Published in final edited form as:
Curr Top Med Chem. 2005 ; 5(14): 1393–1430.

Recent Advances in the Synthesis of *C*-oligosaccharides

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Abstract

This paper reviews the recent advances in the synthesis of catabolically stable sugar mimetics, *C*-oligosaccharides. These compounds are synthetic analogs of the naturally occurring *O*-oligosaccharides, in which the interglycosidic oxygen has been replaced by a methylene group. This review is organized in terms of chemistry used to assemble *C*-oligosaccarides under the sub-headings: anionic approaches, cationic methods, reductive glycosyl samarium chemistry, cyclization methodology, and free radical chemistry.

1. INTRODUCTION

Oligosaccharides (*oligo* means *few* in Greek) are composed of 2 to 10 glycosidically-linked mono-saccharides [1]. Oligosaccharides are hydrolyzed readily by aqueous acid to form an oligosaccharides constituent monosaccharides. Oligosaccharides represent a unique class of glycosides, in which the “aglycon” is also a carbohydrate residue instead of a simple alcohol.

Oligosaccharides and glycocojugates are involved in a multitude of biological processes including cell recognition, cell differentiation and cell adhesion. In addition, a number of protein-carbohydrate interactions mediate critical biological process such as cell signaling in growth and differentiation, and fertilization [2]. While these above processes are generally beneficial, carbohydrates also play major roles in a number of detrimental processes, including inflammation, viral and bacterial infections, and tumor metastasis. Major achievements in the development of carbohydrate based therapeutics include the synthesis of a heparin pentasaccharide, which displays selective antithrombic activity, and the design and synthesis of derivatives of sialyl Lewis X antigen, that are interest as potential anti-inflammatory agents [3].

However, the glycosidic bonds connecting individual saccharides units within carbohydrate-based therapeutics are unstable to mild acid and to glycosidase enzymes *in vivo*, thus agents with enhanced stability need be developed [4]. Considerable research has focused on the synthesis of *C*-glycosides, stable mimics of the naturally occurring *O*-saccharides. These molecules, in which the interglycosidic oxygen has been replaced by a methylene group, can

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be considered as chemically inert isosteres of natural *O*- and *N*-glycosides, and are stable to mild acid *in vitro* and glycosidase enzymes *in vivo* [5].

C-Oligosaccharides are defined as compounds with two or more sugar units linked by one carbon atom through (1→1), (1→2), (1→3) or (1→4) linkages, or linked by two carbon atoms for (1→1) or (1→6) linkages. Synthetically prepared *C*-glycosides have so far proved useful for probing stereoelectronic effects, which can control the conformation of oligosaccharides, and can also prevent viral and bacterial attachment to lectins in adhesion assays, to the same extent as *O*-glycosides [6]. *C*-glycosides can inhibit some carbohydrate processing enzymes. Oligosaccharides and glycoconjugates are biosynthesized through complicated, highly efficient enzyme mediated routes. The structure of the final glycoconjugate is governed by the action of a series of enzymes. Alteration in the regulation of these enzymes is believed to be responsible for the biosynthesis of carbohydrates associated with disease processes. Inhibitors of glycosidase and glycosyltransferase enzymes are currently receiving attention as new pharmaceutical agents. Moreover, a number of enzyme inhibitors have proven therapeutic efficacy for the treatment of diseases such as influenza and AIDS [7].

Biological studies have shown that the natural inhibitors highlighted in Fig. 1, exert their effects on a range of glycosidases and are therefore of limited use as medicinal agents [8]. Consequently, more specific inhibitors are currently being sought that can be engineered to more accurately resemble the substrates that they are mimicking and thereby provide greater selectivity. Early tests on *C*-glycosides have provided evidence for their potential to act as oligosaccharide processing inhibitors [7].

The area of *C*-linked glycoside synthesis has been extensively reviewed over the past 15 years [9]. The organization of this review is based on the type of chemistry used to assemble the target *C*-oligosaccharides. The chemistry involved includes anionic and cationic chemistry, reductive samariation, cyclization methodology and free radical approaches. Methods that afford the *C*-oligosaccharides with high stereoselectivity at the anomeric center (α or β) are clearly desirable. This selectivity can be controlled by either starting with a stereochemically defined *C*-glycoside, which is then coupled with another sugar, or by controlling the stereochemistry of the newly formed center.

2. ANIONIC APPROACHES

2.1. Enolate Anions

Fraser-Reid and Jarosz coupled two monosaccharide units through a directed aldol reaction [10]. Aldehyde **1** was deprotonated with $(Me_3Si)_2NLi$ (LiHMDS) to give the chelated enolate **2**, which was condensed with aldehyde **3** to give **4a** as the major product (Scheme **1**).

The zinc-copper-mediated reaction between **5** and **6** gives rise to the generation of single product **7**, in 78% yield demonstrating a remarkable double stereoselectivity with a strong preference for α-*C*-glycosylation of the ulosyl bromide together with the elaboration of the (*R*) configuration for the CHOH group linking the pyranoid moieties (Scheme **2**) [11].

Vogel utilized a “naked sugar” approach for the synthesis of an aza-*C*-disaccharide. Enolate derived from **8** was coupled with aldehyde **9** to give the adduct **10** in 61% yield. The ketone was reduced and the resulting diol was acetylated. This was followed by selenoxide elimination to afford olefin **11**, which was converted to **12** as shown in Scheme **3** [12].

Cross-aldol reaction of racemic aldehyde 14 with enantiomerically pure lithium enolate of (−)-(1*R*,4*R*,5*R*,6R)- or (−)-(1*S*,4*S*,5*S*,6*S*)-13, results in mixtures composed mostly of enantiomerically pure (+)-**15** and (-)-**15**, respectively, in 37–48% (only one of the isomers is shown in Scheme **4**) [13].

Vogel and co-workers use a novel approach to *C*-disaccharide synthesis that involves conjugate addition and enolate trapping [14]. Levoglucosenone **16** was treated with Me_2AlSPh to give the aluminium enolate **17**. Condensation of **17** with aldehyde **18** gave the aldol product that was reduced with DIBAL to **20**. Treatment of **20** with acidic methanol afforded the (1→3)-*C*-disaccharide **21** (Scheme **5**).

Enone **22** was synthesized and condensation of trapping enolate with aldehyde **23** led to a mixture of aldols **24** and **25** that were separated by column chromatography on silica gel and isolated in 15% and 29% yield, respectively. Reduction of the major aldol **25** with $NaBH_4$ in MeOH/THF was highly stereoselective and provided the *C*-disaccharide **26** in 77% yield (Scheme **6**) [15].

