Pergamon

Tetrahedron 54 (1998) 9913–9959

TETRAHEDRON

Tetrahedron report number 462

RECENT ADVANCES IN STEREOSELECTIVE *C*-GLYCOSIDE SYNTHESIS

Yuguo Du and Robert J. Linhardt

Division of Medicinal and Natural Products Chemistry and Department of Chemical and Biochemical Engineering, University of Iowa, PHAR S328, Iowa City, Iowa, 52242, USA

Iontcho R. Vlahov

Baker-Norton Pharamceuticals, Inc. 4400 Biscayne Blvd., Miami, Florida 33137, USA

Received 10 February 1998

Contents

*E-mail: robert-linhardt@uiowa.edu; FAX: +1 319-335-6634

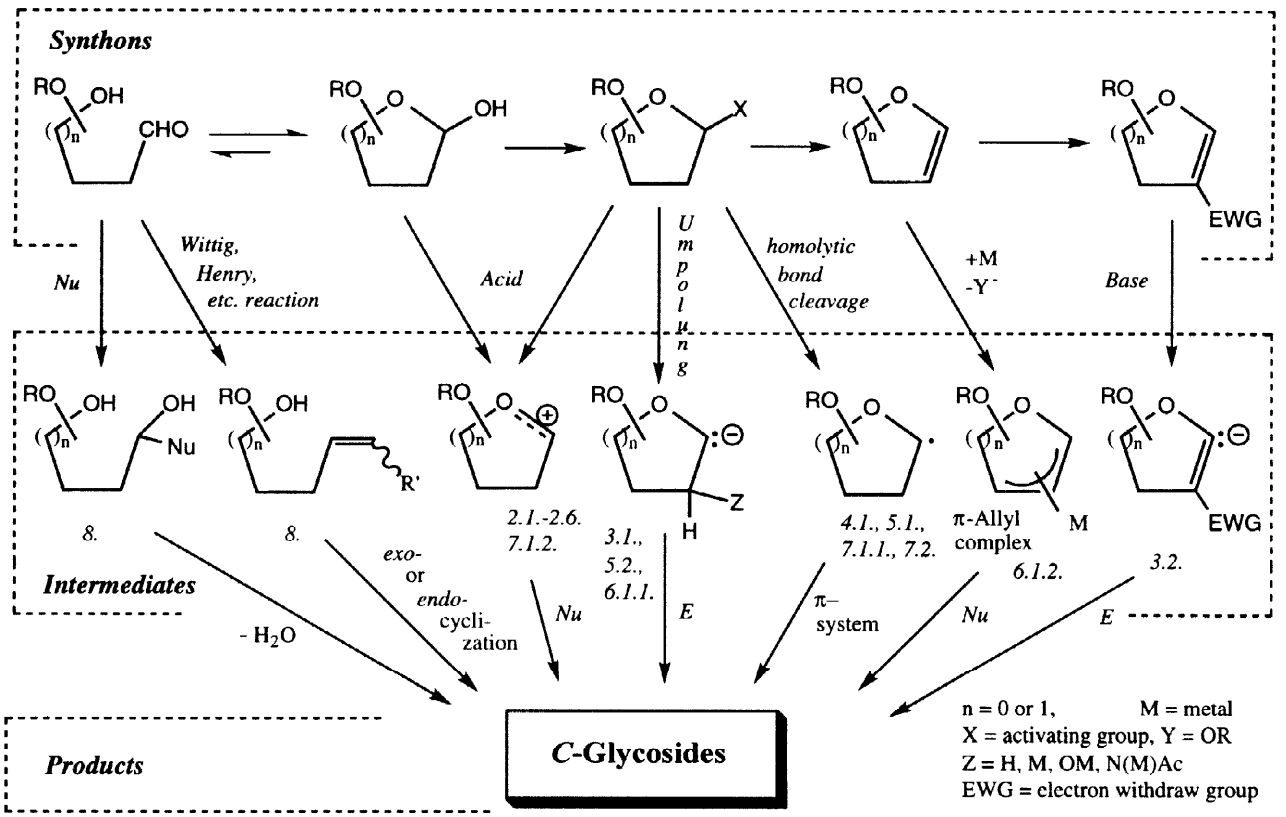
PII: S0040-4020(98)00405-0

1. INTRODUCTION

Carbohydrate analogs in which a carbon atom substitutes for the glycosidic oxygen are called *C*-glycosides. During the last two decades, the synthesis of *C*-glycosides has become an area of intense study among carbohydrate chemists and biochemists because: 1) The discovery of naturally occurring *C*-nucleosides with important pharmacological properties[1] gave impetus to synthetic efforts for preparing active carbohydrate analogs; 2) The requirement of *C*-glycoside chiral building blocks in the synthesis of biologically important macromolecules, such as palytoxin,[2] spongistatin[3,4] and halichondrin B,[5] has stimulated the development of the new synthetic methodologies; 3) *C*-glycosides are potential inhibitors of carbohydrate processing enzymes and are stable analogs of glycans involved in important intra- and inter-cellular processes.[6-9]

C-glycoside synthesis has been reviewed by Postema,[10] Levy,[11] Sinaÿ,[12] Beau[13] and Nicotra.[6] The aim of the present survey is to provide a summary of the recent applications, published since 1994, of stereoselective methods in the synthesis of *C*-glycosides.

A generalized overview of the most common synthons and intermediates in the *C*-glycosylation is shown on Scheme 1. The numbers in italics indicate specific sections in this article that describe each synthetic method presented.



Scheme 1

2. Electrophilic *C*-Glycoside Donors

Electrophilic reactions are probably the most widely used for the formation of *C*-glycosides due to easy accessibility of the electrophilic sugar species, intermediate stability, and reaction simplicity. Methods that involve the electrophilicity of the anomeric center can be applied to electrophilic *C*-glycosidation.[10] Commonly used C-glycoside electrophilic donors are shown in Fig. 1.

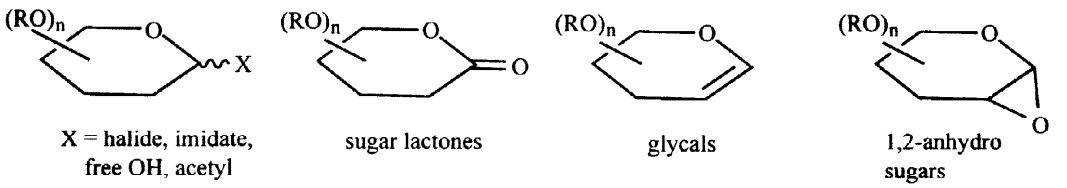
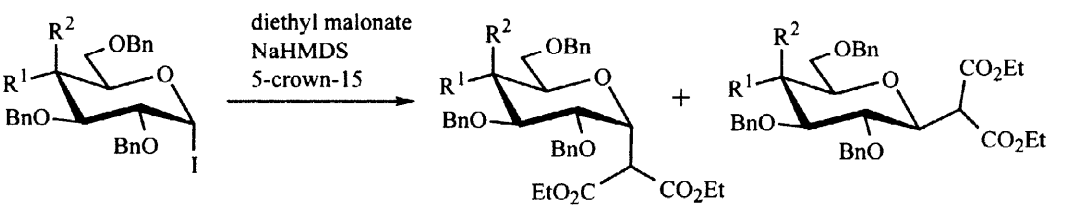


Fig. 1. Electrophilic donors

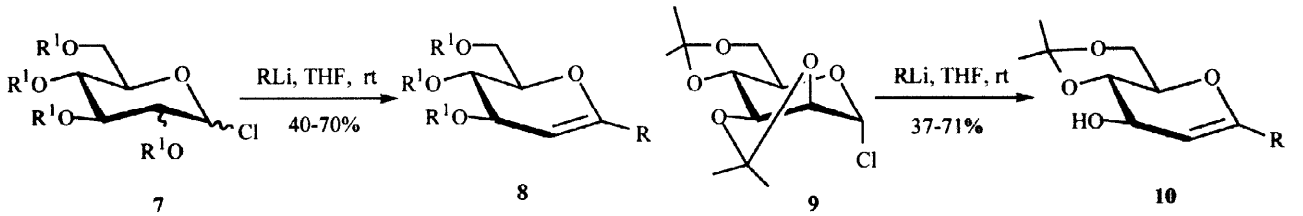
2.1 Glycosyl halides

Glycosyl halides are commonly used as electrophilic donors. The addition of stabilized anions, such as malonate anion [$^-CH(CO_2Et)_2$], to α-glycosyl iodides proceeds with inversion of stereochemistry, by a presumptive S_N2 mechanism, to give *C*-glycosides with good yield and stereoselectivity, even in the absence of a *C*-2 participatory (ester) group.[14] The observed α-selectivity in the *gluco* series, is presumably due to the β-iodide generated through *in situ* anomerization. The galactosyl iodide (**2**) is considerably more reactive than its *gluco* counterpart, directly giving S_N2 product, *C*-galactopyranoside (**6**), with good yield and β-stereoselectivity (Scheme 2). Similar treatment of α-D-glycopyranosyl iodide with tetrabutylammonium cyanide affords a moderate yield of β-D-glycosyl cyanide but is often accompanied by E-2 elimination affording glycal side-product.



Scheme 2

The *C*-glycal with its versatile functional group is an attractive building block in natural product synthesis.[15] *C*-glycals are conveniently prepared by treating ether-protected glycopyranosyl chlorides with organolithium reagents[16] (Scheme 3).

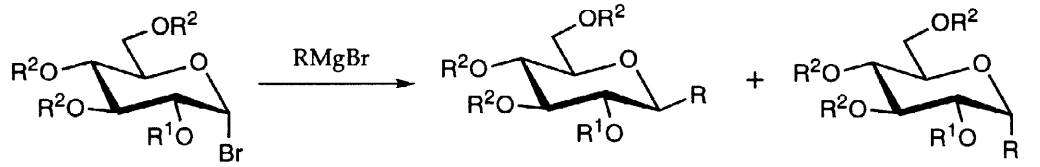


7 8 9 10

R^1 = Me, Bn; R = Me, *n*-Bu, Ph, ^{t}Bu

Scheme 3

Organocuprate, organozinc, organolithium, organotin and Grignard reagents have also been utilized for the *C*-glycosylation of sugar halides.[11] Two examples,[17] in Schemes 4 and 5, exemplify the methodology.



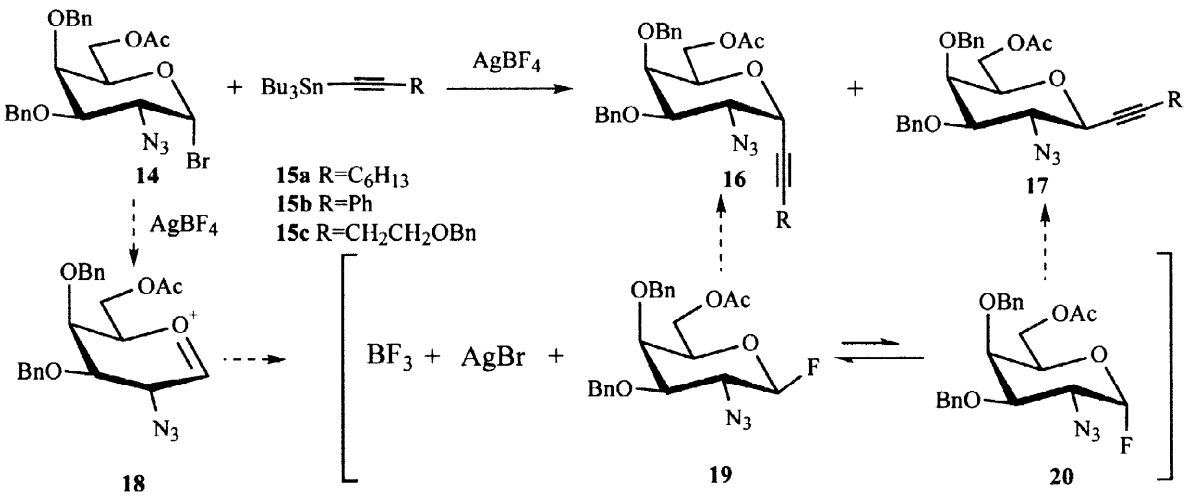
11 12 13

$R^1 = R^2$ = Bn, Me, silyl, α - selectivity R = allyl, vinyl, benzyl, alkynyl, α - selectivity

R^1 = Ac, or Bz, R^2 = Bn, Me, silyl, β - selectivity

Scheme 4

The 2-azido *C*-glycosides **16** and **17** were prepared by reaction of glycosyl bromide (**14**) and organotin complex **15a-c** in the presence of catalytic amount of $AgBF_4$. The lower α-selectivity encountered with metalated phenylacetylene may arise from its higher nucleophilicity causing it to react directly with the oxonium species **18** (Scheme 5). Evidence in support of this mechanism can be taken from Posner's recent publication[18] on the synthesis of antimalarial trioxane derivatives. The coupling of mixed α, β-fluoride sugar derivatives with dimethylaluminum *C*-nucleophiles gave β-*C*-glycosides stereoselectively, implicating the reaction was carried out through a compound **18**-type carbocation intermediate.



14 16 17 18 19 20

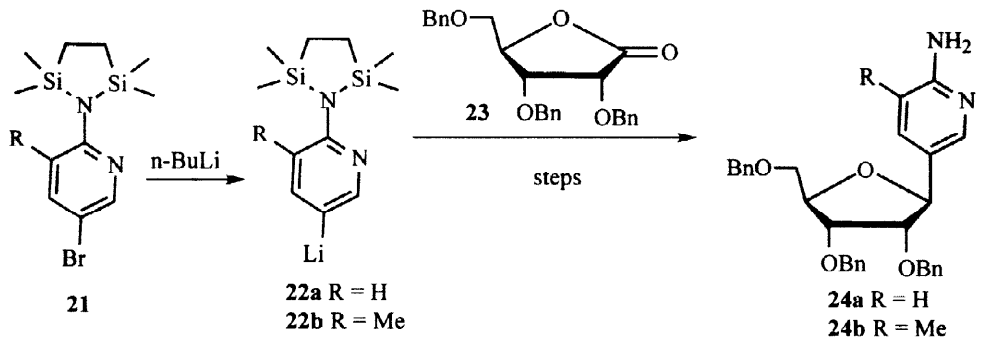
R = C_6H_{13} **16a** : **17a** = 84:16 62%
R = Ph **16b** : **17b** = 60:40 65%
R = $CH_2CH_2OCH_2Ph$ (only **16c**, 46%)

Scheme 5

2.2 C-1 Lactones

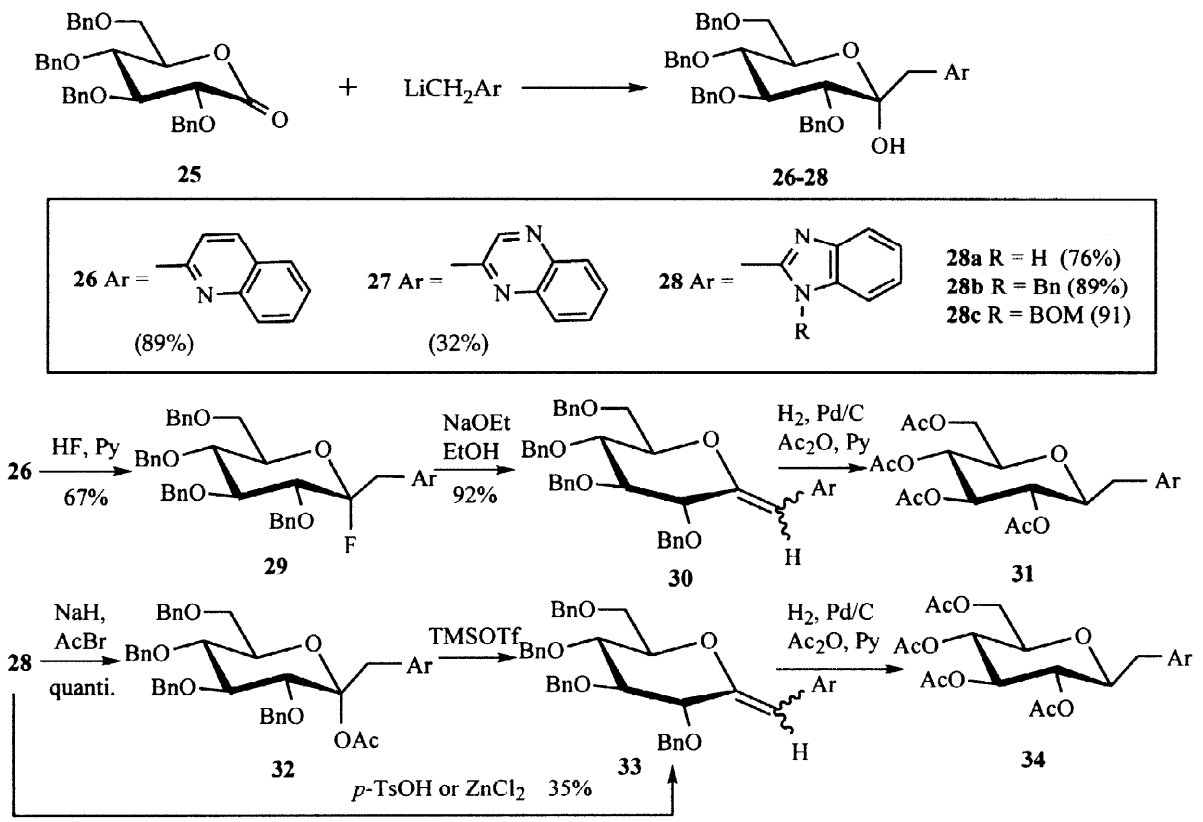
Glyconic acid lactones, useful substrates for the formation of *C*-glycosides, are readily prepared through the oxidation of lactols. A two-step process, nucleophilic addition and reductive removal of the resulting lactol, provides *C*-glycoside in high yield with excellent stereocontrol.

Bromide-lithium exchange of **21** with *n*-BuLi at -75°C forms **22** (Scheme 6). *In situ* phenylation of lactone **23** furnishes a mixture of hemiacetals that can be subsequently reduced with excess $Et_3SiH/BF_3{\cdot}Et_2O$, exclusively providing β-*C*-glycosides **24a-b**.[19,20]



Scheme 6

O-Benzyl protected gluconolactone **25** (Scheme 7) reacts readily with stabilized anions of lithiated 2-methyl quinaldine, quinoxaline, benzimidazole and imidazole at low temperatures to afford *C*-glycosides **26-28, 31, 34** in high yields.

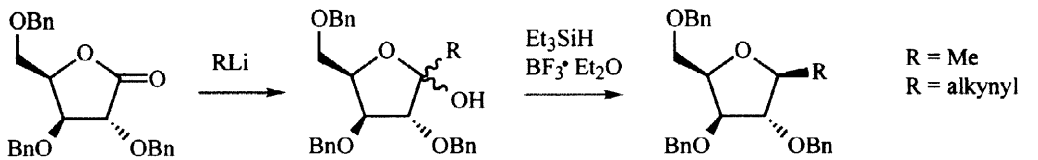


Scheme 7

The direct dehydroxylation of ketopyranose **26-28** with Lewis acid and triethylsilane failed. Schmidt and coworkers[21] designed three alternative routes to obtain the target *C*-glycoside (Scheme 7): 1) formation of glycosyl fluoride, elimination and hydrogenation (**26→31**); 2) acid catalyzed dehydration and hydrogenation (**28→33→34**); and 3) acetylation of the *C*-1 hydroxy group, TMSOTf-catalyzed elimination of AcOH and hydrogenation (**28→32→33→34**), giving the best overall yield.

Grignard reagents have also been used as nucleophiles in β-*C*-glycoside synthesis. Stereoselectivity is considerably reduced when this method is applied to the 2-deoxy sugars.[22]

Nucleophilic addition of organolithium reagents to protected glycofuranolactones **35** and $Et_3SiH/BF_3{\cdot}Et_2O$ induced reductive cleavage of the resulting hemiacetals **36** gives an expedient route to *C*-glycofuranosides[23] (Scheme 8). Stereocontrol results from hydride delivery *cis*- to the adjacent oxygen functional group.

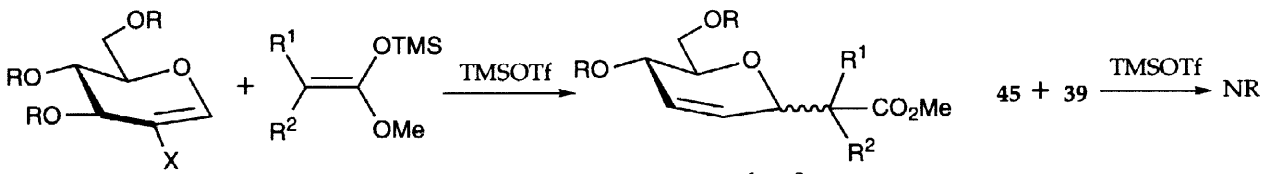


35 **36** **37**

Scheme 8

2.3 Glycals

The direct synthesis of *O*-glycosides from glycals affords high yields and good stereoselectivity. The easy accessibility and versatile functionality of glycals also provides advantages in *C*-glycoside synthesis.[24] Csuk and co-workers reported the formation of 2,3-unsaturated *C*-glycosides from glycals and silyl ketene acetals after allylic rearrangement (Scheme 9).[25] While the benzoylated glucal **43** reacts with **39** to give *C*-glycoside **44** in 98% yield, the 2,3,4,6-tetra-*O*-benzoyl-1,5-anhydro-D-arabino-hex-1-enitol (**45**) does not react under the same coupling conditions (disfavored allylic rearrangement).



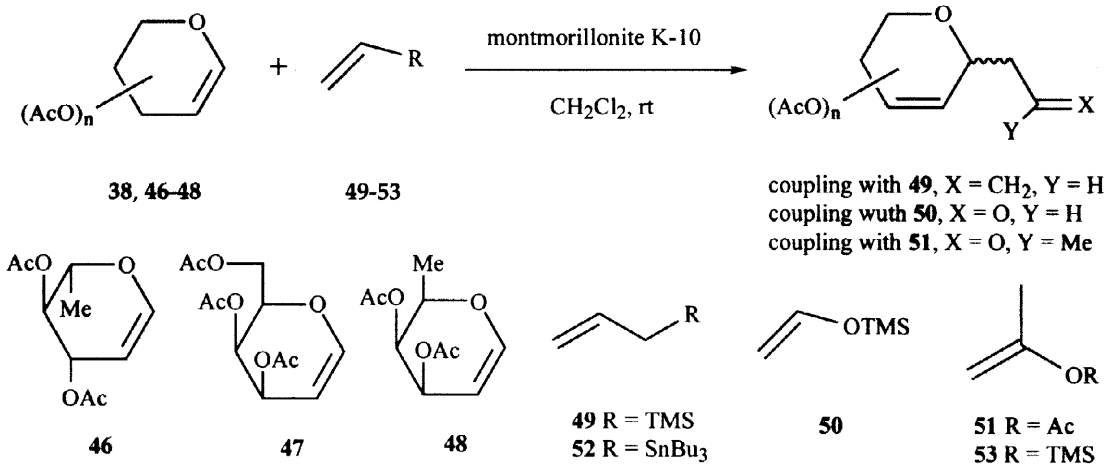
38 R = Ac, X = H
43 R = Bz, X = H
45 R = X = OBz

39 $R^1 = R^2 = Me$
41 $R^1 = R^2 = Et$

40 R = Ac, $R^1 = R^2 = Me$ 68% α:β =1:4
42 R = Ac, $R^1 = R^2 = Et$ 25% only β
44 R = Bz, $R^1 = R^2 = Me$ 98% α:β =1:1.6

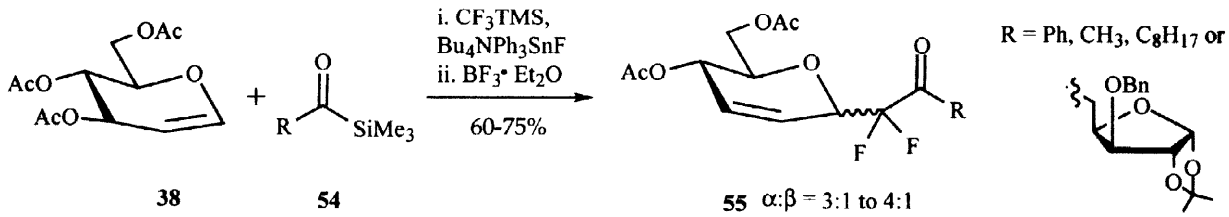
Scheme 9

An inexpensive and reusable acid clay, Montmorillonite K-10, serves as an efficient catalyst for *C*-glycosylation of glycals (**38**, **46-48**) with allylsilane (**49**), vinyloxysilane (**50**) and isopropenyl acetate (**51**) mainly giving α-products (Scheme 10).[26] *C*-glycosidation of glycal **46** with allytributyltin **52** demonstrated that it was much less reactive than allylsilane **49**. In addition, 2-siloxypropene **53** afforded much lower yields than isopropynyl acetate **51**. The same clay has been applied to the aryl *C*-glycosidation of unprotected 2-deoxy monosaccharides and their methyl glycosides with high β-selectivity.[27] These reactions not only employ an environmentally compatible catalyst, but the work-up involves only filtration and evaporation of solvent resulting in easy recovery and re-use of catalyst and solvent.



Scheme 10

Difluoroenoxysilanes, prepared from acylsilanes **54** and CF_3TMS under fluoride activation, can be glycosylated by glucal **38** to yield *C*-glycosides **55** having a difluoromethylene in place of the anomeric oxygen[28] (Scheme 11).

