone **88** gave a mixture of {**90** (α) and **89** (β)} anomers. Acetylation, followed by deacetylation and reacetylation, gave a 50% overall yield of the β-anomer **91**.



Scheme 20

Showdomycin (**92**) is a *C*-glycoside that possesses strong activity against *Streptococcus hemolyticus* and is also found to inhibit Ehrlich ascites tumors in mice. Barret *et al.* used a combination of Wittig chemistry and selenocyclization to achieve its synthesis. Reaction of the ylide **93** with D-ribose (**94**) in refluxing

tetrahydrofuran produced compound **95** in 75% yield. Selenoetherification, followed by oxidative elimination, yielded showdomycin (**92**) and epishowdomycin **96** as a 1:3 mixture.[31]

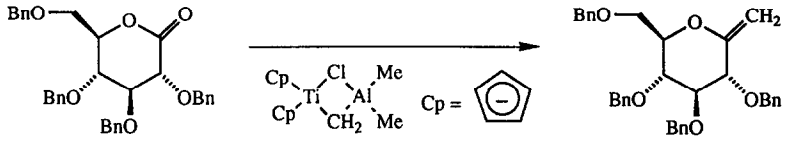


94 93 95

Scheme 21

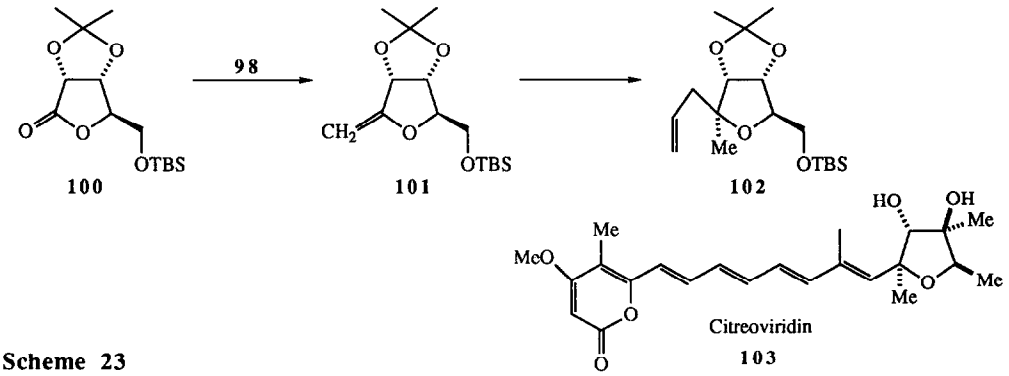
2. Reactions of Sugar Lactones

When lactone **97** is reacted with Tebbe's reagent (**98**) the *exo*-methylenic sugar **99** is produced. It is amenable to further transformations such as organocuprate addition, oxymercuration, and reduction.[32]



Scheme 22 97 98 99

A combination of the use of Tebbe's reagent and Friedel-Crafts chemistry (Scheme 23) was applied in the synthesis of a *C*-glycoside during model studies directed toward the natural product Citreoviridin (**103**). Reaction of the ribonic acid 1,4-lactone **100** with Tebbe's reagent (**98**) gave an 85% yield of the *exo*-methylene sugar derivative **101**. Treatment of this compound with acetic acid followed by Lewis acid-catalyzed allylation afforded **102**.[33]

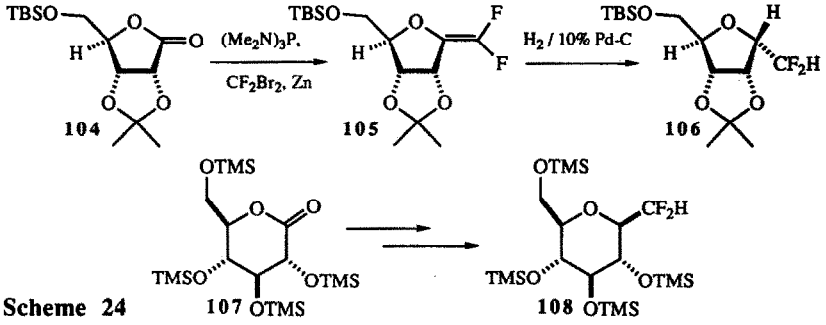


100 101 102 103

Scheme 23

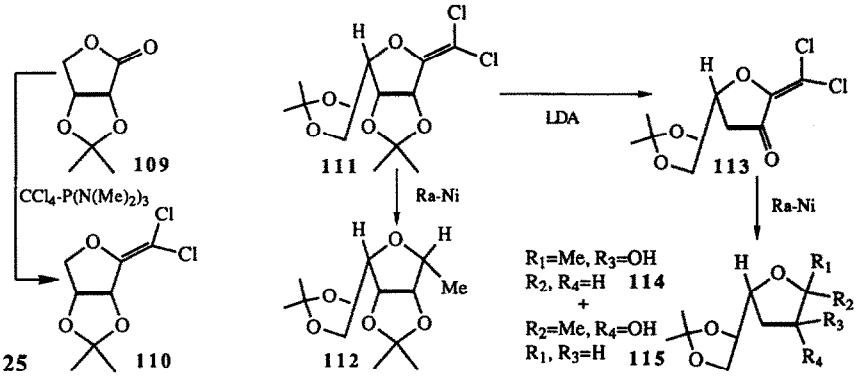
In order to determine if replacement of the anomeric oxygen on a carbohydrate with a difluoro functionality would result in a biologically active compound, Motherwell and co-workers developed technology to produce such materials.[34] Such compounds would possess the ability to hydrogen bond as *O*-glycosides do, and the two fluorine atoms could well mimic the electronic effect of the oxygen lone pairs in the corresponding *O*-glycoside. Scheme 24 shows the synthetic route. Reaction of the D-ribose derivative **104** with tris(dimethylamino)phosphine, dibromodifluoromethane, and zinc dust in refluxing tetrahydrofuran produced

the difluoro enol ether **105**. Hydrogenation then afforded the desired *C*-glycoside **106**. The reaction sequence was also carried out on the protected gluconolactone **107** to give, as a final product, compound **108**.



Scheme 24

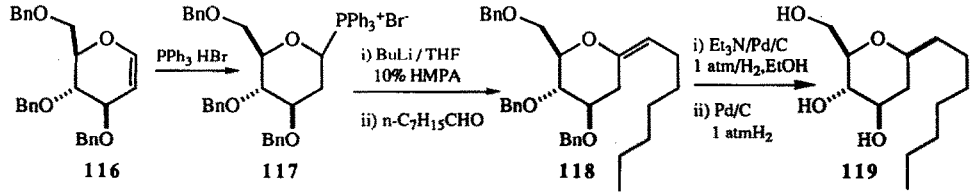
Chapleur and Bandzouzi[35] have found that reaction of sugar lactones with hexamethylphosphorous-triamide-tetrachloromethane gives, in one step, dichloroolefins. Reduction of **111** (Scheme 25) with Raney nickel gave isomer **112** as the sole product. Compound **112** arises by reduction from the less hindered top face. It was also found that treatment of the dichloroolefin **111** with LDA resulted in selective elimination to produce the 4-deoxy-3-*ulo*-*C*-glycoside **113**. Reduction of **113** with Raney nickel afforded the mixture of isomers shown.



Scheme 25

3. Reactions of Anomeric Phosphoranes

Most approaches to *C*-glycosides that are based on Wittig olefination involved condensation of a Wittig reagent with a free sugar (a lactol), but Scheme 26 shows how the Wittig reagent can be derived from the sugar itself, to give, in this case, the phosphonium bromide **117**. This material was then deprotonated and reacted with octanal to form the *C*-glycoside **118**. Reduction of the double bond followed by benzyl group removal afforded the 2-deoxy-*C*-glycoside **119**.[36]

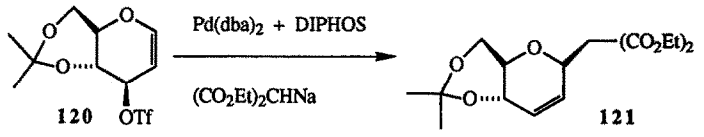


Scheme 26

IV. PALLADIUM MEDIATED REACTIONS

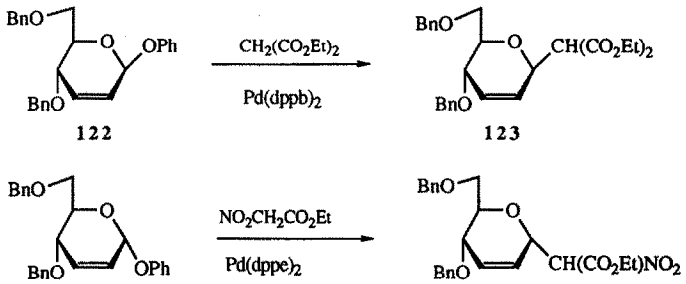
1. π-Allyl Complexes

During the preparation of this manuscript a review on palladium-mediated coupling of aryl mercurials with glycals appeared.[37] The extensive chemistry of allylic systems in the presence of Pd(O) has been applied to the preparation of *C*-glycosides. Scheme 27 shows the reaction of 1,5-anhydro-4,6-*O*-benzylidene-3-*O*-triflyl-D-*arabino*-hex-1-enitol (**120**) in a Michael fashion with the enolate of malonic ester. The process was carried out in THF in the presence of bis(dibenzylideneacetone)-Pd(O) and bis(diphenylphosphino)ethane and gave **121** in 56% yield.[38]



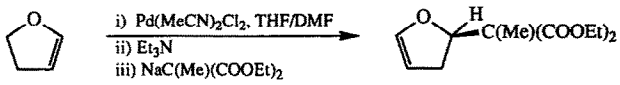
Scheme 27 **120** **121**

A further example of the use of palladium based methodology is illustrated by the next example (Scheme 28) in which a *C*-glycoside is produced in good yield and in a highly stereoselective manner.[39] Reaction of compound **122** with 5 mole % of 1,4-bis(diphenylphosphino)butane in warm acetonitrile containing malonic ester gave the *C*-glycoside **123** in 82% yield. It should be noted that the β-anomer was the exclusive product. Although still not fully understood, the mechanism of this reaction is thought to involve a *syn* addition of the palladium-nucleophile complex to the double bond from the top face. If one begins with the other anomer, compound **124**, reaction with $Pd(dba)_2$ and 1,2-bis(diphenylphosphino)ethane in warm tetrahydrofuran in the presence of ethyl 2-nitroacetate produces the α-anomer **125** exclusively. Again the yield is high (80%). This reaction is limited to the use of ethyl or methyl 2-nitroacetates as the nucleophiles.



Scheme 28 **122** **123** **124** **125**

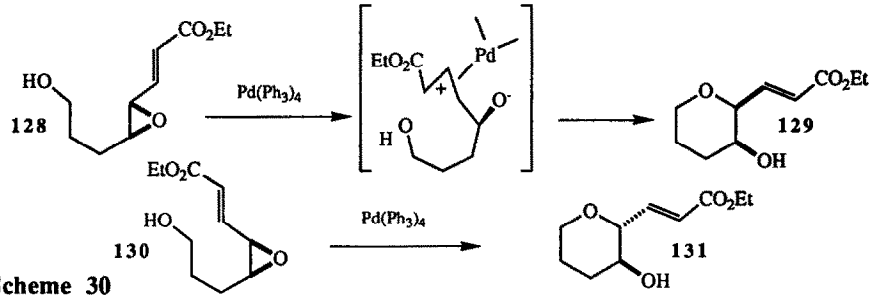
Dunkerton[40] has found a method of coupling malonate derivatives with dihydrofurans to yield cyclic ethers in fair yield. Reaction of dihydrofuran (**126**) with $Pd(MeCN)_2Cl_2$ in 1:1 THF/DMF at room temperature, followed by addition of triethylamine at a low temperature, and finally, addition of sodium diethyl-2-methyl malonate yielded (50%) the so called *C*-glycoside **127** (Scheme 29).



Scheme 29 **126** **127**

Although not *C*-glycosides, compounds **129** and **131** (Scheme 30) possess some resemblance to the skeleton of a *C*-glycoside; they have a pyranoid ring with an adjacent carbon chain and a hydroxyl function.

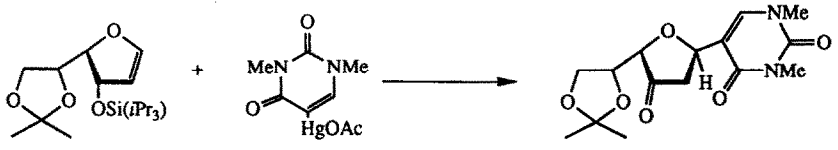
Hirama and co-workers[41] have synthesized these compounds using palladium-mediated cyclization. Exposure of the vinyl epoxide **128** to fluoride ion and then to a catalytic amount of $Pd(Ph_3)_4$ afforded compound **129** in almost quantitative yield with the *cis*-isomer favored 99:1 over the *trans*. Alternatively, exposure of **130** to the same conditions provided the *trans*-isomer **131** as the major (ca. 99:1) product.



Scheme 30

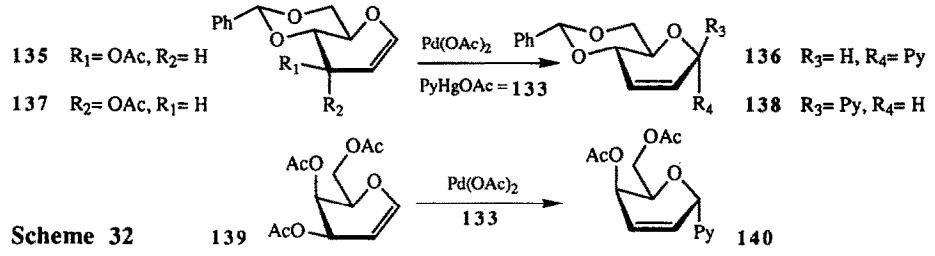
2. Heck Type Couplings

The coupling of the organomercuric salt **133** with the glycal **132** (Scheme 31) in the presence of palladium (II) acetate is a highly regiospecific reaction with bond formation occurring at the electron deficient carbon atom.[42] This is in contrast to the results of the Heck reaction of simple olefins where mixtures of regioisomers are often formed. Daves has used the Heck coupling to join the pyrimidine **133** to the furanoid glycal **132** in a highly stereo- and regiospecific manner. Again the addition of the palladium complex occurs in a *syn*-fashion from the least hindered (top) face to give **134**.



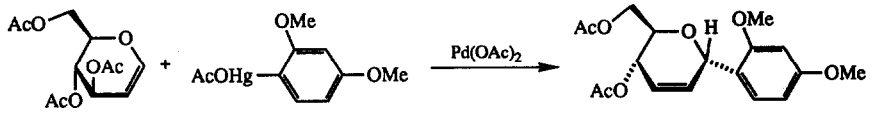
Scheme 31 **132** **133** **134**

Reaction of the protected glycal **135** (Scheme 32) under the same conditions provided the *C*-glycoside **136** (25%). Presumably, in this example, *syn*-addition occurred from the bottom face. Reaction of the glycal **139** gave a slightly higher yield of *C*-glycoside **140** (40%). When glycal **137** was used, the addition occurred from the top face, leading to **138**.[43]



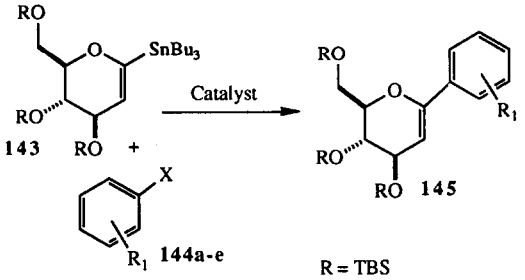
Scheme 32 **139** **140**

Scheme 33 shows another example of palladium coupling. Reaction of **4** with the mercuric halide salt **141** in the presence of palladium acetate furnished compound **142**.[44]



Scheme 33 **4** **141** **142**

Friesen and Sturino[45] used a combination of palladium and tin chemistry to quickly assemble aryl *C*-glycosides. Scheme 34 shows the general reaction of a 1-stannylglycal **143** (see Scheme 103 for preparation) with an aryl bromide under palladium catalysis. Table I shows some of the results. The yields are generally good, except for para chloro- and ortho methyl- aryl halides. Entry e shows that acceptable yields can be obtained even though an ortho substituent is present. This is a significant reaction since many naturally occurring aryl *C*-glycosides contain multiple oxygen functionality on the aromatic ring. The use of $Pd(Ph_3)_2Cl_2$ seemed to give slightly better yields than $Pd(Ph_3)_4$ itself in these couplings.

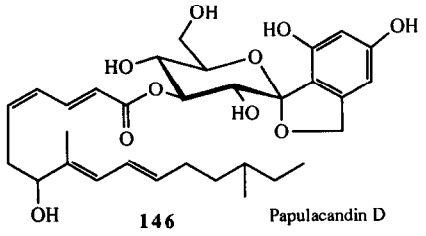


Scheme 34

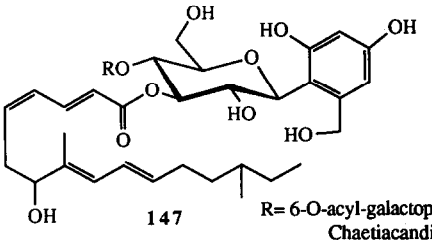
Table I: Palladium Coupling of Glycals.

ArX	Catalyst	Solvent	Yield
a PhBr	$Pd(Ph_3)_4$	THF	70
b 4-CNC_6H_4Br	$Pd(Ph_3)_2Cl_2$	PhMe	81
c 4-ClC_6H_4Br	"	"	49
d 2-MeC_6H_4Br	"	"	49
e 2,5-$(MeO)_2C_6H_3Br$	"	"	65

Papulacandin D (**146**) and chaetiacandin (**147**) are closely related antibiotics isolated from *Paularia sphaerosperma* and *Monochaetia dimorphospora*, respectively.[46] They have been found to possess strong antibiotic activity against yeast, and papulacandin B has the property of inhibiting β-glucan synthesis in various organisms.[47] Therefore, these compounds are important synthetic targets. Chaetiacandin is an aryl *C*-glycoside, while the papulacandins are spiro ketals possessing an anomeric aryl-carbon bond. Beau and Dubois[48] have very recently utilized palladium coupling to synthesize the basic skeletons of these compounds. Coupling of the 1-tri-*n*-butylstannyl glycal **148** with the bromo alcohol **149** produced the aryl *C*-glycoside **150** (Scheme 35). Refluxing a solution of **148** and **149** in toluene containing $Pd(PPh_3)_4$ and sodium carbonate gave a good yield of **151**. The synthesis of the chaetiacandin skeleton was accomplished via hydroboration of **151** to give **152**.