When reacted with $PhMe_2SiZnMe_2Li$ in THF at −78 °C enone **27** afforded a single adduct **28**. Treatment of ketone **28** with dicyclohexylboron chloride and Et_3N at −15 °C followed by addition of **29**, the resulting aldol-borate was oxidized with 35% H_2O_2 giving adduct **30** in 24% yield. Stereoselective reduction of aldol **30** with $Me_4NBH(AcO)_3$ afforded diol **31** in 59% yield (Scheme **7**) [15].

2.2. Nitro Stabilized Anions

Vasella and Martin pioneered the use of nitro-based anions for *C*-saccharide synthesis. Anomeric nitro derivative **32** was treated with TBAF and exposed to aldehyde **33** to give the adduct **34** in 78% yield. Acetylation of **34** followed by reductive denitration afforded **35** (Scheme **8**) [16].

Martin's work has also relied on the Henry reaction. Aldol condensation of nitro sugar **36** with aldehyde **33** gave **37**. Dehydration of **37** and conjugate reduction led to **38**. Removal of nitro group by radical-based reduction followed by the removal of protecting groups gave rise to the (1→6)-β-*C*-disaccharide **40** (Scheme **9**) [17].

An open chain sugar derived aldehyde was used to access a *C*-trehalose derivative through the Henry reaction. Condensation of **36** with aldehyde **41** in the presence of KF and crown ether 18-crown-6, gave adduct **42**, which was immediately converted to **43** with a sequence of reactions in 29% overall yield. The intermediate was finally transformed to the *C*-linked-(1→1)-disaccharide **44** (*C*-β,β-trehalose) (Scheme **10**) [17].

Martin and coworkers applied the same methodology to prepare an *O*,*C*-trisaccharide, namely methyl *O*-β-D-glucopyranosyl-(1→4)-*C*-β-D-glucopyranosyl-(1→6)-D-glucopyranoside **48** [18]. The condensation of compound **45** with 6-aldehydo-glucopyranoside **46** in the presence of KF in an aprotic medium afforded the desired pseudotrisaccharide **47** in 73% yield. Application of the same chemistry to **47** gave the target compound **48** (Scheme **11**).

Kobertz and coworkers utilized Martin's methodology to prepare *C*-allolactose. Nitro sugar **49** was condensed with aldehyde **50** afforded the adduct **51** as a mixture of diastereomers. The hydroxyl group was converted to the corresponding phenyl thiocarbonate ester **52**. Treatment with tin hydride and a radical initiator effected elimination reaction, yielding only *E*-olefin **53**. Finally the olefin was reduced with dimide (generated *in situ*) and benzyl ethers were removed by dissolving metal reduction to afford the target disaccharide **54** (Scheme **12**) [19].

Gurjar *et al*. synthesized the first methyl α-*C*-D-ara*f*-(1→5)-α-D-ara*f* **60**, the *C*-disaccharide segment of motif C of *Mycobacterium tuberculosis*, through nitro-aldol condensation. The coupling reaction between **55** and **56** gave diasteromeric mixture **57**, which was subjected to three subsequent steps, *i.e*. dehydration, selective reduction of conjugated olefin and denitration, to give the penta-*O*-benzyl *C*-disaccharide **59** (Scheme **13**) [20].

Witczak has used nitro anions for *C*-disaccharide synthesis. Michael addition of the nitro anion derived from **61** to levoglucosenone **62** gave adduct **63** in 43% yield. The sterics in **62** dictates the facial bias of the addition, which can only occur from the α-face. Reductive denitration followed by reduction of lactol and ketone afforded **64**. Ring opening, deprotection and acetylation gave **65** (Scheme **14**) [21].

2.3. Sulfur Stabilized Anions

The Taylor group employed the Meyers variant of the Ramberg-Bäcklund reaction to synthesize *C*-disaccharides [22]. The penta-*O*-benzyl thioglucose **66** was coupled with iodide compound **67** followed by oxidation of the formed sulfide gave sulfone **68**. Exposure of the sulfone to the Meyers variant of the Ramberg-Bäcklund reaction afforded *exo*-glycal **69** as a mixture of isomers in 48% yield. Hydrogenation of this mixture stereoselectively reduced double bond and cleaved the benzyl groups. Peracetylated *C*-trehalose **70** was furnished by acetylation of free sugar (Scheme **15**).

This approach is well suited to analog synthesis simply by varying the alkylating agent. Thus, the homologous (1→1')-*C*-disaccharide, containing a two-carbon bridge (“homoisotrehalose”), was readily prepared (Scheme **16**) [23]. Lactol **71** was converted into sulfonate **74** by a straightforward three-step sequence involving Moffat-type *C*-glycosylation to give ester **72**, followed by reduction and mesylation. Next, **74** was coupled with thiol **75** in a similar alkylation-oxidation sequence to that above. The resulting sulfone **77** underwent a halogenative Ramberg-Bäcklund rearrangement (RBR) to give *exo*-glycal **78** as a 88:12 mixture of (*Z*)- and (*E*)-isomers in 57% yield. Subsequent reduction/debenzylation followed by acetylation produced the novel, ethylene-bridged disaccahride **79**.

This group also reported a rapid synthesis of a range of *C*-disaccharides involving a tandem Horner-Wadsworth-Emmons (HWE)/conjugate-addition *C*-glycosylation followed by a tandem halogenation-RBR sequence, utilizing Meyers variant of the RBR [24]. The HWE reagent **81** proceeded the HWE/conjugate-addition sequence with diisopropylidene mannofuranose **80** in 86% yield, to produce the adduct sulfone **82** (as a mixture of diastereomers). The key halogenation-RBR was carried out using the conditions devised by Chan *et al*. giving *E*-alkene **83** as the only isolable product. Alkene hydrogenation and concomitant debenzylation, followed by acetylation for characterization purposes, gave the novel disaccharide **84** in 69% yield over the two reactions (Scheme **17**).

A two-directional variant of this methodology can be used to prepare symmetrical *C*-disaccharides, as shown in Scheme **18** [24]. The double HWE reaction on diisopropylidene mannofuranose **80** worked extremely well in the HWE/conjugation-addition *C*-glycosydation sequence giving diastereomeric sulfones **85**, in a combined yield of 75%. RBR of the major stereoisomer (β,α-**79**) using the Meyers-Chan procedure gave alkene **86** in 66% unoptimized yield, and hydrogenation produced the novel *C*-linked bisfuranose disaccharide **87** in 76% yield.