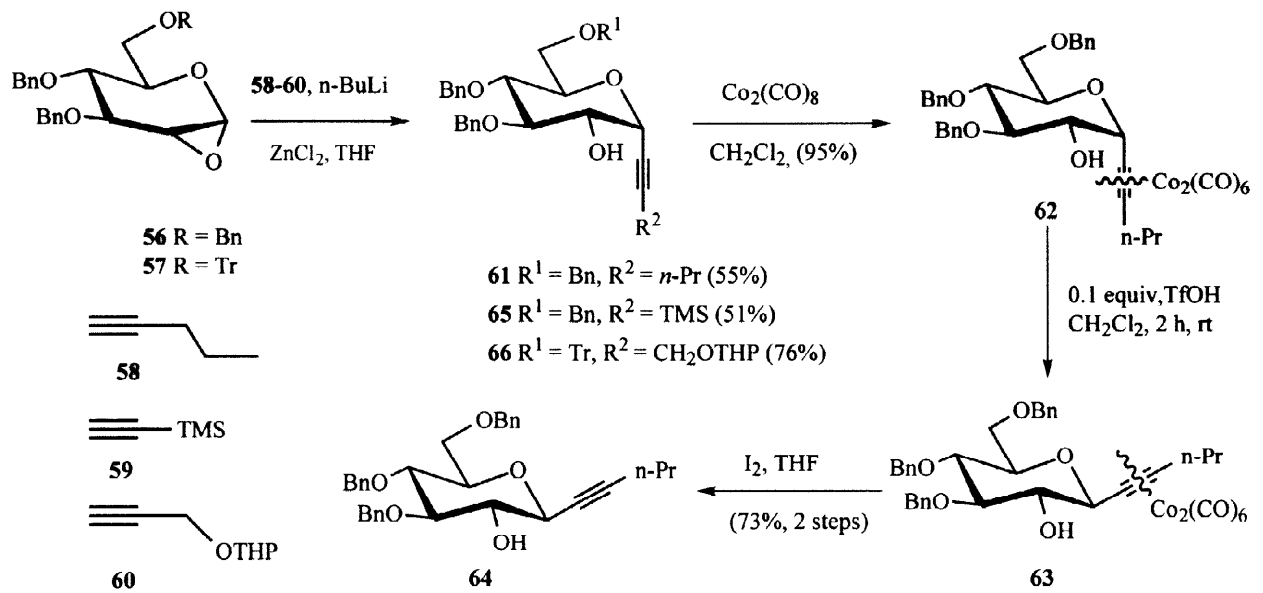


Scheme 11

2.4 1,2-Anhydrosugars

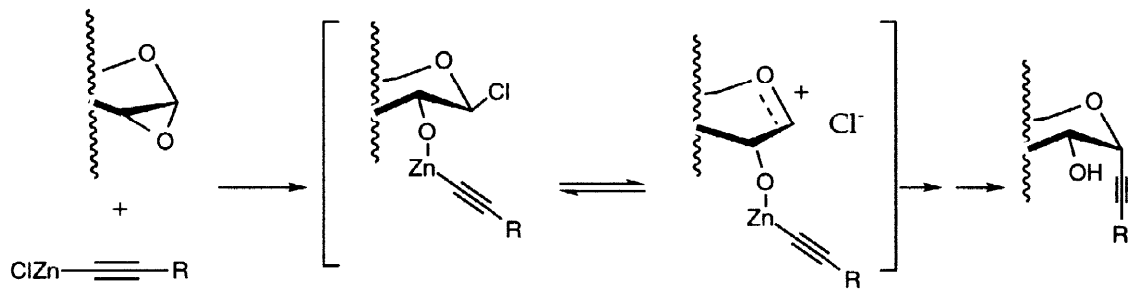
1,2-Anhydro sugars are widely used as donors in *O*-glycosidation reactions resulting in 1,2-*trans* stereoselectivity.[29,30] These 1,2-anhydrosugars can be synthesized from glycals,[31] *C*-1 halide,[32] or *C*-2 tosylated sugars.[33] The last two reactions are typical S_N2 processes with exclusive control of configuration.

Early work using 1,2-anhydrosugars for *C*-glycosidation focused on their reactions with dialkyl (aryl) cuprates in the presence of *n*-BuLi. Van Boom and co-workers[34] extended this reaction to lithiated alkynyl derivatives. The desired ring-opening of 1,2-anhydro 3,4,6-tri-*O*-benzyl-α-D-glucopyranose (**56**) in the presence of zinc chloride proceeds with retention of configuration to afford α-*C*-(alkynyl)-glycosides **61**, **65**, and **66**. (Scheme 12)



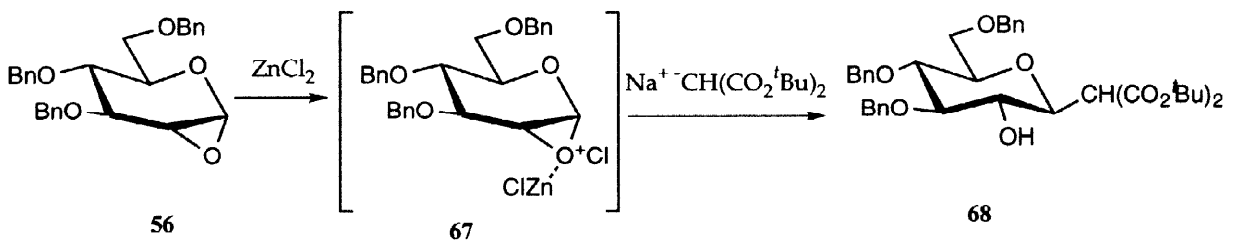
Scheme 12

The high α selectivity can be rationalized by the mechanism shown in Scheme 13.



Scheme 13

Epimerization of the α- to β-configuration was also investigated. Protection of the yne system in **61** with dicobaltoctacarbonyl resulted in the complex **62**, which was epimerized with catalytic amounts of triflic acid. Decomplexation of **63** with iodine led to the isolation of β-*C*-glycoside **64** (Scheme 12). Ring-opening of 1,2-anhydrosugar **56** with $ZnCl_2$ and excess sodium/di-*tert*-butyl malonate proceeds stereoselectively to give the β-*C*-glucoside **68** (Scheme 14).

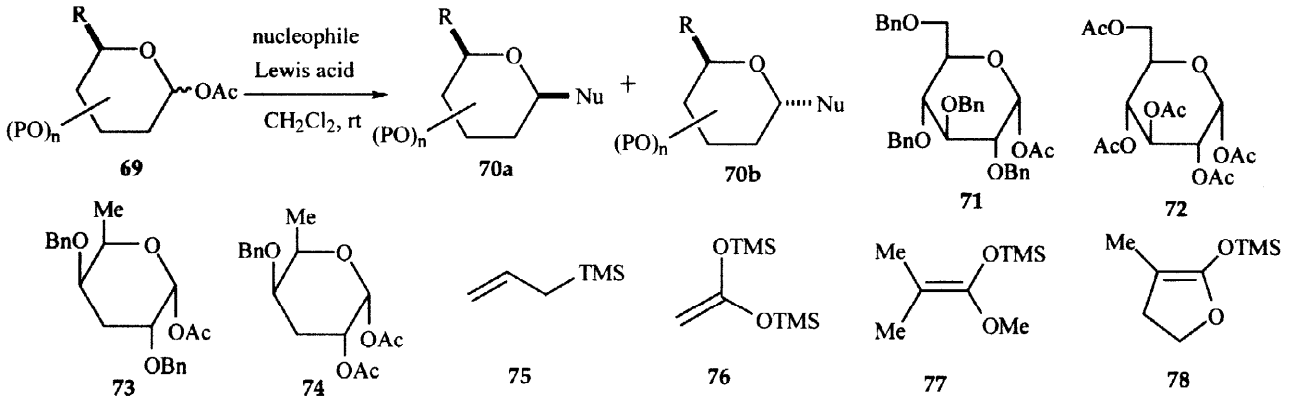


Scheme 14

2.5 C-1 Acetylated carbohydrates

Most of *C*-1 acetylated sugars react directly with allyl and acetylenic silanes in the presence of Lewis acids (TMSOTf or $BF_3 \cdot Et_2O$) to generate α-*C*-glycopyranosides in good yield (Scheme 15).[35-39] Kishi and

Minehan[40] used glycosyl-1-*O*-acetates and silyl ketene acetals to obtain *C*-glycosides. The stereochemical outcome of these reactions can be controlled by exploiting the electronic and/or steric properties of the nucleophiles (Table 1).



Scheme 15

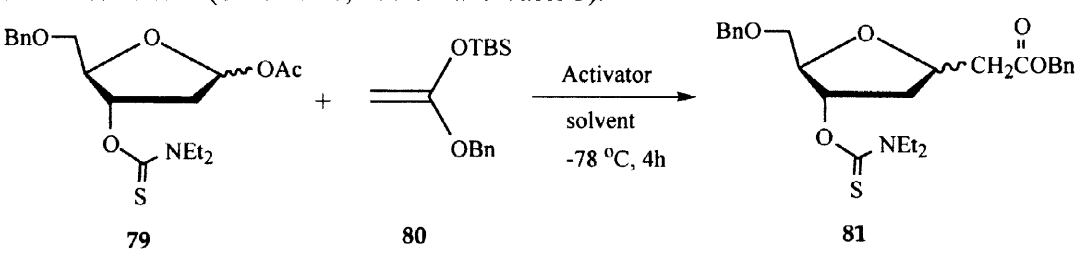
Table 1. The Electronic Effect of the Silyl Ketene Nucleophiles.

Substrate	Nucleophile	β : α	Yield%	Method*	Substrate	Nucleophile	β : α	Yield%	Method*
71	**75**	<1 : 10	55	A	**73**	**75**	<1 : 10	96	A
71	**76**	1.4 : 1	57	A	**73**	**76**	1.1 : 1	72	A
71	**77**	3 : 1	64	A	**73**	**77**	2 : 1	78	A
71	**78**	3 : 1	65	A	**73**	**78**	8 : 1	72	A
72	**75**	<1 : 10	50	B	**74**	**75**	<1 : 10	50	A
72	**76**	>10 : 1	47	B	**74**	**76**	>10 : 1	52	A
72	**77**	>10 : 1	53	B	**74**	**77**	>10 : 1	71	A
72	**78**	NR	--	B	**74**	**78**	>10 : 1	60	A

* Method A: 1 eq of TMOTf was used; Method B: 1 eq of TMSOTf and 9 eq of BF_3•OEt_2 were used.

These studies showed that silyl ketene acetals preferentially formed β-*C*-glycosides. Allylsilanes, having lower relative nucleophilicity, gave α-*C*-glycosides. An increase in the steric hinderence at the nucleophile's reaction terminus results in enhanced β-selectivity. The presence of a neighboring participating group (such as OAc) on C-2 can also greatly increase the β-selectivity.

Finding effective activators and solvents can be important for improving the yield and stereoselectivity in *C*-glycoside synthesis. In a case study, Mukaiyama and co-workers[41] systematically investigated the influences of these factors (Scheme 16, Table 2 and Table 3).



Scheme 16

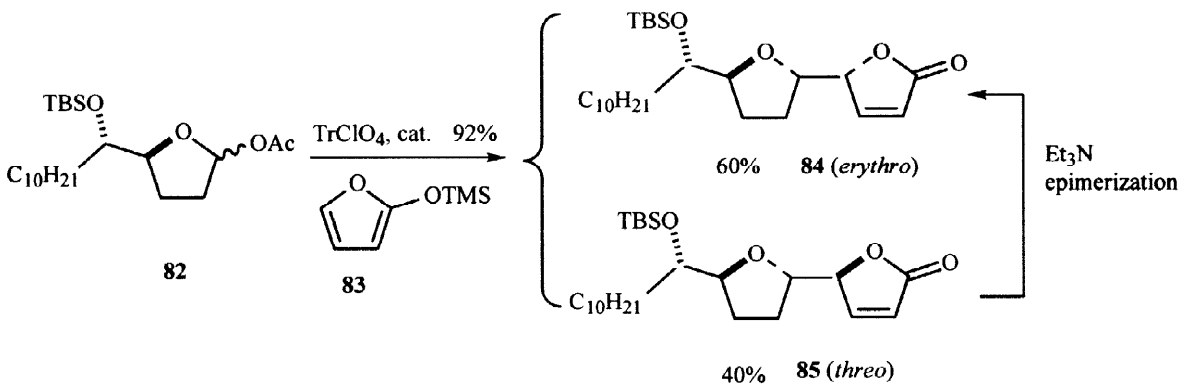
Table 2. Effect of Activator in *C*-Glycosylation Performed in CH_2Cl_2

Activator	mol/100	Yield%	α/β
$SnCl_2(OTf)_2$	100	9	28/72
$TiCl_2(OTf)_2$	100	5	25/75
$SiCl_2(OTf)_2$	100	86	3/77
$SiCl_2(OTf)_2$	200	82	10/90
$SiCl(OTf)_3$	50	86	19/81
$SiCl(OTf)_3$	100	89	4/96
$SiCl(OTf)_3$	200	81	2/98

Table 3. Effect of Solvent in *C*-Glycosylation Using $SiCl(OTf)_3$ Activator(100 mol/100)

Solvent	Yield	α/β
toluene	64	20/80
CH_2Cl_2	89	4/96
$EtNO_2$	54	33/67
$EtNO_2$	21	15/85
CH_3CN	59	31/69

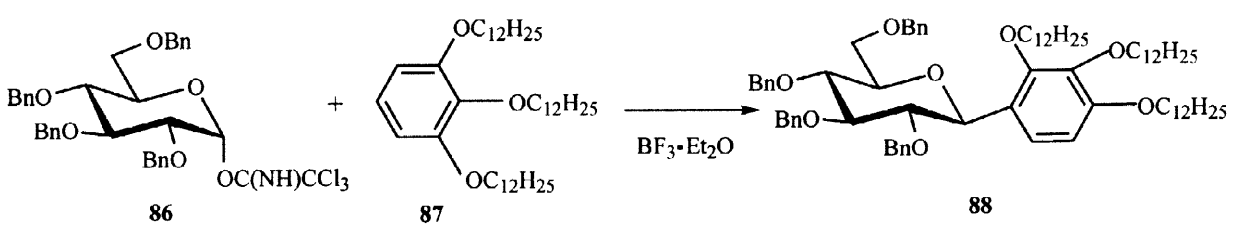
$TrClO_4$ (0.1 eq) and TMSOTf (1 eq) are excellent co-promotors in the *C*-glycosidation of furanose acetate (**82**) with [(trimethylsilyl)oxy]furan (**83**) (Scheme 17).[42]



Scheme 17

2.6 Anomeric trichloroacetimidates

Schmidt and co-workers[43,44] have demonstrated that anomeric trichloroacetimidates are useful glycosyl donors in the synthesis of β-*C*-glycosides, particularly in aryl *C*-glycosidations. Glycosyl imidate **86** reacts with electron-rich aromatic compounds such as **87** in the presence of $BF_3 \bullet Et_2O$ or TMSOTf, to stereoselectively afford β-*C*-aryl glycosides in good to excellent yields (Scheme 18).[22] The *N*-tetrachlorophthalimido (*N*-TCP) protected glucosaminyl trichloroacetimidate can react to form *C*-glycosides under similar conditions.[43]



Scheme 18

3. *C*-glycosylation Through Anomeric Anionic Intermediates

The "umpolung" strategy is complementary to the electrophilic methods described in Section 2. Most of the applications, based on the deprotonation of the anomeric center, rely on the use of lithiated glycosyl nucleophiles to prepare *C*-glycosides.[45]

3.1 Reductive lithiation-dianion method

Paulsen and co-workers[46] first reported the carbon-elongation of open-chain carbohydrates by polarity inversion (umpolung) at the anomeric center using dianions of hydroxylated 1,3-dithianes. This idea has more recently been applied to 1-nitronates **89**, 2-deoxysugars **90**, glycals **91** and dilithiated sugars **92** (Fig. 2).[13]

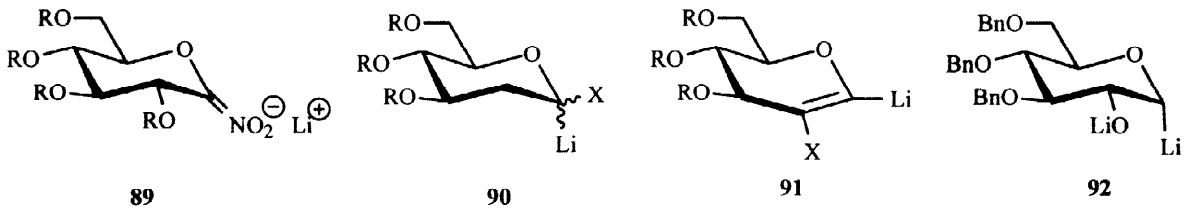
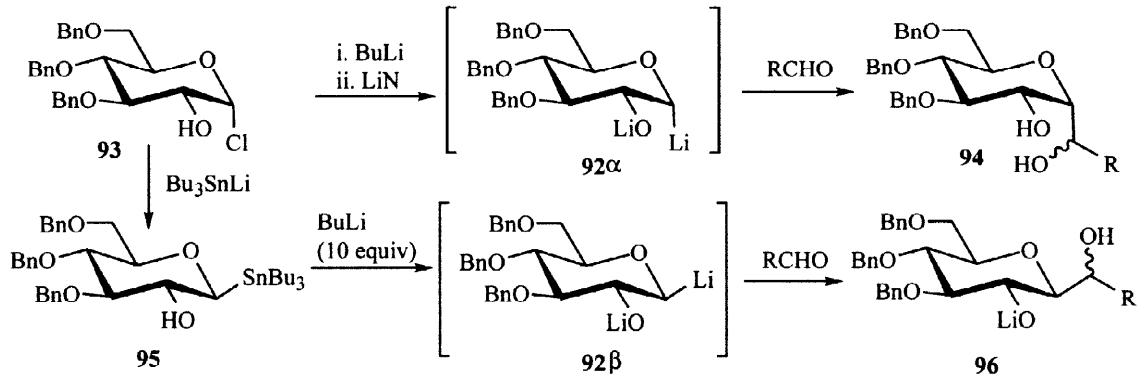
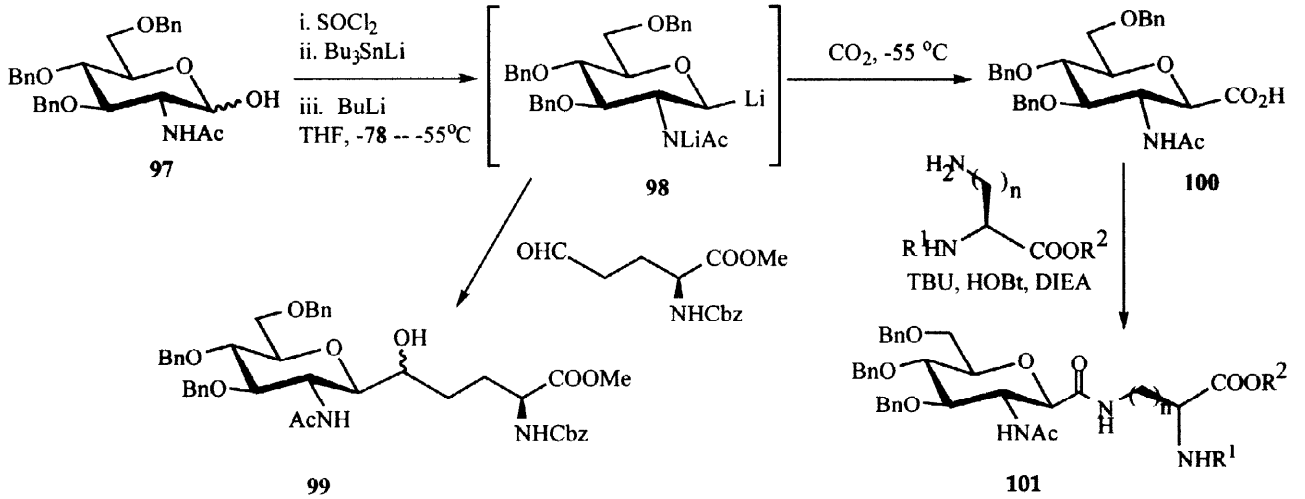


Fig. 2. Anomeric anionic species used in *C*-glycosidation

Kessler[47-50] generated the α-dianion **92α** from the vicinal halohydrin **93** by treatment with *n*-BuLi and lithium naphthalenide. The presence of *C*-2-lithium alkoxide effectively prevents 1,2-elimination thus blocking the formation of the undesired glycal (Scheme 19). The lithiation of the corresponding β-glucosyl stannane **95** provides the β-dianion **92β**. The same approach has also been applied to amino sugars to prepare *C*-glycopeptides.[51-53] (Scheme 20)



Scheme 19

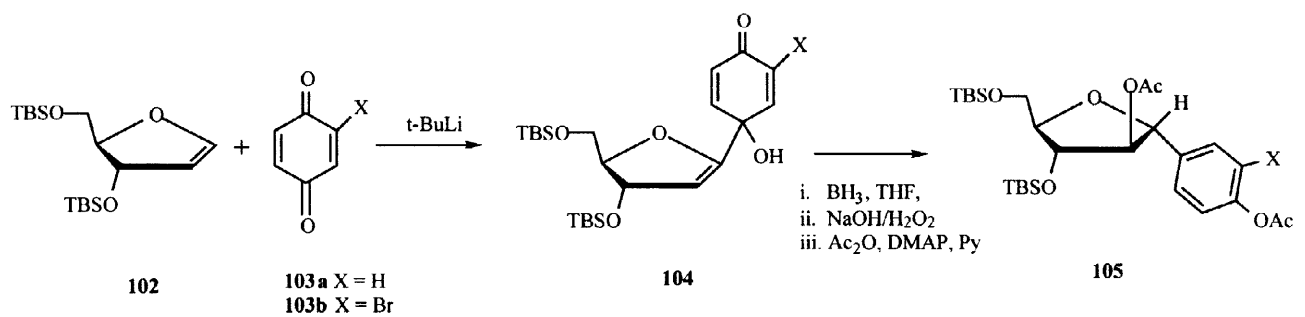


Scheme 20

3.2 Lithiated 1-alkoxyvinyl anions

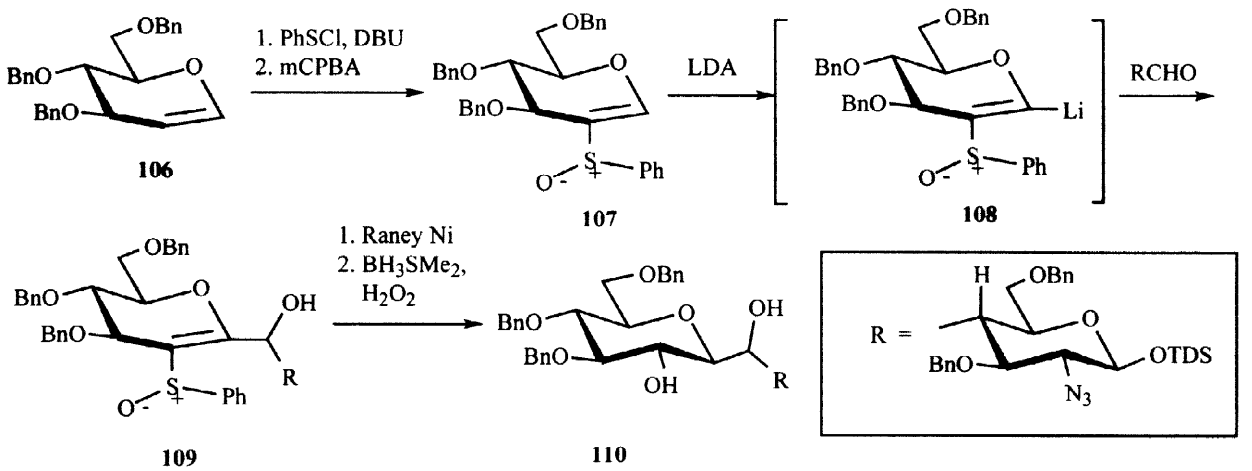
3.2.1 Alkoxyvinyl deprotonation

The addition of a lithiated glycal derivative to a quinol ketal or quinone followed by aromatization and hydroboration affords *C*-aryl arabinofuranosides (Scheme 21). The 3,4 *trans*-disubstituted dihydrofuran derivative gave α-*C*-glycoside **105** while *cis*-isomer gave the corresponding β-*C*-xylofuranoside.[54-56]



Scheme 21

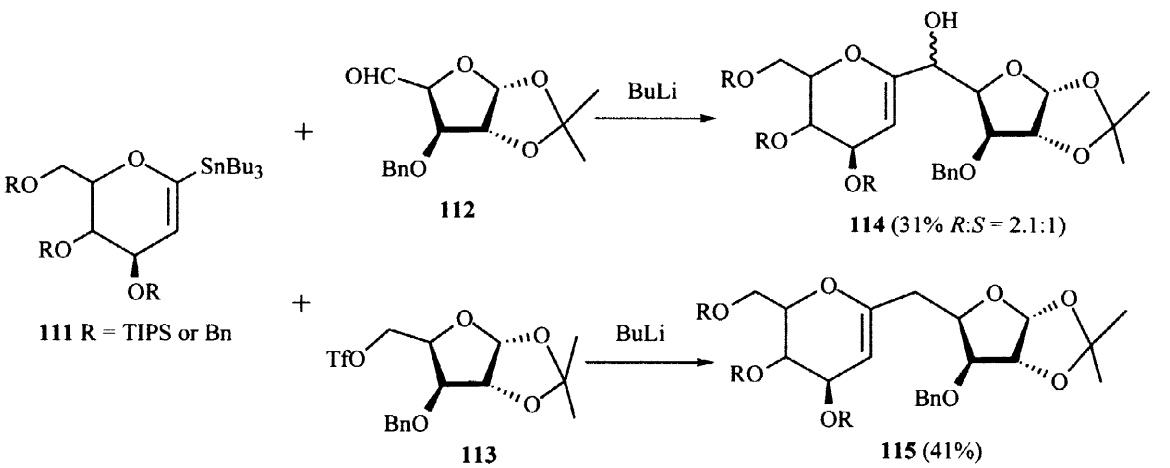
Schmidt and co-workers[57] have used *C*-2 sulfoxide-stabilized 1-*C*-lithiated glucal **108** as C_6 nucleophile. Its reaction with various C_7 aldelyde electrophiles provides high yields of hydroxy-methylene-bridged *C*-glycosides. The lithiated intermediate **108** is readily prepared from glycal **106** (Scheme 22). Raney nickel removal of the phenylsulfinyl group in **109** and stereospecific hydroboration affords the β-*C*-glycoside target **110**.