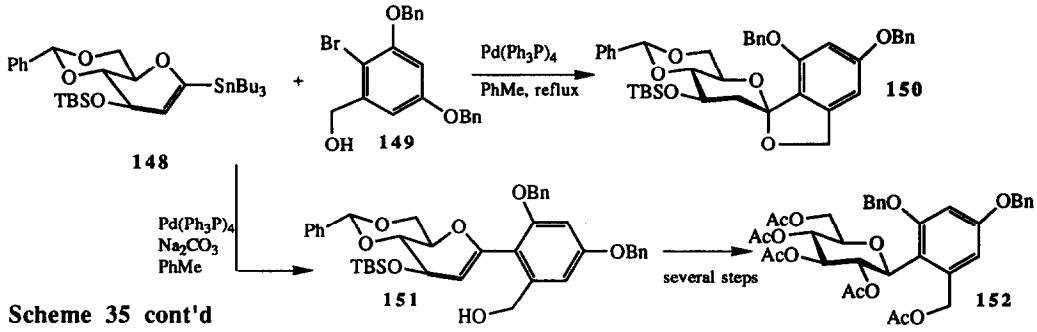


146 Papulacandin D



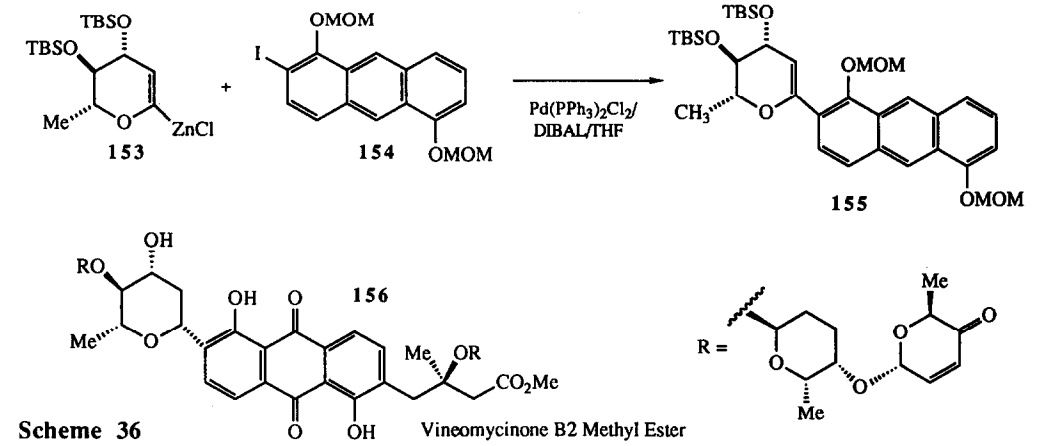
147 R= 6-O-acyl-galactopyranosyl Chaetiacandin

Scheme 35



Scheme 35 cont'd

The key step in the synthesis of vineomycinone B2 methyl ester by Tius *et al.*[49] was a palladium mediated coupling of the *C*-1 zinc glycal **153** with the aromatic iodide **154**. Several reaction conditions were tried including both nickel and palladium based catalysts. The optimum conditions were found using $Pd(PPh_3)_2Cl_2$ with DIBAL in THF to give a 78.5% yield of the *C*-aryl Glycoside **155** which was then transformed via several steps into the methyl ester of vineomycinone B2 **156**.



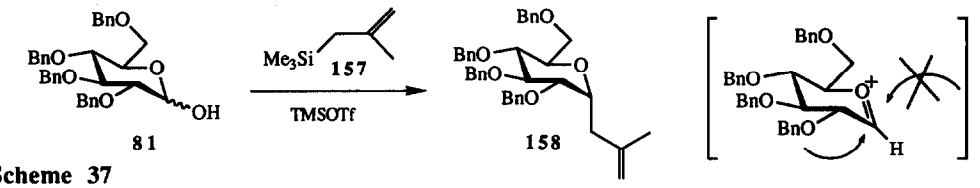
Scheme 36 Vineomycinone B2 Methyl Ester

V. SUGAR ELECTROPHILES

The most popular method for *carbon-carbon* bond formation at the anomeric site relies on the natural electrophilicity of this center. Cationic reactivity at the anomeric position is involved largely in glycosylation reactions. Several types of sugar derivatives have been utilized in *C*-glycoside synthesis such as lactols, esters, glycosides, glycosyl halides, lactones, imidates, glycals, enitols and 1,5-anhydro sugars. A Lewis acid is usually used to form an oxonium ion species which which is then captured by an external carbon nucleophile. With pyranose sugars attack is often from the α-face leading to the α-*C*-glycoside. This is due to the anomeric effect of the ring oxygen which directs the incoming nucleophile to the α-face. In furanoses the steric bias of the two faces usually dictates the product ratio. A wide variety of carbon nucleophiles have been used this includes allylsilanes, allylstannanes, silyl enol ethers, 1,3-dicarbonyl compounds, aromatics, and organometallics.

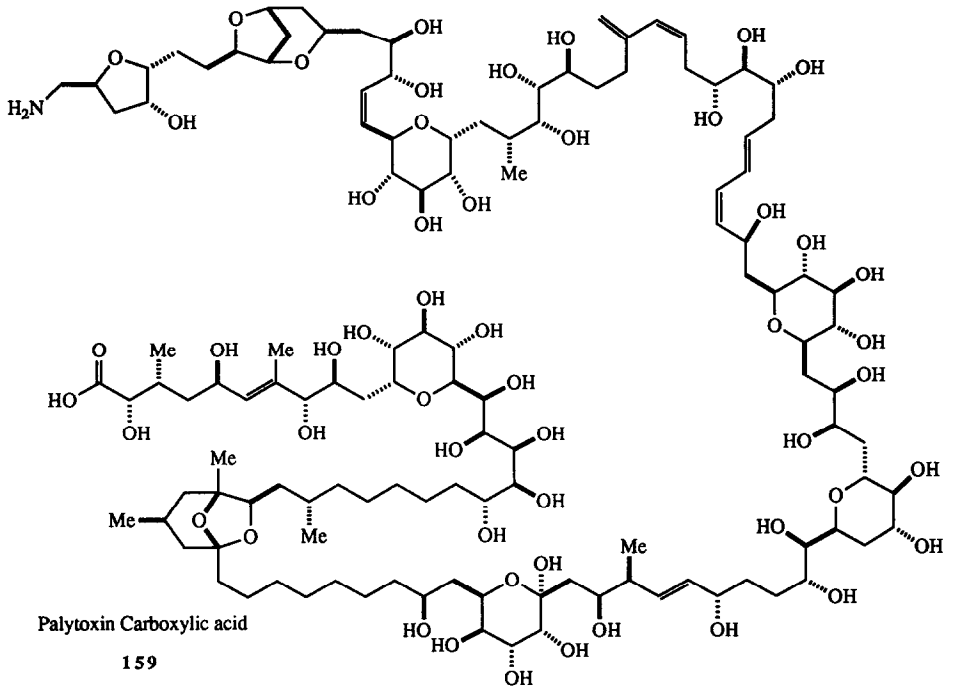
1. Lactols

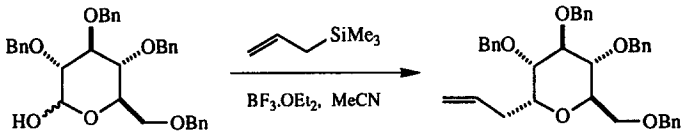
Alkylations are not limited to aromatic nucleophiles and Scheme 37 shows the Lewis-acid mediated reaction of compound **81** with 2-methyltrimethylallylsilane (**157**).[50] The main product is the α-isomer **158**, formed in 82% yield. This facial preference is due to axial attack, under the influence of the anomeric effect, on the pyroxonium triflate.



Scheme 37

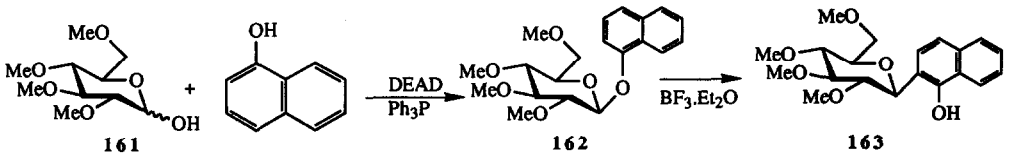
During the synthesis of palytoxin (**159**), Kishi developed methodology for access to α-anomers of allyl *C*-glycosides.[51] Reaction of **81** with allyltrimethylsilane in the presence of boron trifluoride etherate in acetonitrile gave (Scheme 38) a 10:1 ratio of anomers, in favor of the α-anomer **160**.





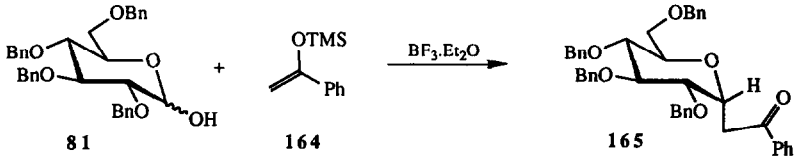
Scheme 38

Mitsonobu coupling reactions are quite popular in synthetic carbohydrate chemistry for selective protection.[52] Treatment of 2,3,4,6-tetra-*O*-methyl*gluco*pyranose (**161**) (Scheme 39) with 1-naphthol in the presence of diethyl azidodicarboxylate and triphenylphosphine provided **162** in 66% yield. Further reaction of **162** with boron trifluoride etherate yielded the rearranged product **163**.[53]



Scheme 39

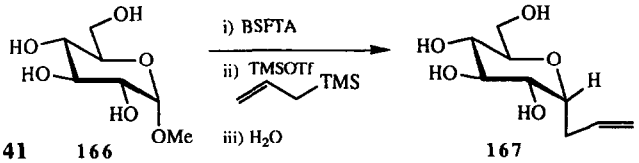
Scheme 40 shows that the anomeric hydroxyl group need not be derivatized for a carbon glycosylation to occur. Reaction of **81** with the silyl enol ether **164** in the presence of a Lewis acid catalyst led to the α-product **165**.[54]



Scheme 40

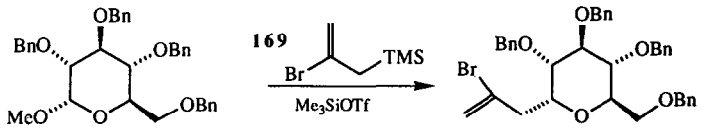
2. Glycosides

Of the examples of allylation reactions presented above, all have used protected sugars as starting materials. Bennek and Gray developed a method that allows for the generation of the α-allyl glycoside without use of a protected sugar. Treatment of methyl glucoside (**166**) with bis(trimethylsilyl)trifluoroacetic anhydride, [BSTFA] (1.5 equivalents per hydroxyl group), followed by exposure to allyltrimethylsilane in the presence of trimethylsilyl triflate, and finally exposure to water provided the free *C*-glycoside **167**. The BSTFA served to silylate the hydroxyl groups *in situ*, and once the allylation was complete the silyl groups were removed.[55] This method avoids the need for debenzylation (if the starting material is a perbenzylated sugar) by hydrogenation, a process which may sometimes cause partial loss of the double bond in the allyl group.



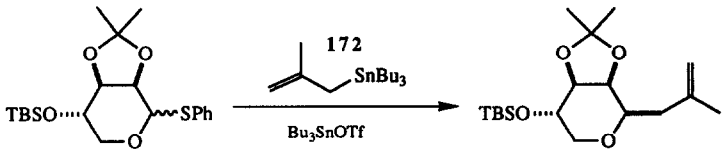
Scheme 41

Allylation of the glucose derivative **168** with the bromo silyl compound **169** gave the α-anomer **170** exclusively.[56]



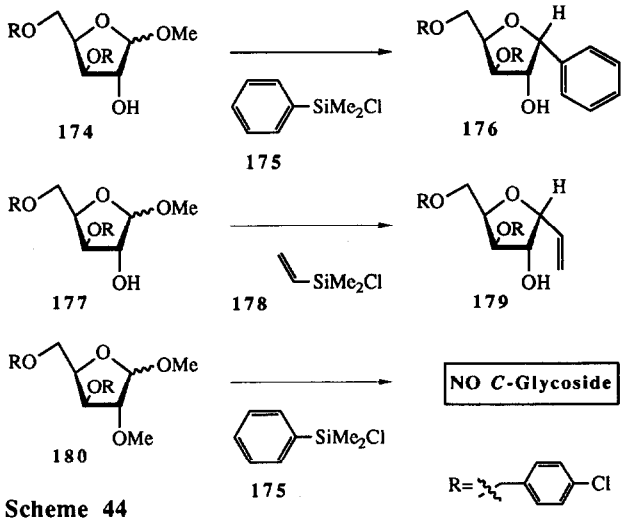
Scheme 42

Keck and co-workers[57] have found that reaction of **171** with methylallyltri-*n*-butylstannane (**172**) in the presence of tri-*n*-butylstannyl triflate at high temperature gave a 95% yield of the β-anomer **173**. The preference for this isomer was very high (99:1) and this result stands in contrast to standard allylation reactions in which the α-anomer is formed preferentially.



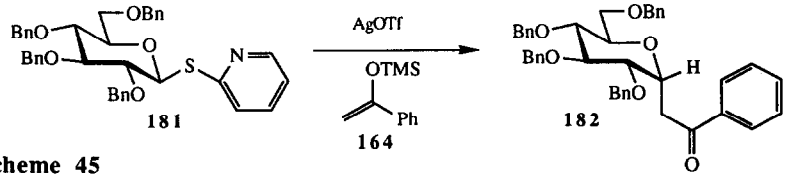
Scheme 43 171 173

Martin and co-workers[58] have synthesized *C*-glycosides stereospecifically through the use of internal nucleophile delivery. Scheme 44 shows that when the *C*-2 hydroxyl is free, as in **174**, the product formed is the *C*-glycoside **176** with the aryl unit and the hydroxyl *syn*. However, when the hydroxyl is protected, as in **180**, no *C*-glycoside is formed. Conversion of **177** to **179** provides another example that supports the effect of a free hydroxyl.



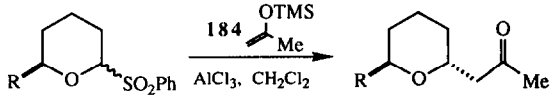
Scheme 44

Williams and Stewart[59] have used pyridyl glycosides (Scheme 45) as starting materials for the synthesis of *C*-glycosides. Reaction of the glycoside **181** with the silyl enol ether **164** in the presence of silver triflate produced the *C*-glycoside **182**.



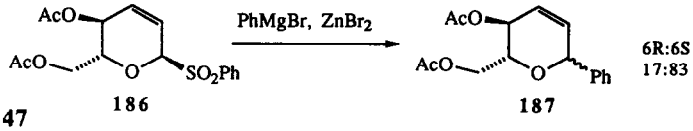
Scheme 45

Using methodology developed in his own laboratories, Ley[60] has found that reaction of sulfone **183** with silyl enol ether **184** under aluminum trichloride catalysis produced the *trans*-cyclic ether **185**.



Scheme 46

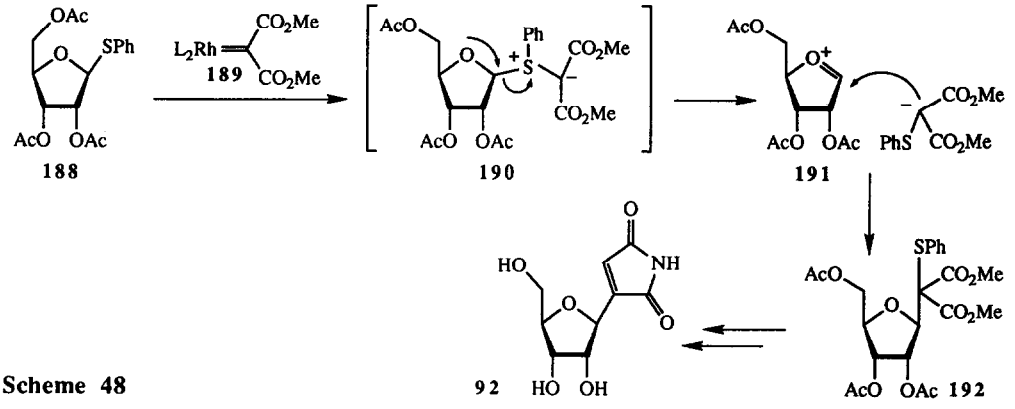
Ley has developed[61] a method of making *C*-glycosides that involves treating anomeric sulfones with a Lewis acid and an appropriate nucleophile. Reaction of sulfone **186** (Scheme 47) with phenylmagnesium bromide and zinc bromide gave a mixture of anomers (6*R*:6*S* :: 17:83) **187** in 71% yield (based on recovered starting material).