Norris *et al*. deprotonated **88** with *n*-BuLi and the resulting anion was coupled with an excess lactone **89** at low temperature to afford the adduct **90** in 77% yield. SPh groups were removed with Raney nickel, and lactol **91** was isolated as a syrup that contained two components in approximately a 4:1 ratio. The two compounds were thought to be α- and β-lactols with the latter being major. It was straightforward to reduce the lactols with a high degree of stereocontrol to afford the *C*-disaccharide **92** with a 51% isolated yield (Scheme **19**) [25].

2.4. Phosphorous Stabilized Anions

The most common type of reaction discussed in this section is Wittig approach to *C*-oligosaccharide synthesis. This methodology is particularly suited for synthesis of (1→6)-*C*-saccharides, since one sugar can hold the aldehyde while the other the ylid or phosphonate anion.

Dondoni has utilized this approach to prepare a variety of β-D-(1→6)-*C*- disaccharides. The general approach is shown in Scheme **20**. Coupling of β-linked galactopyranosyl or mannofuranosyl derivative (**93**, **94**, **95**, or **96**) with ylide from phosphonium iodide **97** or **98** gave alkene **99**. Alkene was reduced and removal of deprotecting groups gave the corresponding β-D-(1→6)-*C*- disaccharide **100** [26].

α-D-(1→6)-*C*-disaccharide **103** was also synthesized using the approach (Scheme **21**).

Dondoni applied this methodology in an iterative fashion to prepare the corresponding β-(1→6)-*C*-trigalactosides and β-(1→6)-*C*-tetragalactosides [27]. Starting with coupling of ylide **104**, generated *in situ* with aldehyde **33**, gave adduct **105** (*E*/*Z* 1:9). Removal of silyl protecting group followed by oxidation led to aldehyde **106**, which was coupled with the ylide from **104** to give *C*-trisaccharide **107** in 36% yield. The same sequence was repeated with **107** afforded the protected *C*-tetrasaccharide alkene **108**. Compounds **108** was

desilylated and exposed to hydrogen over $Pd(OH)_2$ on carbon followed to peracetylation gave protected *C*-tetrasaccharide **109** (Scheme **22**).

Taking advantage of their experience on the stereo-selective synthesis of *C*-oligosaccharides by iterative Wittig olefination, this group developed new building blocks and a modified protocol for the straightforward assembly of *C*-α-(1→5)-ᴅ-oligoarabinofuranosides [28]. While the two monofunctionalized sugar moieties, **110** and **111** were suitable precursors to the head and tail of the oligosaccharidic chain, the difunctionalized compound **114** was a repeating unit (Scheme **23**). Building block **114** was designed to allow, after the Wittig coupling, for regeneration of the formyl group in a single step under conditions that do not affect the chemical and stereochemical integrity of the growing saccharidic chain (Scheme **24**).

Colinas *et al*. reported a method for the synthesis of *C*-disaccharides by a sequence involving the Wittig reaction as key step and further glycosydation of these compounds to afford new *C*, *O*-trisaccharides [29]. The enol ether **122a-b** were prepared by the Wittig reaction of the α, β mixture of 2-deoxiglycosyl phosphonium salts **120a-b** with aldehyde **121**. Hydrogenation of the *exo*-glycals afforded the β-*C*-disaccharides with good yields. The *O*-glycosidation employing the *exo*-glycals and the glycosyl acceptor **124** is illustrated in Scheme **25**.

2.5. C-1 Vinyl Anions

Schmidt was the first to explore the addition of sulfoxide-stabilized vinyl C-1-organolithiums to carbohydrate-based carbonyl compounds [30]. The vinyl sulfoxide **126** was deprotonated with LDA to give **127**. Addition of **127** to aldehyde **128** gave a mixture of diastereoisomers, of which the major **129** was formed in a 10:1 ratio. Desulfurization, hydroboration and removal of benzyl groups gave the (1→5)- β–*C*-disaccharide **130** (Scheme **26**).

Schmidt and coworkers used this methodology for a highly efficient synthesis of an analog of *C*-trehalose **134**, Scheme **27** [31]. Anion **131** was converted to aldehyde **132** and condensation of this aldehyde with the same anion gave adduct **133**, which was then converted to the target *C*-disaccharide **134**.

2.6. Acetylide-Based Anions

Sinaÿ was the first to prepare a *C*-disaccharide. His approach involved the coupling of a C-6 alkyne with an anomeric lactone followed by reduction of the formed hemiacetal [32] Aldehyde **135** was converted to the dibromoalkene **136**, which was treated with *n*-butyllithium to give an intermediate acetylide **137**. The latter, upon nucleophilic addition to lactone **138**, gave a mixture of lactol **139** in high yield. Stereoselective reduction of lactol **139** was followed by hydrogenation of benzyl groups and the triple bond, affording the (1→6)-β-*C*-disaccharide **140** (Scheme **28**).

The lactone-addition methodology was later applied by Sinaÿ and co-workers in an iterative fashion for the preparation of higher homologues [33]. Hydroxylmethylene in compound

141 was converted to acetylide lithium in compound **142** by a sequence of reactions. Condensation of compound **142** with the galacto lactone **143** gave **144** as mixture of anomers. The lactol were stereoselectively reduced to and triple bond was hydrogenated to give **145**. Methyl glycoside **145** was hydrolyzed to the corresponding lactols, which were oxidized to lactone **146**. The same sequence was then repeated twice to give *C*-trisaccharide **147** and *C*-tetrasaccharide **148** (Scheme **29**).

The di-, tri- and tetrasaccharide derivatives (**145**, **147** and **148**) were all debenzylated and tested for their binding affinity to three different monoclonal immunoglobulins with specificity for different *O*-β-(1→6)-D-galactopyranosyl determinants. These *C*-saccharide analogs had similar binding properties to the corresponding *O*-saccharides.

Schmidt has also used acetylide-lactone condensation to assemble *C*-disaccharides of ketoses [34]. Lithium acetylide **149** was condensed with ketone **150** to give a mixture of alcohol **151** after removal of the pivoloyl group. Attempted cyclization under Lewis acid catalysis resulted only in the removal of the acetonide. Accordingly, the diol was tied back as the carbonate and the acetylene complex as the dicobalt species **152**. The isomers were then separately cyclized to give a 1:1 mixture of *C*-disaccharide **153**. The cobalt complex on α-*C*-disaccharide was removed under standard conditions to give **154** and deprotection of the carbonate was followed by hydrogenation and peracetylation to give **155** (Scheme **30**). Similar chemistry was also carried out with the corresponding β-isomer.

Van Boom and co-workers used lithiated alkynyl derivative **156** in presence of $ZnCl_2$ to selectively open ring of the 1,2-anhydrosugar **157**, affording the α-*C*-(alkynyl)-glycoside **158**. Hydrogenolysis of the benzyl groups was followed by peracetylation to give the (1→6)-α-*C*-disaccharide **159** (Scheme **31**) [35].