Scheme 22

3.2.2 Tin-lithium transmetallation

Reaction of stannane **111** with electrophiles, such as aldehyde **112** or triflate **113**, in the presence of *n*-BuLi affords *C*-disaccharides **114** and **115** (Scheme 23). Tin-lithium exchange takes place during the reaction and the lithiated sugar generated *in situ* is believed to act as the nucleophile in *C*-glycosidation[58] (also see Schemes 19 and 20).



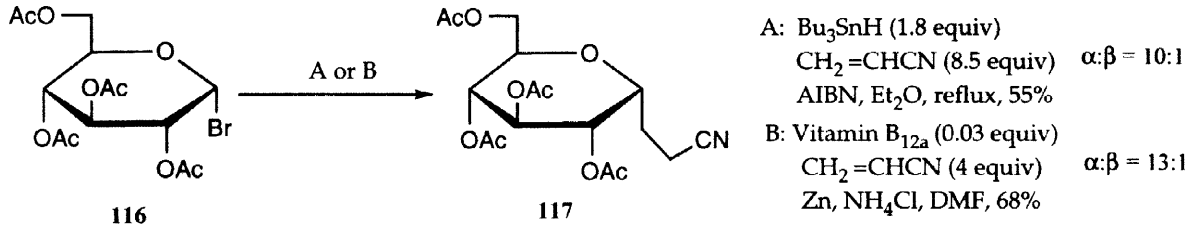
Scheme 23

4. Intermolecular Free Radical Approaches

An anomeric free radical is a common α-alkoxyalkyl radical. Its elevated HOMO can interact with the LUMO of an electron-poor alkene, such as acrylonitrile, acrolein, to form a *C-C* bond. The merits of intermolecular free radical approaches are: 1) Their compatibility with a wide range of protecting groups, and 2) Undesired elimination and/or epimerization reactions are suppressed since no anion is generated in the carbohydrate moiety.

4.1. Radical C-glycosylation using glycosyl bromide

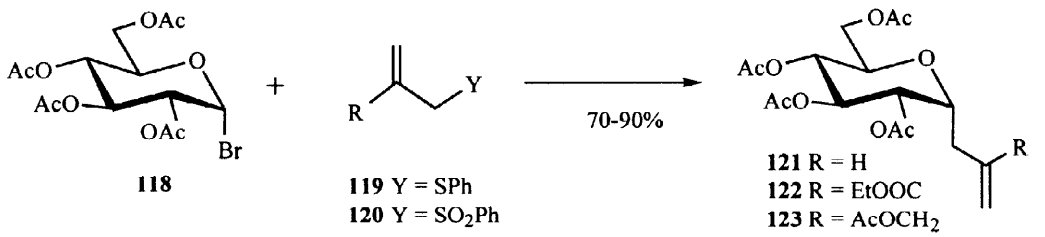
The most commonly used approach for radical *C*-glycosidation is the reaction of the radicals, generated from glycosyl bromides, tributyltin hydride and AIBN, with conjugated electrodeficient alkenes.[59] In a case study, Schäfer[60] showed that vitamin B_{12a} (in place of AIBN as radical reaction initiator) together with Zn and NH_4Cl (as co-catalysts) improved the yield and stereoselectivity of radical *C*-glycosylation (Scheme 24).



116 **117**

Scheme 24

Similarly, allylic sulfides **119** or sulfones **120** in the presence of hexabutyldistannane[61] give the corresponding α-*C*-allyl glycosides **121-123** in good yields (Scheme 25).



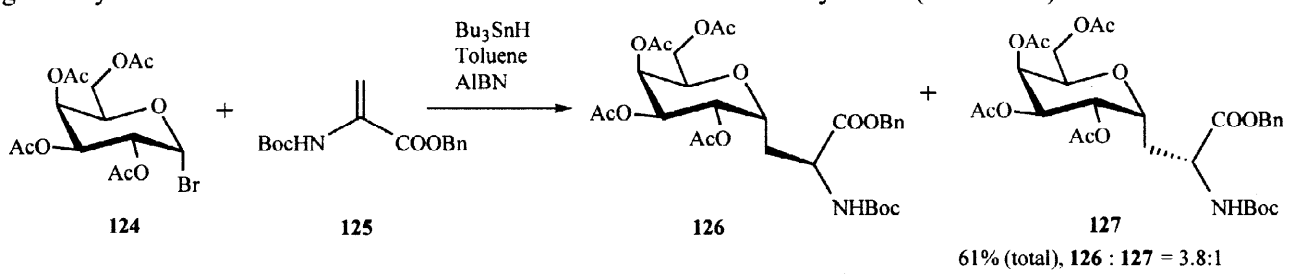
118

119 Y = SPh
120 Y = SO_2Ph

121 R = H
122 R = EtOOC
123 R = $AcOCH_2$

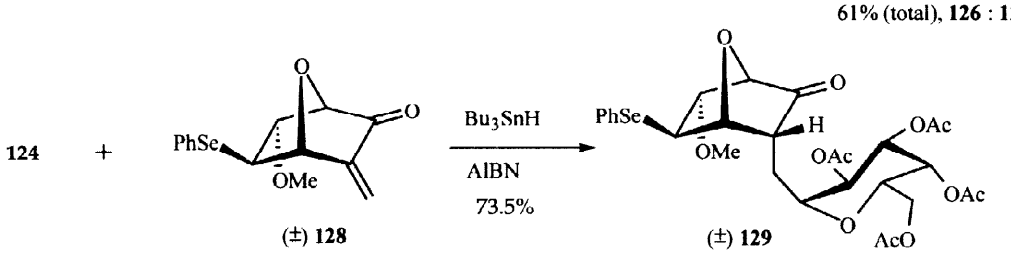
Scheme 25

Radical reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**124**) and Boc-dehydroalanine-OBn (**125**) in the presence of tributyltin hydride and AIBN gives a mixture of the epimeric *C*-galactosyl alanine derivatives **126** and **127** in a ratio of 3.8:1 with 61% yield.[62] (Scheme 26)



124 **125** **126** **127**

61% (total), **126** : **127** = 3.8:1

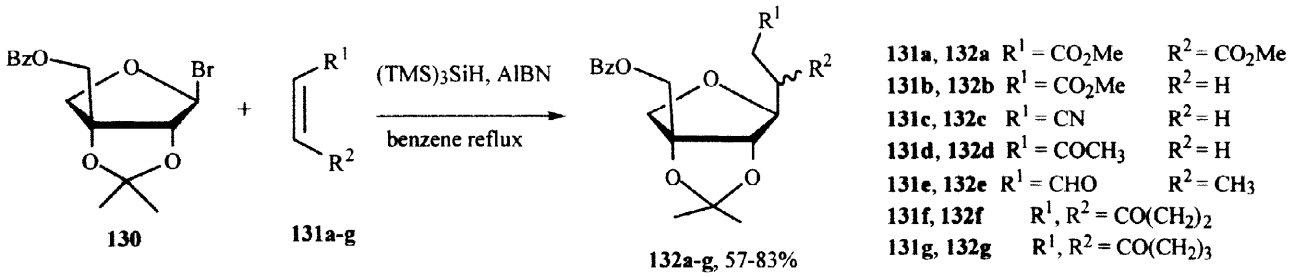


(±) **128** (±) **129**

Scheme 26

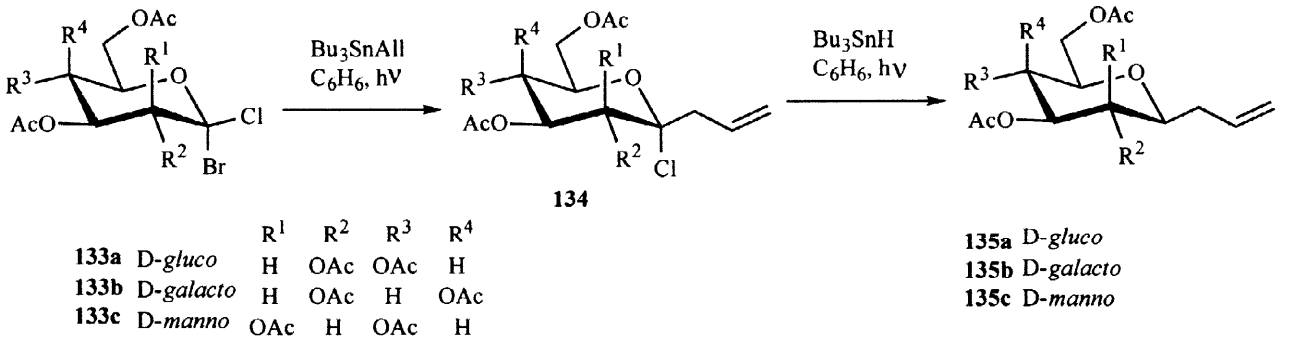
Radical glycosylation of (±)**128** with **124** gives a diastereomeric mixture of (±)**129** (Scheme 26).[63]

Apiosyl bromide **130**, refluxed in benzene with a large excess of olefin derivatives **131a-g** in the presence of TMS_3SiH and AIBN, gave a good yield of *C*-glycosides **132a-g** (Scheme 27).[64]



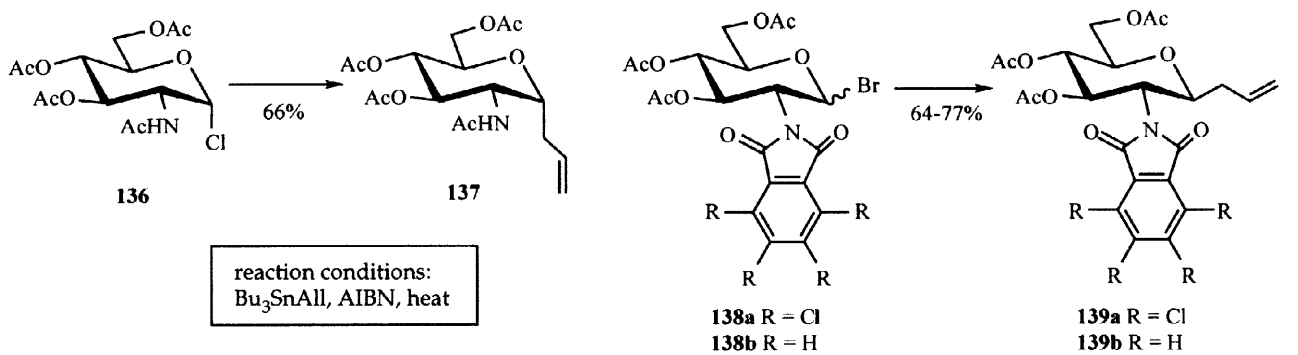
Scheme 27

Keck reaction of the 2,3,4,6-tetra-*O*-acetyl-1-bromide-β-D-glycopyranosyl chlorides (**133a-c**) was investigated by Praly and co-workers[65] under photolytic conditions (UV light irradiation). This reaction is carried out under very mild conditions and gives good yield and stereoselectivity. (Scheme 28).



Scheme 28

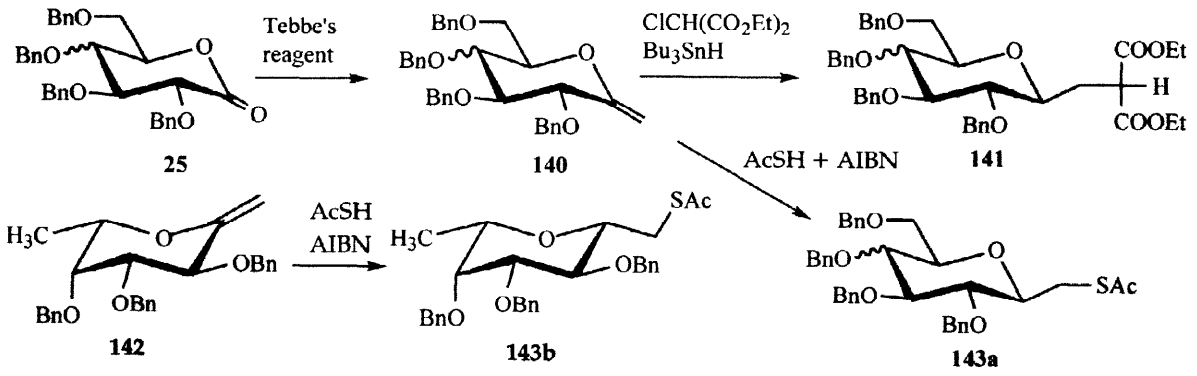
Keck reaction of the glycosyl chloride derivative of *N*-acetylglucosamine **136** affords the α-*C*-glycoside **137**. The same allylation of **138**, directed by the sterically hindered 2-phthalimido protecting group, provides the β-*C*-glycosides in good yield and high stereoselectivity (Scheme 29).[66]



Scheme 29

4.2 Radical C-glycosylation with exomethylenic carbohydrates

Glyco-*exo*enitol **140**, obtained by reaction of the corresponding lactone **25** with Tebbe's reagent, reacts with a malonyl radical to give the stable *C*-glycoside (**141**) with β-steroselectivity based on the preferred configuration of the anomeric radical (Scheme 30). Reaction of the same malonyl radical with *exo*-methylenic furanose gives the corresponding β-*C*-furanoside.[67] Similarly, radical addition of thiol acetic acid to compound **140** or **142**, with AIBN initiator, generate β-*C*-glycosides **143a** or **143b** in good to excellent yields.[68]



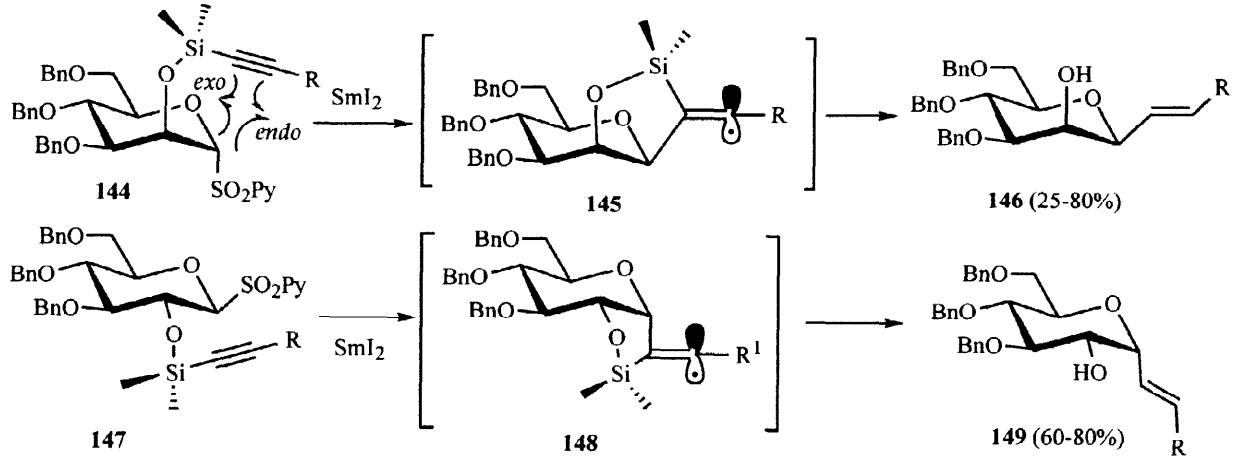
Scheme 30

5. Samarium Iodide Mediated *C*-Glycosylation

SmI_2 has played an increasing role in organic synthesis since its introduction in the late 1970's. SmI_2 promotes a number of important reactions in organic synthesis *via* one- and two- electron transfer processes including: radical cyclizations, ketyl-olefin coupling reactions, pinacolic coupling reactions, Barbier-type reactions, and aldol-type reactions.[69] Sinaÿ and Beau can be credited with the major contribution of introducing SmI_2-mediated reactions for *C*-glycoside synthesis.

5.1. Single electron transfer reactions

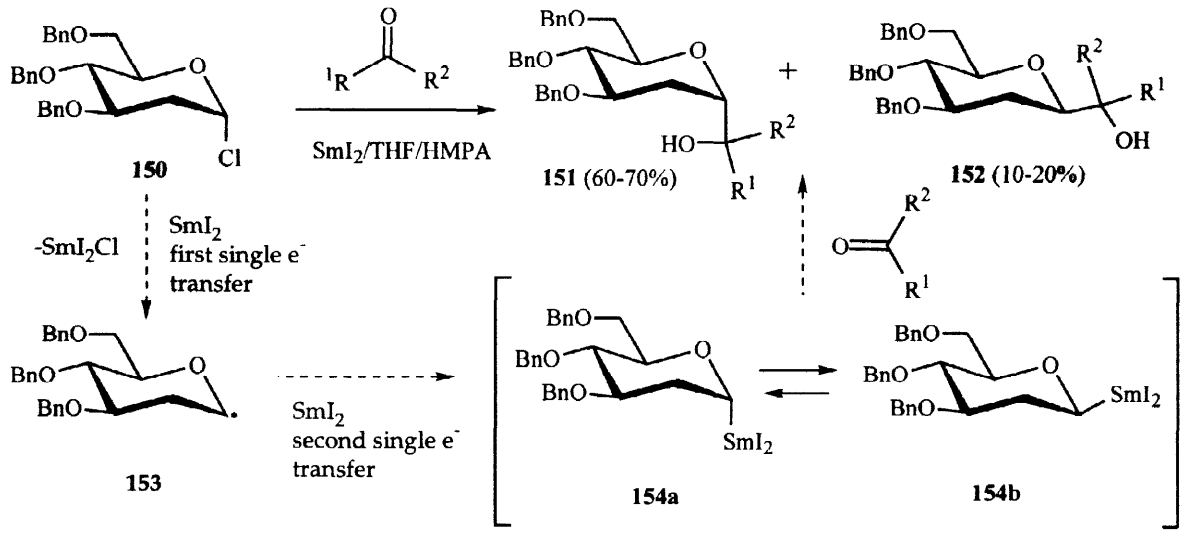
The stereospecific synthesis of 1,2-*cis*-*C*-glycosides was accomplished using a silicon-tethered unsaturated group at the C-2 hydroxyl group.[70,71] These reactions proceed through an anomeric radical generated *in situ* followed by *exo* cyclization (Scheme 31).



Scheme 31

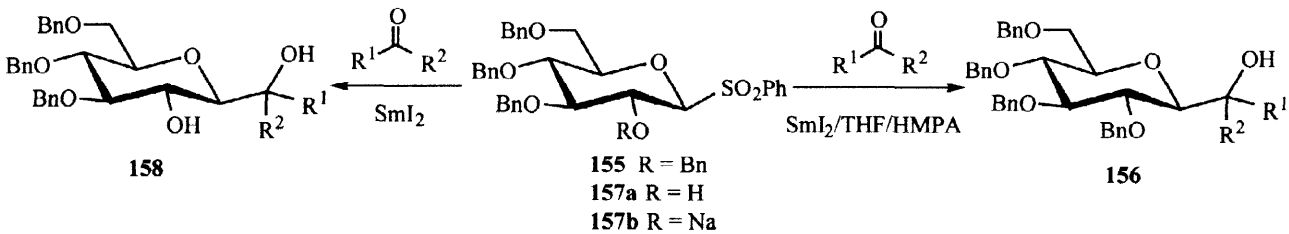
5.2. Sequential single electron transfer reactions

Glycosylsamarium (III) derivatives, generated from glycosyl chlorides or sulfones, undergo Barbier-type condensation with carbonyl compounds to form *C*-glycosides. These reactions are believed to proceed through two consecutive one-electron transfers to form a glycosyl anion intermediate.



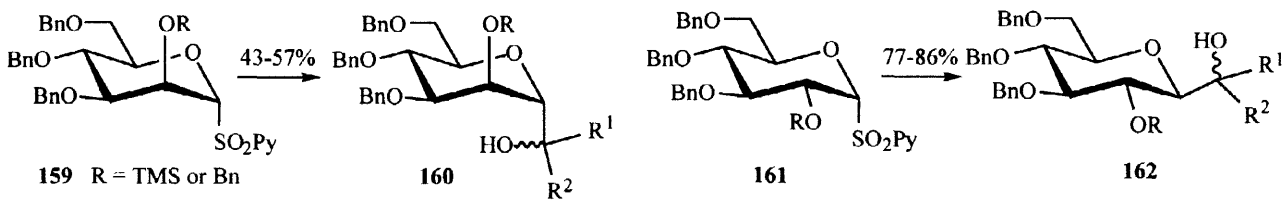
Scheme 32

Sinaÿ and co-workers[72] demonstrated that reductive samariation of 2-deoxy glycopyranosyl chloride (Scheme 32) and perbenzylated glucopyranosyl phenyl sulfone (Scheme 33) with SmI_2/THF/HMPA in the presence of carbonyl compounds afforded the desired *C*-glycosides (α-product for 2-deoxy sugar, β-product for glycopyranoside). The presence of a protecting group at the *C*-2 hydroxyl group is a limitation of this approach because the intermediate glycosyl samarium species can collapse into a glycal. The use of a *C*-2-alkoxide, such as **157b**, can overcome this potential problem (Scheme 33).



Scheme 33

By using glycosyl aryl sulfones, Beau and co-workers[73] prepared the corresponding 1,2-*trans*-*C*-glycosides under Barbier conditions. Ether protected *manno*-2-pyridyl sulfone **159** provides the α-*C*-mannopyranosides **160** in good yields while the ether protected *gluco*-2-pyridyl sulfone **161** generates the β-*C*-glucopyranosides **162** in moderate yields, together with glucal side-product (Scheme 34).

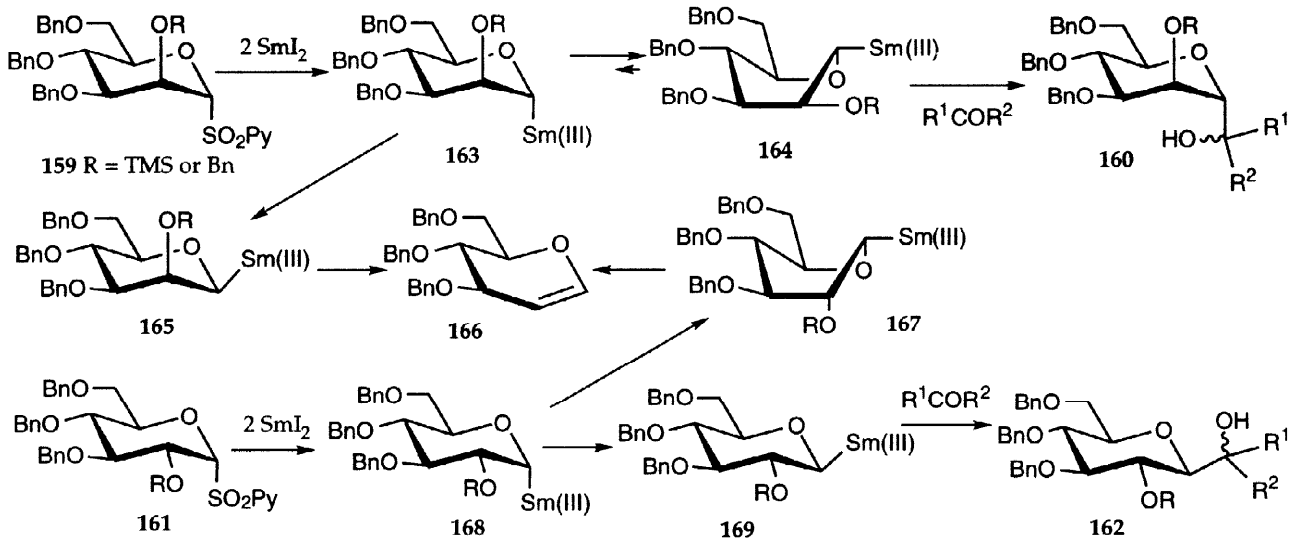


reaction condition: R^1COR^2, SmI_2, THF; If R = Ac, glucal is the major product

Scheme 34

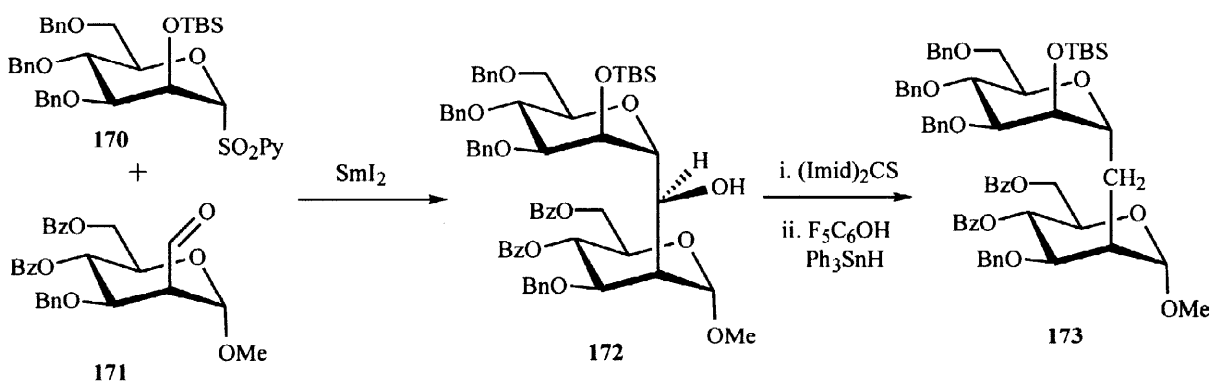
An explanation for the observed stereochemical outcome of the reaction is that the Sm^{3+}-substitutent in the intermediate is bulky and tries to adopt the thermodynamically more stable equatorial position. In the

manno-series this is possible through a boat-like conformation **164**, while in the *gluco*-series a $^4C_1$-conformation **169** fulfills such a requirement (Scheme 35).