186 187

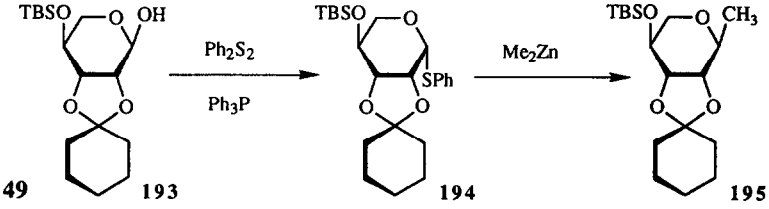
Scheme 47

The use of transition metals in the formation of *C*-glycosides has proven to be a good method of *carbon-carbon* bond formation at the anomeric site. For example, the thioglycoside **188** was reacted (Scheme 48) with the carbene precursor **189** to yield, presumably, intermediate **190**, which then underwent rearrangement as shown to **192**. Compound **192** was elaborated further to afford the natural product showdomycin (**92**).[62]



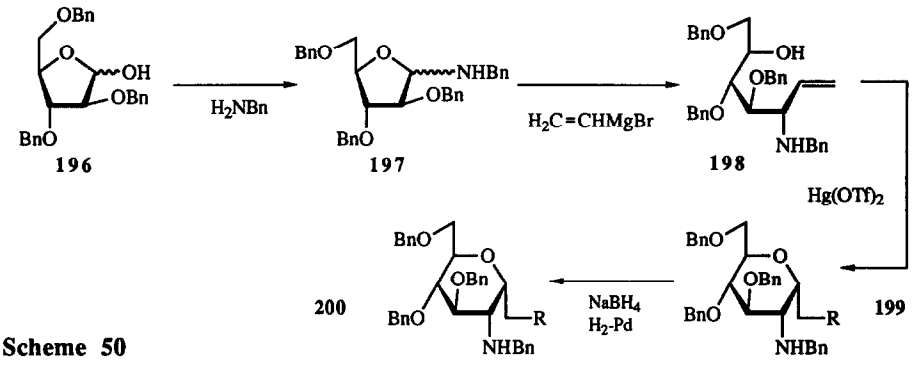
Scheme 48

Another application of organometallic chemistry is given in Scheme 49. The protected L-lyxose derivative **193** was reacted with diphenyl disulfide and tributylphosphine to furnish the thio-glycoside **194** in good yield. Reaction with dimethylzinc in chloroform then generated the methyl glycoside **195**.[63]



Scheme 49 193 194 195

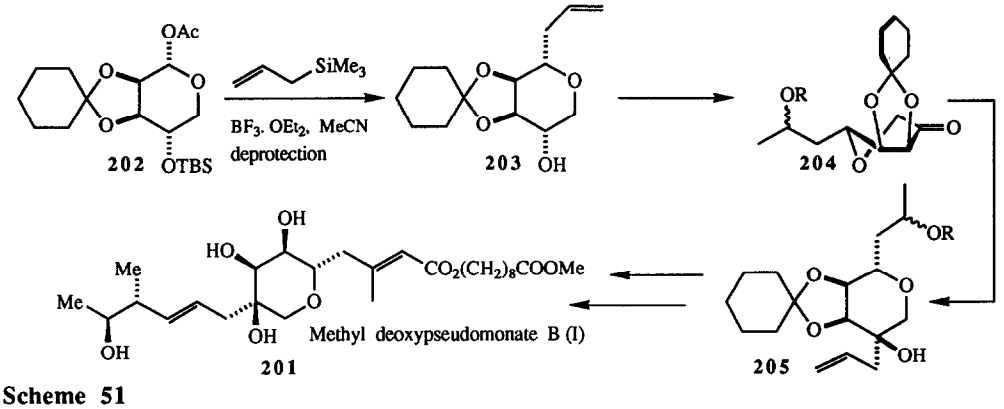
Furanose derivatives are also convenient starting materials for making *C*-glycosides. For example, reaction of 2,3,5-tri-*O*-benzyl-D-*arabinose* (**196**) with benzylamine gives **197** in quantitative yield. Further reaction of **197** with vinylmagnesium bromide then gave the intermediate **198**, which, when exposed to mercuric triflate, yielded **199**. This was easily reduced to the *C*-glycoside **200**.[64]



Scheme 50

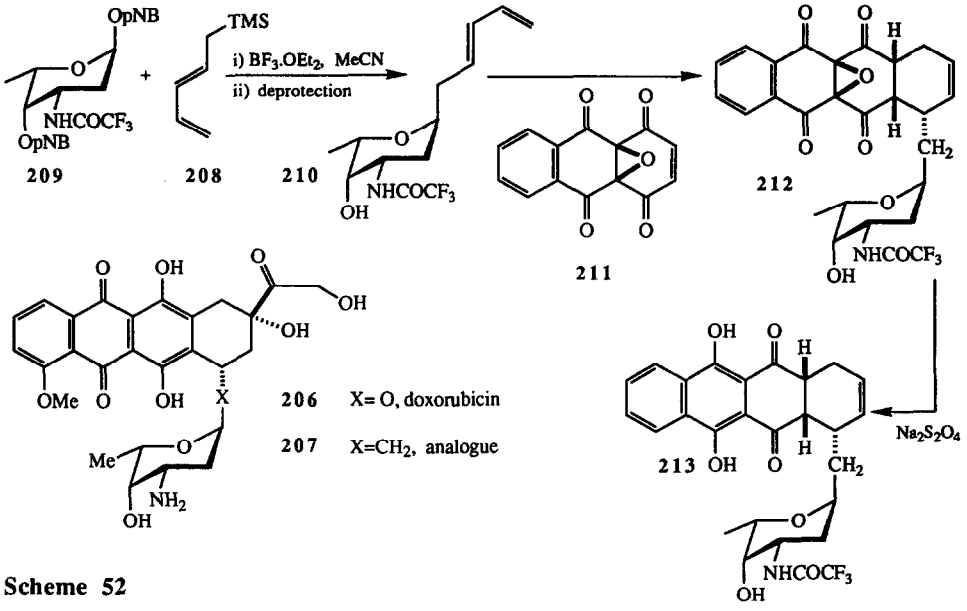
3. Anomeric Esters

Similar methodology was used by Kozikowski[65] during the synthesis of methyl deoxypseudomonate B (**201**). Reaction of acetate **202** with allyltrimethylsilane in acetonitrile in the presence of boron trifluoride etherate gave the expected product **203**. Its stereochemistry is a result of the anomeric effect as well as the steric influence of the ketal group which blocks the top face. Oxymercuration followed by selective protection and oxidation gave the ketone **204**, and this ketone was then treated with allylmagnesium bromide. The tertiary alcohol **205**, resulting from attack from the less hindered face, was elaborated into methyl deoxypseudomonate B (**201**).



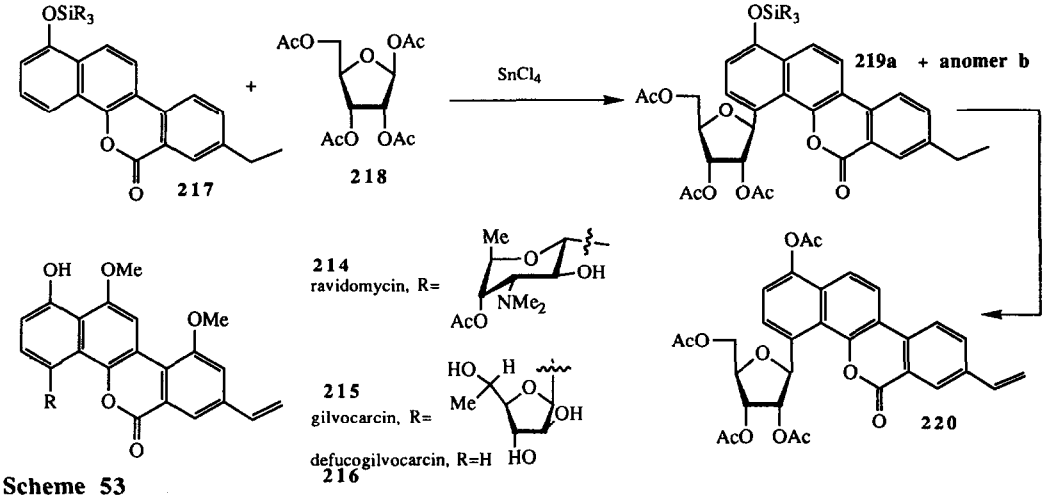
Scheme 51

In an effort to synthesize an analogue of the anticancer agent, doxorubicin (**206**), Acton and co-workers[66] chose to replace the anomeric oxygen by a methylene unit. Their work is summarized in Scheme 52. Reaction of the diene **208** with the dideoxy amino sugar **209** gave the *C*-glycoside **210**. Diels-Alder reaction of **210** with **211** then yielded adduct **212**. Finally, reduction with sodium dithionite produced the doxorubicin analogue **213**.



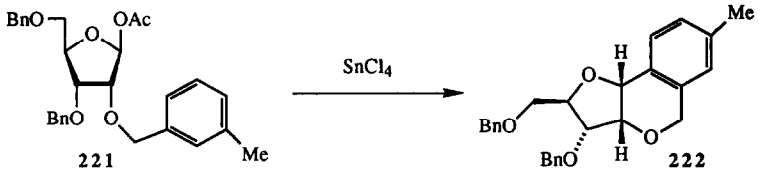
Scheme 52

Ravidomycin (**214**) and gilvocarcin V (**215**) are two aryl *C*-glycosides that possess potent antitumor activity.[67] Daves recently applied Friedel-Crafts coupling in the synthesis of an analogue of gilvocarcin. Reaction of the naphthobenzopyranone **217** with the peracetylated furanose **218** in the presence of stannic chloride provided an 80% yield of a 1:1 mixture of anomers **219a** and **219b** (Scheme 53). Desilylation, acetylation, and benzylic bromination of **219a** was then followed by dehydrogenation using tetrakis(triphenylphosphine)palladium to afford compound **220**.[68]



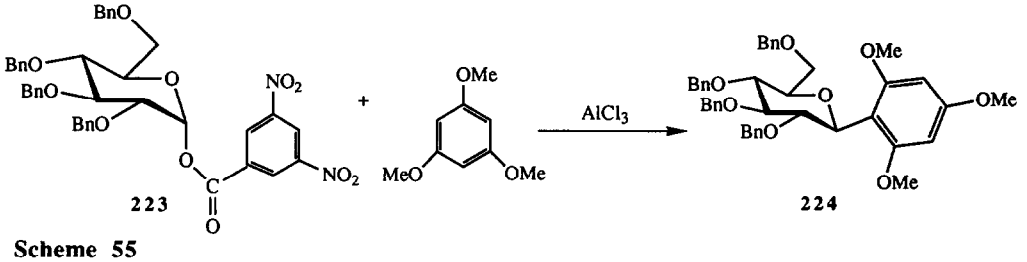
Scheme 53

Work by Martin[69] provides an intramolecular example of Friedel-Crafts chemistry. Scheme 54 shows the cyclization of compound **221** in the presence of stannic chloride catalysis to provide **222**.



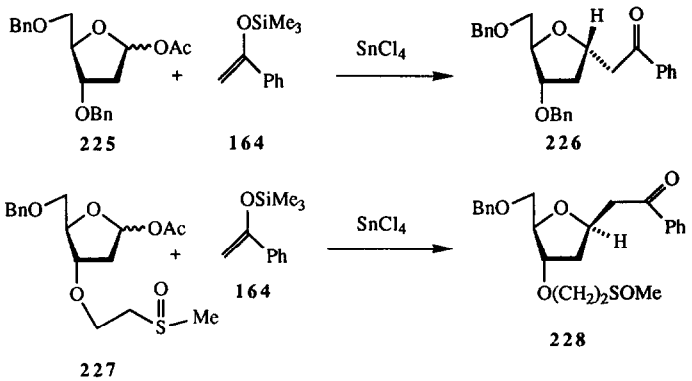
Scheme 54

Scheme 55 shows the reaction of the activated glucopyranose **223** with 1,3,5-trimethoxybenzene in the presence of aluminum trichloride. The β-anomer **224** is formed in 80% yield. This type of methodology provides access to oxygenated aryl *C*-glycosides.[70]



Scheme 55

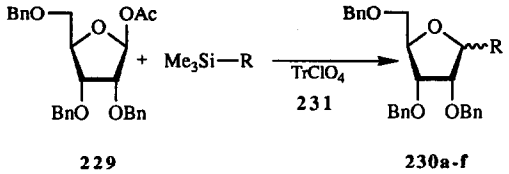
The two examples of Scheme 56 show how neighboring group participation can affect the stereochemical outcome of such reactions. Transformation of **225** into **226** under stannic chloride catalysis gave a mixture of epimers in 92% yield.[71] The α:β ratio was 82:18. When the 3-*O* protecting group was changed to ethyl methyl sulfoxide, as in **227**, the α:β ratio shifted drastically to 32:68. This is due to participation of the sulfoxide oxygen in oxonium ion stabilization. Such participation preferentially shields the α-side of the molecule and so the β-product **228** is obtained.



Scheme 56

Many examples are known in which silicon chemistry has been used in the synthesis of *C*-glycosides. Scheme 57 illustrates the use of triphenylmethyl perchlorate (**231**) as a Lewis acid catalyst. The reaction gives good yields and acceptable stereoselectivities of *C*-glycosides. Reaction of **229** with the trimethylsilyl enol ether of various ketones in the presence of the catalyst **231** gave an almost quantitative yield of *C*-glycosides with the

α-anomer predominating (99:1). Table II shows the variety of nucleophiles studied. The authors also succeeded in converting polystyrene-bound triphenylmethanol into its perchlorate salt, thereby creating a polymer bound catalyst. Flow reactions with compound **229**, entry a (silyl enol ether of pinacolone), and the immobilized catalyst gave an 86% yield of *C*-glycoside **230a** with an α:β ratio of 24:1. The method proved to be very convenient since the catalyst can be recycled. This methodology is also well-suited to large-scale operations.[72]

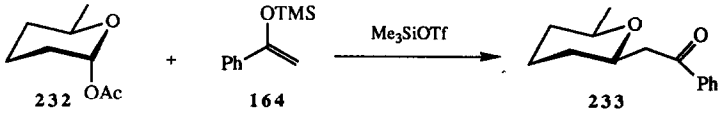


Scheme 57

Table II: Perchorate Mediated Couplings.

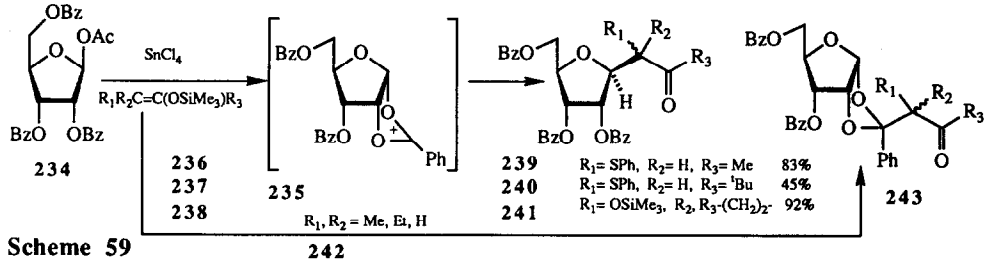
R Group	Solvent	Yield	Ratio α:β
a t-BuC(O)=CH_2	$(MeO)_2C_2H_4$	93	99:1
b PhC(O)=CH_2	$(MeO)_2C_2H_4$	97	100:1
c C_6H_9-O-	"	93	96:4
d CH_2=CH-CH_2-	"	90	100:1
e CN	"	97	63:37
f CN	Et_2O	93	93:7

Condensation of enol silyl ether **164** with the 2-acetoxytetrahydropyran **232** (Scheme 58) in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate gave the *cis* condensation product **233** exclusively. This method allows stereoselective access to carbonyl-containing tetrahydropyranyl compounds.[73]



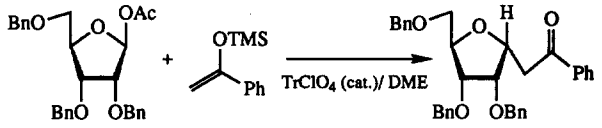
Scheme 58

Exposure of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl acetate (**234**) to stannic chloride in dichloromethane (Scheme 59) presumably gave the intermediate **235**, which, when treated with the enol ethers **236-238** gave compounds **239-241**, respectively. The presence of an α-hetero substituent in the enol ether decides the site of attack on the intermediate **235**. If no α-heteroatom is present the enol ether preferentially attacks the *C*-2 benzoyl carbon to produce ketals **243**. Apparently, when no α-heteroatom is present silyl-stannyl exchange occurs to produce the α-trichlorostannyl carbonyl compound, which prefers to react selectively on the benzoyl group.[74] Introduction of the α-heteroatom seems to prevent this exchange causing reaction to occur at the anomeric carbon atom.[75]



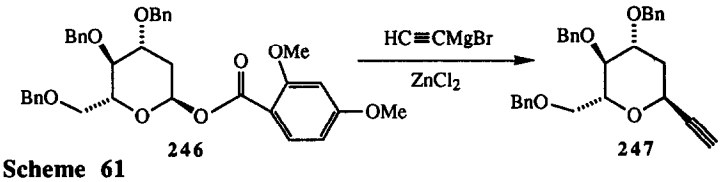
Scheme 59

The furanosyl acetate **244** was reacted with the enol ether **164** in the presence of a catalytic amount of trityl perchlorate in dimethoxyethane to give the α-anomer **245**.[76]



Scheme 60 244 164 245

Addition of magnesium acetylide to the *O*-glycoside **246** in the presence of zinc chloride gave compound **247**, a result of addition with retention of configuration. This stereochemical outcome is due to the anomeric effect which directs attack of the organometallic on the intermediate oxonium species. In the absence of zinc chloride no reaction was observed.[77]

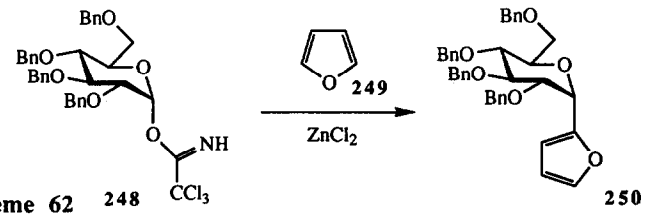


246 247

Scheme 61

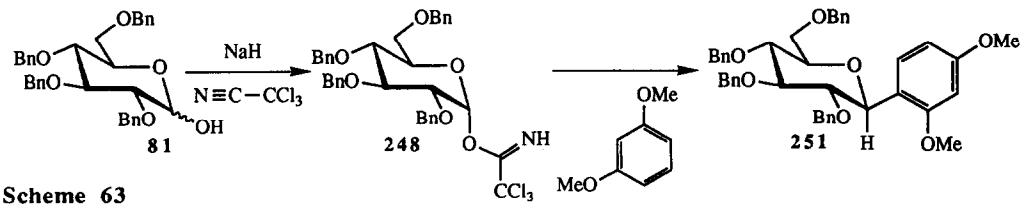
4. Anomeric Imidates

Glycosyl imidates have also been utilized in the synthesis of *C*-glycosides.[78] Scheme 62 shows the reaction between a glucose imidate **248** and furan (**249**), a reactive electron-rich aromatic, under Lewis acid catalysis. In the presence of zinc chloride the α-anomer **250** is formed in good yield. This process involves formation of a cationic intermediate which undergoes addition to the furan π electron system.