Normally, attack of the nucleophile proceeds from an equatorial direction to give the β-isomer. The unexpected stereochemical outcome is rationalized by the generation of an initial zinc acetylide species, which facilitates intramolecular delivery to the α-face (Scheme **32**).

Wightman synthesized *C*-disaccharide analogs of the α-D-arabinofuranosyl-(1→5)-α-D-arabinofuranosyl motif of mycobacterial cell walls through alkynyl intermediates [36]. The lactone **164** was treated with lithio(trimethylsilyl)ethyne at low temperature to give lactol in 66% yield of **165**. Treatment of this with triethylsilane and $BF_3{\cdot}Et_2O$ gave the separable isomers, **166**α (60%) and **166**β (13%). Desilylation of the major isomer, **166**α gave **167** in 97% yield. Treatment of **167** with *n*-BuLi, followed by addition of lactone **164** gave 85% yield of the hemiacetal **168**, which on reduction with Et_3SiH and $BF_3{\cdot}Et_2O$ gave the disubstituted alkyne **169** (83%) as the major product. Reduction-hydrogenolysis of **169** then gave the *C*-disaccharide **170** in near-quantitative yield (Scheme **33**).

3. REDUCTIVE GLYCOSYL SAMARIUM SPECIES

The introduction of SmI_2 as reducing agent can be credited to Kagan and has since been utilized in numerous synthetic schemes [37]. Sinaÿ and Beau introduced SmI_2 chemistry into *C*-glycoside synthesis through intermolecular reactions with appropriate electrophiles,

and intramolecular reactions of silyl tethered substrates [38]. Anomeric samarium species are highly stable and not likely to undergo β-elimination. Treatment of the aryl sulfone **171** with SmI_2 affords the nucleophilic intermediate **172** through two single electron transfer processes. Introduction of a suitable electrophile (carbonyl compounds), affords the α-*C*-mannopyrannoside **173** in good yield and with excellent stereo-selectivity (Scheme **34**) [38a].

Preparation of *C*-glycosides of ulosonic acids using SmI_2 was pioneered by Linhardt and coworkers [39]. Coupling of pyridyl sulfone **174** with aldehyde **175** in the presence of SmI_2 gave an excellent yield of the *N*-acetylneuraminic acid *C*-disaccharide **176** as single isomer. This stereochemical outcome was rationalized on the basis of the Felkin-Anh model for predicting the stereochemical outcome of a kinetically controlled addition of a nucleophile to a chiral adehyde (Scheme **35**, **A**).

Reductive samarium method was utilized to synthesize sialo-antigen *C*-analogs by the Linhardt group. A fully protected *C*-analogue of the SialylTn antigen, α-D-Neu5Ac-(2→6)α-D-GalNAc-(1→*O*)-Ser **182**, was prepared [40]. *C*-glycosylation of the neuraminic acid sulfone donor with aldehyde acceptor in presence of excess SmI_2 afforded the α-*C*-glycoside **180** as an *R*/*S* mixture (1:1). The critical intermediate, aldehyde acceptor **178**, was prepared in 13 steps. Chemoselective resolution to compound **180** was undertaken by oxidation with DMSO/Ac_2O to keto-bridged compound **181**, followed by stereoselective reduction with $Zn(BH_4)_2$ to regenerate the bridge hydroxyl function, gave **182** in >90% de (Scheme **36**).

A common versatile *N*-acetylneuraminic acid *C*-disaccharide precursor of the *C*-glycoside analogs of gangliosides GM4 and GM3 has been synthesized [41]. Samarium(II) iodide coupling of *N*-acetylneuraminic acid sulfone **179** with a 3-formyl galactopyranoside derivative **183** afforded the corresponding *C*-disaccharide **184** as a mixture of (*R*) and (*S*) isomers at the newly formed hydroxymethylene bridge. This diastereoisomeric mixture was resolved after debenzylation of the galactoside residue, and the chirality of each isomer assigned after acetylation. Conversion of the *p*-methoxyphenyl group in the peracetylated (*S*) isomer **187** into the corresponding thiophenyl glycoside **188** was accomplished, affording the key intermediate for the synthesis of *C*-glycoside analogs of GM4, GM3, and other related gangliosides (Scheme **37**).

Ganglioside GM4 is a very important cell adhesion molecule. The *C*-disaccharide of GM4 is currently being synthesized in Linhardt's lab using standard *O*-glycosylation of *C*-disaccharide with protected ceramide. Once the ceramide has been attached, it can be oxidized to afford an aldehyde group for coupling to keyhole limpet hemocyanin (KLH) by reductive amination for use as carbohydrate-based vaccine. GM3, a related trisaccharide containg ganglioside, plays an important role in cell growth and differentiation, Fig. 2. The synthesis of *C*-oligosaccharide GM3 is currently underway following a similar route to that of *C*-GM4 synthesis [42].

Beau also reported a sialyl *C*-disaccharide synthesis which relied on the unprecedented use of a stable and crystalline 2-pyridyl sulfide of the *N*-acetylneuraminic acid derivative **189** as

the anomeric precursor in a samarium-Reformastky procedure [43]. The coupling procedure with sulfide **189** and aldehyde **190** afforded the carbon-linked dimer **191** in 93% yield as a 1:1 diastereomeric mixture.

Alcohols **191** were converted into thiocarbonates and deoxygenated by employing triphenyltin hydride, catalytic AIBN, and pentafluorophenol, which yielded *C*-disaccharide **192** as a single compound in 65% yield for the 2 steps. Desilylation, hydrogenolysis, acetylation, and final acetolysis of the methyl glycoside provided the carbon-linked mimic **193** of the disaccharidic component of the sialylTn tumor antigen (Scheme **38**).

4. CATIONIC METHODS

This section is categorized according to reactions that involve the generation of anomeric ions followed by the capture with sugar-based nucleophiles.

4.1. *Exo*-glycals as Nucleophiles

Nitotra *et al*. have found that treatment of exo-glycal **194** with $BF_3{\cdot}OEt_2$ followed by a water quench, afforded the *C*-disaccharide **195** (Scheme **39**). It is noteworthy to noteworthy that the attack of the enol ether on the anomeric oxonium ion occurs with high stereoselectivity on the α-face, only **195** was obtained [44].

4.2. Silyl-based Nucleophiles

Isobe has designed and developed alkynylation as a key reaction for the introduction of a carbon chain onto sugars. Those alkynylated compounds are called “sugar acetylenes” [45]. The mechanism includes eliminative formation of cation to which silylacetylene can coordinate on the α-face (Scheme **40**).