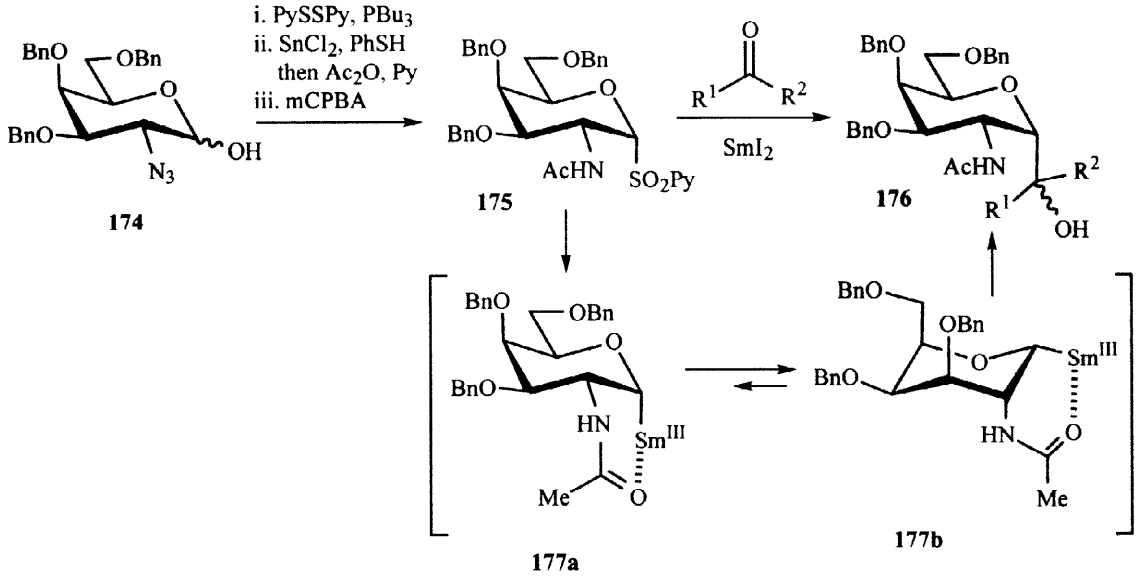


Scheme 35

The same approach was exploited for the synthesis of Man α-(1→2)-Man *C*-disaccharide[74] (Scheme 36). An unexpected outcome of SmI_2-promoted *C*-glycosidation of the pyridylsulfone of *N*-acetyl galactosamine **175** with aldehydes or ketones was the selective formation of the 1,2-*cis*-product[75] (Scheme 37). The observed α-selectivity can be explained by the chelate involvement of the *N*-acetyl group at C-2 as shown in compound **177**.

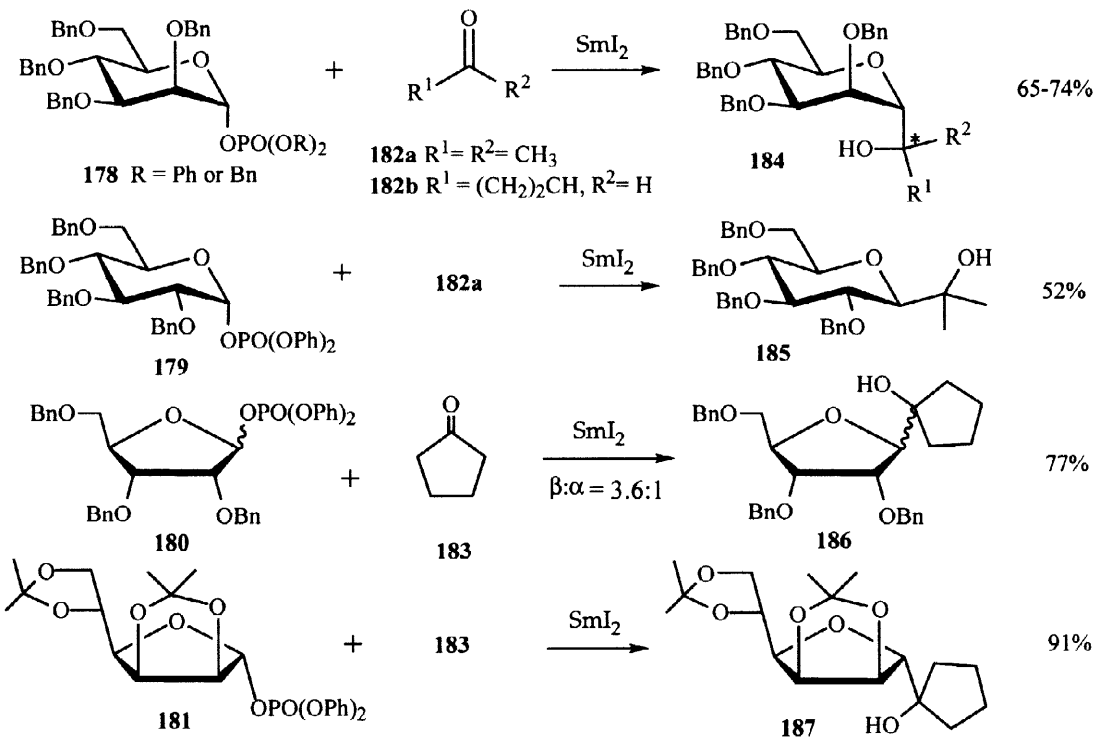


Scheme 36



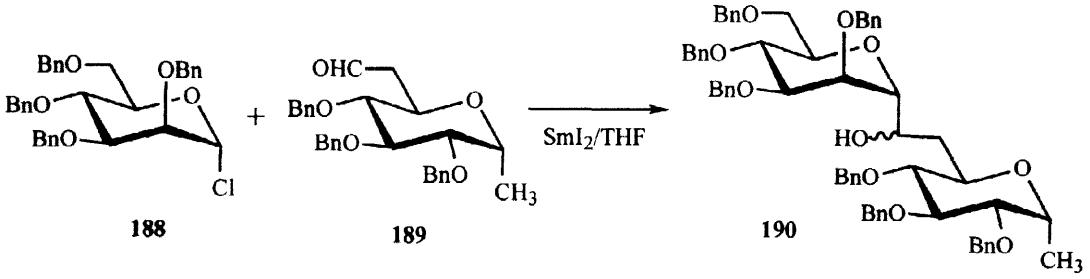
Scheme 37

The use of a phosphate group as an acceptor in the initial electron transfer from SmI_2 had been described for α-cyanophosphates[76] and allylic phosphates.[77] Wong[78] first applied this approach to the coupling of pyranosyl and furanosyl phosphates with a carbon radical or anion acceptor in the presence of SmI_2. Generally, 1,2-*trans*-linked *C*-glycosides are the major products, similar to the results obtained with the aryl sulfone substrates (Scheme 38).



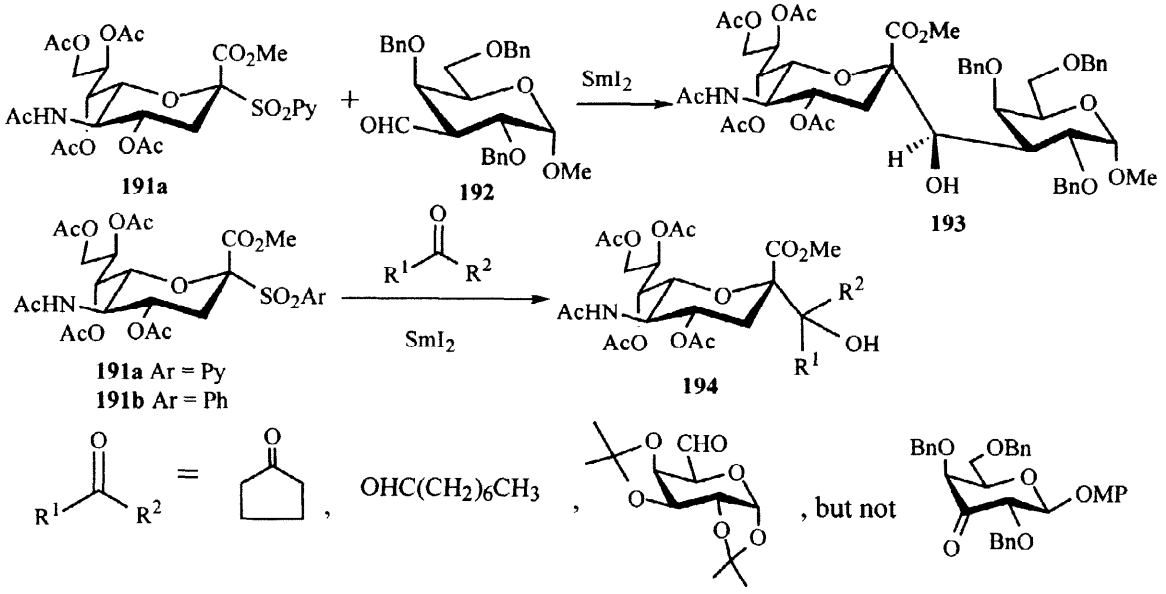
Scheme 38

Perbenzylated α-D-mannopyranosyl chloride **188** can be coupled with sugar aldehyde **189** in the presence of SmI_2 to furnish *C*-disaccharide **190** in 57% yield and with good α-selectivity (α : β = 6 : 1)[79] (Scheme 39).



Scheme 39

We have reported a diastereocontrolled synthesis of α-linked *C*-glycosides of *N*-acetylneuraminic acid (Neu5Ac) *via* glycosyl samarium(III) intermediates (Scheme 40).[80,81] Neu5Ac pyridyl sulfone (**191a**) and phenyl sulfone (**191b**) were coupled with carbonyl compounds under Barbier conditions to give Neu5Ac α-*C*-glycosides (**193**, **194**) in excellent yields and α stereoselectivity. Compound **193** represents the first *C*-disaccharide derivatives of an ulosonic acid. *C*-glycoside formation, in this case, resulted in a quaternary anomeric center in the Neu5Ac-portion. Using this approach it was even possible to generate a new bond between two quaternary centers in **194**.



Scheme 40

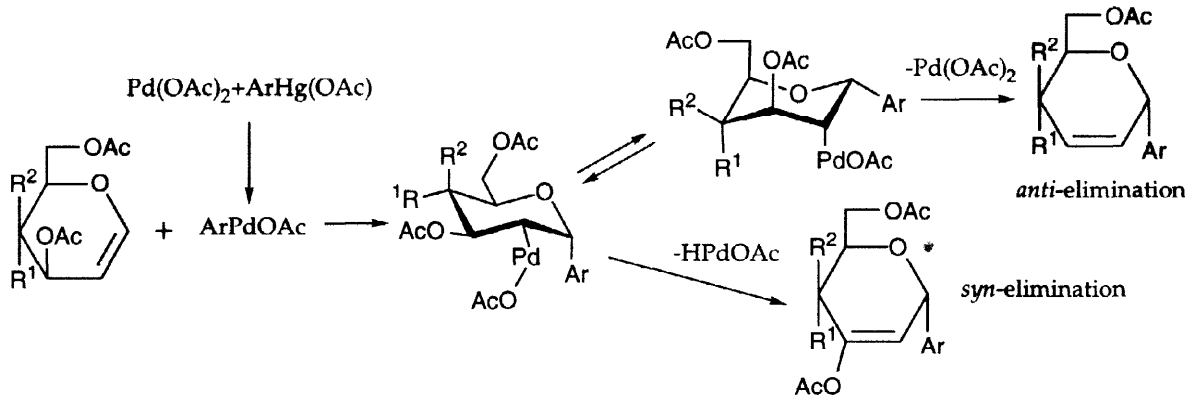
6. Transition Metal Mediated *C*-Glycosylation

6.1. Palladium mediated C-glycosylation

6.1.1 Heck type couplings

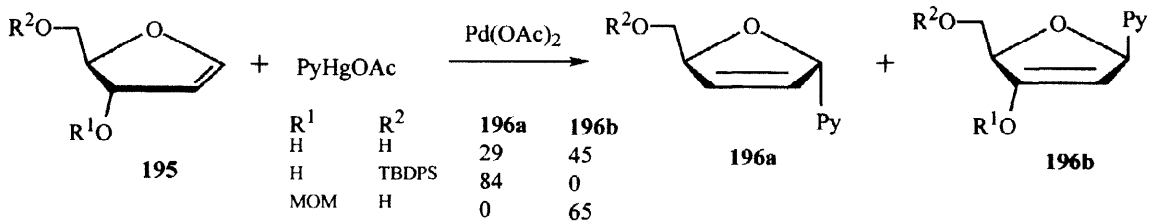
The Heck reaction, the palladium-catalyzed arylation or alkenylation of alkenes, has been extensively used in organic synthesis.[82] Daves[83] has applied the Heck reaction on carbohydrate molecules. The reaction of

glycal derivatives and an arylpalladium complex provides *C*-glycosides under mild condition and with high regioselectivity at the anomeric center. The proposed mechanism for the Heck type *C*-glycosidation is illustrated in Scheme 41.



Scheme 41

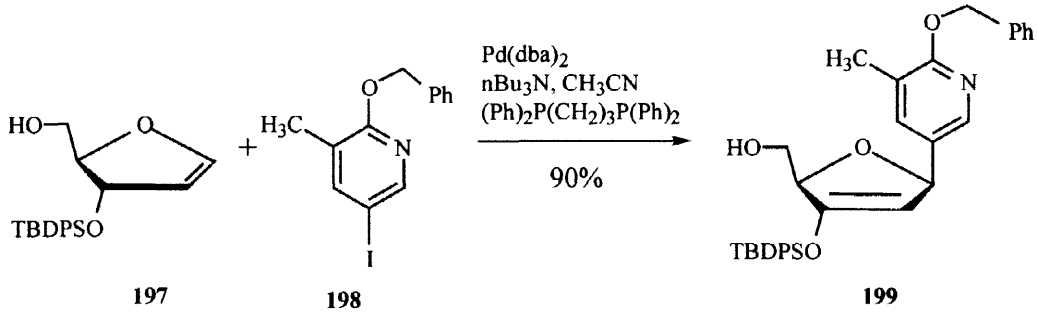
The stereochemistry of this reaction is determined by the relative accessibility of the two faces of the glycal double bond to the organopalladium reagent forming the π-complex. The nature of the substituent at the other hydroxyl groups dominates the *C*-1 stereochemistry, particularly in the case of furanoid glycals **195** (Scheme 42).[84]



R^1	R^2	**196a**	**196b**
H	H	29	45
H	TBDPS	84	0
MOM	H	0	65

Scheme 42

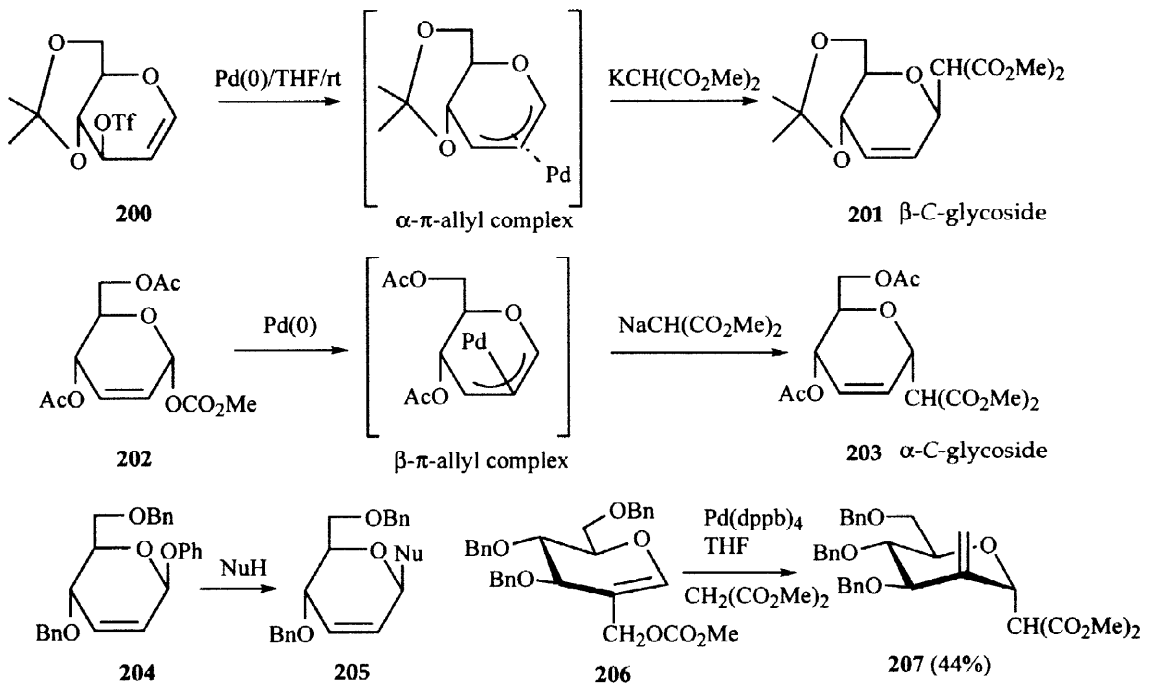
The appropriate selection of an ancillary ligand is another critical factor for the Pd-mediated Heck-type coupling. The Pd-mediated coupling of glycal **197** and 2-(benzyloxy)-3-methyl-5-iodopyridine **(198)** was studied using various ancillary ligands.[85] The use of tris-(pentafluorophenyl) phosphine ($P(C_6F_5)_3$), triphenylarsine ($AsPh_3$) or 1,1'-bis (diphenylphosphin) ferrocene (dppf) resulted in only moderate yields of *C*-glycoside product, while the use of bidentate ligand 1,3-bis(diphenylphosphino) propane (dba) resulted in an estimated 90% yield of β-*C*-nucleoside (Scheme 43).



Scheme 43

6.1.2 π-Allyl complexes

Dunkerton and coworkers[86] pioneered the use of π-allylpalladium complexes in synthetic carbohydrate chemistry. More recently, the chemistry of the allylic system in the presence of Pd(0) has been extensively applied to the synthesis of *C*-glycosides because of its very high stereoselectivity and very mild experimental conditions.[87]

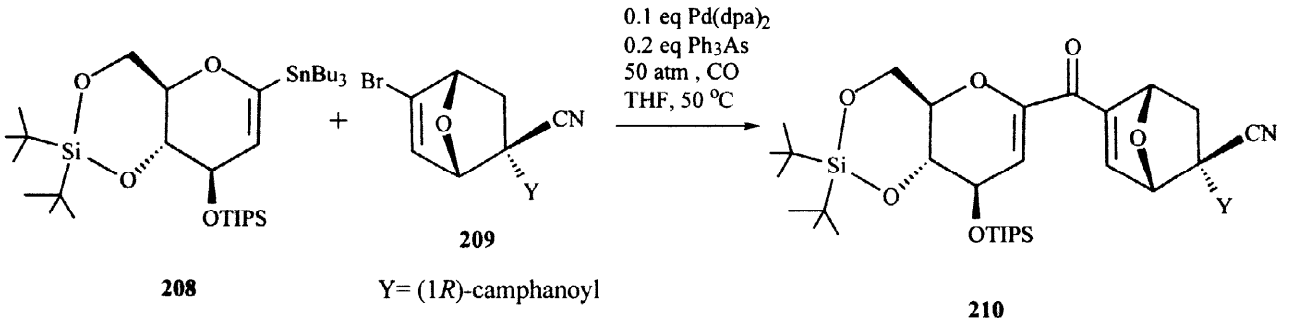


Scheme 44

Three different types of unsaturated sugars can be used as π-allyl palladium complexes precursors (Scheme 44): 1) A glycal with C-3 bearing a strong electron withdrawing group (**200**); 2) 2,3-unsaturated α and β glycosyl carbonates or aryl glycosides (**202**, **204**) (α-phenylglycosides may generate α, β-mixtures of *C*-glycoside due to a retro-Michael addition but this is highly dependent on the nature of the nucleophile); 3) A *C*-2 carbomethoxymethyl glycal **206**, an analogue of **200**, generates *C*-glycoside having a *C*-2 *exo*methylene structure.[88]

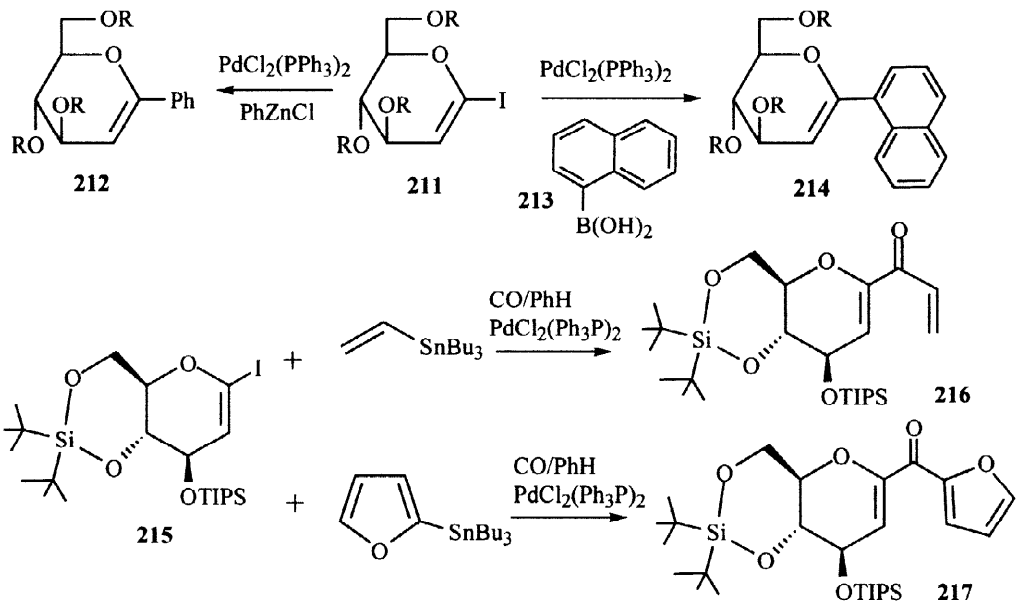
6.1.3 Palladium-catalyzed vinylic substitution

The Stille reaction (palladium-catalyzed vinylic substitution) is a cross-coupling between an organotin compound (or another organometallic compound) and an aryl or vinyl halide. This reaction is used to make 1,2-unsaturated *C*-glycosides[89] (also see Scheme 3). The tin glucal derivative **208** reacts with vinylbromide **209** to give a 47% yield of dienone **210**. Replacement of Ph_3As with Ph_3P failed to produce product[90] (Scheme 45).



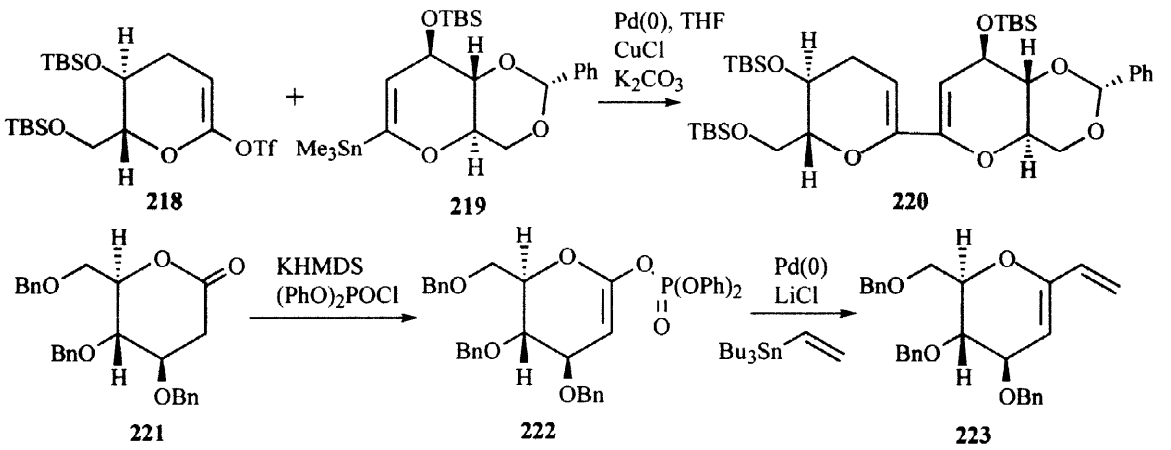
Scheme 45

A complementary approach reverses the polarity by reacting metallated vinyl or aryl groups with the 1-iodo-glycals **211**[91] and **215**,[90] affording *C*-glycosides under mild reaction conditions and in good yields (Scheme 46).



Scheme 46

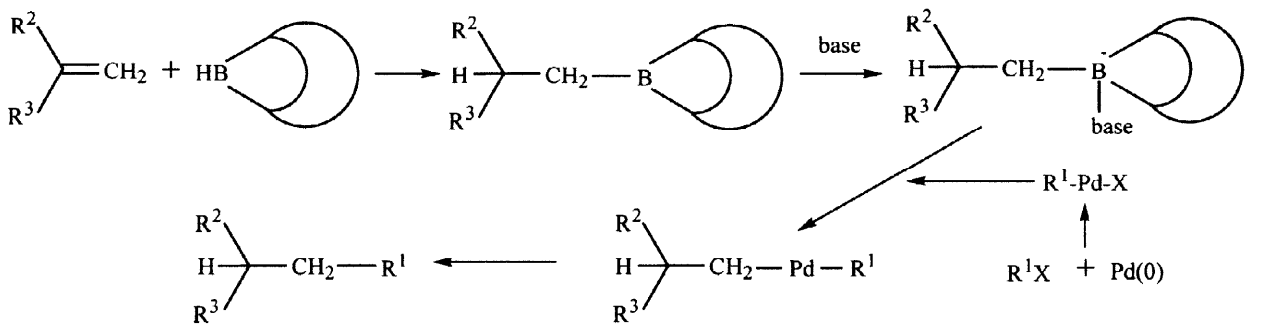
Nicolaou and co-workers[15] investigated the use of Stille cross-coupling in *C*-glycoside synthesis. Initial attempts at cross-coupling of the appropriate glycal partners, following standard Stille reaction conditions, failed due to low reaction rates and the formation of homodimers. The $Pd(Ph_3P)_4$-catalyzed cross-coupling of enol triflate **218** and stannyl enol ether **219** was best carried out in the presence of CuCl and K_2CO_3 giving the desired bisglycal **220** in 80% yield (Scheme 47). CuCl may act as a scavenger of free Ph_3P ligands or may be involved in a transmetalation of tin to copper. Subsequently, the more stable enol phosphate[92] counterpart of **221** was used in place of triflate with vinyl tin reagent under standard Stille cross-coupling conditions to give high yield of *C*-vinyl glycal derivative **223**. This method is more general for the construction of medium to large cyclic ethers (Scheme 47).