Scheme 62 248 250

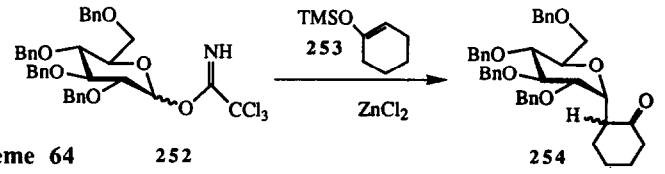
Reaction of the glucose imidate **248** (produced by reaction of **81** with trichlororacetonitrile and sodium hydride) with 1,3-dimethoxybenzene in the presence of boron trifluoride etherate gave the β-isomer **251** exclusively.[79]



81 248 251

Scheme 63

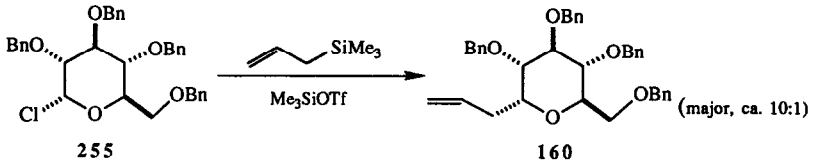
The reaction of silyl enol ethers with glycosyl imidates has also found use in the synthesis of *C*-glycosides (Scheme 64).[80] The anomeric imidates **252** were reacted with compound **253**, again in the presence of a Lewis acid, to furnish **254** in 80% overall yield. The α:β ratio was found to be 7:1.



Scheme 64 **252** **254**

5. Glycosyl Halides

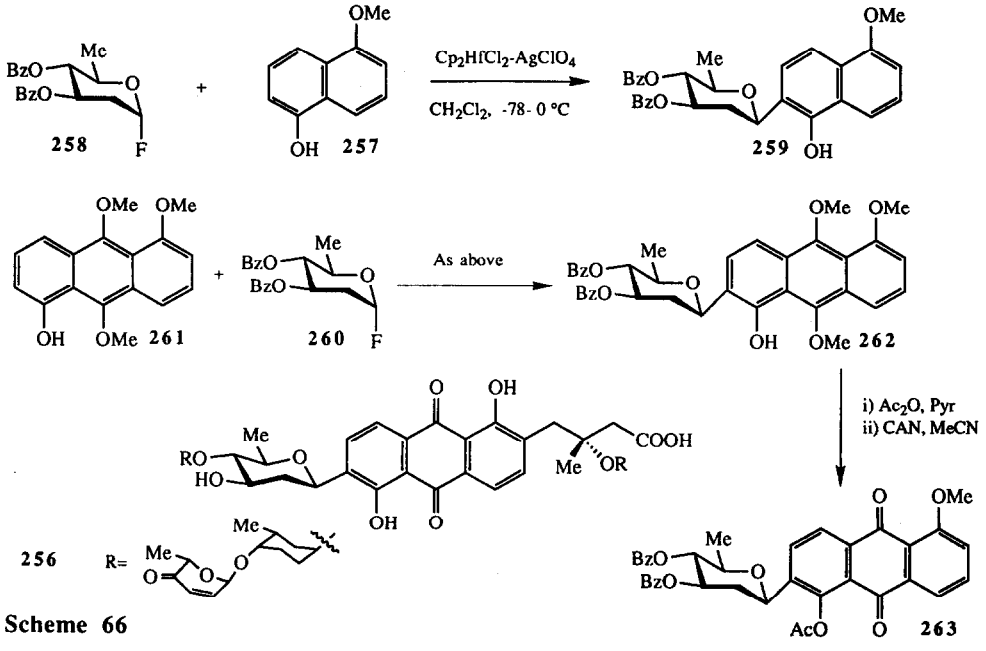
The use of pyranosyl chlorides in Lewis-acid catalyzed allylations also provides good yields of α-anomers. Reaction of compound **255** (Scheme 65) with trimethylallylsilane in the presence of trimethylsilyl triflate provides a 75% yield of anomers, with the α-anomer **160** favored by a factor of 10:1.[81]



255 **160**

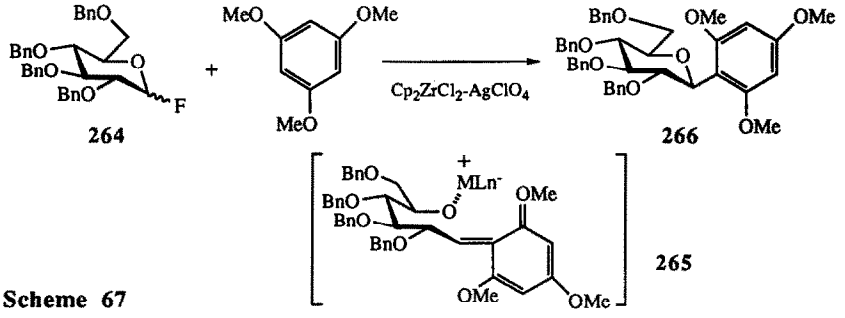
Scheme 65

Vienomycin (**256**) is an aryl *C*-glycoside that possesses antitumor activity. It was isolated from *Streptomyces matensis veneus* and its structure is shown below (Scheme 66).[82] Model studies[83] on the Cp_2HfCl_2-$AgClO_4$ mediated coupling of 5-methoxy-1-naphthol (**257**) with the 2-deoxyglycosyl fluoride **258** gave a 78% yield of the β-anomer **259** exclusively. No *O*-glycoside formation was observed; however the use of boron trifluoride etherate gave only the *O*-glycoside in 39% yield. Based on this success, coupling of the glycosyl fluoride **260** with anthrufin (**261**) in the presence of 3 equivalents of Cp_2HfCl_2-$AgClO_4$ furnished an 86% yield of the β-glycoside **262**. Acetylation followed by treatment with ceric ammonium nitrate then yielded the aryl *C*-glycoside **263**.



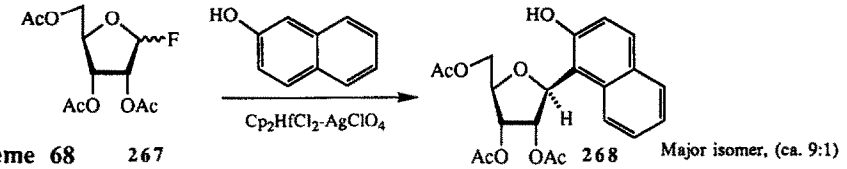
Scheme 66

2,3,4,6-Tetra-*O*-benzyl*glucosyl* fluoride (**264**) was allowed to react with 1,3,5-trimethoxybenzene in the presence of Cp_2ZrCl_2-$AgClO_4$ to afford **266** in 96% yield.[84] It has been proposed that this type of reaction involves the intermediary structure **265**, for which ring closure is not influenced by the anomeric effect, therefore, giving rise to the thermodynamically favored product, the equatorial *C*-glycoside.



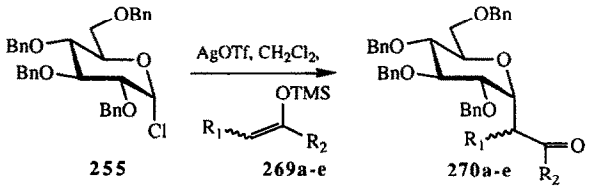
Scheme 67

The furanosyl fluorides **267** were coupled with 2-naphthol in the presence of a catalytic amount of Cp_2HfCl_2-$AgClO_4$. The aryl *C*-glycoside **268** was the major epimer. The α:β ratio for this reaction was found to be 1:9.[85]



Scheme 68 **267**

Enol ethers will also condense with glycosyl halides to afford *C*-glycosides. Allevi[86] has made use of glycosyl chlorides in reactions with enol silyl ethers to produce *C*-glycosides that carry a carbonyl-containing side chain. Reaction (Scheme 69) of the glycosyl halide **255** with enol ethers **269a-e** under silver triflate catalysis gave **270a-e**. Table III shows that the reactions proceeded in good yield and in each case the α-anomer was the major product formed. This is presumably due to the fact that the intermediate pyranoxonium triflate accepts nucleophiles preferentially from the axial side under the influence of the anomeric effect.

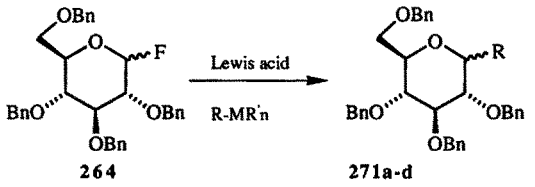


Scheme 69

Table III: Silyl Enol Ethers.

Enol Ethers	Yields
a $EtOCOCH{=}C(OSiMe_3)OEt$	75
b $CH_2{=}C(OSiMe_3)Ph$	88
c $CH_2{=}C(OSiMe_3)C_6H_4Cl$-p	80
d $CH_2{=}C(OSiMe_3)Bu^t$	83
e $CH_2{=}C(OSiMe_3)Me$	85

Although glycosyl bromides and chlorides have found considerable use in the synthesis of carbon glycosides, the corresponding fluorides have received considerably less attention. Nicolaou has found the glycosyl fluorides **264** to be quite useful for the synthesis of carbon glycosides. Scheme 70 shows the general reaction of the perbenzylated glucosyl fluorides **264** with various silanes in the presence of a Lewis acid catalyst. The *C*-glycosides are formed in good yield.[87] Table IV shows the variety of reaction conditions that allow for *C*-glycoside formation.

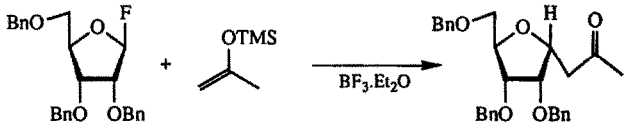


Scheme 70

Table IV: Glycosyl Fluorides and Silane Couplings.

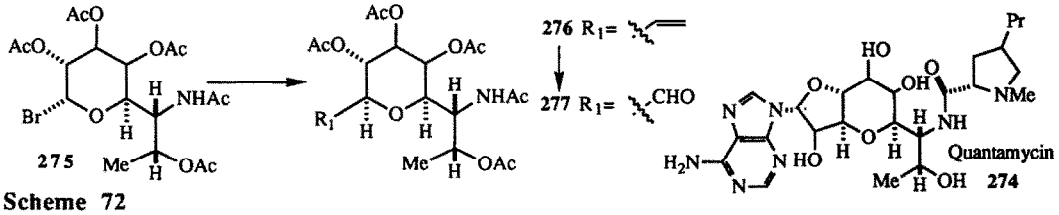
R. Conditions	Yield	Ratio α:β
a Me_3SiR, $BF_3.Et_2O$, R=allyl	95,	(>20:1)
b AlR_3, R=Me	95,	(>20:1)
c Me_3SiR, R=CN	90,	(ca. 3:1)
d Me_3SiR, R=CH_2CN	85,	(ca. 3:1)

The glycosyl fluoride **272** (Scheme 71) was reacted with silyl enol ether **184** under Lewis acid catalysis to afford the α-anomer **273** as the sole product of the reaction.[88]



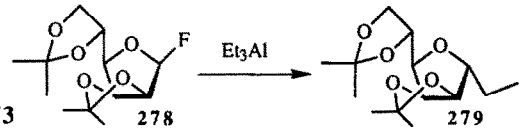
Scheme 71 **272** **184** **273**

During the synthesis of quantamycin (**274**), a computer designed antibiotic, an intermediate *C*-glycoside was required. Treatment of **275** with vinylmagnesium bromide gave compound **276**. The double bond was oxidatively cleaved to give **277** and this material was then elaborated into quantamycin (**274**).[89]



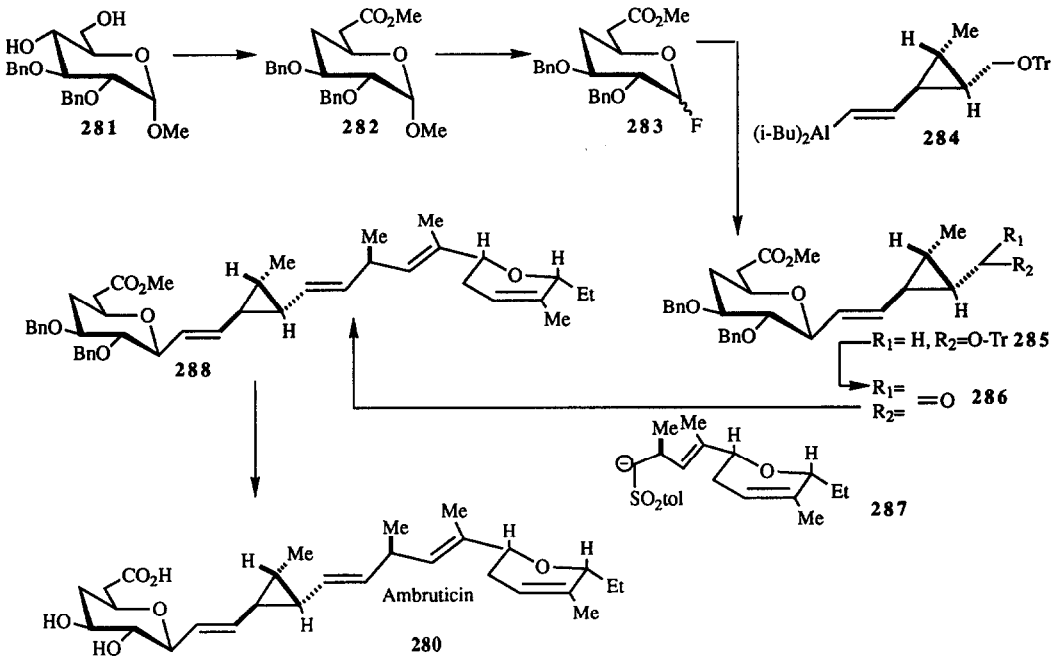
Scheme 72

Aluminum reagents have also been used to generate *C*-glycosides.[90] Reaction of **278** with triethylaluminum afforded (79%) a mixture of anomers. The ratio was 20:1 in favor of the α-anomer **279**. The reaction proceeded with inversion of configuration at the anomeric site.



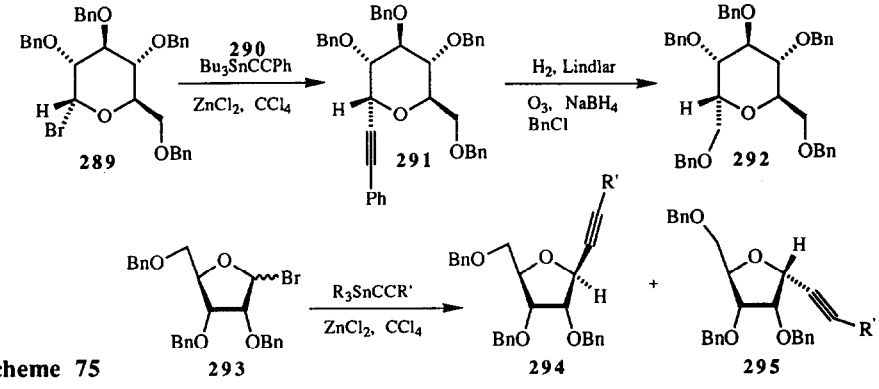
Scheme 73 **278** **279**

Aluminum mediated coupling served as the key step (Scheme 74) in the synthesis of naturally occurring ambruticin (**280**).[91] Ambruticin has been found to be active against the diseases plasmosis and coccidiomycosis.[92] The synthesis of the left hand portion began with the methyl α-glucopyranoside **281**. Barton deoxygenation at *C*-4 followed by oxidation of the primary alcohol to the acid and Arndt-Eister homologation gave the ester **282**. Anomeric hydrolysis and treatment of the free anomeric hydroxyl with Et_3NSF_3 provided a 73:27::β:α of glycosyl fluorides **283**. Coupling of the glycosyl fluorides with synthon **284** (available by a combination of an extension of Yamamoto's dianion chemistry and hydroalumination) provided the β-*C*-glycoside **285** in 49% yield. Detritylation and Dess-Martin oxidation provided the aldehyde **286**, which was condensed with anion **287** to give the *E*-tetraene **288** as the major product. Ester hydrolysis and Birch debenzylation then furnished natural ambruticin.[93]



Scheme 74

The protected *gluco*-pyranosyl bromide **289** (Scheme 75) was treated with the organotin acetylide **290** in the presence of two equivalents of zinc chloride to furnish **291** Degradation of the triple bond was accomplished by routine manipulations and protection of the resulting primary alcohol produced an optically active compound **292**. The β-anomer of **292** would have given an optically inactive (meso) compound. The furanosyl bromide **293** was also coupled with the organotin acetylide, but the α:β ratio was quite sensitive to the identity of the terminal group on the triple bond. When R = *n*-hexyl the α-isomer was formed exclusively. When R = phenyl the β-isomer was favored by a 3:1 ratio, and when R = methoxymethyl a 1:1 mixture of anomers was obtained.[94]

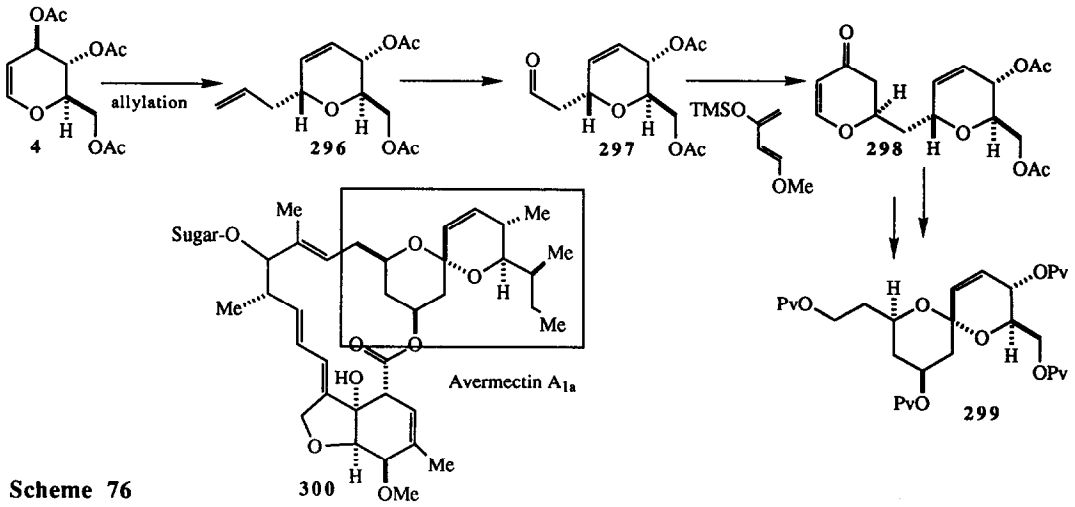


Scheme 75

6. Glycals

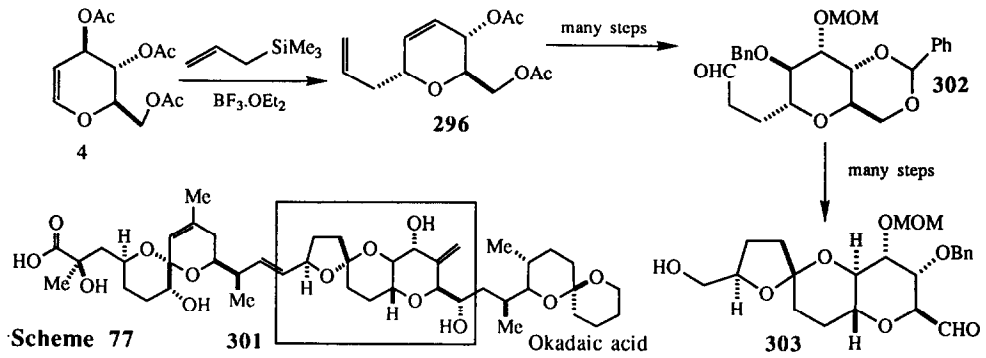
During model studies related to Avermectins A_{1a}, Danishefsky[95] utilized a *C*-glycoside as a synthetic intermediate for construction of the spiro portion of the natural product. Reaction of compound **4** under

standard allylation conditions (Scheme 76) furnished compound **296** in excellent yield. The terminal double bond was selectively osmylated and the resulting diol oxidatively cleaved with periodate to provide **297**. Diels-Alder reaction of **297** with Danishefsky's diene afforded **298**, which was then elaborated into the spiroketal **299**.