Double *C*-glycosylation between glycal **198** and bis (silylacetylene) gave C-disaccharide “like” compounds **199** and **200** (Scheme **41**).

Silylpropargyl-sugar **201** smoothly reacted with D-glucal to furnish exclusively the α-acetylene glycoside product **202** in 88% (Scheme **42**) [46].

5. CYCLIZATION METHODOLOGY

This approach to *C*-oligosaccharide synthesis relies on the coupling of an open chain fragment with an intact monosaccharide to give an intermediate that is then cyclized to deliver the *C*-oligosaccharide target. This section is divided by the type of chemistry used to initially assemble the two pre-cyclization fragments.

5.1. Wittig Reaction-Cyclization

The Kishi group was the first to use Wittig-cyclization approach to synthesize *C*-disaccharides. Starting with Wittig reaction between **203** and **204**, the intermediate **205** was afforded as a single stereoisomer in 82% yield. Osmylation then gave a mixture of diols with the major one formed in a 6:1 ratio. Selective protection of the diols gave **206a** and **206b**. The mono-*para*-methoxybenzyl ether **206a** was then transformed into the hemiketal **207** in

75% overall yield in three steps, i.e., (1) Swern oxidation, (2) acetonide hydrolysis (4 N HCl/THF/rt), and (3) benzoylation (3 equiv of PhCOCl/py/CH_2Cl_2/rt). Silane reduction of **207** in an acidic medium should preferentially yield the equatorially substituted β-*C*-glycoside which was deblocked and converted to the methyl- β-*C*-disaccharide, **209**. Exact parallel experiments, applied to the minor isomer, gave the corresponding *C*-disaccharide **210** (Scheme **43**) [47].

Armstrong has employed Wittig-osmylation protocol for the preparation of a small library of α-*C*-(1→6)-disaccha-rides [48]. Readily available allyl *C*-glycoside **211** was homologated to diene ester **212** and subjected to osmylation followed by reduction to afford a 5:1 mixture (**213**/**214**: **215**/**216**) of lactols that were readily separable by chromatography. Following a deprotection of an equimolar mixture of **213** and **214**, **217** and the D/L hybrid *C*-disaccharide of D-glucose-*O*-(1→6)-L-galactose **218** were obtained. The D/D and D/L derivatives **219** and **220** of glucose-α-(1→6)-idose were also obtained as a near equimolar mixture after deprotection of **215** and **216** (Scheme **44**).

5.2. Anion Addition-Cyclization

Kishi developed an approach for the synthesis of the *C*–trehalo sugars, which relied on nucleophilic addition of one intact sugar fragment to a fundamental aldehyde, *i.e.*, Kishi-Nozaki reaction [49]. Coupling of monosaccharide **221** and aldehyde **222** gave **223**. The triple bond was partially reduced and osmylation was followed by selective protection to afford **224**. The acetonide was converted to epoxide **225** by standard methods and removal of the PMB group. Acid-catalyzed cyclization followed by aglyconic hydrolysis and protection of hydroxyl group with (*p*-methoxyphenyl)diphenylmethyl chloride (MMTrCl) gave **226**. Inversion of the C-2 hydroxyl and removal of protecting groups delivered α, α-*C*-trehalose **227** (Scheme **44**).

Kishi and co-workers also employed aldol reactions as an efficient access to the *C*-trisaccharide related to the type II ABO(H) blood group determinant [50]. Aldol condensation of the enolate of methyl ketone **228** with aldehyde **229** gave a 4:1 mixture of hydroxy ketones **230** and **231**. The major ketol was cyclized, desulfurized and oxidized to afford the disaccharide ketone **233**. The ketone in THF was treated with LiHMDS (3 equiv) and TMEDA, followed by the addition of $MgBr_2$. Addition of the aldehyde **234** led to almost exclusive formation of the equatorial products **235** and **236** in a 1:2 ratio. Mesylation of **235** and **236** followed by treatment with liquid ammonia gave enones **237a** and **237b**, which were reduced to yield exclusively the C-2'-equatorial ketone **238**. Sodium borohydride reduction of the C-3' carbonyl proceeded with the desired stereoselectivity to yield the protected *C*-trisaccharide **239**, which was deblocked to provide the polyol **240** (Scheme **46**).

Sutherlin and Amstrong cleverly applied a recursive stereochemical deconvolution (RSD) combinatorial approach for the synthesis of a small library of C-trisaccharides as potential inhibitors for the cell surface proteins of bacterium *Helicobactor pylori* [51]. The workers chose to carry out variations in galactose ring of these trisaccharides. An efficient Nozaki-Kishi coupling of vinyl bromide **241** with aldehyde **242** in a diasteromeric ratio of 1:2,

followed by protection with TBSOTf led to **243** and **244**. Hydroboration followed by oxidation gave aldehydes **245** and **246**, respectively. Addition of allylmagnesium bromide to aldehyde **245** followed by removal of the silyl group afforded **247**, to **246** giving **248** and **249**. Epoxidation gave a 1:1 mixture of the corresponding epoxides which were cyclized, to give the *C*-trisaccharide **250**–**255**, after removal of the benzyl groups (Scheme **47**).

Schmidt reported a stereoselective, 6-*exo*-*trig* selective, electrophilic cylization approach for *de novo* synthesis of a methylene-bridged Neu5Ac-α-(2,3)-Gal *C*-disaccharide, the *C*-analog of an important motif in glycosphingolipids [52]. The open chain precusors **259a**/**b** (a 3:2-mixture of diaseteromeric alcohols) were formed by the addition of lithiated iodide **256** to open chain aldehyde **258**. Subsequent C_1 incorporation using Tebbe-reagent, formation of a cyclic carbonate, and deprotection of the two isopropylidene ketals afforded tetrol **264** which, upon treatment with phenylselenyl trifilate, was steroselectively cyclized in a 6-*exo*-*trig* selective manner, affording a diasteromeric mixture of **251** and **252** in a ratio of 7:1. A *seleno*-Pummerer rearrangement to afford aldehyde **267** in 5 steps in 90% overall yield. Oxidation of the aldehyde and subsequent steps led to the desired *C*-disaccharide **268** (Scheme **48**).