Scheme 47

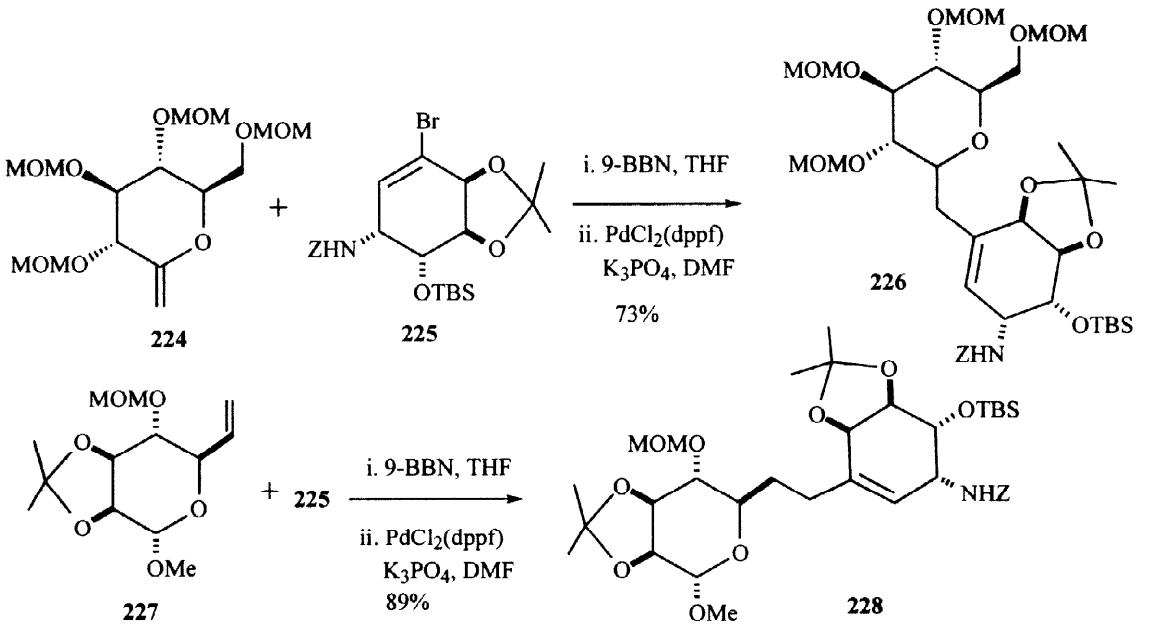
6.1.4 Palladium-catalyzed Suzuki coupling

The cross-coupling reaction of β-alkyl-9-borabicyclo[3.3.1]nonane (β-R-9-BBN), readily obtainable from alkenes by hydroboration, with 1-*halo*-1-alkenes or haloarenes in the presence of a catalytic amount of $PdCl_2$(dppf) and base (NaOH or K_2CO_3) gives the corresponding alkenes or arenes.[93] The proposed mechanism for above Suzuki coupling reaction is shown in Scheme 48.



Scheme 48

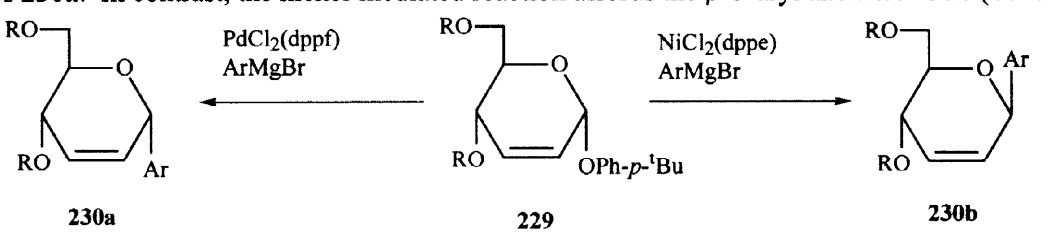
Thus, hydroboration of *exo*methylene pyranose **224** or vinyl glycoside **227** (9-BBN, THF, reflux), followed by Suzuki coupling of the products with vinyl bromide **225** ($PdCl_2$(dppf) and K_3PO_4, in aq. DMF), affords *C*-glycoside **226** or **228**, respectively, as a single diasteresomer (Scheme 49).[94]



Scheme 49

6.2 Other Transition Metal Complexes

An excellent example of transition metal mediated *C*-glycosidation was reported recently by Sinou and co-workers.[95] The palladium-catalyzed coupling of *p-tert*-butylphenyl-α-*O*-Δ^2-glycopyranoside **229** with various substituted arylmagnesium bromides stereospecifically affords the corresponding α-*C*-aryl-Δ^2-glycopyranosides **230a**. In contrast, the nickel-mediated reaction affords the β-*C*-aryl anomers **230b** (Scheme 50).



R=Bn, TBDMS, Ar=Ph, 2-MeOPh, 4-MeOPh, 3,4-(CH_2O_2)Ph-, 2-MePh, 4-MePh, 4-ClPh, Bn

Scheme 50

7. *C*-Glycosylation Through Intramolecular Aglycon Delivery

Tethering represents an elegant method of using a C-Si or a C-O bond as a temporary connection, which enhances stereoselectivity through the formation of a cyclic structure, to unequivocally guarantee a predictable reaction course.

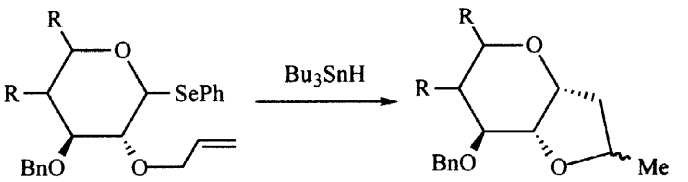
A sugar-based temporary (tether) connection strategy to synthesize molecule A-B typically includes three steps: 1) attachment of the desired subunit (molecule B) to a stereochemistry-controlling hydroxyl group on sugar A through a tether T, affording A-T-B; 2) intramolecular transfer of subunit B to the anomeric center of sugar A by cyclization *cis* to the controlling hydroxyl group; and 3) removal of the temporary tether T

without destroying the newly formed bond in the A-B portion of the molecule. To date, C-O and Si-O tethers have given the most promising results and thus are widely used in synthetic carbohydrate chemistry.

7.1. Through a temporary C-O connection

7.1.1. Radical induced cyclization

Temporary C-O connections are a valuable tool for stereocontrolled radical reactions. This is exemplified when C-2 *O*-allyl tethered seleno glycoside **231** undergoes an intramolecular radical cyclization with complete regio- (only *exo* ring closure was observed) and stereospecificity to furnish α-*C*-glycoside **232** in 80-95% yields[96] (Scheme 51).

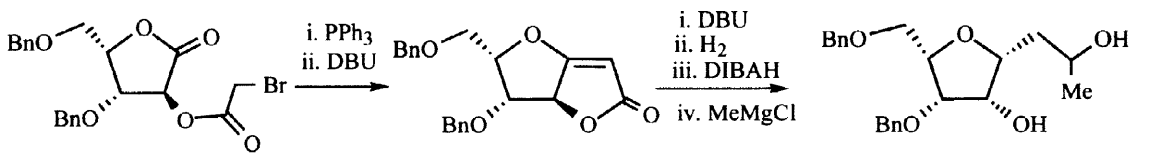


231 **232**

Scheme 51

7.1.2. Ionic cyclization

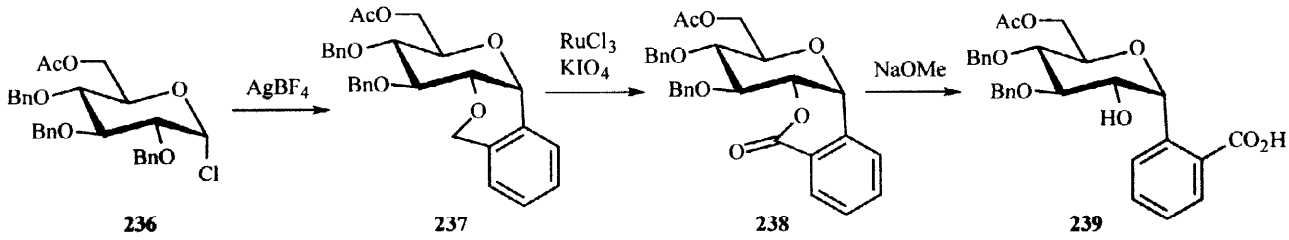
In addition to the radical reactions, intramolecular Wittig-like reactions have also been used in a C-O tether strategy[97] (Scheme 52). Reaction of the *O*-tethered compound **233** with triphenylphosphine followed by addition of DBU affords **234**. Treatment with a catalytic amount of DBU gave the tetronate epimer. Reduction to the hemiacetal followed by nucleophilic opening gave α-L-*C*-ribofuranoside **235** in 81% yield with 3:1 ratio of isomers (*S*:*R*).



233 **234** **235** *S*:*R*=3:1

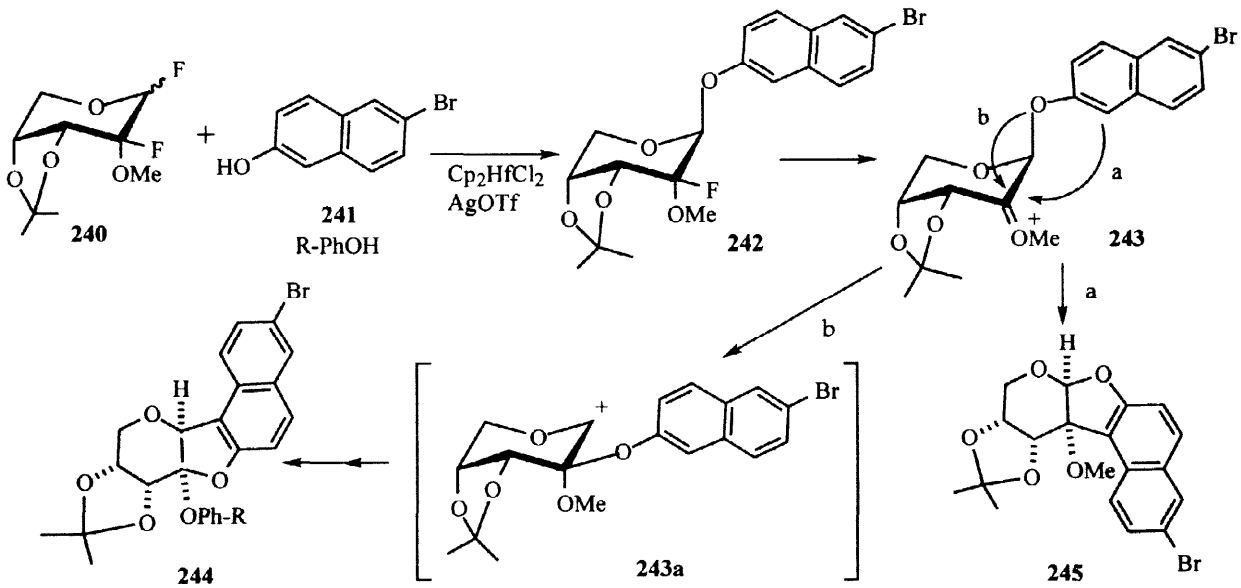
Scheme 52

Friedel-Crafts arylation is one of the approaches used for the synthesis of *C*-aryl glycosides. A variety of Lewis acid promoters have been applied, based on the nature of the donor leaving group and the nucleophilicity of the aromatic compound. As a rule, pyranoses are less reactive and usually give the thermodynamically more stable 1,2-*trans* anomer.[18] The more flexible furanoses often afford a mixture of anomers. The most important breakthrough in the stereoselective preparation of 1,2-*cis* *C*-aryl glycosides resulted from the use of a tethered 2-*O*-benzyl substituent in an intramolecular *C*-glycosylation by Friedel-Crafts reaction. For example, the 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl chloride (**236**) was treated with silver tetrafluoroborate to give the intermediate **237**. Regioselective oxidation of **237** followed by hydrolysis of the resulted lactone generated *C*-glycoside **239** with complete α-stereoselecitivity[98] (Scheme 53).



Scheme 53

Matheu and co-workers[99] investigated the intramolecular Friedel-Crafts reaction in the synthesis of naphtho-and benzo-dihydrofuran derivatives (Scheme 54).



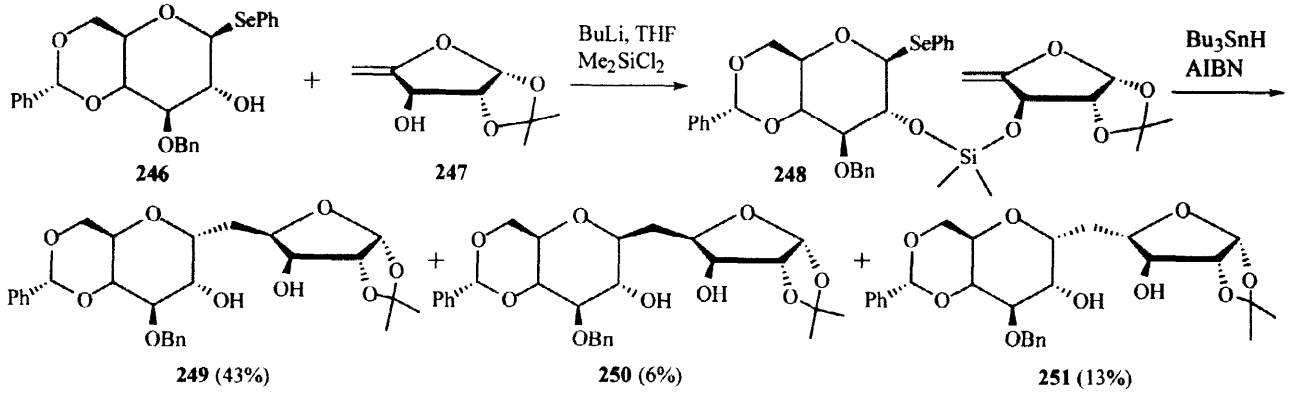
Scheme 54

When 2-fluoro-3,4-isopropylidene-2-*O*-methyl-D-ribo-pento-pyranosyl fluoride **240** was reacted with 6-bromo-2-naphthol (**241**) in the presence of co-catalyst Cp_2HfCl_2/AgOTf, a mixture of *C*-glycoside derivative **244** and compound **245** were formed *via* intramolecular Friedel-Crafts reaction in the yield of 21% and 44%, respectively. This four-step process involves *O*-glycosidation, C-2-oxocarbenium ion generation, 1,2-migration of the anomeric substituent and Friedel-Crafts arylation.

7.2 Silicon tether method

The pioneering work of Stork[100] on intramolecular aglycon delivery using silyl ethers suggested its utility in free-radical processes. Sinaÿ and co-workers[12] also demonstrated general application of this approach. The intermolecular regio- and stereocontrolled condensation of a nucleophilic anomeric radical donor with an *exo*methylene containing sugar constitutes a potentially general and expeditious strategy for *C*-

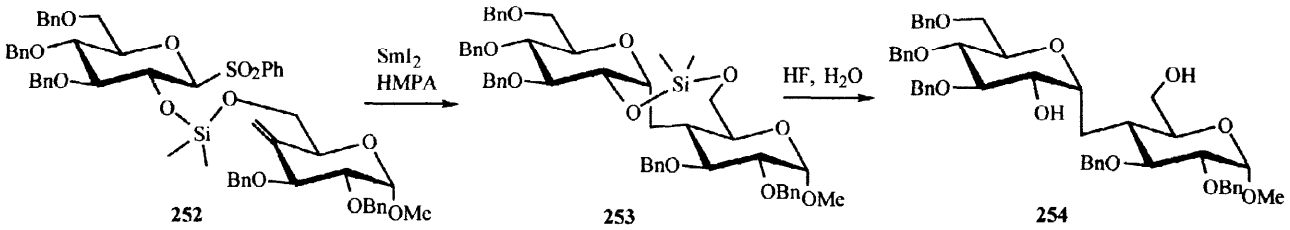
disaccharide synthesis. Temporary covalent connection between the donor and acceptor counterparts by means of easily cleavable ketal or silylketal tethers strongly facilitates C-C bond formation between the reacting vicinal centers. An application[101] exemplifying this methodology is shown in Scheme 55.



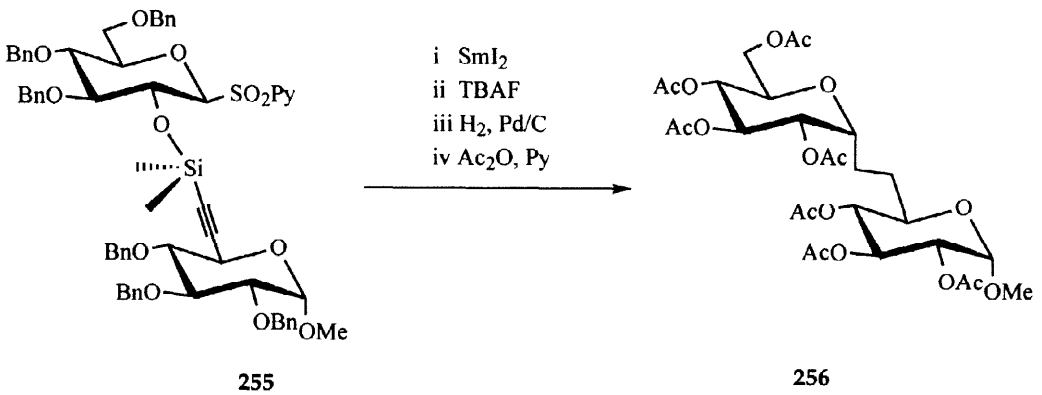
Scheme 55

Tethering of selenoglucopyranoside **246** and exomethylene furanose **247** was achieved *via* the silylketal **248**. Intramolecular 8-*endo-trig* radical cyclization of **248** with AIBN and Bu_3SnH, followed by removal of the silyl tether, yields a mixture of *C*-disaccharides **249** (43%), **250** (6%) and **251** (13%) (Scheme 55).

Two additional excellent applications[102,103] of this methodology are shown in Schemes 56 and 57.



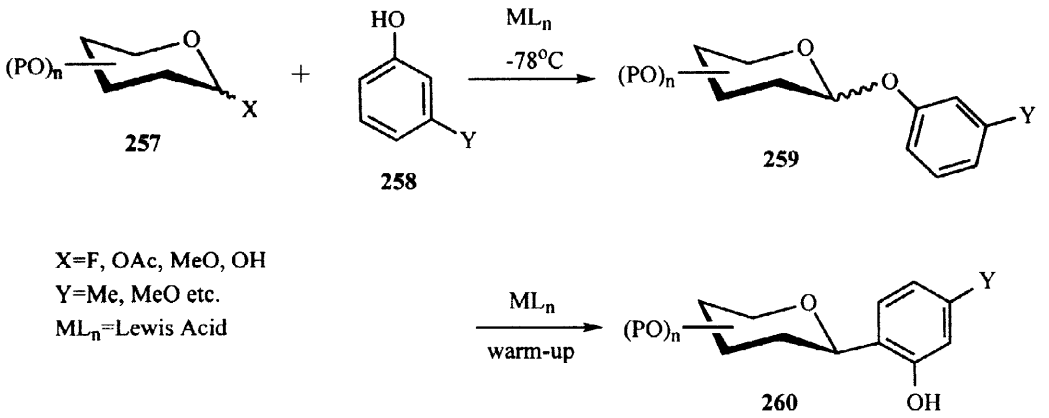
Scheme 56



Scheme 57

7.3 O→C-glycoside rearrangements

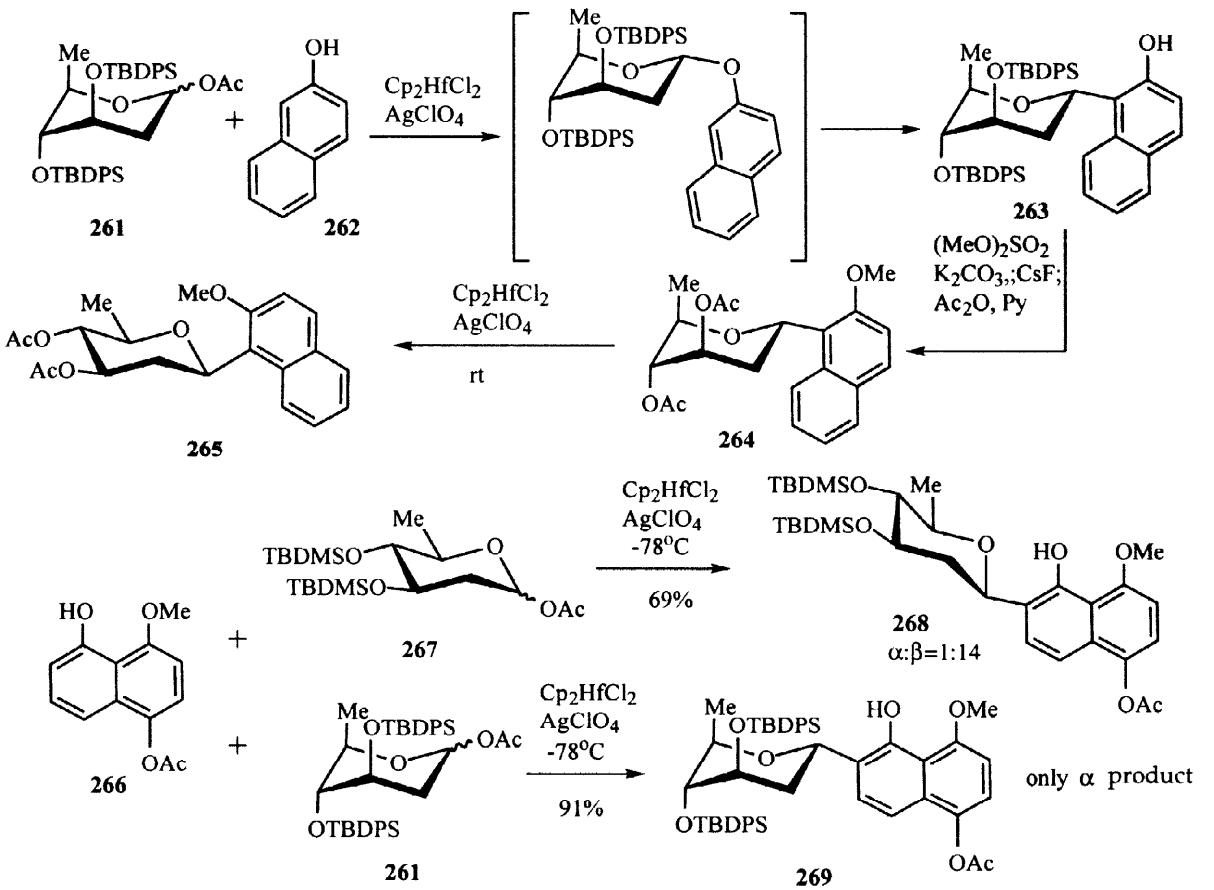
An effective method for the synthesis of aryl *C*-glycosides was exploited by Suzuki and co-workers.[104] This reaction is proposed to proceed through initial formation of an *O*-glycoside that rearranges, in the presence of Lewis acids, to a *C*-glycoside (Scheme 58).



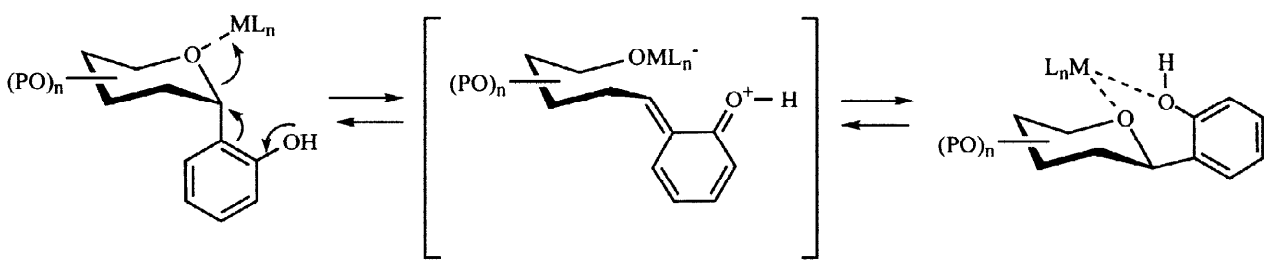
Scheme 58

The stereochemical outcome of the initial *O*-glycosidation is of little importance since, the stereochemistry at the anomeric center is rebuilt during the formation of the *C*-glycoside.[105] The yield and stereoselectivity of the *O*→*C*-glycosidation is strongly dependant on the reaction conditions (*i.e.*, catalyst, temperature, etc.).[106,107] The co-catalyst, Cp_2HfCl_2-$AgClO_4$, proved to be the best promoter for the formation of β isomer *via* *O*→*C*-glycosidation. Suzuki and co-workers[108,109] have applied this methodology to the synthesis of variety of aryl *C*-glycosides.