Scheme 76

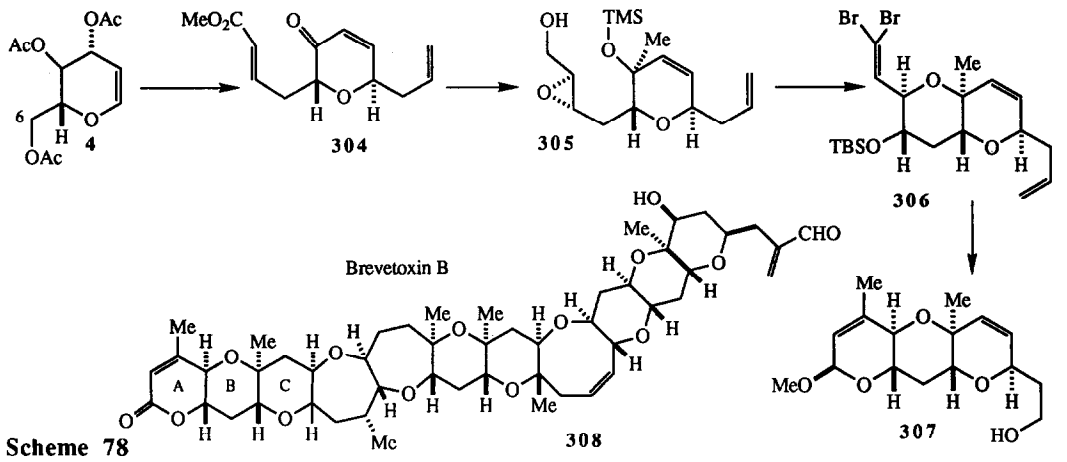
The complex polyether toxin, Okadaic acid (**301**), contains several spiroketals which, from a synthetic point of view, may be derived from sugars of defined chirality. During the synthesis of the midportion of this natural product, Isobe and co-workers (Scheme 77) used a *C*-glycoside as the starting point. Allylation of **4** under standard conditions gave the expected product **296**. Cleavage of the exo-cyclic double bond to the aldehyde, diol protection, and epoxidation of the cyclic double bond followed by ring opening gave **302**. Coupling of a four carbon fragment followed by ketalization and appropriate manipulations gave intermediate **303**.[96]



Scheme 77 **301**

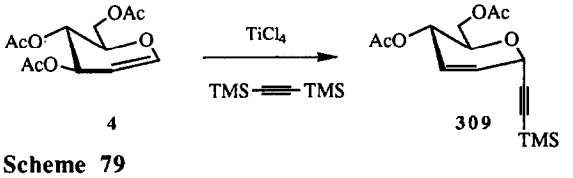
During the synthesis of the ABC ring system of the marine natural product, Brevetoxin B, a nemotoxin produced by the "red-tide" dinoflagellate *Ptychodiscus brevis*,[97] Nicolaou and co-workers[98] also used the allylation of **4** as the starting point. Allylation followed by standard manipulations at *C*-6 gave **304**. Treatment of **304** with $AlMe_3$, silylation of the *C*-5 hydroxyl, and DIBAL reduction of the ester produced an allylic alcohol, which was subjected to Sharpless epoxidation to bring the synthesis as far as **305**. Swern oxidation of **305**, reaction with Ph_3P-CBr_4, and treatment with camphorsulfonic acid gave the product of 6-*endo* cyclization

306. Further synthetic steps then gave **307**, a compound corresponding to the ABC ring system of brevetoxin B.



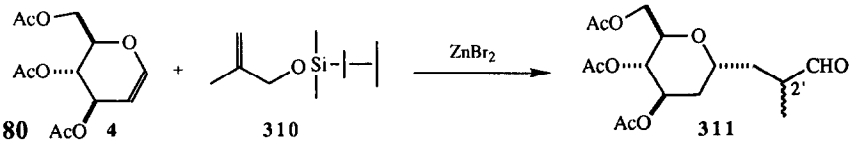
Scheme 78

Reaction of the glycal **4** with bis(trimethylsilyl)acetylene (Scheme 79) under Lewis acid catalysis gave the α-anomer **309** in 75% yield. This example shows yet another carbon nucleophile that can be used to prepare *C*-glycosides.[99]



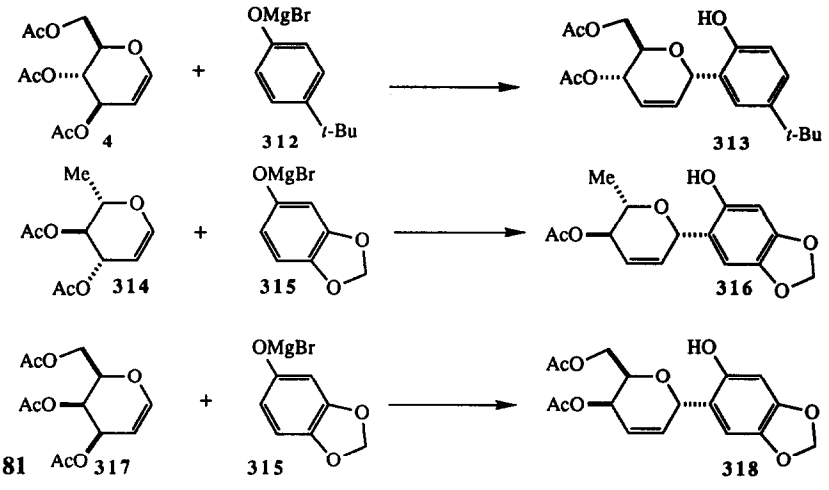
Scheme 79

Homoenolate chemistry was used for the synthesis of the *C*-glycoside **311**. The glycal **5** reacted with the allylsilane **310** under zinc bromide catalysis to furnish the α-anomer **311** (as a mixture of epimers at *C*-2') as the major product.[100]



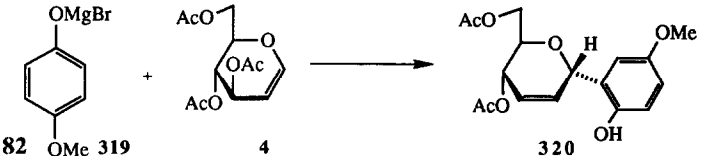
Scheme 80

Treatment of the glycal **4** (Scheme 81) with four equivalents of the bromomagnesium salt **312** followed by ultrasonic irradiation, gave in 71% yield, the α-anomer **313**. Reaction of 2,4-di-*O*-acetyl-L-rhamnal **314** with **315** produced both the α and β-anomers in a ratio of 8:1. Reaction of the galactal **317** under similar conditions gave only the β-anomer **318**, but in low yield.[101]



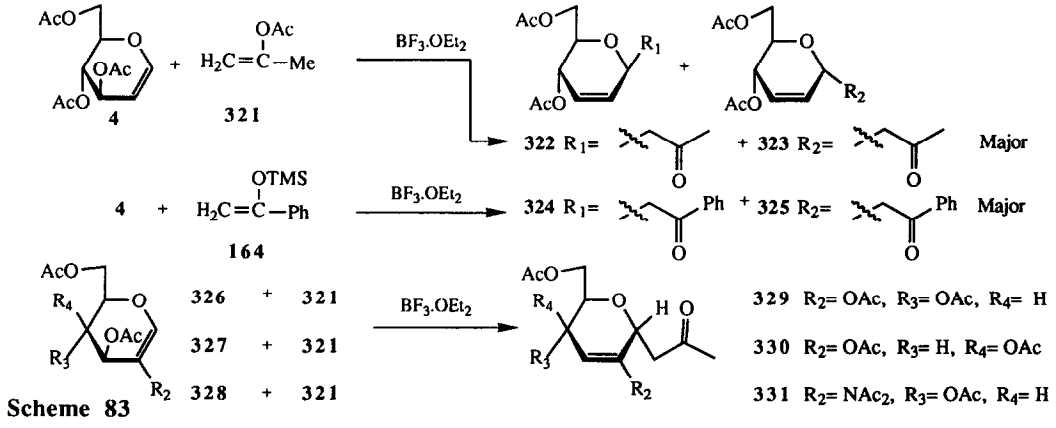
Scheme 81

When **4** was treated with the bromomagnesium salt of 4-methoxyphenol (**319**) the α-anomer **320** was formed as almost the exclusive product.[102]



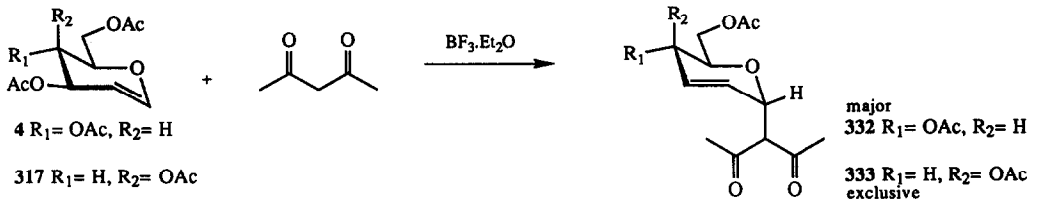
Scheme 82

Scheme 83 shows the addition of enol ethers to glycals to produce *C*-glycosides. A mixture of the protected glycal **4** and isopropenyl acetate (**321**) was treated with boron trifluoride etherate, and compound **323** was formed in 85% yield. A small amount of the other epimer **322** was also produced. Similarly, reaction of **4** with the silyl enol ether **164** gave the α-anomer **325** as the major product. Three other glycals were also studied: **326, 327**, and, **328**. In each case the α-anomer was the major product formed. It is interesting to note that introduction of a heteroatom at *C*-3 affords a *C*-glycoside with a masked *C*-3 carbonyl group.[103]



Scheme 83

Enol ethers are not the only nucleophiles that react with glycals to produce *C*-glycosides. Reaction of **4** with acetylacetone under Lewis acid catalysis (Scheme 84) produced the α-anomer **332** as the major product (α:β::5:1). When one begins with the galactal **317** the α-anomer **333** is the exclusive product.[104]

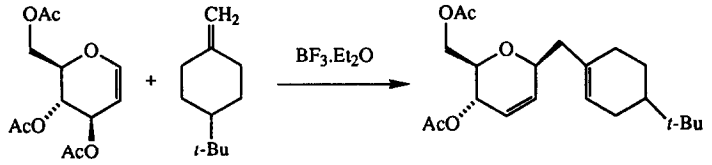


4 R_1= OAc, R_2= H

317 R_1= H, R_2= OAc

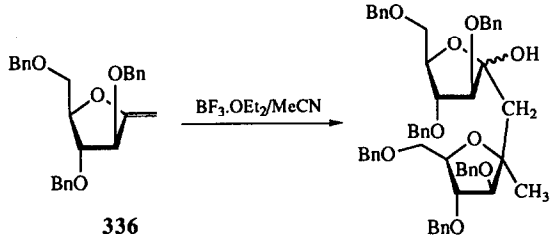
Scheme 84

Simple olefins can also be used in forming *carbon-carbon* bonds at the anomeric center. Reaction of glycal **4** with the *exo*-methylene cyclohexane derivative **334** (Scheme 85) in the presence of boron trifluoride etherate provided compound 335 in 92% yield with the α-anomer predominating over the β-anomer by a factor of 15:1.[105]

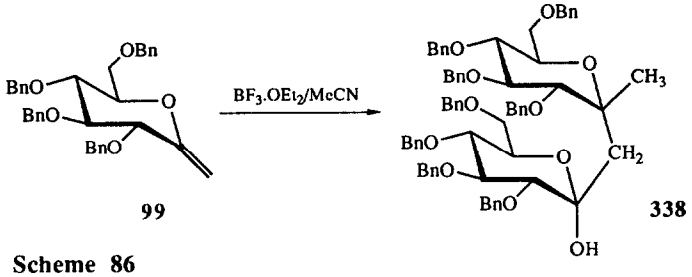


Scheme 85 **4** **334** **335**

Nicotra *et al.* have found that exo-methylenic glycals can be made to dimerize to furnish *C*-disaccharides as shown in Scheme 86.[106]



336 **337**

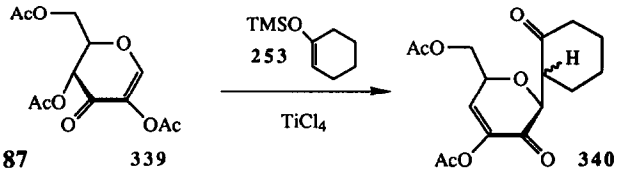


99 **338**

Scheme 86

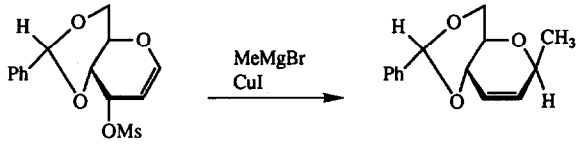
7. Enitols & Anhydro Sugars

Scheme 87 shows a Michael reaction of **339** with enol ether **253** under titanium tetrachloride catalysis affording compounds **340** in good yield.[107]



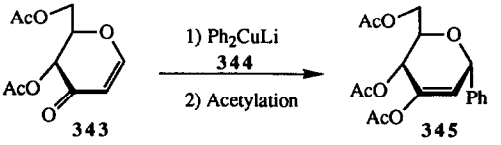
Scheme 87 **339** **340**

1,5-Anhydro-enitols are convenient starting materials for the formation of *C*-glycosides since they are amenable to reactions typical of alkenes. One such process is addition to a double bond using cuprate reagents, as shown in Scheme 88.[108] The product is the β-anomer **342**, resulting from attack on the least hindered face. In this type of process a *carbon-carbon* bond is formed at the anomeric site and the resulting 2,3-double bond provides a good point for controlled introduction of further hydroxyl groups.



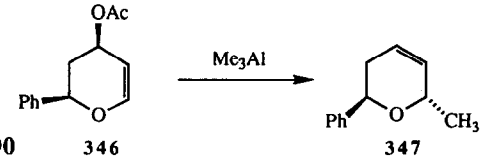
Scheme 88 **341** **342**

The next example, involving a 1,5-anhydro-enitol (Scheme 89), shows a reversal in product stereochemistry.[109] Reaction of 4,6-di-*O*-acetyl-1,5-anhydro-D-*erythro*-3-hexulo-1-enitol (**343**) with organocuprate **344** gave **345** in 74% yield.



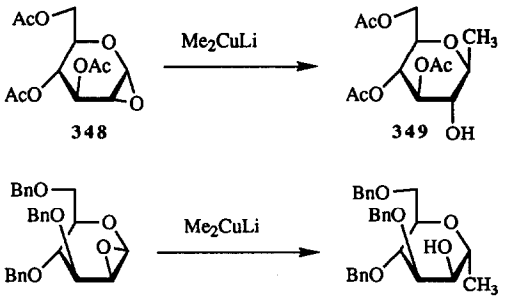
Scheme 89 **343** **345**

S_N2' displacements are not limited to organocuprates. Scheme 90 shows the use of trimethylaluminum for the same purpose. The addition proceeds from the least hindered face and the product **347** is formed in good yield.[110]



Scheme 90 **346** **347**

1,2-Anhydro sugars can also serve as useful precursors to *C*-glycosides. Reaction of 3,4,6-tri-*O*-acetyl-1,2-anhydro-α-D-*gluco*pyranose (**348**) with lithium dimethylcuprate in diethyl ether provided **349** in good yield (Scheme 91).[111] The reaction proceeds by attack at *C*-1. Likewise in the *manno* series, reaction of **350** gave compound **351**.