5.3. Esterification-Cyclization

Work from the Postema group has focused on a ring closing metathesis (RCM) approach for the synthesis of *C*-saccharides [53a]. The chemistry is versatile and has been used for the synthesis of a small library of differentially linked β-*C*-disaccharides through a radical allylation-RCM strategy [53b]. The synthesis of the β-(1→4)-glucopyranosyl glucopyranoside **280** represents an example of this chemistry. The known triacetyl glucopyranoside **269** was converted to iodide **270** in good yield. Radical allylation of **271** proceeded to afford a mixture of equatorial and axial allylation products in a 6:1 ratio. Oxidative cleavage of the double bond gave the corresponding aldehydes **273**a and **273b**, which were separable. Pinnick oxidation of the major aldehyde **273a** then gave the C-4 equatorial acid **274**. DCC-mediated coupling of alcohol **275** and acid **274** proceeded to afford ester **276** in good yield. Methylenation of **276** gave **277** and exposure to catalysist **278** gave a 41% yield of the *C*-disaccharide glycal, which was exposed to an excess of BH_3·THF to give 64% yield of the β-*C*-disaccharide **279**. Removal of the benzyl groups and global peracetylation gave the peracetylated (1→4)-β-*C*-disaccharide **281** in good yield (Scheme **49**).

5.4. Ring Expansion-Cyclization

Nelson developed a new strategy for asymmetric and stereoselective synthesis of *C*-linked disaccharide mimetics, the C58-C71 fragment of palytoxin [54]. The diol (*R*,*R*)-**282** was converted into the di-dihydropyran (DHP) template **283**, **284** and **285**. The di-DHPs were functionized in a two directional sense using dihydroxylation reactions. The two-directional approach was often very efficient indeed: for example, in the synthesis of **286**, six new stereogenic centers were introduced with almost complete stereocontrol using a reduction and a dihydroxylation reaction. The approach is not restricted to the synthesis of C2-symmetrical disaccharide mimetics. Using the unsymmetrical template **285**, which has both

a pseudo-axial and a pseudo-equatorial hydroxyl groups, the unsymmetrical mimetics **289** and **290** were prepared (Scheme **50**).

6. RADICAL APPROACHES

The radical approach for C-C bond formation is a popular method within organic chemistry. The use of radical chemistry in carbohydrate synthesis has certain advantages. Firstly, the reaction conditions are very mild and tolerant of a range of functional and protecting groups. Second, anomeric radicals are stable with respect to elimination and epimeration. Most significantly, the chemistry required to incorporate an appropriate substitute at C-1, employed in the initial hemolytic cleavage step, is common within carbohydrate chemistry [55]. The use of such radical technique can be subdivided into two classes, intermolecular and intramolecular approaches.

6.1. Intermolecular Radical Approaches

Giese was the first to employ an intermolecular radical-based approach for synthesis of *C*-disaccharides [56]. Addition of an alkene to an anomeric radical, under appropriate conditions, allowed exclusive entry to the α-linked *C*-glycoside, a result which was mirrored by the work of Baldwin [57]. The high α-selectivity of the reaction was in contrast with other reports. Thus radicals generated at the C-2, C-3 and C-4 centers all preferred to occupy equatorial positions [58]. When the anomeric bromide **291** was treated with tin hydride and AIBN, resulting anomeric radical, and reacted with lactone **292** in a Michael addition, it afforded **293**. In this reaction hydrogen abstraction at the resulting radical center occurs from axial face to selectively generate the equatorial C-2' substituent. Reduction and acetylation of **293** furnished *C*-disaccharide **294** (Scheme **51**) [59].

Witczak used the facial bias of levoglucosene to stereoselectively add a carbohydrate-based radical in the preparation of the 3-deoxy-(1→4)-β-*C*-disaccharide **299** [60]. Addition of the radical derived from iodide **295** to **296** gave adduct **297** in 26% yield. Removal of the anomeric hydroxyl of **297** was achieved by treatment with triethyl silane, borontrifluoride ether complex followed by stereoselective reduction of the keto function at C-2' with the formation of **298** in 89% yield. Debenzylation followed by acetolysis of 1,6-anhydro ring produced the peracetylated target *C*-disaccharide **299** in 19% overall yield from **295** (Scheme **52**).

Vogel has developed general methods to transform enantiomerically pure 7-oxabicyclo[2,2,1]heptyl derivatives (“naked sugars”) into *C*-disaccharides. Because of these chiral bicyclic skeletons, they undergo highly stereoselective reactions with predictable diasteroselectivities. An arsenal of methods is available that allow to substitute these “naked” carbon centers with a variety of functional groups with all possible relative configurations. The methods allow preparation of both enantiomers of a given target with the same ease. Predictably high stereoselectivity of the reactions of the bicyclic chirons adds to the flexibility of approach, which can lead to high molecular diversity [61].

α-*C*-(1→3)-mannopyranoside of *N*-acetyl-galactosamine, potent β-galactosidase inhibitors, was synthesized by this approach [61]. Enone **302** was readily prepared from **300**. The

addition of the radical derived from bromide **303** to enone **302** afforded the α-isomer **304**. The ketone was then reduced and the selenide eliminated *via* the intermediacy of the selenoxide, to give **305**. Acid-promoted (CF_3SO_3H) 7-oxa ring opening of **305** in MeCN produced the amino-conduritol derivative **306** resulting from the quenching of the allylic cation intermediate by the solvent (Ritter reaction). Ozonolysis of the chloroalkene **306** generated an acyl chloride-aldehyde intermediate that reacted with MeOH to produce a mixture of methyl uronates. The major compound **307** was silylated and reduced. The crude polyol obtained was acetylated to produce **308**. Desilylated and ammonolysis afforded a mixture of α-/β-pyranoses **309** and corresponding α-/β-furanoses (Scheme **53**).

Similar chemistry was carried out to synthesize non-protected α-*C*(1→2)-L-fucopyranoside of D-galactopyrano-side, corresponding to a blood group mimetic [62]. Giese's radical fucosidation of racemic enone **310** with α-L-bromoacetofucose **311**, provided the mixture of diastereomeric α-*C*-fucoside **312a** and **312b** in reproducible yield of 78%. Reduction of the mixture gave a 1:1 mixture of endo-alcohols **313** and **314**, which were isolated pure in 40% and 35.5% yield, respectively. Oxidative elimination of the benzeneselenyl group of **313** followed by acetylation gave *endo* acetate **315** in 85% yield. Acid-promoted ring opening of **315** and ozonolysis of the resulted chloroalkene gave methyl uronic ester **316** in modest yield (10%). Treatment of **316** with Cl_3CCN and NaH, followed with $BF_3{\cdot}OEt_2$ furnished the totally protected *C*-disaccharide **317** in 79%. The reduction of **317** and treatment with DOWEX-H^+ resin provided the desired *C*-fucoside **318** in 70% (Scheme **54**).