Glycosyl acetate **261** was subjected to *O*→*C*-glycoside rearrangement to form the aryl *C*-glycoside.[110] On treatment of acetate **261** with 2-naphthol (**262**) in the presence of Cp_2HfCl_2 and $AgClO_4$, *O*-glycoside preceedes formation of α-*C*-glycoside **263** in the $^1C_4$ conformation in 91% yield. Interestingly, the 3,4-di-*O*-TBDMS-subsituted acetate **267** reacted with naphthol derivative **266** to give β-*C*-glycoside **268** in the $^4C_1$ conformation in 69% yield. The 3,4-di-*O*-TBDPS-substituted sugar **261** gives α-*C*-glycoside **269** in the $^1C_4$ conformation in 91% yield under the same reaction conditions (Scheme 59). This α-configuration can not be epimerized to β isomer by Cp_2HfCl_2-$AgClO_4$ while the corresponding diacetate **264** cleanly anomerized to give β-*C*-glycoside **265**. These results are rationalized by the ring flipping of the pyranoside ring ($^1C_4$) in the glycosyl donor and the *C*-glycoside product, due to the severe repulsion of the siloxy groups. (Scheme 60)

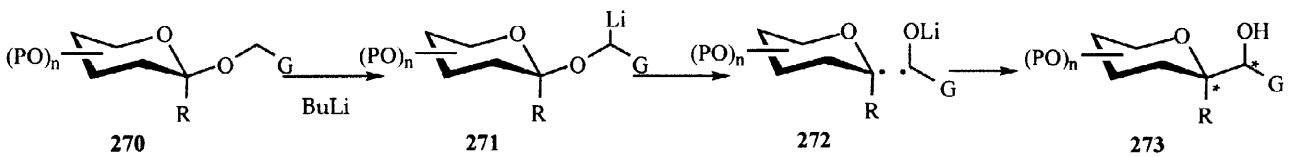


Scheme 59



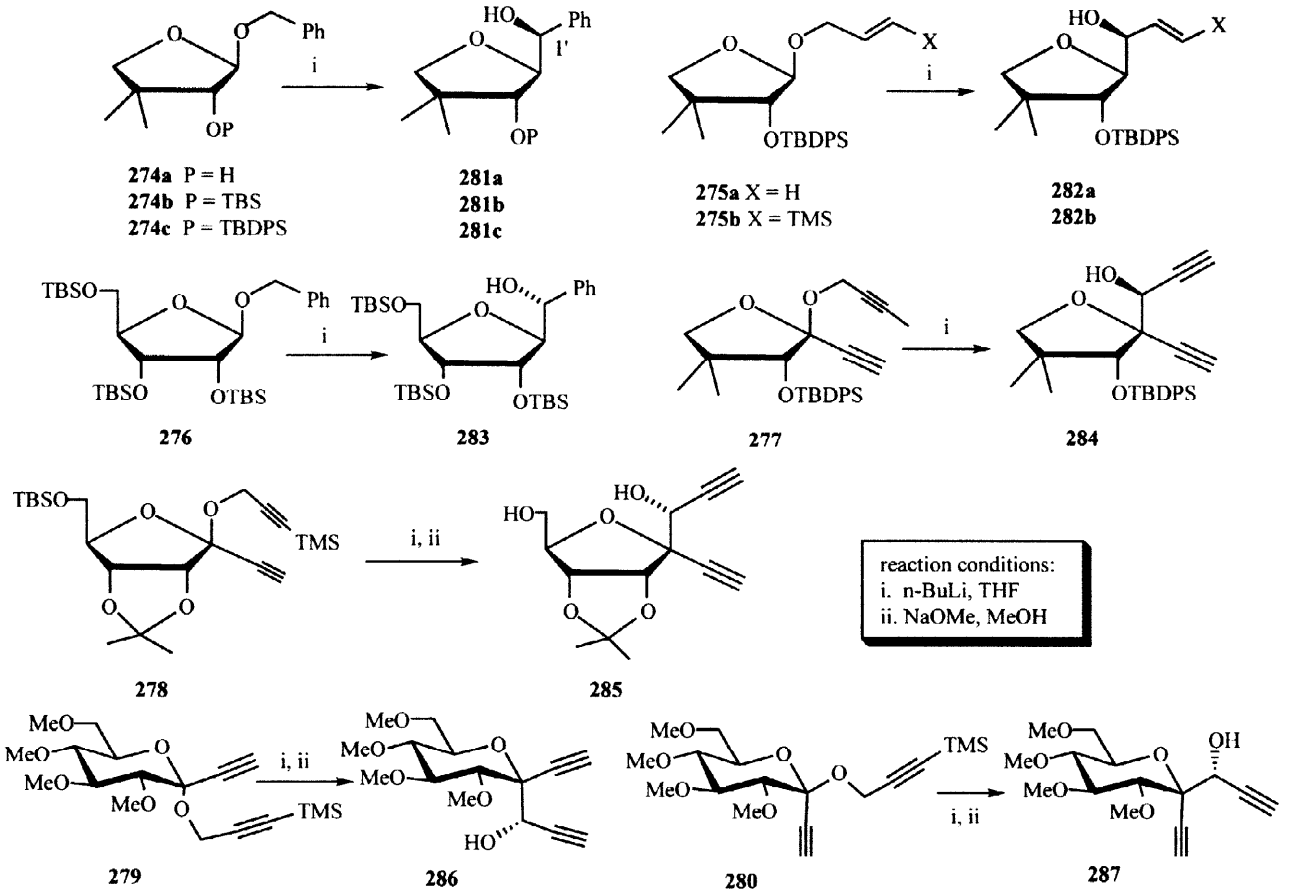
Scheme 60

O→*C* glycosidation through 1,2-Wittig rearrangement is well recognized to proceed *via* a radical dissociation-recombination mechanism. Nakai and co-workers[111-113] found that the [1,2]-Wittig rearrangement of *O*-glycosides proceeds with efficient stereocontrol, at both the anomeric center and the newly formed chiral center on the side chain, to give the stereo-defined *C*-glycosides in high yield. This high stereoselectivity was mainly attributed to the relative stability of the α-oxa radical generated in the rearrangement (Scheme 61).



Scheme 61

When the furanoside acetals and ketals **274-278** were treated with *n*-BuLi, the reaction proceeded with complete retention of the β-anomeric configuration to give the [1,2]-Wittig products (**281-285**). These products are a mixture of the *C*1'-epimers, and both the yields and isomeric ratios are strongly dependent on steric factors from the sugar protecting groups. The rearrangements of the acetal **276** and ketal **278** were found to give *C*-glycoside **283** and **285** as the only stereoisomer. Interestingly, the configuration of these products at the *C*1' is opposite to that in compounds **281, 282** and **284**. These results suggest that the choice of a proper siloxy group as protecting group greatly affects the *C*-glycosidation stereoselectivity and yield. The same effect was shown for hexose ketals **279** and **280** (Scheme 62 and Table 4).



Scheme 62

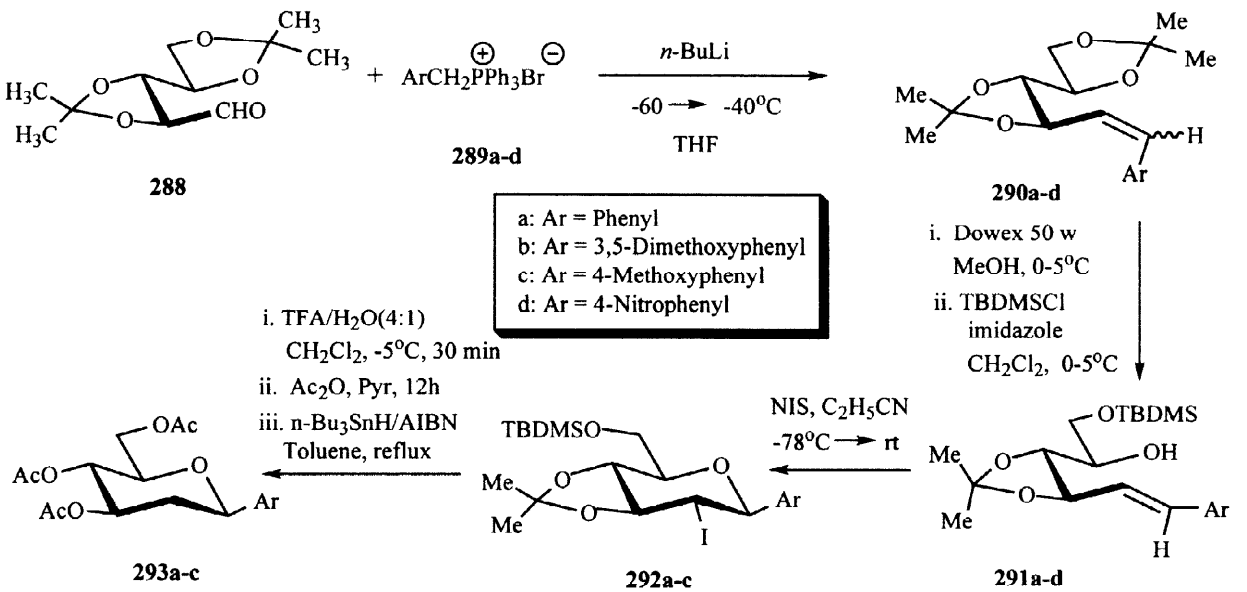
Table 4. [1,2]-Wittig Rearrangements of β-*O*-Glycosides

Substrate	Major product	Yield%	C1'-epimers	Substrate	Major product	Yield%	C1'-epimers
274a	**281a**	44	40 : 60	**276**	**283**	40	>98 : <2
274b	**281b**	71	89 : 11	**277**	**284**	81	96 : 4
274c	**281c**	77	>98 : <2	**278**	**285**	90	90 : 10
275a	**282a**	35	>98 : <2	**279**	**286**	71	87 : 13
275b	**282b**	60	>98 : <2	**280**	**287**	71	87 : 13

8. *C*-Glycoside Synthesis Through Intramolecular Cyclization

Wittig and Grignard reactions have been applied to the anomeric center of carbohydrates to give a ring open sugar that can be cyclized under a judicious choice of conditions to generate *C*-glycosides.[114,115]

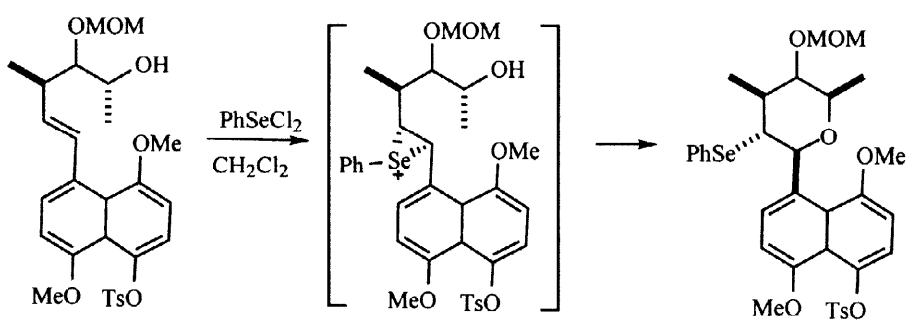
Schmidt and co-workers[116] reported a convenient approach for the synthesis of *C*-(2-deoxy-β-glycosyl) arenes based on electrophile-induced cyclization of carbohydrate-derived arylalkenols (Scheme 63). First, D-arabinose derivative (**288**) is converted by a Wittig reaction into a mixture of *E*/*Z* olefin **290a-d**. Selective deprotection of the 5,6-*O*-isopropylidene followed by silylation of primary alcohol afforded the separable *Z*-,*E*-isomers (**291a-d**). NIS-induced, stereoselective cyclization of compounds *Z*-**291c** and *E*-**291a-c**, followed by protecting group exchange, furnished the β-D-*C*-glucopyranosylarenes (**293a-c**). Electron donating aryl derivatives and *E*-oriented olefins are preferred in this cyclization.



288 **289a-d** **290a-d** **291a-d** **292a-c** **293a-c**

Scheme 63

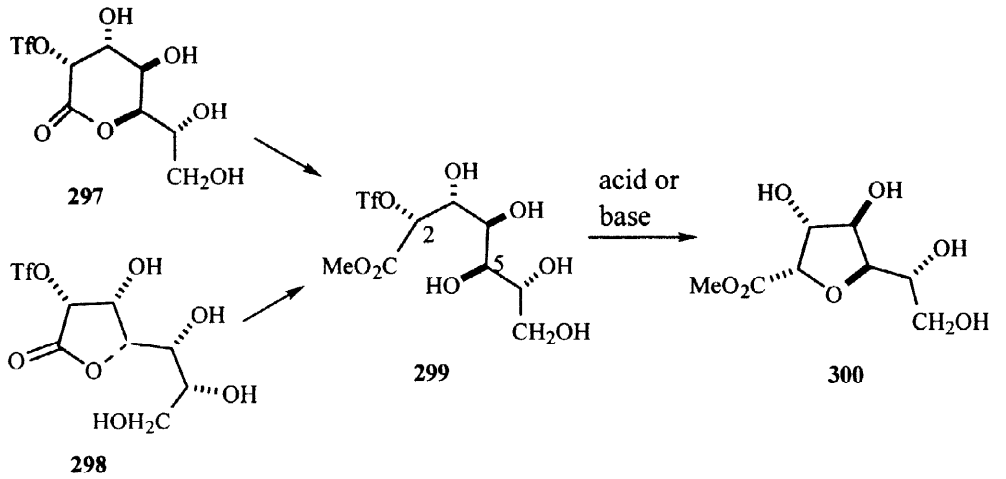
Hart and collaborators[117] have applied a similar approach to the synthesis of *C*-aryl glycosides related to the chrysomycins *via* selenium induced cyclization (Scheme 64).



294 **295** **296**

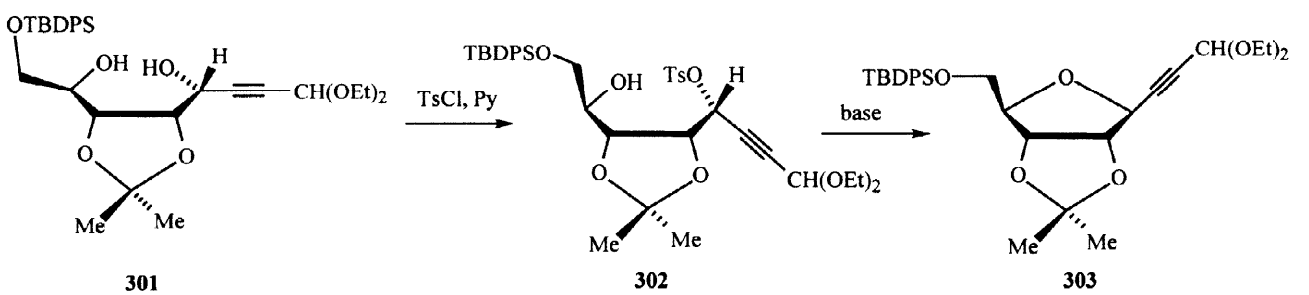
Scheme 64

Ring closure of the α-triflates of γ- and δ-glucoheptonolactones[118,119] (**297**, **298** in Scheme 65) leads to the formation of *C*-glucofuranoses **300** through nucleophilic attack of the C-5 hydroxyl group.



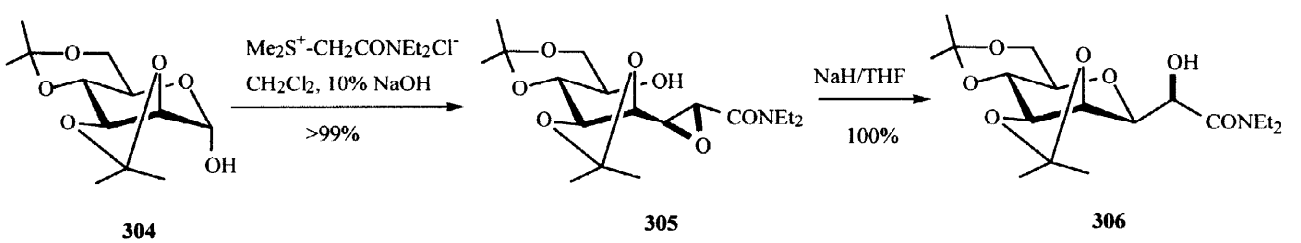
Scheme 65

A tosyl leaving group has also been applied to the cyclization shown in Scheme 66.[120]



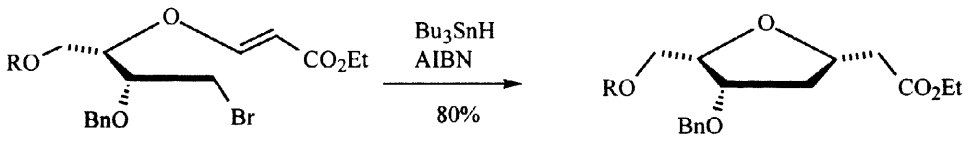
Scheme 66

Condensation of mannopyranose **304** with a sulfur ylide[121] generated *in situ* quantitatively affords epoxy amide **305** with complete stereoselectivity (Scheme 67). Epoxide ring opening with concomitant intramolecular cyclization of **305** leads to *C*–glycopyranosides, such as **306**.[122,123] This method provides an easy and efficient stereoselective two-chiral carbon atoms elongation of pyrannose.



Scheme 67

Radical induced cyclization of bromides **307** generates *C*-furanosides **308** in approximately 80% yield[124] (Scheme 68).

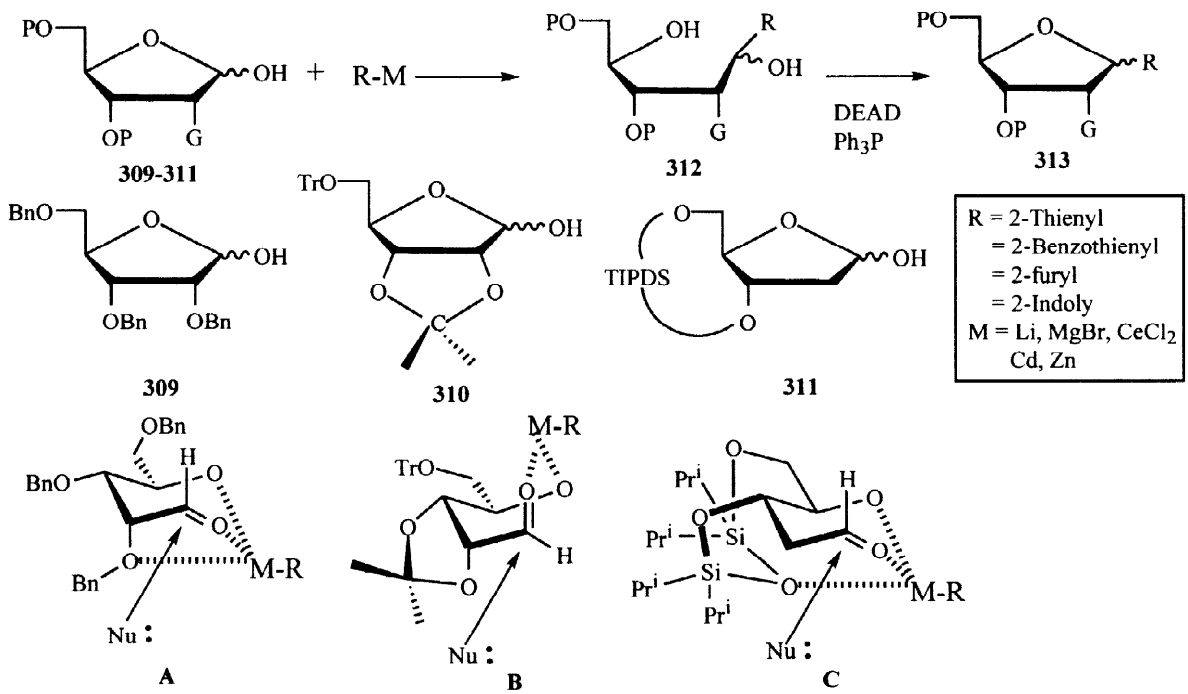


307a R = TBS
307b R = TBDPS

308a
308b

Scheme 68

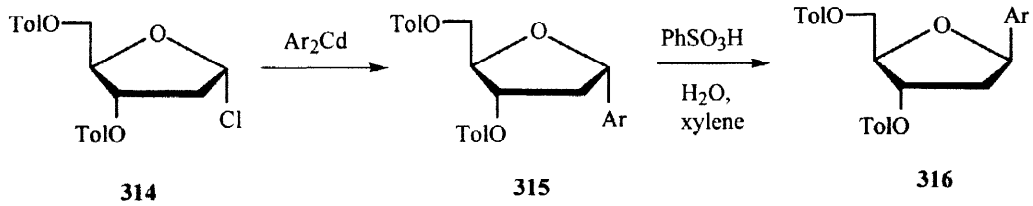
A number of organometalic reagents have been used to synthesize *C*-glycosides.[125,126] The coupling of 2,3,5-tri-*O*-benzyl-D-ribofuranose (**309**) with less basic (compared to Li) Mg, Cd and Zn salts of aromatic heterocycles affords diols, which under Mitsunobu conditions condense to the corresponding β-*C*-nucleosides.[127] This stereoselectivity may be due to an easy attack of heterocycles on *re*-face of the carbonyl group of the intermediate metal chelate (Scheme 69, **A**).



Scheme 69

When ribofuranose **310** was coupled with the magnesium salt of thiophene, only α-*C*-glycoside was obtained. This can be rationalized by nucleophilic attack on the carbonyl group proceeding exclusively *via* the more stable complex **B** (Scheme 69). Reaction of 2-deoxy ribofuranose **311** with the Cd and Zn salts showed predominant *S*-stereoselectivity affording the β-*C*-glycosides (Li salts give α-selectivity). This β-stereoselectivity may be due to attack of the nucleophile on the *re*-face of carbonyl group in the more stable complex **C** (Scheme 69).

Reaction of ribofuranosyl chloride (**314**) with arylcadmium derivatives affords the α-*C*-glycoside **315** as the major product.[128] Interestingly, this product can be easily isomerized to β-*C*-glycoside **316** by acidic epimerization at the C-1 position through a reversible ring-opening pathway (Scheme 70).



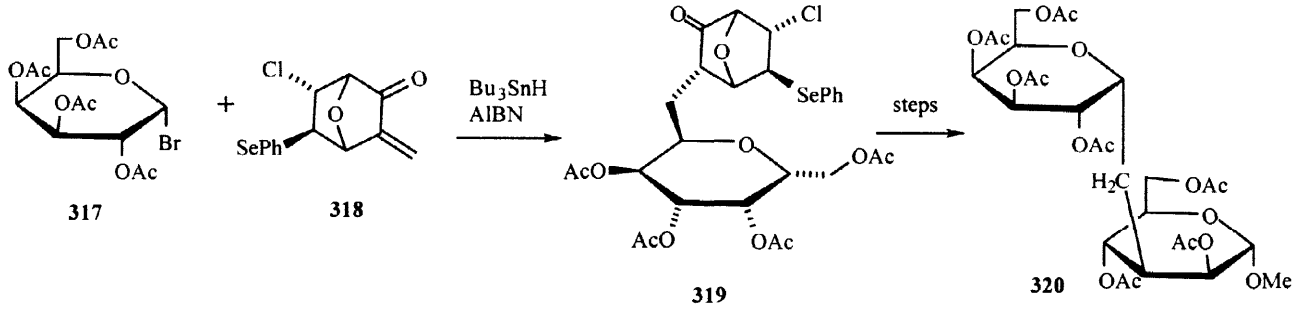
Scheme 70

9. *C*-Oligosaccharide Synthesis

9.1 C-Disaccharides

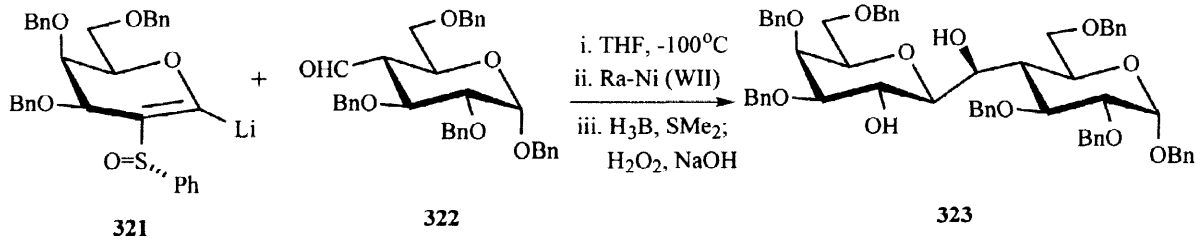
The first *C*-disaccharide was described by Sinaÿ and Rouzad[129] in 1983. Since then, the *C*-disaccharides have been the continuous pursuit of synthetic carbohydrate chemists. In Sections 1 through 8, the synthesis of many *C*-glycosides are discussed as various *C*-glycosidation methods are described. In this section, selected examples of *C*-disaccharide syntheses are presented illustrating a number of important and interesting targets.

Methylene-linked 3-α-D-galactopyranosyl-D-mannose (**320**) was prepared by radical coupling of **317** with the enone **318** followed by refunctionalization of intermediate **319**[130] (Scheme 71).



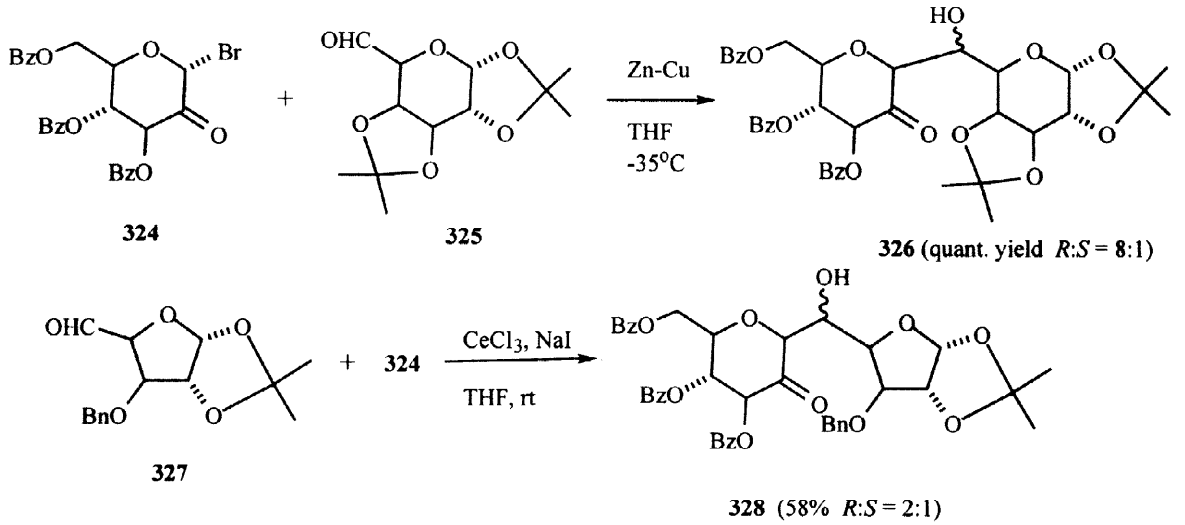
Scheme 71

Schmidt and co-workers[131,132] reported the preparation of *C*-lactose and *C*-cellobioside derivatives with methylene, hydroymethylene and carbonyl group linkages. The key step in the synthesis of *C*-lactose analog **323** is the condensation of nucleophilic 1-*C*-lithiated 2-(phenylsulfinyl)-D-galactal **321** with 4-*C*-formyl-4-deoxy glucose compound **322** (Scheme 72).