Scheme 91

8. Sugar Lactones

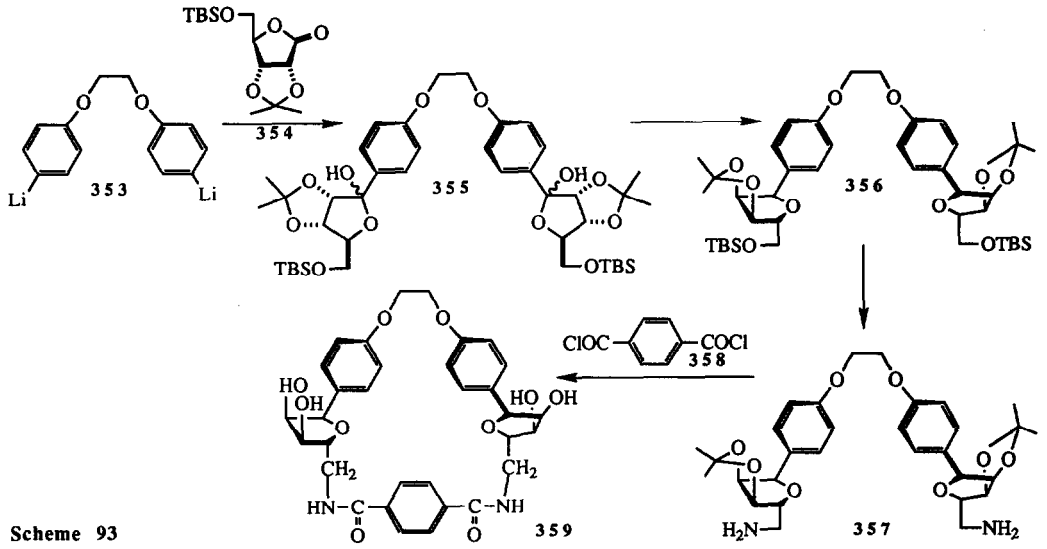
Kraus and Molina[112] have conducted a study on the addition of organometallic reagents to sugar lactones. Addition of organometallics to the gluconyl lactone **97** gives lactols. These where then reduced by the triethylsilane/boron trifluoride etherate method to give good yields of β-*C*-glycosides (Table V). Benzyl groups serve as adequate protecting functions and the addition of vinylmagnesium bromide is useful since the double bond can be stereoselectively hydroxylated to provide an eight carbon sugar precursor.

Scheme 92

Table V: Organolithium Addition.

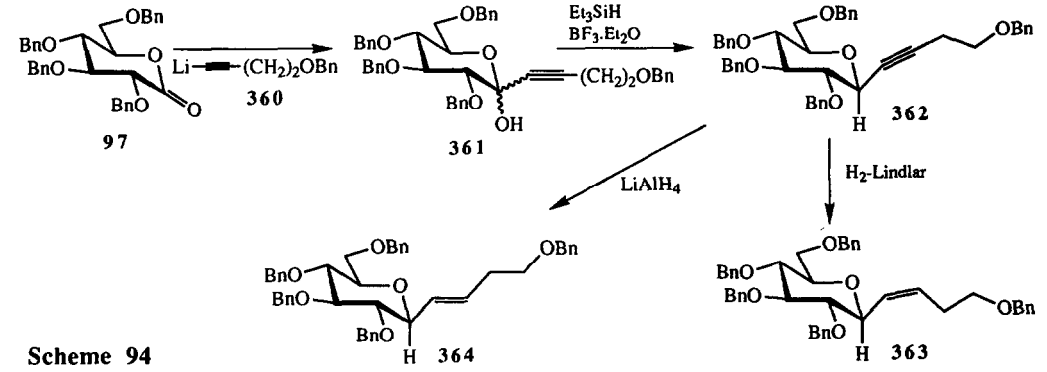
R-M	Yield
a Phenyl magnesium chloride	88
b 2-furyllithium	65
c 2-pyridyllithium	60
d vinyl magnesium bromide	60

Wilcox and Cowart[113] recently synthesized a macrocyclic *C*-glycosyl compound in order to produce a water-soluble cyclophane (Scheme 93). Reaction of the dilithium species **353** with the lactone **354** produced the bis(*C*-glycosyl) compound **355** exclusively, and reduction of the hemiacetal with sodium cyanoborohydride then furnished the bis(*C*-glycoside) **356**. Routine manipulations subsequently afforded the diamine **357**, which reacted with the dicarboxylic acid chloride **358** to furnish, after acetal removal, the *C*-glycoside-containing macrolide **359** incorporating two *C*-glycoside units.



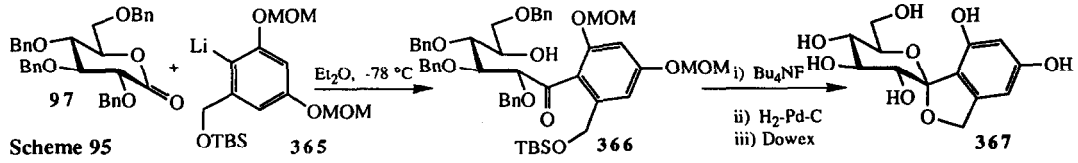
Scheme 93

Addition of the lithium acetylide **360** to the protected gluconolactone **97** gave a mixture of epimers **361**. Stereoselective reduction with triethylsilane and boron trifluoride etherate then gave β-anomer **362** as the exclusive product. Scheme 94 shows how the triple double bond may manipulated to give either the *Z*-isomer **363** or the *E*-isomer **364**.[114]



Scheme 94

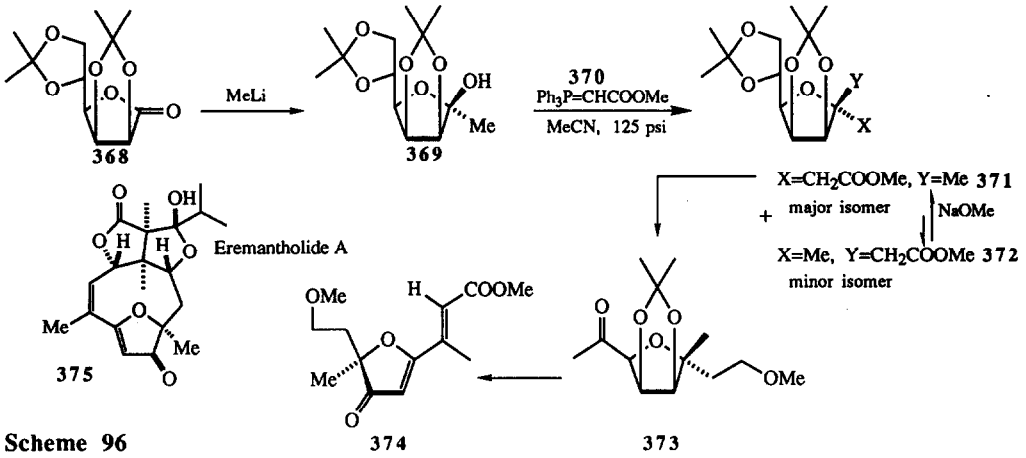
The spiroketal portion of the papulacandin skeleton was easily assembled by addition of the aryllithium **365** to the gluconolactone **97** to yield the ketone **366**. Desilylation and protective group removal then afforded the spiroketal **367**.[115]



Scheme 95

During the course of model studies directed at the germacrolide sesquiterpenes, Fraser-Reid[116] used a combination of organometallic and Wittig chemistry to synthesize the needed precursor *C*-glycoside. Reaction

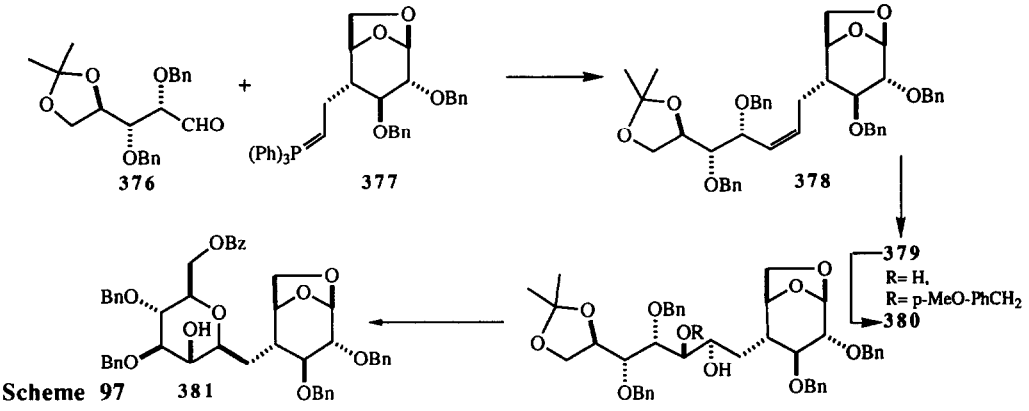
(Scheme 96) of lactone **368** with methyllithium in THF gave the lactol **369**. Wittig reaction with the ylide **370** in acetonitrile gave a mixture of isomers **371** and **372** which were then equilibrated in sodium methoxide/methanol to give a 2.5:1 mixture of **371** and **372**. Compound **371** was then elaborated to **374**.



368 369 375 373 374

Scheme 96

During the synthesis of palytoxin, a *C*-disaccharide was needed as one of the sub-units.[117] Wittig reaction (Scheme 97) of **376** with **377** gave a 60% yield of the desired *cis*-olefin **378**. Osmylation then afforded **379** which was selectively protected to give **380**. Ring closure was effected by the following steps: Swern oxidation, acetonide hydrolysis, and benzoylation. Finally silane reduction afforded the required *C*-disaccharide **381**.



376 377 378 381

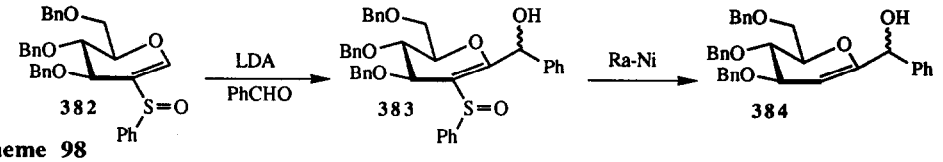
Scheme 97

VI. NUCLEOPHILIC GLYCOSIDES

A few workers have reversed the character of the anomeric carbon atom from electrophilic to nucleophilic. Examples of nucleophilic sugars include *C*-1 lithiated glycals, both directed and non-directed, stannyl glycals, stannyl glycosides, copper glycosides, nitro sugars and anomeric complexes derived from transition metals.

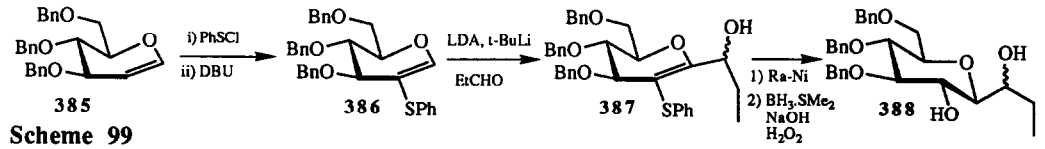
1. C-1-Lithio Derivatives

Scheme 98 shows an unsaturated sulfoxide **382** which was deprotonated with LDA and subsequently treated with benzaldehyde to afford the *C*-glycosides **383**.[118] The action of Raney nickel on **383** gave the desulfurized product **384**.



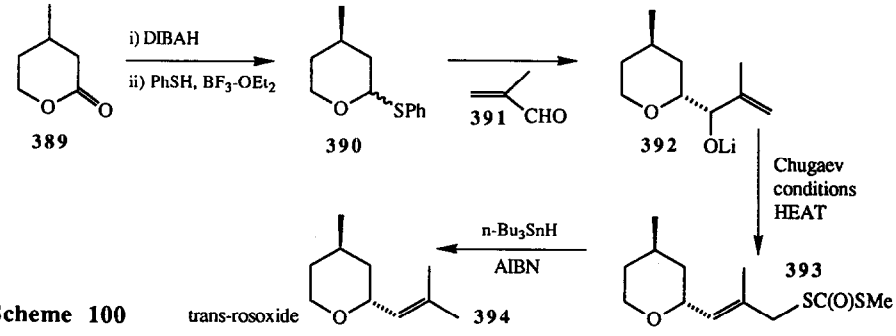
Scheme 98

Work by Schmidt[119] took advantage of the directing ability of the sulfur atom to facilitate anomeric lithiation. Reaction of the glycal **385** (Scheme 99) with phenyl sulfenylchloride and subsequent elimination with DBU afforded the vinylic sulfide **386** in good yield. Deprotonation with LDA/*t*-BuLi and treatment with propanol gave a mixture of isomers **387**. The *C*-glycosides **387** were then desulfurized with Raney nickel and hydroborated to yield the *C*-glycosides **388**.



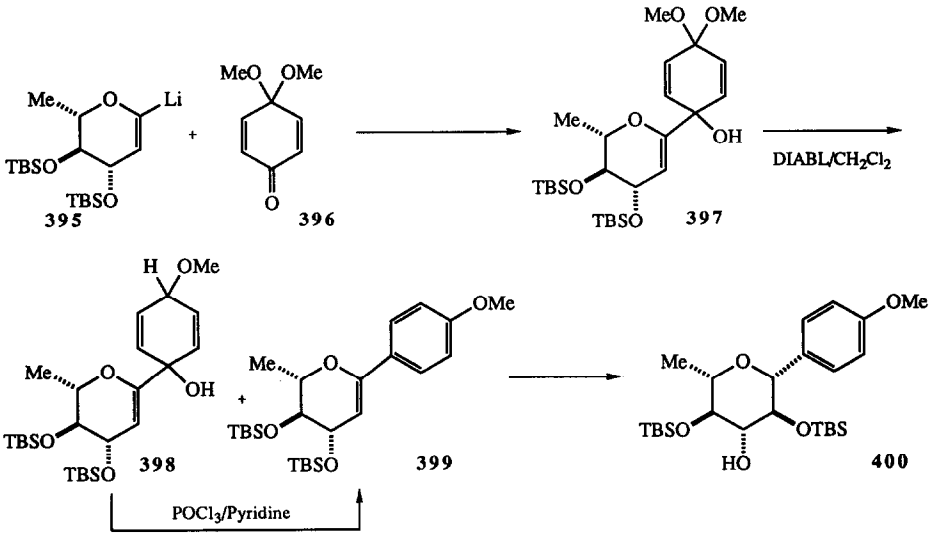
Scheme 99

Although not a carbohydrate, compound **389** bears a strong resemblance to the anomeric portion of lactonic sugars and its conversion to racemic *trans*-rosoxide typifies a *C*-glycoside synthesis (Scheme 100).[120] Reduction of lactone **389** with DIBAL followed by treatment with thiophenol in the presence of a Lewis acid gave a mixture of stereoisomers **390**, with the *trans*-isomer formed in 71% and the *cis*-isomer in 29%. Reductive lithiation with lithium 1-(dimethylamino)naphthalenide yielded only the *trans*-lithio-4-methyltetrahydropyran which added in a 1,2-manner to methacrolein (**391**) to yield **392**. The latter was not isolated, but subjected to Chugaev conditions and the resulting xanthate was heated to produce **393**, obviously the result of a [3,3]-sigmatropic rearrangement. Finally, stannane reduction gave *trans*-rosoxide (**394**).



Scheme 100

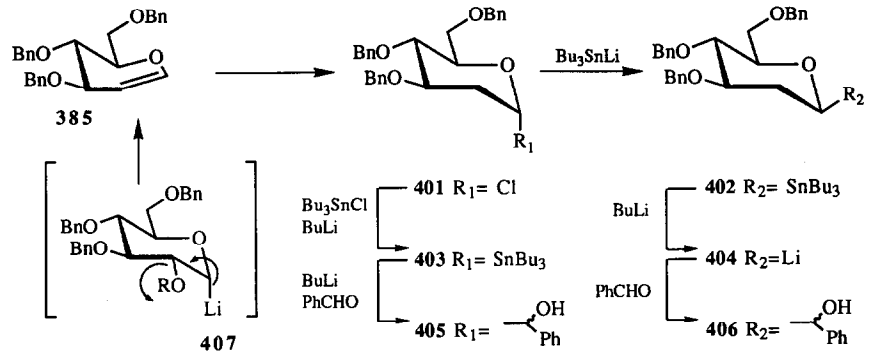
Parker[121] has devised a method for the quick assembly of aryl *C*-glycosides. Reaction of the *C*-1 lithiated glycal[122] **395** with the quinol ketal **396** provided **397**. Addition of **397** to DIBAL in dichloromethane gave a mixture of **398** and **399**. This mixture was treated with $POCl_3$ in pyridine to give **399**. Hydroboration and subsequent oxidation furnished the aryl *C*-glycoside **400** in 94% overall yield (in which silyl migration had occurred).



Scheme 101

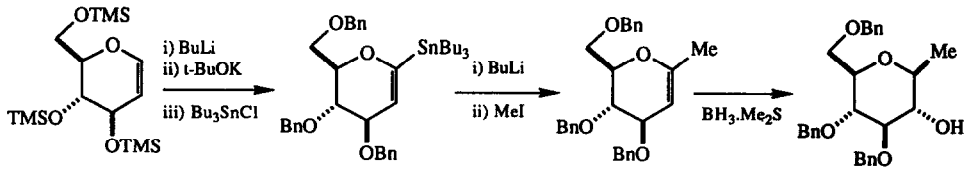
2. Anomeric Stannanes

Sinaÿ[123] has developed a powerful method based on reversing the character of the anomeric center from electrophilic to nucleophilic. This approach provides access to both the α and β-anomers of *C*-glycosides. Scheme 102 illustrates how the pyranosyl chloride **401** can be converted either to the α or β-tin glycoside. Treatment of **402** or **403** with *n*-butyllithium and reaction with an appropriate electrophile then yields **406** and **405**, respectively. It should be noted that both the α and β-tin glycosides are available from the same readily available α-pyranosyl chloride. However, this method is restricted to 2-deoxyglycosides since an intermediate anion of structure **407** would undergo elimination as shown below.



Scheme 102

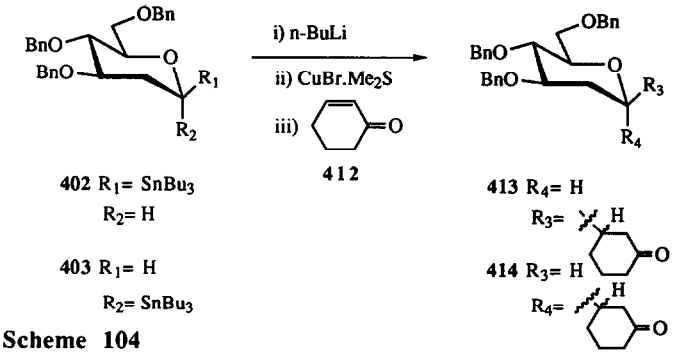
Stannyl glycals have also served as *C*-glycoside precursors as shown in Scheme 103. The protected glycal **408** was treated with butyllithium and potassium *t*-butoxide to yield the *C*(1)-anion which was then allowed to react with tributyltin chloride to form the anomeric stannane **409**.[142] Reaction of **409** with *n*-butyllithium and methyl iodide then gave the *C*-glycoside **410**. This was reduced with borane methyl sulfide complex and the intermediate borane was oxidized with alkaline hydrogen peroxide to yield 1-*C*-methyl anhydro-D-glucitol **411**.