6.2. Intramolecular Radical Approaches

One disadvantage with the intermolecular approaches is that during such radical mediated reactions, electron deficient alkenes are required to facilitate C-C bond formation. The intramolecular approach of Sinaÿ overcomes this drawback by bring two substrates together *via* a temporary covalent silaketal connector. This enables the use of a wider range of alkenes, which can include alkene-functionalized sugars, thus leading to the generation of *C*-disaccharides [63]. Based on the early work of Stork, Sinaÿ employed the tether reaction in the synthesis of both α- and β-*C*-disaccharides, with this work subsequently being employed in the synthesis of biologically significant natural products [64]. The availability of different hydroxyl groups on each monosaccharide unit allowed the fine-tuning of stereochemical outcome by selective positioning of the silyl tether [65]. Development of this early stereochemical control led to the tethering of the donor **320** with alcohol **319** through a di-isopropyl silicon tether **321**. Subsequent treatment with Bu_3SnH and AIBN, led to a 9-*endo-trig* cyclization to form the *C*-disaccharide **322** in an 80% yield with exclusive formation of the α-product. The silyl tether was removed with Bu_4NF, and deprotection under standard conditions afforded the desired disaccharide **323** in excellent yield (Scheme **55**).

In parallel, the development of a 3,2' silyl tether allowed access to the β-linked product as demonstrated in Sinaÿ's synthesis of methyl β-*C*-lactoside **328** [66]. Alcohol **324** and **320** were connected *via* the dimethylsilyl tether, an 8-*endo-trig* cyclization followed to exclusively afford the β-disaccharide **326** in 45% yield. Removal of the tether and deprotection of benzyl ether gave β-*C*-disaccharide **328** (Scheme **56**).

This group also selected iodosugars bearing a free hydroxyl group as progenitors of the radical donors [67]. In a typical experiment, the radical donor **329** was connected to the radical acceptor **330** through a silaketal tether, following their procedure. Tributyltinhydride mediated 8-*endo*-*trig* radical cyclization of compound **331** gave, after detethering of the non isolated intermediate **332**, the protected β-*C*-disaccharide **333** in 37% overall yield (from starting materials **330** and **329**). Peracetate **335** was achieved after hydrogenolysis. The *C*-laminaribioside **334** is of potential biological interest as it mimics the repeating disaccharide unit of fungal β-(1→3)-glucans, which have antitumor and immunomodulating properties (Scheme **57**).

CONCLUSIONS

In this paper, the biological importance of *C*-oligosaccharides as subunits of natural products and as a new generation of carbohydrate based on therapeutics has been illustrated. Different methods are available for the synthesis of *C*-oligosaccharides. As with traditional saccharide synthesis, it has been necessary to develop a number of specific approaches to facilitate the regioselective and stereoselective preparation of the desired targets. Work in this area continues and it is expected that many interesting new *C*-oligosaccharides will be prepared using the chemistry described in this review. It is also likely that new chemistry will be developed in the future for the preparation of these biologically important targets.

Acknowledgments

The authors thank Dr. Sultan Baytas for her critical reading of this manuscript.

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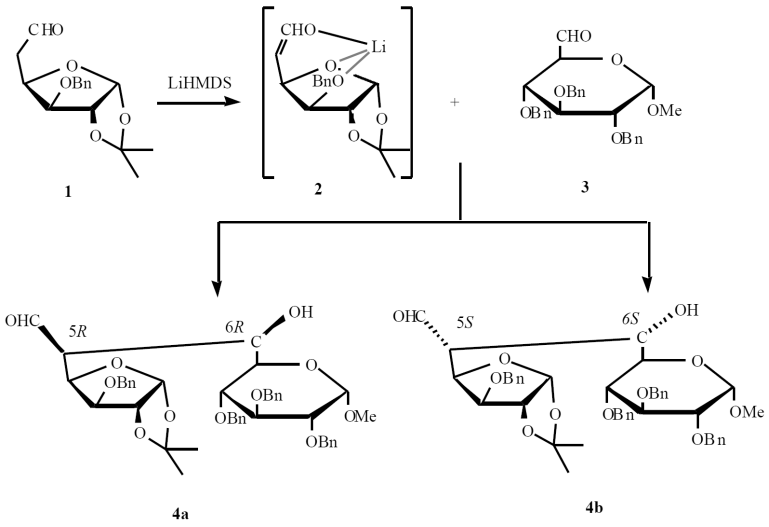
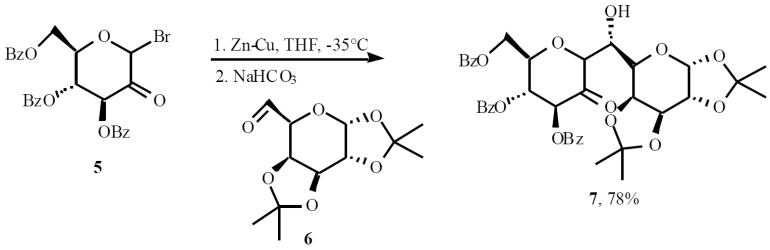


Scheme (1).



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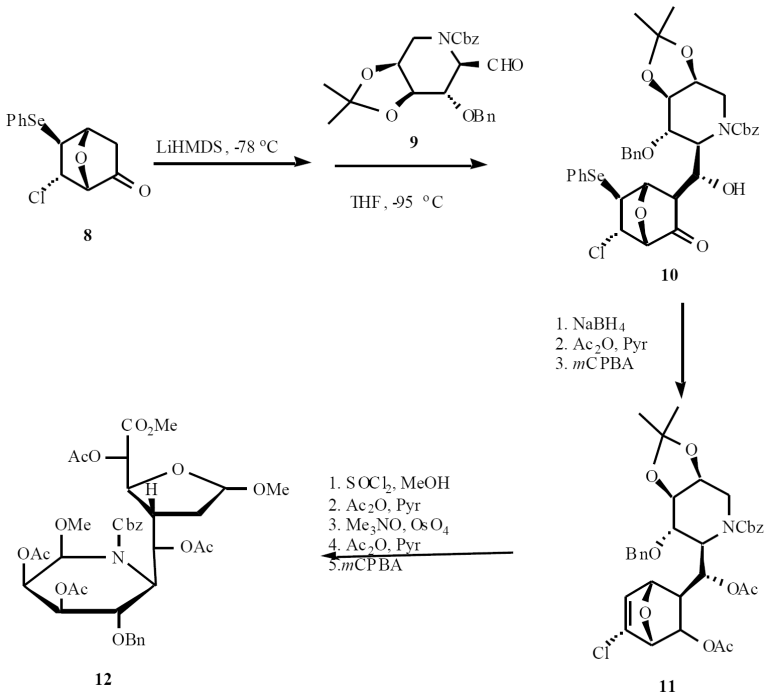