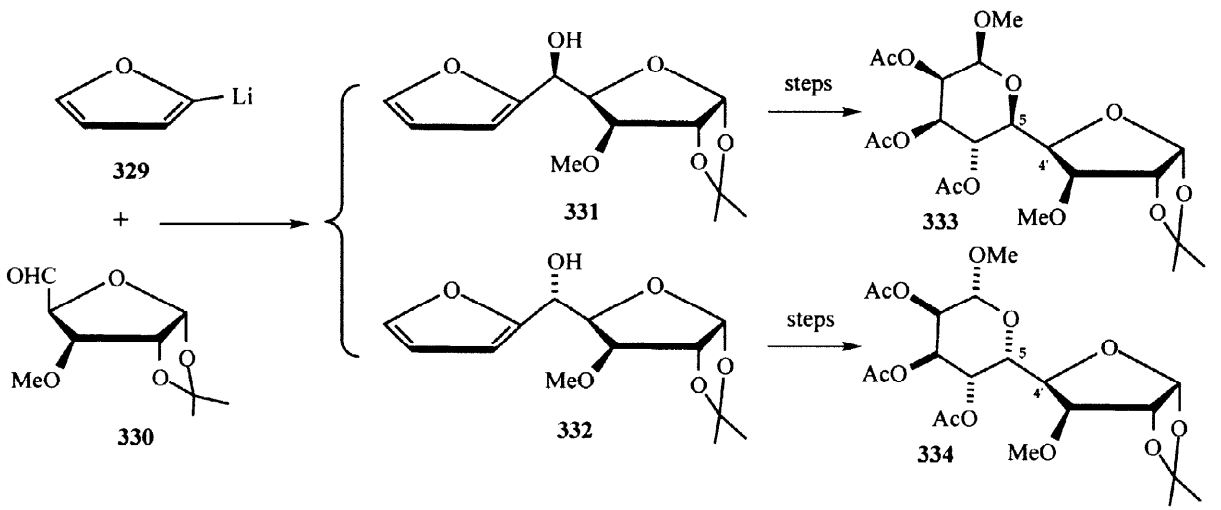
Scheme 72

The carbohydrate-derived α-bromo ketone **324** undergoes reductive cleavage using either Zn-Cu or $CeCl_3$-NaI co-catalyst[126] and the resulting enolate can be trapped by the aldehydes **325** and **327** to give *C*-disaccharides **326** and **328**, respectively (Scheme 73).



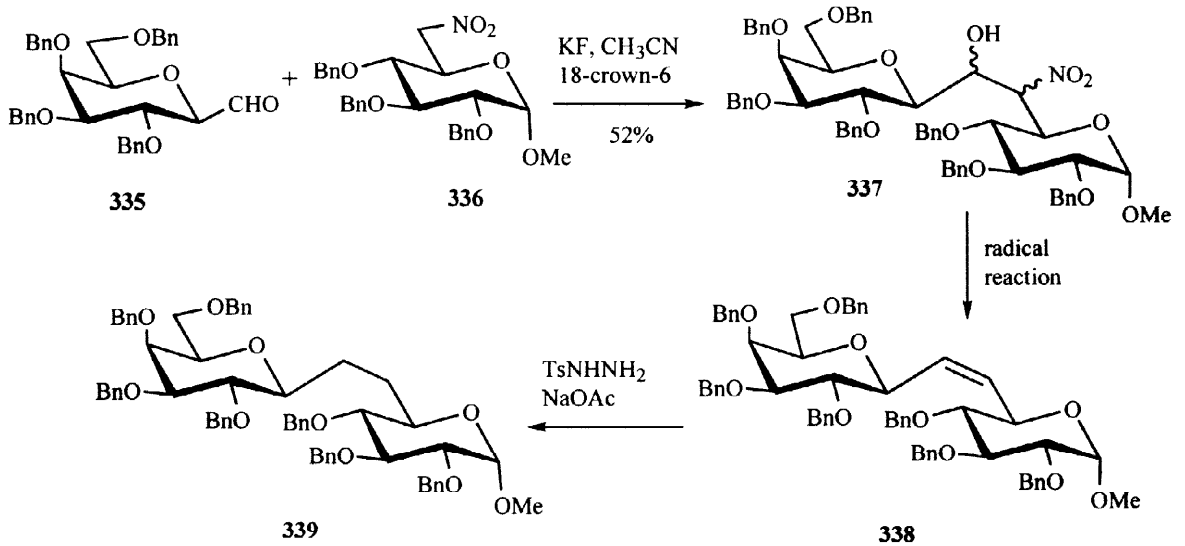
Scheme 73

Employing a conceptually related stratagem,[133] furyllithium **329** was condensed with the aldehyde **330** to give $C_{4'}$-C_5 directly linked disaccharides **333** and **334** (Scheme 74).



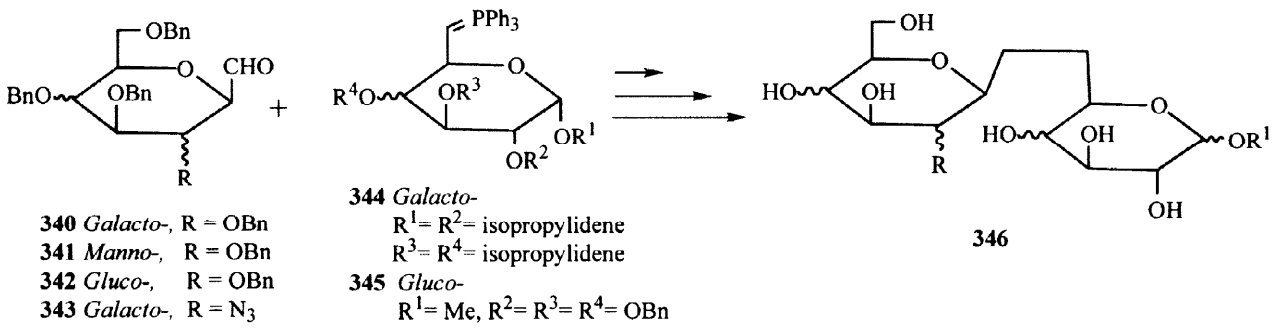
Scheme 74

Carbohydrate-derived aldehydes are also useful synthons for the preparation of *C*-disaccharides.[134] Aldehyde **335** was condensed with 6-nitroglucose derivative **336** using Martin's procedure to afford the *C*-disaccharide precursor **337** as a mixture of diastereomers.[135] Radical-promoted elimination followed by diimide reduction afforded 1→6 linked *C*-disaccharide **339** (Scheme 75).



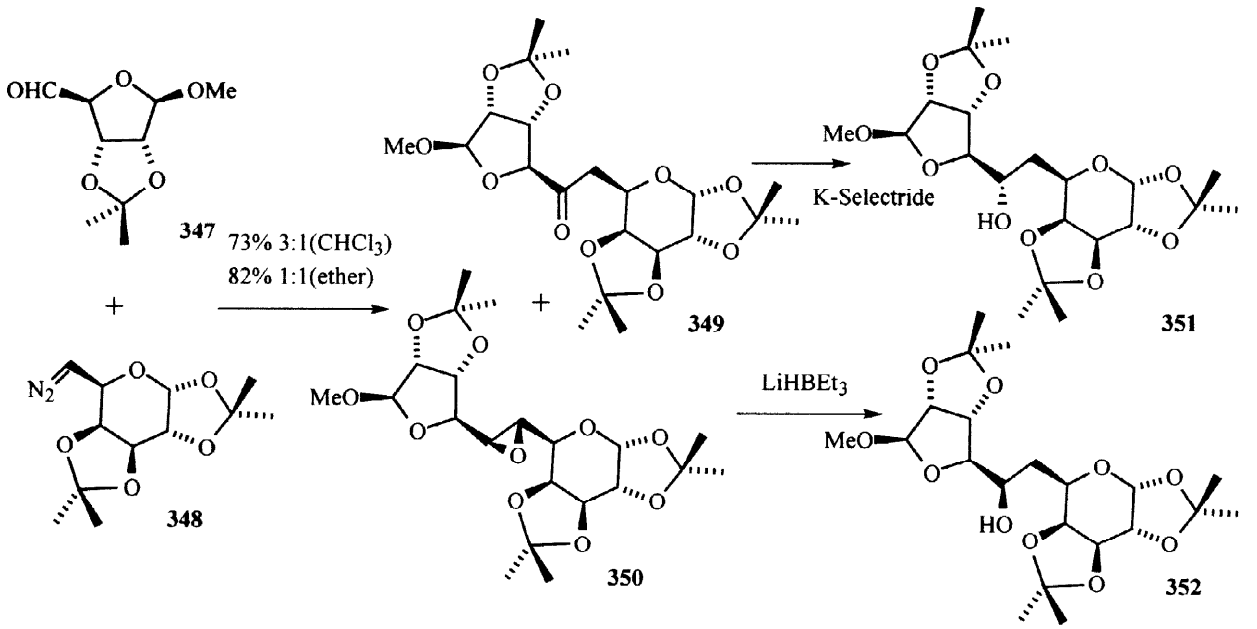
Scheme 75

Dondoni and co-workers[136,137] reported that Wittig olefination of carbohydrate C-1 aldehydes (Scheme 76, **340-343**) with C-6 phosphoranes (**344** and **345**), followed by Pd/C hydrogenation, provides β-(1→6)-linked *C*-disaccharides **346** in very good total yields. The same procedure can not be used for the synthesis of α-isomer due to the easy epimerization of anomeric formyl group under the reaction conditions.



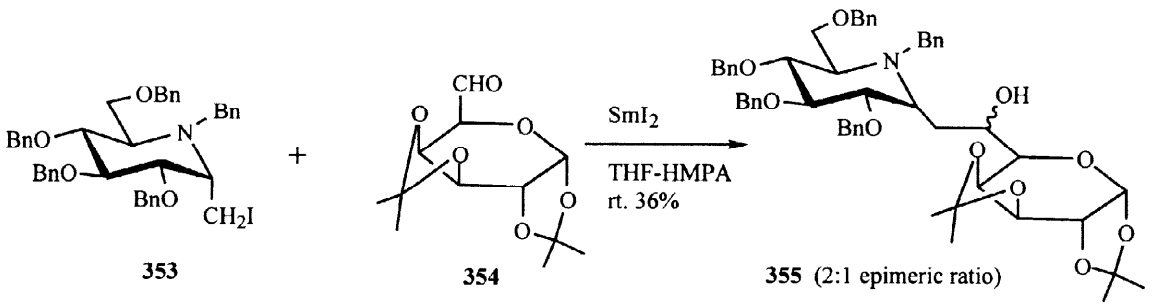
Scheme 76

Condensation of a 6-deoxy-6-diazo sugar **348** with sugar aldehyde **347** gives a mixture of a ketone and an epoxide bridged *C*-disaccharides **349** and **350**.[138,139] Compounds **349** and **350** were reduced to **351** and **352**, respectively, with high stereoselectivities (Scheme 77).



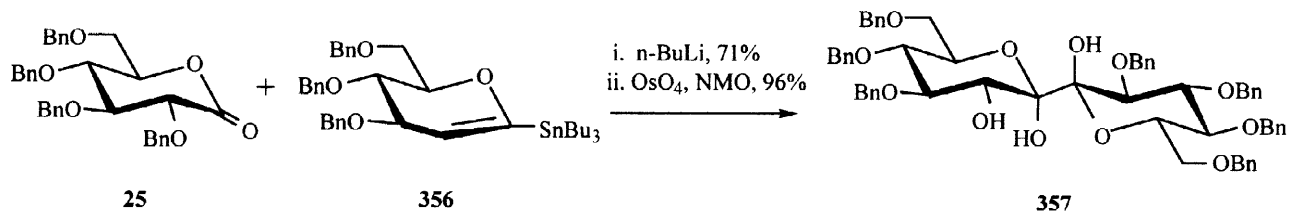
Scheme 77

Aza-sugars[140] and carba-sugars[130,141,142] are growing into one of the most attractive classes of carbohydrate mimetics due to their proposed glycosidase inhibitory activity. Several groups have reported the synthesis of aza-sugar *C*-disaccharides.[143-145] The synthetic approaches, described by Martin,[145] for forming (1→6) aza-sugar *C*-glycoside is shown in Scheme 78. Conversion of aza-*C*-glycosyl iodomethyl derivative **353** into an organosamarium species and reaction with C-6 sugar aldehyde **354** provides aza-*C*-disaccharide analog **355** in 36% yield.



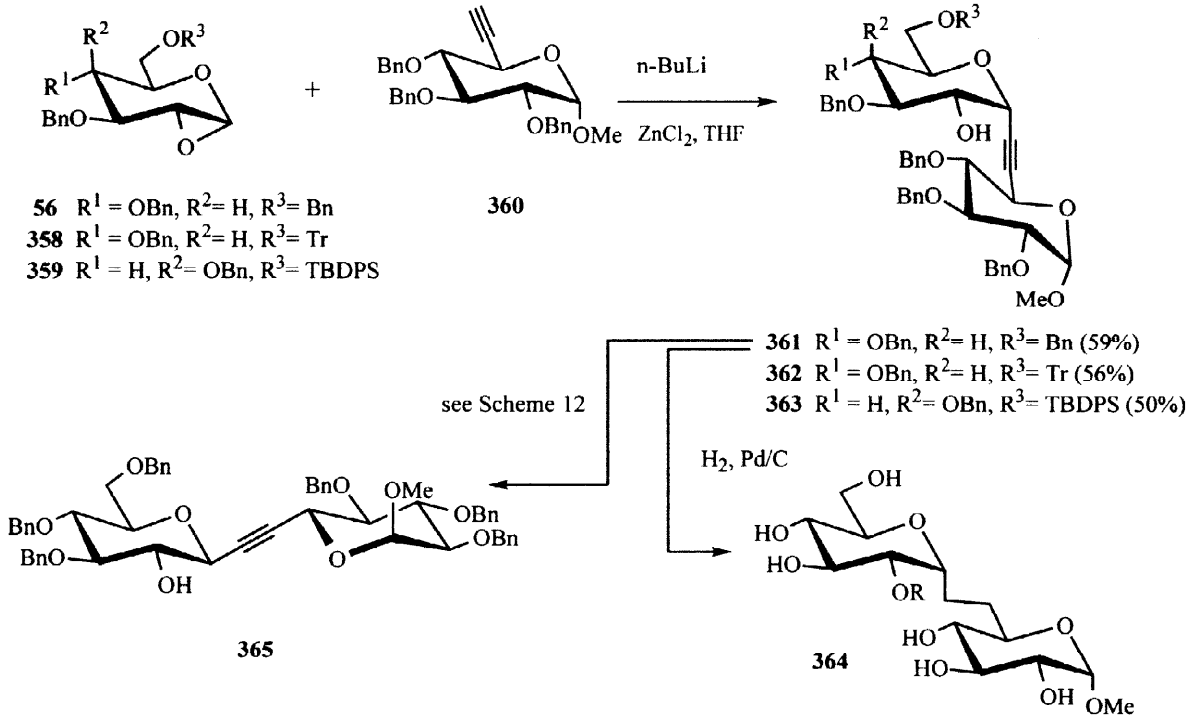
Scheme 78

The kinetic controlled reaction of 1,5-glucuronolactone **25** with glucal **356** in the presence of *n*-BuLi, following dihydroxylation, gives 1,1'-directly linked pseudo *C*-disaccharide **357**. The diastereoselectivity in the dihydroxylation step can be explained by the presence of the 3-*O*-benzyl group in the glucal moiety.[146]



Scheme 79

Ring opening of 1,2-anhydro sugars **56**, **358**, **359** with the acetylenide anion, generated from perbenzylated methyl 6,7-dideoxy-α-D-*gluco*-hept-6-ynopyranoside **360**, led to precursors **361-363** in fair yields.[34] Hydrogenation of **361** gave α-(1→6)-*C*-disaccharide **364** (Scheme 80, see also Scheme 12).



56 R^1 = OBn, R^2= H, R^3= Bn
358 R^1 = OBn, R^2= H, R^3= Tr
359 R^1 = H, R^2= OBn, R^3= TBDPS

360

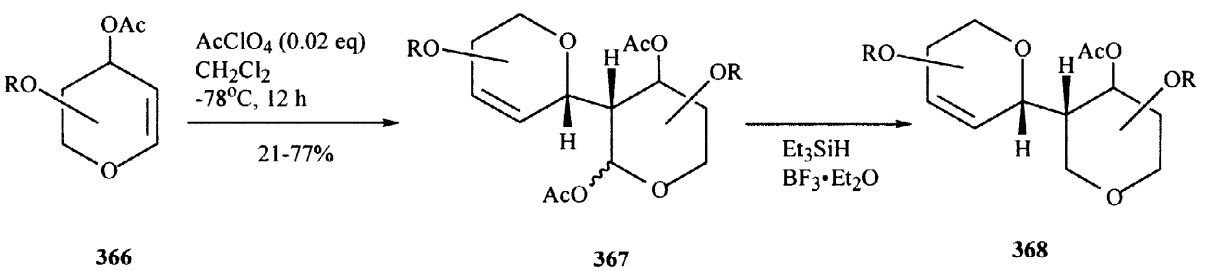
361 R^1 = OBn, R^2= H, R^3= Bn (59%)
362 R^1 = OBn, R^2= H, R^3= Tr (56%)
363 R^1 = H, R^2= OBn, R^3= TBDPS (50%)

365

364

Scheme 80

Glycals have been widely utilized as the electrophilic components in *C*-glycoside synthesis notably *via* the " carbon Ferrier rearrangement". Steel and co-workers[147] reexamined this process with a number of cationic polymerization initiators and found that acetyl perchlorate, an effective initiator for the polymerization of dihydrofuran, results in efficient coupling of 3-*O*-acyl glycals **366** with high stereoselectivity representing an excellent route to 1→2 linked pseudo *C*-disaccharides **368** (Scheme 81).



366

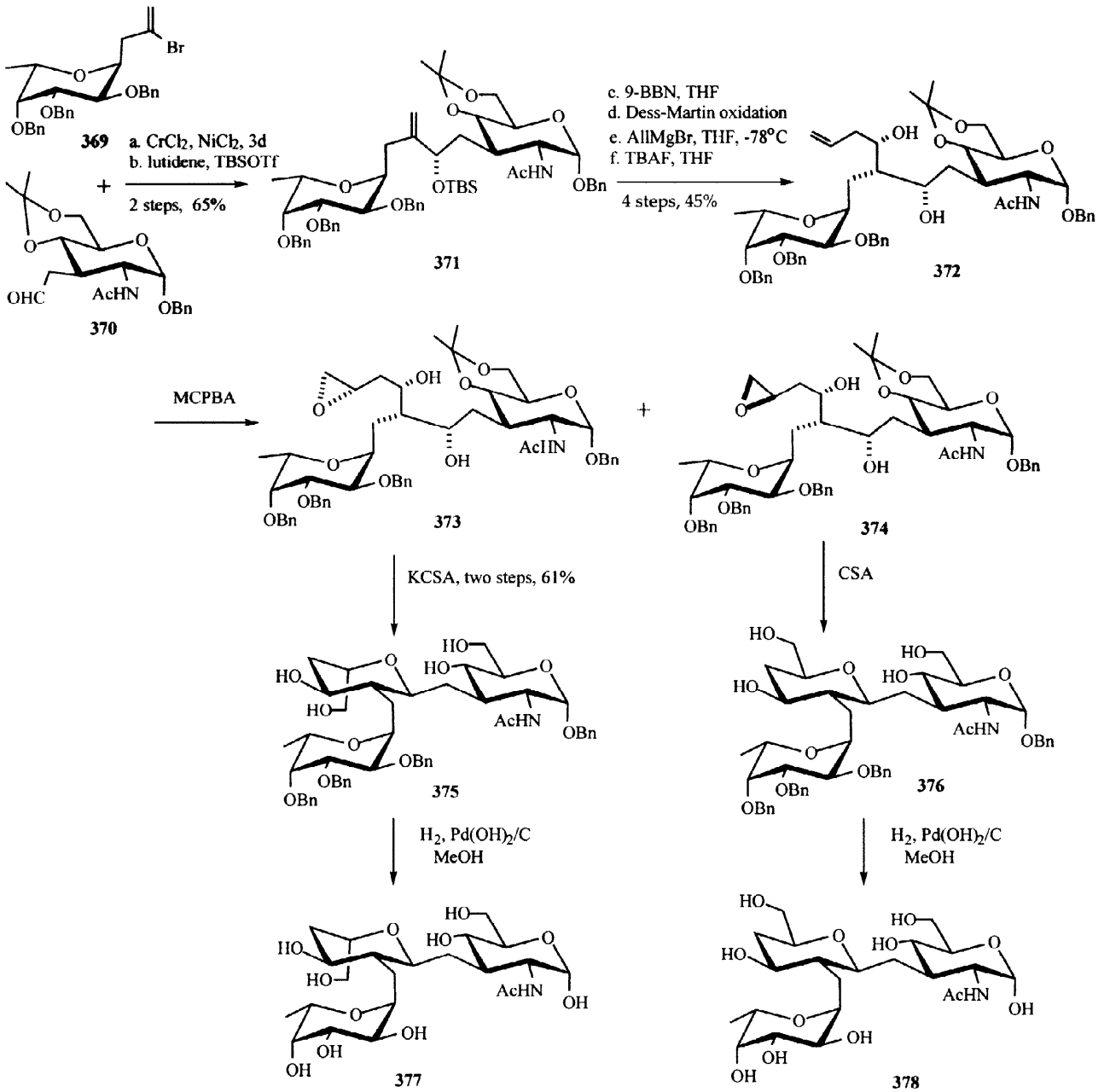
367

368

Scheme 81

9.2 C-Oligosaccharides

An elegant example of *C*-oligosaccharide synthesis, the preparation of twelve stereochemically and structurally diverse *C*-trisaccharides, was recently reported by Armstrong and co-workers.[9,148] Their synthetic strategy involved: 1) The synthesis of a trisaccharide precusor with fucose and *N*-acetylglucosamine at each terminus; and 2) the central core hexose was synthesized *de novo* with complete regio- and stereo-control. The synthesis of two (**377** and **378**) of a total of twelve target compounds is shown in Scheme 82.

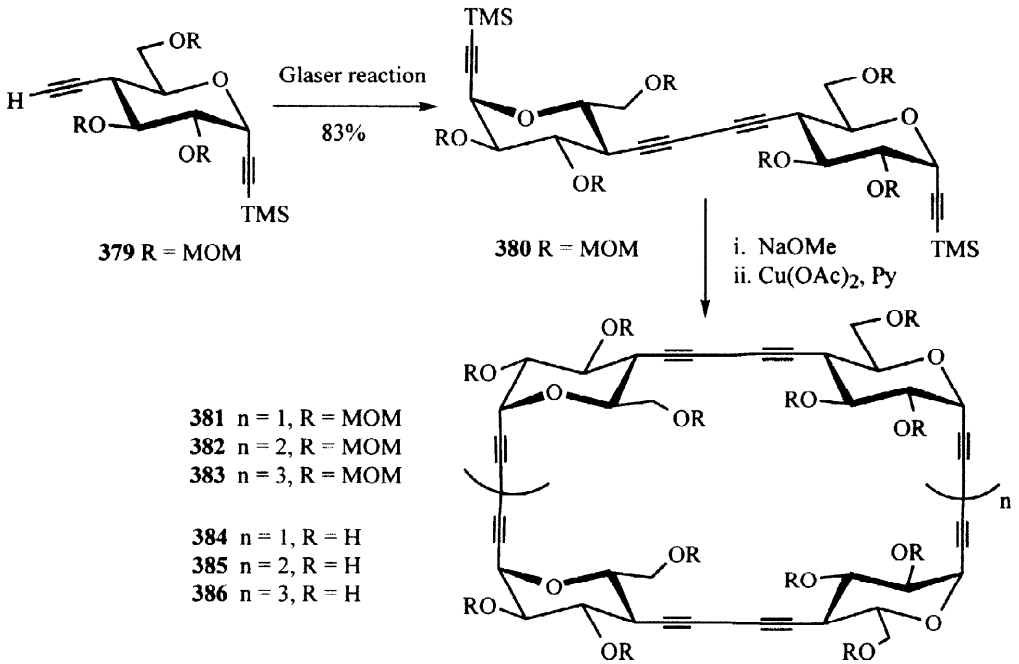


Scheme 82

Hydroboration of the tethered disaccharide **371** with 9-BBN, followed by Dess-Martin oxidation afforded aldehyde. Grignard allylation and desilylation gave olefin **372**. Its oxidation and subsequent acid-catalyzed cyclization furnished two separable *C*-trisaccharides **375** and **376** that after deprotection gave the target *C*-trisaccharides **377** and **378**, respectively.

Another interesting example of *C*-oligosaccharide synthesis, reported by Vasella and coworkers,[149,150] is the preparation of cyclic acetylenosaccharides. These *C*-oligosaccharides have a hydrophobic cavity making them important mimics of cyclodextrins (Scheme 83). Mono-*C*-silylated dialkyne **379** can be converted to the

butadiyne **380** in excellent yield by homo-dimerization under Glaser conditions. Disilylation of **380** followed by treatment with $Cu(OAc)_2$ in pyridine gave cyclotetramer **381**. Cyclohexamer **382** and cyclooctamer **383** were also obtained as by-products. Deprotection leads to the cyclodextrin mimics **384-386**.