408 **409** **410** **411**

Scheme 103

Hutchinson and Fuchs[125] have gained access to both the α and β-anomers produced by Michael addition of an anomeric cuprate to 2-cyclohexen-1-one (**412**) (Scheme 104). If one begins with the α-tin glycoside **403** one obtains the α-*C*-glycoside **414**, while the β-tin glycoside **402** gives the corresponding β-product **413**. This sequence is an application of the technology that Sinaÿ had developed earlier (*vide supra*).



402 R_1= $SnBu_3$, R_2= H

403 R_1= H, R_2= $SnBu_3$

412

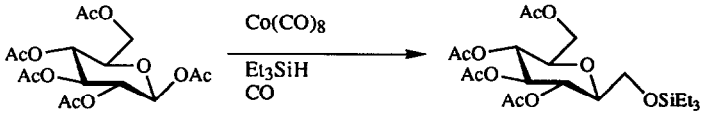
413 R_4= H, R_3=

414 R_3= H, R_4=

Scheme 104

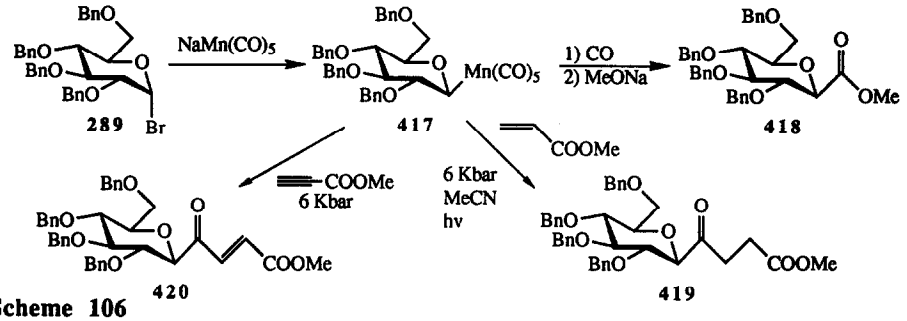
3. Transition Metal Anomeric Complexes

A number of other transition metals have been used to construct *C*-glycosides, and Scheme 105 shows a simple method for generating a *C*-glycoside in a highly stereospecific manner. Reaction of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucose (**415**) with $Co(CO)_8$ in the presence of triethylsilane and carbon monoxide gave the *C*-glycoside **416**.[126]



Scheme 105 **415** **416**

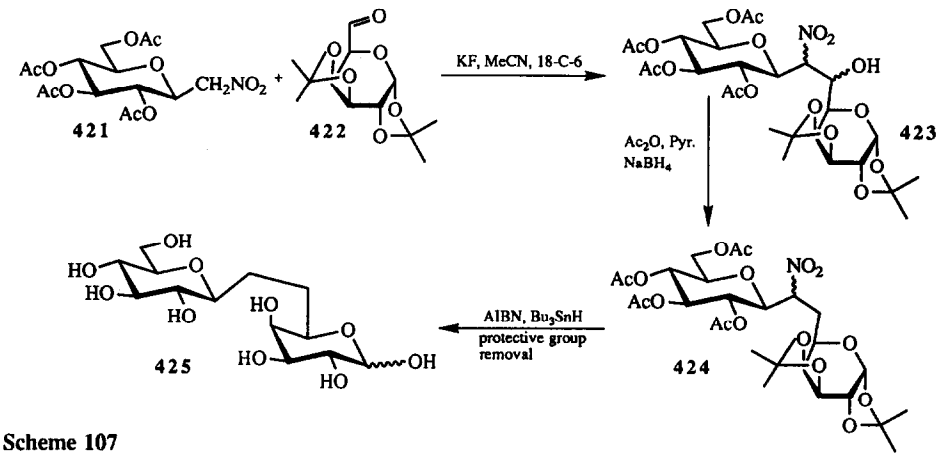
Manganese chemistry has also been used for *carbon-carbon* bond formation at the anomeric center. The glucopyranosyl bromide **289** was treated with sodium pentacarbonyl manganate [$NaMn(CO)_5$] to give the anomeric organometallic complex **417**.[127] Scheme 106 also illustrates the synthetic possibilities of this versatile intermediate. Reaction with carbon monoxide and subsequent treatment with sodium methoxide yields the ester **418**. Reaction with methyl methacrylate under pressure gives the keto-ester **419**, while treatment with methyl propiolate yields the unsaturated keto-ester **420**.



Scheme 106

4. Nitro Compounds

If the interglycosidic oxygen in a disaccharide is replaced with a methylene unit, one obtains a non-metabolizable *C*-disaccharide. Nitroaldol condensation (Scheme 107) of **421** with aldehyde **422** in acetonitrile, containing potassium fluoride and 18-Crown-6, afforded the aldol products **423**. Acetylation, elimination, and reduction of the double bond by the action of sodium borohydride furnished **424** as a mixture of epimers. Tin hydride reduction of the nitro group followed by deprotection gave the *C*-glycosides **425**.[128]



Scheme 107

VII. FREE RADICAL APPROACHES

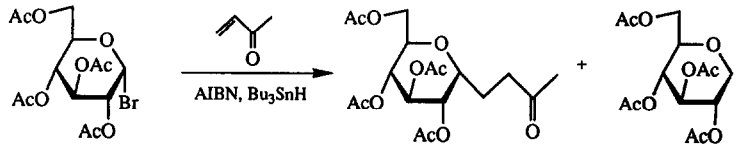
Free radical addition reactions are very popular and important methods for *carbon-carbon* bond formation at the anomeric center of carbohydrates. This approach towards the synthesis of *C*-glycosides via intermolecular additions is in large part due to the work of Giese. The advantages of free radical chemistry include mild reaction conditions, facile generation of anomeric radicals from available glycosyl halides, and the predictable reactivity of pyranosyl radicals.[129] Although a useful synthetic method, reduction of the radical by tributyltin hydride prior to addition or cyclization can sometimes be a problem.

This category can be divided into two sections intermolecular additions and intramolecular additions. The stereochemistry of the intermolecular addition is controlled by the anomeric effect (for pyranoses) and it has been found that for glucose the α-anomer is almost always the exclusive product. The intramolecular additions

have the potential yield either the α or β configuration, and some workers have developed very efficient methodologies to address this problem.

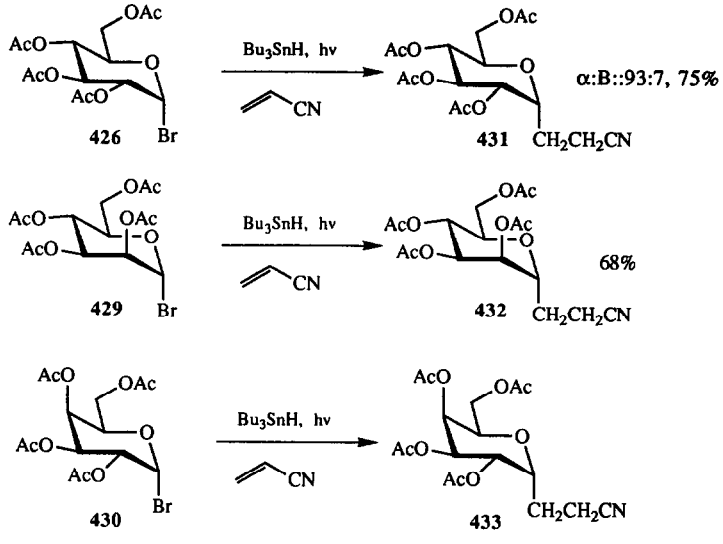
1. Intermolecular Additions

Scheme 108 shows the reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-*gluco*pyranosyl bromide (**426**) with tributyltin hydride to give an α-free radical. This radical then reacted with the Michael acceptor 3-butene-2-one to furnish compound **427** in 40% yield. The rest of the product is the reduced form of compound **426**, i.e., the 1,5-anhydro-glucitol **428**.[130]



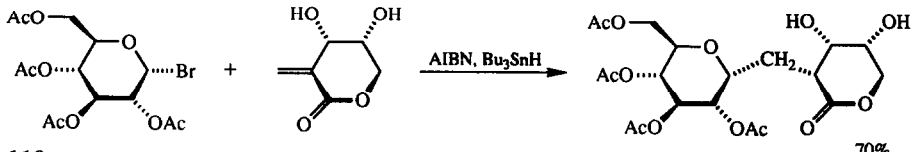
Scheme 108 **426** **427** **428**

Giese has utilized the *gluco*, *manno* and *galacto* pyranosyl bromides in the synthesis of *C*-glycosides. Reaction of bromides **426**, **429**, and **430** with acrylonitrile and tributyltin hydride under photolytic conditions gave the *C*-glycosides **431**, **432**, and **433**.[131]



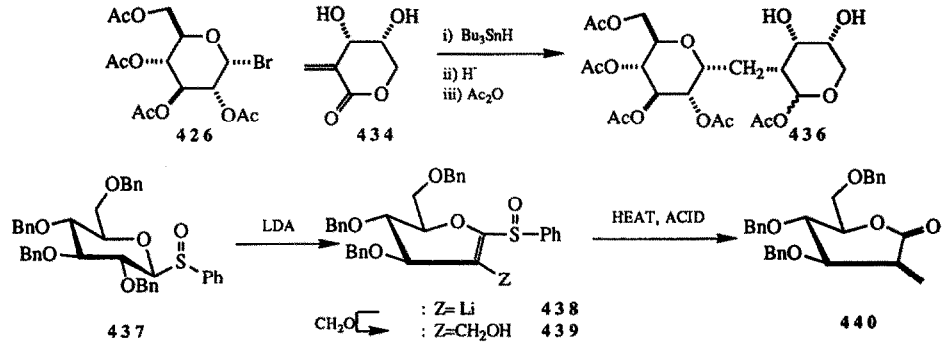
Scheme 109 **426** **429** **430** **431** **432** **433**

Work by Giese[132] has also dealt with the formation of *C*-disaccharides. Reaction of the glucopyranosyl bromide **426** under free radical conditions in the presence of the unsaturated lactone **434** afforded **435** in 70% yield.



Scheme 110 **426** **434** **435**

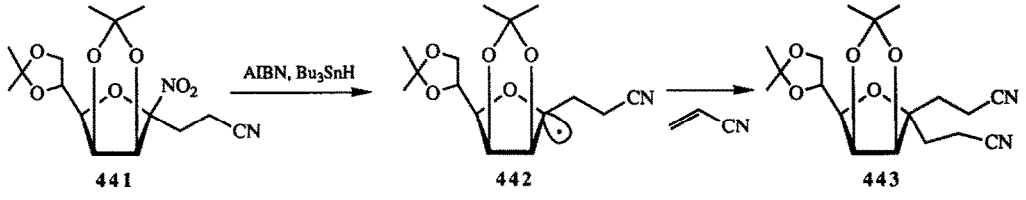
Addition of a glycosyl radical to an α-methylene-γ-lactone is a viable method of producing *C*-disaccharides however the supply of these types of lactones is quite limited. Scheme 111 summarizes a convenient synthesis of these compounds. Treatment of sulfoxide **437** with two equivalents of LDA generated the lithiated species **438**, and reaction with formaldehyde followed by exposure to trace amounts of acid gave the α-methylene-γ-lactone **439**.[133]



426 434 436 437 438 439 440

Scheme 111

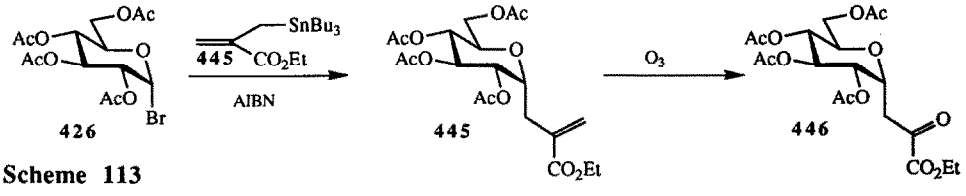
It was recently discovered that secondary and tertiary nitro compounds can be reduced via a free radical pathway by the action of tributyltin hydride.[134] Giese[135] reacted the nitro sugar **441** with a twenty-fold excess of acrylonitrile in the presence of tributyltin hydride and AIBN to produce **443**. The stereochemistry of attack shown in Scheme 112 has been proven by deuteration studies.



441 442 443

Scheme 112

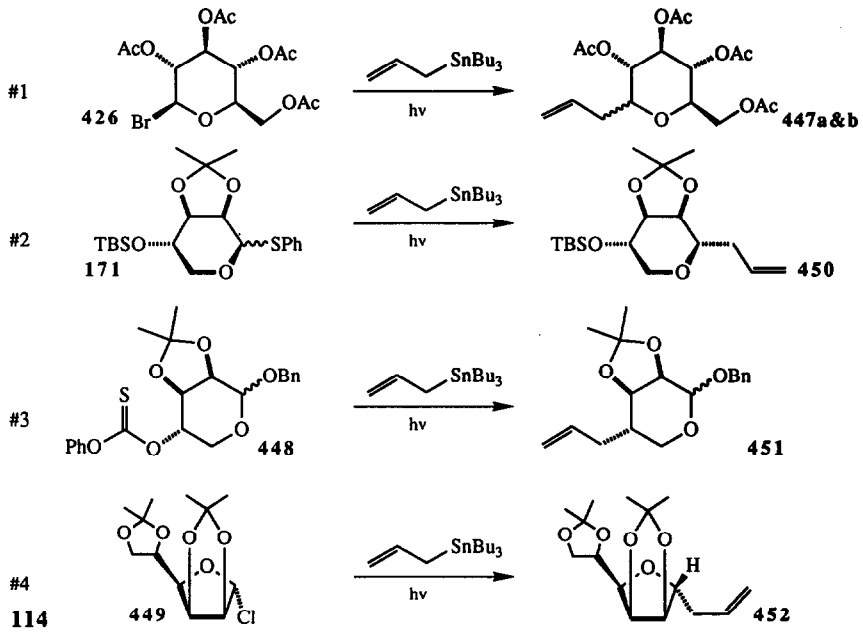
Glycosyl radicals have also been used to mimic the enzymatic aldol reaction between phosphoenol pyruvate and carbohydrates. Scheme 113 shows the reaction of **426** with the alkene **444** in the presence of AIBN to afford the *C*-glycoside **445**. Exposure of **445** to the action of ozone then gave the ketoester **446**.[136]



426 445 446

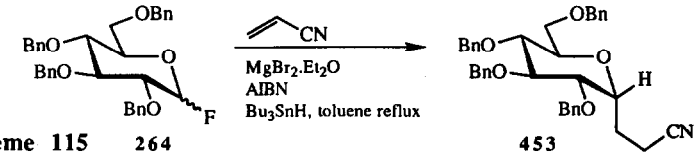
Scheme 113

Keck has employed allylstannanes in his synthesis of *C*-glycosides and Scheme 114 shows some examples. Irradiation of a mixture of glycosyl bromide **426** and allylstannane produced the anomers **447a** and **447b**. Treatment of the thioglycoside **171** under similar conditions produced **450**. Finally irradiation of the furanosyl chloride **449** gave the the product of retention of configuration **452**.[137]



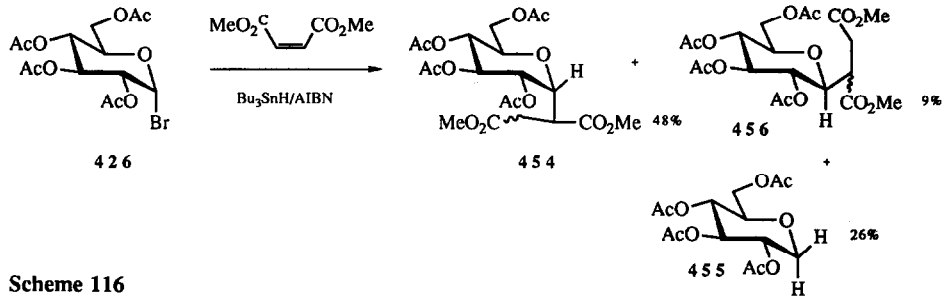
Scheme 114

Glycosyl fluorides can also be used as radical precursors. Exposure of the glycosyl fluoride **264** to AIBN, tributyltin hydride, an excess of acrylonitrile and magnesium bromide etherate in refluxing toluene gave the *C*-glycoside **453**. The action of magnesium bromide etherate alone on compound **264** gave a glycosyl bromide; presumably this is the free radical precursor.[138]



Scheme 115 **264** **453**

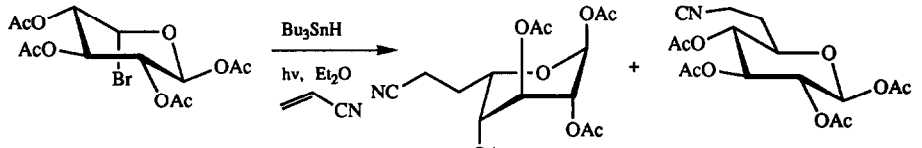
Araki[139] has studied radical coupling of the glucosyl bromide **426** with dimethyl maleate. Radical generation by the tin hydride method and trapping with an excess of the Michael acceptor gave three products. The major product, the α-anomer **454**, was formed in 46% yield, while the β-anomer **456** was formed in 9% yield, and the reduced halide **455** in 26% yield.