Scheme 83

10. Conclusions

Direct carbon-carbon bond formation reactions have always been among the most challenging and yet most important tasks in synthetic organic chemistry. Their application to carbohydrate molecules poses additional complications. The stereocontrol at the anomeric center, affording either α- or β-*C*-glycoside, is in itself a daunting task. *C*-Glycoside synthesis is further complicated by the high degree of chiral functionality in carbohydrates. The presence of multiple protective groups also results in severely steric congestion in these molecules. Despite the complexity associated with their synthesis, the biological and pharmacological significance of *C*-glycosides continues to promise a substantial growth in new methods in this area. Future challenges in *C*-glycoside synthesis include: 1) applications on structurally complex targets; 2) a reduction in the number of the required synthetic steps is inevitable if these targets are ever to serve as therapeutic agents; 3) better control of stereoselectivity and elimination of side-reactions to reduce the need for chromatographic purification; and 4) the introduction of more environmentally friendly reagents and catalysts, particularly in cases where the ultimate goal is commercialization.

Acknowledgements

The authors thank Professors J. Gervay, F. Kong and Z. Jin for their critical reading of this manuscript.

References

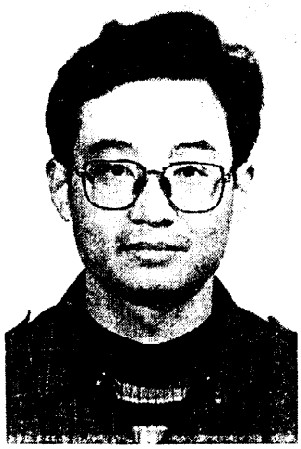
(1) Suhadolnik, R. J. *Nucleoside Antibiotics*; Wiley-Interscience: New York, 1970.
(2) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976-4978.
(3) Paterson, L.; Keown, L.E. *Tetrahedron Lett.* **1997**, *38*, 5727-30.
(4) Smith, III., A.B.; Zhuang, L.; Brook, C.S.; Boldi, A.M.; McBriar, M.D. et. al. *Tetrahedron Lett.* **1997**, *38*, 8667-8678 (3 consecutive papers).
(5) Horita, K.; Sakkkurai, Y.; Nagasawa, M.; Hachiya, S.; Yonemitsu, O. *Synlett* **1994**, 43-45.
(6) Nicotra, F. *Topics Curr. Chem.* **1997**, *187*, 55-83.
(7) Weatherman, R. V.; Mortell, K. H.; Chervenak, M.; Kiessling, L. L.; Toone, E. J. *Biochemistry* **1996**, *35*, 3619-3624.
(8) Weatherman, R.; Kiessling, L. L. *J. Org. Chem.* **1996**, *61*, 534-538.
(9) Sutherlin, D. P.; Stark, T. M.; Hughes, R.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 8350-8354.
(10) Postema, M. H. D. *C-Glycoside Synthesis*; CRC press: Boca Raton, 1995.
(11) Levy, D. E.; Tang, C. *The Chemistry of C-glycosides*; Pergamon: Oxford, 1995.
(12) Sinaÿ, P. *Pure & Appl. Chem.* **1997**, *69*, 459-463.
(13) Beau, J.-M.; Gollagher, T. *Topics Curr. Chem.* **1997**, *187*, 1-54.
(14) Gervay, J.; Hadd, M. J. *J. Org. Chem.* **1997**, *62*, 6961-6967.
(15) Nicolaou, K. C.; Sato, M.; Miller, N. D.; Gunzner, J. L.; Renaud, J.; Untersteller, E. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 889-891.
(16) Gomez, A. M.; Casillas, M.; Valverde, S.; Lopez, J. C. *Chem. Commun.* **1996**, 2357-2358.
(17) a). Wong, M. F.; Weiss, K. L.; Curley, R. W. *J. Carbohydr. Chem.* **1996**, *15*, 763-768. b). Leteux, C.; Veyrieres, A. *J. Chem. Soc. Perkin Trans. 1* **1994**, 2647-2655.
(18) Woo, S. H.; Parker, M. H.; Ploypradith, P.; Northrop, J.; Posner, G. H. *Tetrahedron Lett.***1998**, *39*, 1533-1536.
(19) Hildbrand, S.; Laser, A.; Parel, S. P.; Leumann, C. J. *J. Am. Chem. Soc.* **1997**, *119*, 5499-5511.
(20) Gudmundsson, K. S.; Drach, J. C.; Townsend, L. B. *J. Org. Chem.* **1997**, *62*, 3453-3459.
(21) Streicher, H.; Reiner, M.; Schmidt, R. R. *J. Carbohydr. Chem.* **1997**, *16*, 277-298.
(22) a). Streicher, H.; Geyer, A.; Schmidt, R. R. *Chem. Eur. J.* **1996**, *2*, 502-510. b). Veber, M.; Cheylan, E.; Czernecki, S.; Xie, J. *Liquid Crystals* **1996**, *21*, 197-201.
(23) Calzada, E.; Clarke, C. A.; Roussin-Bouchard, C.; Wightman, R. H. *J. Chem. Soc. Perkin Trans. 1* **1995**, 517-518.
(24) Deshpande, P. P.; Price, K. N.; Baker, D. C. *J. Org. Chem.* **1996**, *61*, 455-458.
(25) Csuk, R.; Schaade, M.; Krieger, C. *Tetrahedron* **1996**, *52*, 6397-6408.
(26) Toshima, K.; Miyamoto, N.; Matsuo, G.; Nakata, M.; Matsumura, S. *Chem. Commun.* **1996**, 1379-1380.
(27) Toshima, K.; Ushiki, Y.; Matsuo, G.; Matsumura, S. *Tetrahedron Lett.* **1997**, *38*, 7375-7378.
(28) Brigaud, T.; Lefebvre, O.; Plantier-Royon, R.; Portella, C. *Tetrahedron Lett.* **1996**, *37*, 6115-6116.
(29) Seeberger, P. H.; Bilodeau, M. T.; Danishefsky, S. J. *Aldrichimica Acta* **1997**, *30*, 75-92.
(30) Du, Y.; Kong, F. *J. Carbohydr. Chem.* **1995**, *14*, 341-352.
(31) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661-6665.
(32) Du, Y.; Kong, F. *Carbohydr. Res.* **1995**, *275*, 259-273.
(33) Du, Y.; Kong, F *Tetrahedron Lett.* **1995**, *36*, 427-430.
(34) Leeuwenburgh, M. A.; Timmers, C.M.; van der Marel, G.A.; van Boom, J.H; Mallet, J.-M.; Sinaÿ, P.G. *Tetrahedron Lett.* **1997**, *38*, 6251-4.
(35) Bombard, S.; Maillet, M.; Capmau, M.-L. *Carbohydr. Res.* **1995**, *275*, 433-440.

(36) Marron, T. G.; Woltering, T. J.; Weitz-Schmidt, G.; Wong, C.-H. *Tetrahedron Lett.* **1996**, *37*, 9037-9040.
(37) Uchiyama, T.; Vassilev, V. P.; Kajimoto, T.; Wong, W.; Huang, H.; Lin, C.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1995**, *117*, 5395-5396.
(38) Uchiyama, T.; Woltering, T. J.; Wong, W.; Lin, C.-C.; Kajimoto, T.; Takebayashi, M.; Weitz-Schmidt, G.; Asakura, T.; Noda, M.; Wong, C.-H. *Bioorg. & Med. Chem.* **1996**, *4*, 1149-1165.
(39) Woltering, T. J.; Weitz-Schmidt, G.; Wong, C.-H. *Tetrahedron Lett.* **1996**, *37*, 9033-9036.
(40) Minehan, T. G.; Kishi, Y. *Tetrahedron Lett.* **1997**, *38*, 6815-6818.
(41) Mukaiyama, T.; Uchiro, H.; Hirano, N.; Ishikawa, T. *Chem. Lett.* **1996**, 629-630.
(42) Figadere, B.; Peyrat, J.-F.; Cave, A. *J. Org. Chem.* **1997**, *62*, 3428-3429.
(43) Castro-Palomino, J. C.; Schmidt, R. R. *Liebigs Ann. Chem.* **1996**, 1623-1626.
(44) Mahling, J.-A.; Jung, K.-H.; Schmidt, R. R. *Liebigs Ann. Chem.* **1995**, 461-466.
(45) Ermolenko, M. S.; Olesker, A.; Lukacs, G. *Tetrahedron Lett.* **1994**, *35*, 715-718.
(46) Paulsen, H.; Roden, K.; Sinnwell, V.; Luger, P. *Liebigs Ann. Chem.* **1981**, 2009-2027.
(47) Frey, O.; Hoffmann, M.; Wittmann, V.; Kessler, H. *Helv. Chim. Acta* **1994**, *77*, 2060-2065.
(48) Frey, O.; Hoffmann, M.; Kessler, H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2026-2028.
(49) von Roedern, E. G.; Lohof, E.; Hessler, G.; Hoffmann, M.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 10156-10167.
(50) Wittman, V.; Kessler, H. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1091-3.
(51) Burkhart, F.; Hoffmann, M.; Kessler, H. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1191-1192.
(52) Hoffmann, M.; Kessler, H. *Tetrahedron Lett.* **1994**, *35*, 6067-6070.
(53) Hoffmann, M.; Burkhart, F.; Hessler, G.; Kessler, H. *Helv. Chim. Acta* **1996**, *79*, 1519-1532.
(54) Parker, K. A.; Koh, Y.-H. *J. Am. Chem. Soc.* **1994**, *116*, 11149-11150.
(55) Parker, K. A.; Coburn, C. A.; Koh, Y. *J. Org. Chem.* **1995**, *60*, 2938-2941.
(56) Parker, K. A.; Su, D.-S. *J. Org. Chem.* **1996**, *61*, 2191-2194.
(57) Eisele, T.; Ishida, H.; Hummel, G.; Schmidt, R. R. *Liebigs Ann. Chem.* **1995**, 2113-2121.
(58) Bearder, J. R.; Dewis, M. L.; Whiting, D. A. *J. Chem. Soc. Perkin. Trans. 1* **1995**, 227-233.
(59) Hanessian, S. In *Preparative Carbohydrate Chemistry*; Marcel Dekker, Inc.: New Youk, 1997; pp 507-526.
(60) Harenbrock, M.; Matzeit, A.; Schafer, H. J. *Liebigs Ann. Chem.* **1996**, 55-62.
(61) Ponten, F.; Magnusson, G. *J. Org. Chem.* **1996**, *61*, 7463-7466.
(62) Michael, K.; Wittmann, V.; Konig, W.; Sandow, J.; Kessler, H. *Int. J. Peptide Protein Res.* **1996**, *48*, 59-70.
(63) Cossy, J.; Ranaivosata, J.-L.; Bellosta, V.; Ancerewicz, J.; Ferritto, R.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 8351-8359.
(64) Drescher, M.; Hammerschmidt, F. *Synthesis* **1996**, 1451-1454.
(65) Praly, J.-P.; Chen, G.-R.; Gola, J.; Hetzer, G.; Raphoz, C. *Tetrahedron Lett.* **1997**, *38*, 8185-8188.
(66) Roe, B. A.; Boojamra, C. G.; Griggs, J. L.; Bertozzi, C. R. *J. Org. Chem.* **1996**, *61*, 6442-6445.
(67) a). Cipolla, L.; Liguori, L.; Nictora, F.; Torri, G.; Vismara, E. *Chem. Commun.* **1996**, 1253-1254.
b). Cipolla, L.; Nicotra, F.; Vismara, E.; Guerrini, M. *Tetrahedron* **1997**, *53*, 6163-6170.
(68) Gervay, J.; Flahert, T. M.; Holmes, D. *Tetrahedron*, **1997**,*48*, 16355-16364.
(69) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307-338.
(70) Mazeas, D.; Skrydstrup, T.; Doumeix, O.; Brau, J.-M. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1383-1386.
(71) Skrydstrup, T.; Mazeas, D.; Elmouchir,M.; Doisneau,G.; Riche, C.; Chiaroni, A.; Beau, J.-M *Chem. Eur. J.* **1997**, *3*, 1342-56.
(72) de Pouilly, P.; Chenede, A.; Mallet, J.-M.; Sinaÿ, P. *Bull Soc. Chim. Fr.* **1993**, *130*, 256-265.

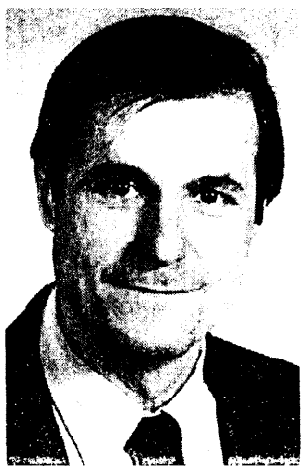
(73) Mazeas, D.; Skrydstrup, T.; Beau, J.-M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 909-912.
(74) Jarreton, O.; Skrydstrup , T.; Beau, J.-M. *Chem. Commun.* **1996**, 1661-1662.
(75) Urban, K.; Skrydstrup, T.; Riche, C.; Chiaroni, A.; Beau, J.-M. *Chem. Commun.* **1996**, 1883-1884.
(76) Yoneda, R.; Harusawa, S.; Kurihara, T. *Tetrahedron Lett.* **1989**, *30*, 3681-3684.
(77) Araki, S.; Hatano, M.; Ito, H.; Butsugan, Y. *J. Organomet. Chem.* **1987**, *333*, 329-331.
(78) Hung, S.-C.; Wong, C.-H. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2671-2674.
(79) Hung, S.-C.; Wong, C.-H. *Tetrahedron Lett.* **1996**, *37*, 4903-4906.
(80) Vlahov, I. R.; Vlahova, P. I.; Linhardt, R. J. *J. Am. Chem. Soc.* **1997**, *119*, 1480-1481.
(81) Du, Y.; Linhardt, R. J. *Carbohydr. Res. in press.* **1998**,
(82) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley, Chichester: 1995.
(83) Daves, G. D. J. *Acc. Chem. Res.* **1990**, *23*, 201-204.
(84) Frappa, I.; Sinou, D. *J. Carbohydr. Chem.* **1997**, *16*, 255-276.
(85) Hsieh, H.-P.; McLaughlin, L. W. *J. Org. Chem.* **1995**, *60*, 5356-5359.
(86) Dunkerton, L. V.; Euske, J. M.; Serino, A. J. *Carbohydr. Res.* **1987**, *171*, 89-94.
(87) Engelbrecht, G. J.; Holzapfel, C. W. *Heterocycles* **1991**, *32*, 1267-1275.
(88) Bouoit, S.; Goux, C.; Sinou, D. *Carbohydr. Lett.* **1997**, *2*, 267-272.
(89) Abas, A.; Beddoes, R. L.; Conway, J. C.; Quayle, P., Urch, C. J. *Synlett.* **1995**, 1264-6.
(90) Jeanneret, V.; Meerpoel, L.; Vogel, P. *Tetrahedron Lett.* **1997**, *38*, 543-546.
(91) Friesen, R. W.; Loo, R. W.; Sturino, C. F. *Can. J. Chem.* **1994**, *72*, 1262-1265.
(92) Nicolaou, K. C.; Shi, G.Q.; Gunzner, J.L.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 5467-8.
(93) a). Miyarea, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314-321. b). Johnson, C. R.; Johns, B. A. *Synlett.* **1997**, 1406-1408.
(94) Johns, B. A.; Pan, Y. T.; Elbein, A. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 4856-4865.
(95) Moineau, C.; Bolitt, V.; Sinou, D. *J. Chem. Soc. Chem. Commun.* **1995**, 1103-1104.
(96) Mesmaeker, A. D.; Waldner, A.; Hoffmann, P.; Winkler, T. *Synlett* **1994**, 330-332.
(97) Rossin, R.; Jones, P. R.; Murphy, P. J.; Worsley, W. R. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1323-1325.
(98) Verlhac, P.; Leteux, C.; Toupet, L.; Veyrieres, A. *Carbohydr. Res.* **1996**, *291*, 11-20.
(99) Matheu, M. I.; Echarri, R.; Domenech, C.; Castillon, S. *Tetrahedron* **1996**, *52*, 7797-7806.
(100) a). Stork, G.; Suh, H.; Kim, G. *J. Am. Chem. Soc.* **1991**, *113*, 7054-7056. b). Stork, G.; La Clair, J. J. *J. Am. Chem. Soc.* **1996**, *118*, 247-248.
(101) Fairbanks, A. J.; Perrin, E.; Sinaÿ, P. *Synlett* **1996**, 679-691.
(102) Chenede, A.; Perrin, E.; Rekai, E. D.; Sinaÿ, P. *Synlett* **1994**, 420-423.
(103) Mazeas, D. S. T.; Doumeix, O.; Beau, J-M. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1383-1386.
(104) Suzuki, K.; Matsumoto, T.; Hosoya, T. *J. Synth. Org. Chem., Jpn.* **1995**, *53*, 1045-1054.
(105) Matsuo, G.; Matsumura, S.; Toshima, K. *Chem. Commun.* **1996**, 2173-2174.
(106) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004-1015.
(107) Hua, D. H.; Saha, S. *Recl.Trav.Chim. Pays-Bas* **1995**, *114*, 341-355.
(108) Matsumoto, T.; Sohma, T.; Yamaguchi, H.; Suzuki, K. *Chem. Lett.* **1995**, 677-678.
(109) Matsumoto, T.; Sohma, T.; Yamaguchi, H.; Kurata, S.; Suzuki, K. *synlett* **1995**, 263-6.
(110) Hosoya, T.; Ohashi, Y.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1996**, *37*, 663-666.
(111) Tomooka, T.; Nakamura, Y.; Nakai, T *Synlett* **1995**, 321-2.
(112) Tomooka, K.; Yamamoto, H.; Nakai, T. *J. Am. Chem. Soc.* **1996**, *118*, 3317-3318.
(113) Tomooka, K.; Nakai, T. *J. Synth. Org. Chem., Jpn.* **1996**, *54*, 1000-1008.
(114) Norrild, J. C.; Pedersen, C.; Sotofte, I. *Carbohydr. Res.* **1997**, *297*, 261-272.
(115) Railton, C. J.; Clive, D. L. J. *Carbohydr. Res.* **1996**, *281*, 69-77.
(116) Khan, A. T.; Ahmed, W.; Schmidt, R. R. *Carbohydr. Res.* **1996**, *280*, 277-286.

(117) Hart, D. J.; Merriman, G. H.; Young, D. G. J. *Tetrahedron* **1996**, *52*, 14437-14458.
(118) Bichard, C. J. F.; Brandstetter, T. W.; Estevez, J. C.; Fleet, G. W. J.; Hughes, D. J.; Wheatley, J. R. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2151-2156.
(119) Estevez, J. C.; Saunders, J.; Besra, G. S.; Brennan, P. J.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymm.* **1996**, *7*, 383-386.
(120) Rycroft, A. D.; Singh, G.; Wightman, R. H. *J. Chem. Soc. Perkin Trans. 1* **1995**, 2667-2668.
(121) Lopez-Herrera, F. J.; Pino-Gonzalez, M. S.; Sarabia-Garcia, F.; Heras-Lopez, A.; Ortega-Alcantara, J. J.; Pdraza-Cebrian, G. M. *Tetrahedron Asymmetry* **1996**, *7*, 2065-2074.
(122) Lopez-Herrera, F. J.; Heras-Lopez, A. M.; Pino-Gonzalez, M. S.; Garcia, F. S. *J. Org. Chem.* **1996**, *61*, 8839-8848.
(123) Lopez-Herrera, F. J.; Sarabia-Garcia, F.; Heras-Lopez, A.; Pino-Gonzalez, M.S. *J. Org. Chem.* **1997**, *62*, 6056-59.
(124) Lee, E.; Park, C. M. *J. Chem. Soc. Chem. Commun.* **1994**, 293-294.
(125) Belosludtsev, Y. Y.; Bhatt, R.K.; Falck, J. R. *Tetrahedron Lett.* **1995**, *36*, 5881-5882.
(126) Binch, H. M.; Griffin, A. M.; Schwidetzky, S.; Ramsay, M. V. J.; Gallagher, T.; Lichtenthaler, F. W. *J. Chem. Soc. Chem. Commun.* **1995**, 967-968.
(127) Yokoyama, M.; Toyoshima, H.; Shimizu, M.; Togo, H. *J. Chem. Soc. Perkin Trans. I* **1997**, 29-31.
(128) Ren, R. X.-F.; Chaudhuri, N. C.; Paris, P. L.; Rumney IV, S.; Kool, E. T. *J. Am. Chem. Soc.* **1996**, *118*, 7671-7678.
(129) Rouzad, D.; Sinaÿ, P. *J. Chem. Soc. Chem. Commun.* **1983**, 1353-1354.
(130) Ferritto, R. V. P. *Tetrahedron:Asymmetry* **1994**, *5*, 2077-2092.
(131) Dietrich, H. S.; Schmidt, R. R. *Liebigs. Ann. Chem.* **1994**, 975-981.
(132) Khan, A. T.; Sharma, P.; Schmidt, R. R. *J. Carbohydr. Chem.* **1995**, *14*, 1353-1367.
(133) Sharma, G. V. M.; Hymavathi, L.; Krishna, P. R. *Tetrahedron Lett.* **1997**, *39*, 6929-6932.
(134) a). Martin, O. R.; Lai, W. *J. Org. Chem.* **1993**, *58*, 176-185. b). Zhu, Y-H.; Vogel, P. *Tetrahedron Lett.* **1998**, *39*, 31-34.
(135) Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. D. *J. Org. Chem.* **1996**, *61*, 1894-1897.
(136) Dondoni, A.; Boscarato, A.; Zuurmond, H. *Tetrahedron Lett.* **1996**, *37*, 7587-7590.
(137) Dondoni, A.; Zuurmond, H. M.; Boscarato, A. *J. Org. Chem.* **1997**, *62*, 8114-8124.
(138) Sarabia-Garcia, f.; Lopez-Herrera, F. J.; Gonzalez, M. S. P. *Tetrahedron* **1995**, *51*, 5491-5500.
(139) Sarabia-Garcia, F.; Lopez-Herrera, F. J. *Tetrahedron* **1996**, *52*, 4757-4768.
(140) Frerot, E.; Marquis, C.; Vogel, P. *Tetrahedron Lett.* **1996**, *37*, 2023-2026.
(141) Barbaud, C.; Bols, M.; Lundt, I.; Sierks, M. R. *Tetrahedron* **1995**, *51*, 9063-9078.
(142) Angelaud, R. L. Y.; Parra-Rapado, L. *Tetrahedron Lett* **1997**, *38*, 8845-8848.
(143) Baudat, A.; Vogel, P. *J. Org. Chem.* **1997**, *62*, 6252-60.
(144) Fuchss, T.; Streicher, H.; Schmidt, R. R. *Liebigs. Ann./Recueil* **1997**, 1351-1321.
(145) Martin, O. R.; Liu, L.; Yang, F. *Tetrahedron Lett.* **1996**, *37*, 1991-1994.
(146) Mochizuki, T.; Shiozaki, M. *Chem. Lett.* **1997**, 801-2.
(147) a). Byerley, A. L. J.; Kenwright, A. M.; Steel, P. G. *Tetrahedron Lett.* **1996**, *37*, 9093-9096. b). Byerley, A. L. J.; Kenwright, A. M.; Lehmann, C. W.; MacBride, J. A. H.; Steel, P. G. *J. Org. Chem.* **1998**, *63*, 913-194.
(148) Sutherlin, D. P.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 5267-5283.
(149) Burli, R.; Vasella, A. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1852-1853.
(150) Xu, J.; Egger, A.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1996**, *79*, 2004-2022.

Biographical sketch



Yuguo Du



Robert J. Linhardt

Iontcho R. Vlahov

Yuguo Du received his B.S. (1987) in Environmental Chemistry from Tsinghua University, M.S. (1990) in Ecology and Environmental Chemistry and his Ph.D. (1995) in Organic Chemistry from the Research Center of Eco-Environmental Sciences, Academia Sinica in Beijing, China. His doctoral research with Professor Fanzuo Kong was on the synthesis, conformational analysis and glycosidic reaction of anhydrosugars. From 1995-1998, Dr. Du was a postdoctoral fellow in Professor Linhardt's laboratory at the University of Iowa, where he worked in the synthesis of acidic carbohydrates. He has recently returned to China as an assistant professor in Academia Sinica.

Robert J. Linhardt received his B.S. (1975) from Marquette University and his M.A. (1977) and Ph.D. (1979) from Johns Hopkins University. His doctoral research was in physical-organic chemistry with Professor B.L. Murr. In 1979, Dr. Linhardt joined Professor R. Langer's group in Biochemical Engineering at MIT as a postdoctoral fellow where he purified and characterized the heparin lyases. On joining the faculty at the University of Iowa in 1982, Dr. Linhardt focused his research on the structure and activity of heparin for which he received the 1994 Isbell Award in Carbohydrate Chemistry from the American Chemical Society. Most recently, his research has included developing methods for the synthesis of acidic carbohydrates. Dr. Linhardt is currently the F. Wendell Miller Distinguished Professor of Medicinal and Natural Products Chemistry and Professor of Chemical and Biochemical Engineering at the University of Iowa.

Iontcho R. Vlahov received his M.Sc. (1980) diploma from the University of Sofia in Bulgaria and his Ph.D. (1984) with Professor G. Snatzke from Ruhr University in Bochum, Germany. In 1990, Dr. Vlahov was awarded an Alexander von Humboldt Research Fellowship to study in Germany with Professor R.R. Schmidt at the University of Konstanz where he worked on the stereospecific synthesis of neuraminic acid analogues. From 1993 to 1996, Dr. Vlahov was a postdoctoral fellow in Professor Linhardt's laboratory at the University of Iowa where he worked in the synthesis of acidic carbohydrates. In 1996 he was a industrial postdoctoral fellow at Hercules Corporation working on the synthesis of modified polysaccharides. He is currently leading the medicinal chemistry research at Baker-Norton Pharmaceuticals in Miami, Florida.