426 454 456 455

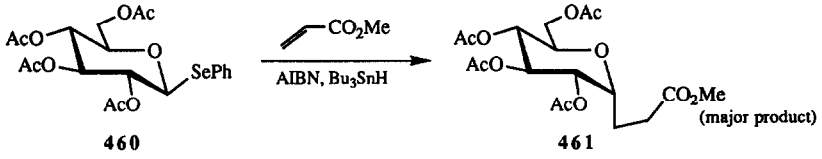
Scheme 116

Exposure of the bromide **457** to tributyltin hydride (Scheme 117) in refluxing diethyl ether with visible light irradiation in the presence of acrylonitrile gave two compounds, the L-*ido*-adduct **458** and the D-*gluco*-isomer **459**.[140]



Scheme 117 **457**

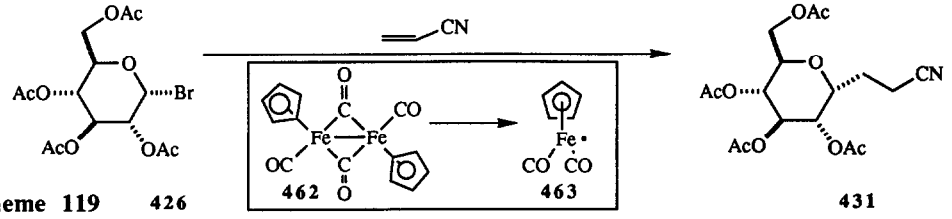
Baldwin[141] has also used anomeric radicals to construct *C*-glycosides, using phenylseleno sugars as precursors (Scheme 118).



460 **461**

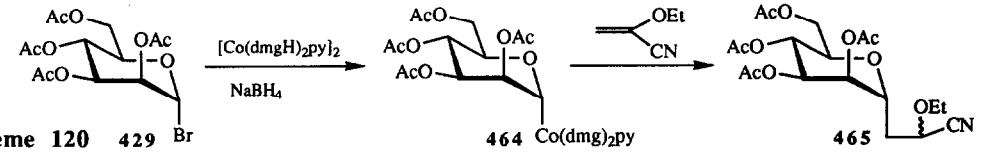
Scheme 118

Giese has also found that the free radical reaction may be initiated by photolyzing the dimeric iron complex **462** to give **463**, which then reacts with a halide to produce the carbon radical. Scheme 119 shows the application of this initiator to the synthesis of the *C*-glycoside **431**.[142]



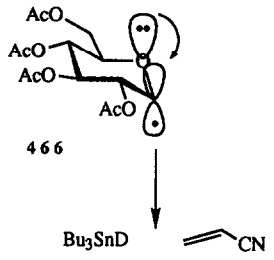
Scheme 119 **426** **462** **463** **431**

Scheme 120 shows that photolysis of glycosyl cobalt complexes can also be used as a source of anomeric radicals.[143]



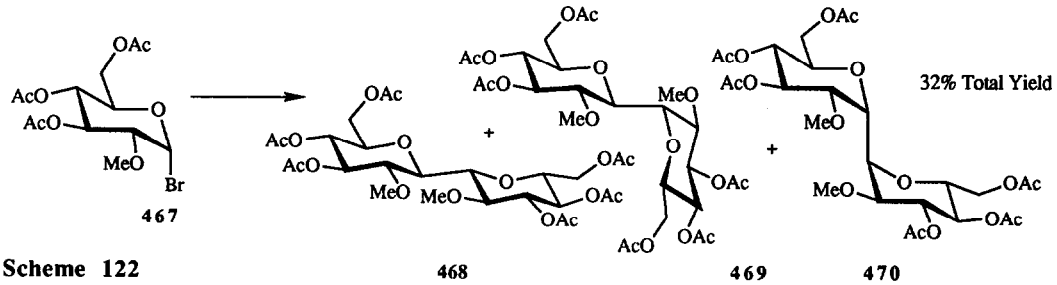
Scheme 120 **429** **464** $Co(dmg)_2py$ **465**

As seen by the above examples the major product of addition of anomeric radicals to alkenes (or reduction by Bu_3SnD) leads almost exclusively to the axial product. Giese has described this as the radical anomeric effect. The anomeric radical is somewhat stabilized in the axial position by stereoelectronic effects from the ring oxygen (Scheme 121) which directs attack axially.[143, 129]



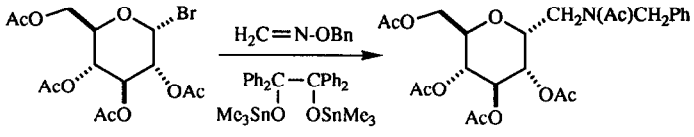
Scheme 121

Dimerization of anomeric radicals leads to the production of *C*-glycosides. Irradiation of the glycosyl bromide **456** in the presence of hexamethylditin gave the three dimers **457**, **458**, and **459**, the main product being **458**.[144]



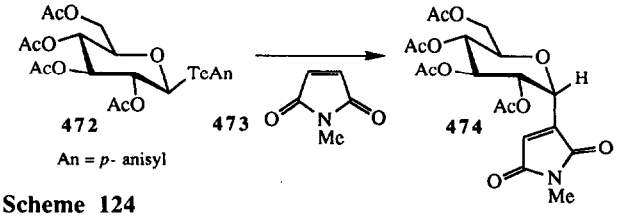
Scheme 122

Hart[145] has used a free radical one carbon homologation to produce a *C*-glycoside. Heating a benzene solution of the glucosyl bromide **426** and bis(trimethylstannyl)benzopinacolate in the presence of *O*-benzylformaldoxime furnished the *C*-glycoside **471**.

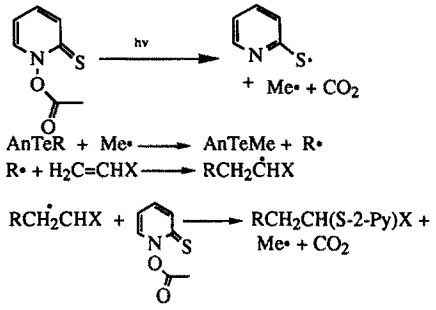


Scheme 123

Barton and Ramesh[146] have employed tellurides as radical precursors to synthesize *C*-glycosides. The glycosyl telluride **472** (obtained from the reaction of a suitably functionalized glucose with anisyl telluride anion) was photolyzed in the presence of **473** to give the *C*-glycoside **474**. The mechanism is shown below in Scheme 124.

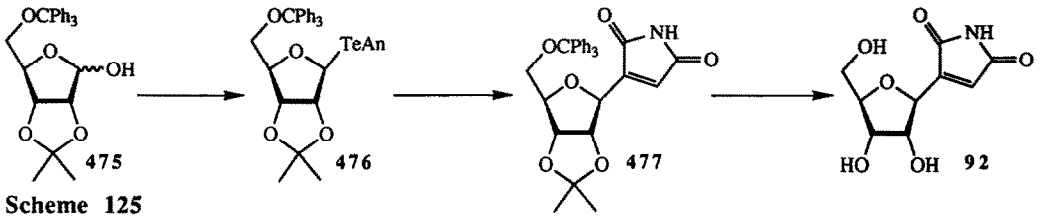


Scheme 124



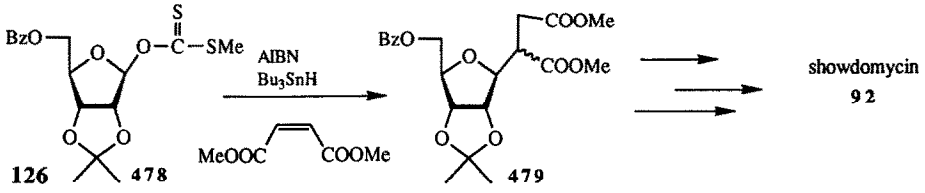
Scheme 124 cont'd

To demonstrate the usefulness of this methodology, a short synthesis of showdomycin (**92**) was carried out (Scheme 125).[146]



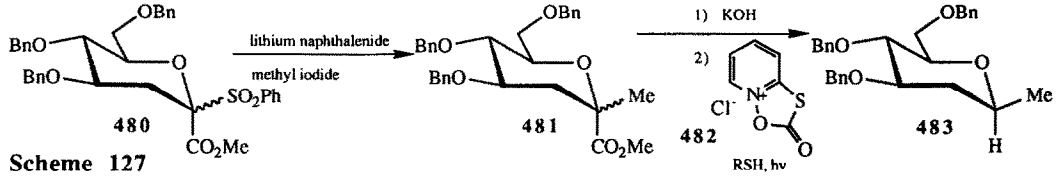
Scheme 125

Araki[147] has also synthesized showdomycin via anomeric radicals. Reaction of **478** with dimethyl maleate in the presence of tributyltin hydride and AIBN as initiator gave a mixture of diastereomers **479**. These were then elaborated to afford showdomycin.



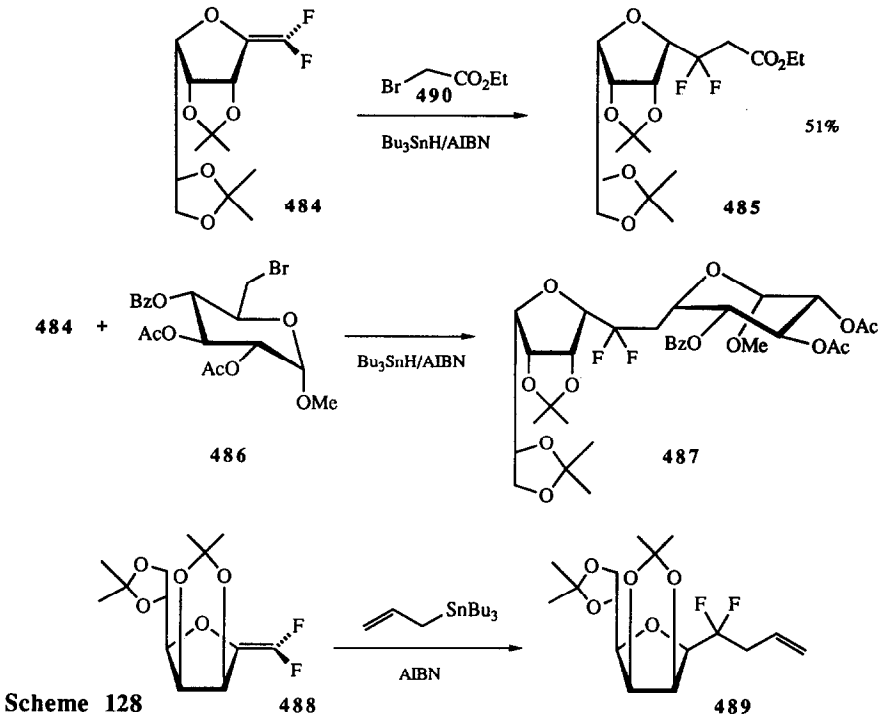
Scheme 126

Using technology developed by Sinaÿ,[61] Crich[148] alkylated the *C*-1 anion resulting from **480** with methyl iodide to give **481**. Ester hydrolysis and Barton decarboxylation using **482** afforded the β-*C*-glycoside **483**.[129]



Scheme 127

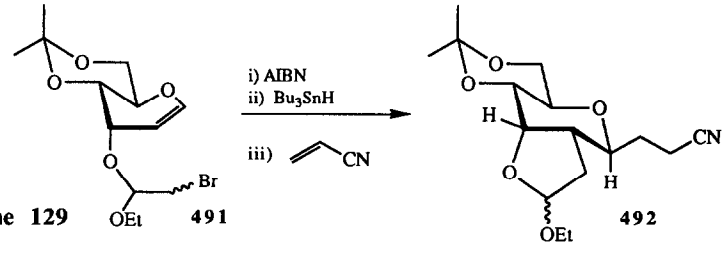
Difluoroenol ethers have also been found to be suitable radical acceptors. The addition of the electrophillic radical derived from **490** to **484** gave **485** in 51% yield. Similar radical addition of the radical derived from **486** to **484** afforded the bridged *C*-disaccharide with the same anomeric configuration as **485**. Keck allylation of **488** provided the addition product **489**.[149]



Scheme 128

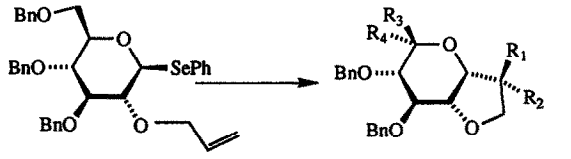
2. Intramolecular Additions

Work by Fraser-Reid[150] using enitols has provided β-*C*-glycosides. Scheme 129 summarizes the strategy involved. Reaction of **491** under free radical conditions with acrylonitrile afforded in good yield compound **492**.



Scheme 129

De Mesmaeker[151] has used an intramolecular radical cyclization to produce a *C*-glycoside. The seleno - glycoside **493** was subject to standard radical conditions to yield a mixture of three compounds **494, 495**, and **496**. Compound **496** was produced as a result of hydrogen abstraction from *C*-5.[152] This was proven by deuteration studies in which tributyltin deuteride was employed. Deuterium was incorporated at *C*-5. Table VI shows the effect of concentration on the component ratios.

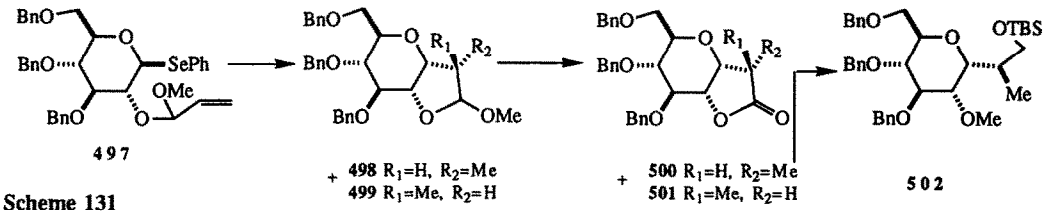


Scheme 130

Table VI: Concentration Effect.

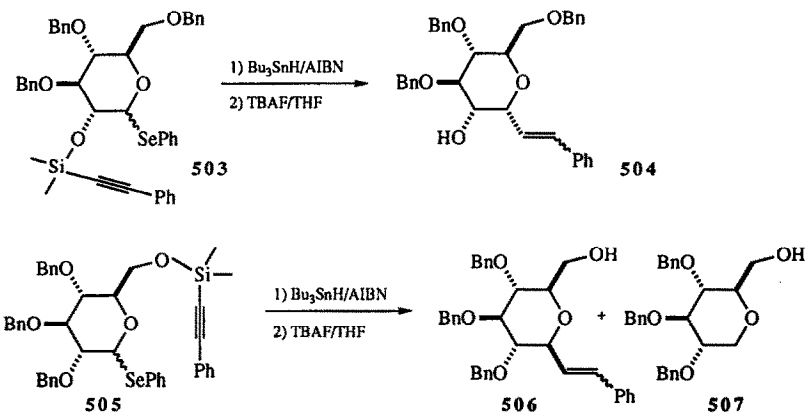
Concentration (M)	Isomer Ratio 494	495	496
0.001	22	23	55
0.01	29	15	56
0.1	43	2	55
0.2	47	not detected	53

In a similar study (Scheme 131),[153] cyclization of the radical derived from the selenide **497** (0.3 M) gave a 1:1 mixture of **498** and **499**. Oxidation with *m*-CPBA furnished the isomeric lactones **500** and **501** which were separated. Compound **500** was then carried on to afford the *C*-glycoside **502** by standard manipulations.

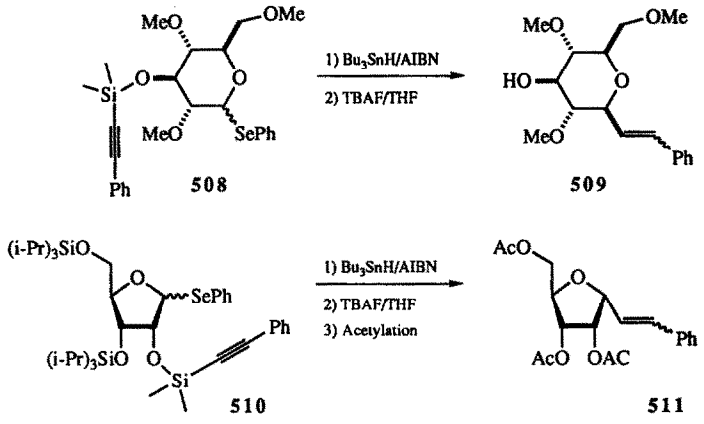


Scheme 131

Stork [154] has also used intramolecular radical cyclization onto silicon tethered alkynes to stereoselectively synthesize *C*-glycosides. Both the α or β *C*-glycoside are available from a suitably protected glucose derivative as shown below in Scheme 132 The method is also applicable to furanose sugars.

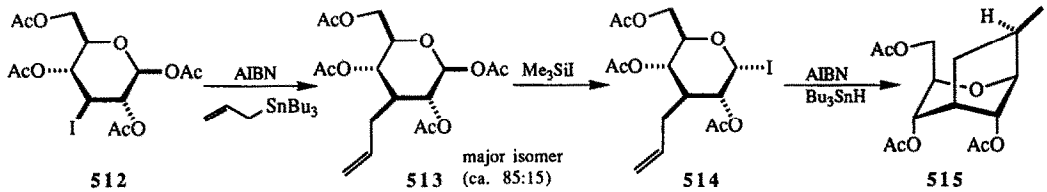


Scheme 132



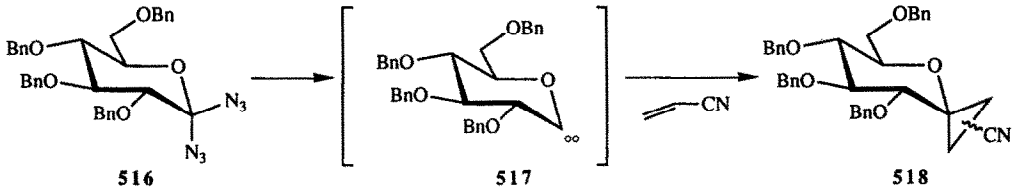
Scheme 132 cont'd

Giese and co-workers[155] have employed intramolecular radical cyclization to produce a *C*-glycoside. Keck allylation (Scheme 133) of **512** afforded **513** as the major isomer, and this was then treated with trimethylsilyl iodide to furnish the glycosyl iodide **514**. Exposure of **514** to tributyltin hydride and AIBN in refluxing benzene gave a mixture of isomers with **515** predominating, a result indicating that the methyl group adopts the less crowded *exo* position during reduction.



Scheme 133

Although not a free radical process, the final example does involve an electron deficient species, a carbene. Photolysis of **516** (available from anomeric dihalo sugars or glycono-1,5-lactones) [156] in the presence of acrylonitrile gave a mixture of isomers of the spiro sugar **518**, a bis (*C*,*C*-glycoside).[157]



Scheme 134

VIII. CONCLUSION

This review has summarized the modern methods available for the synthesis of *C*-glycosides. The field is expanding rapidly and it is certain that many useful developments are yet to come.

ACKNOWLEDGEMENT

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