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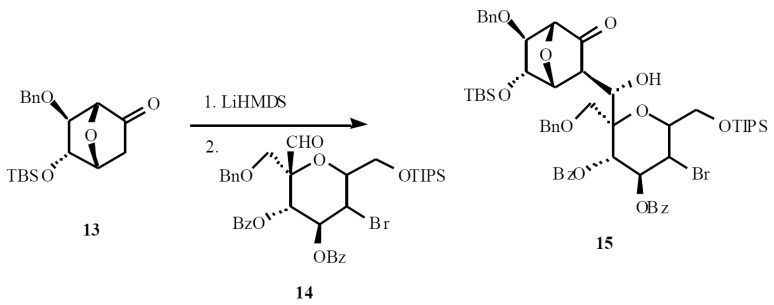

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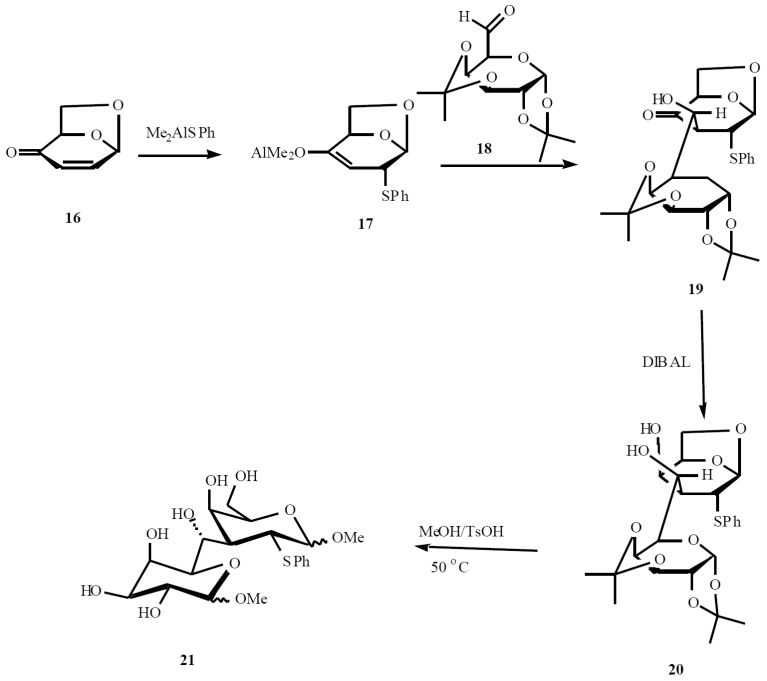
Scheme (4).



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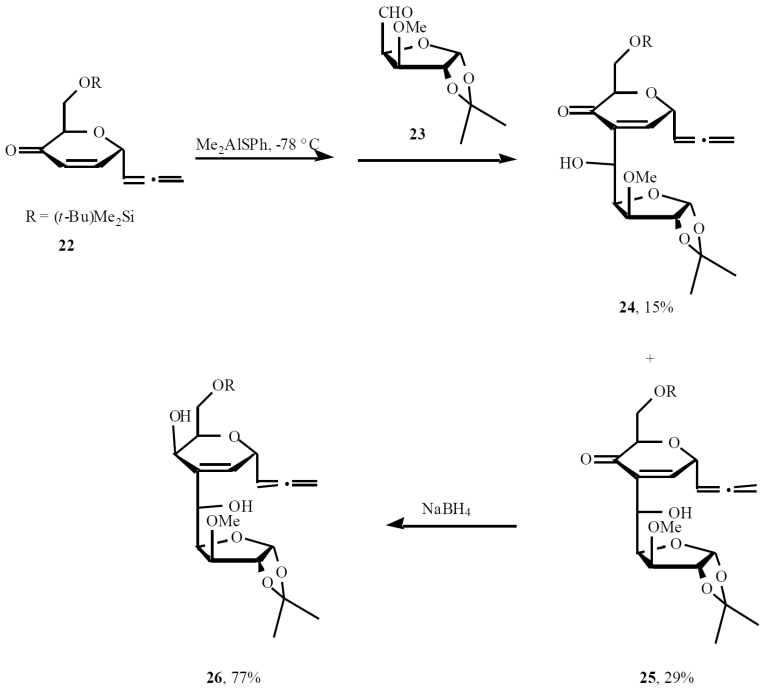

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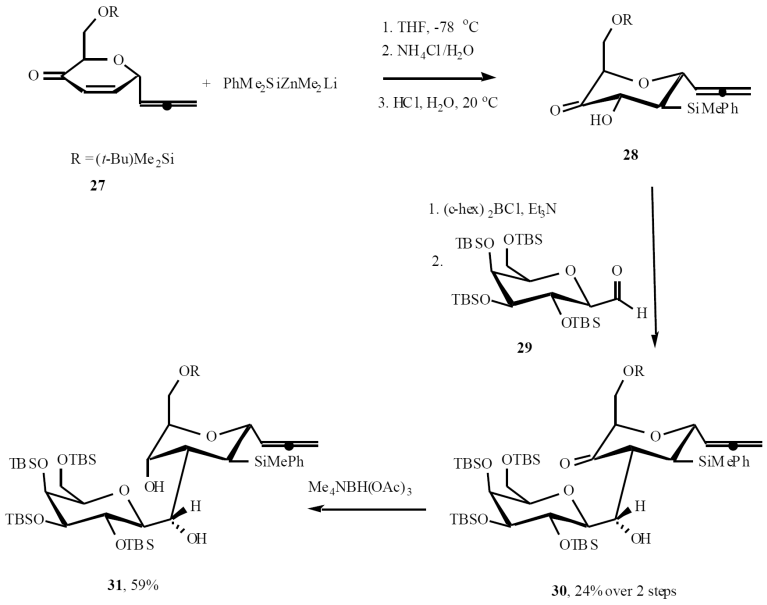

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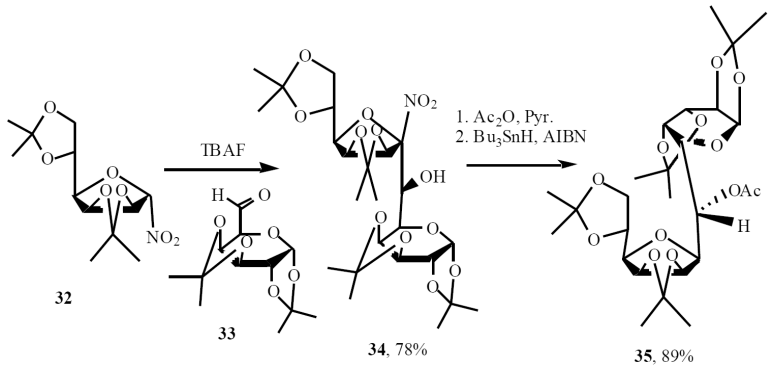

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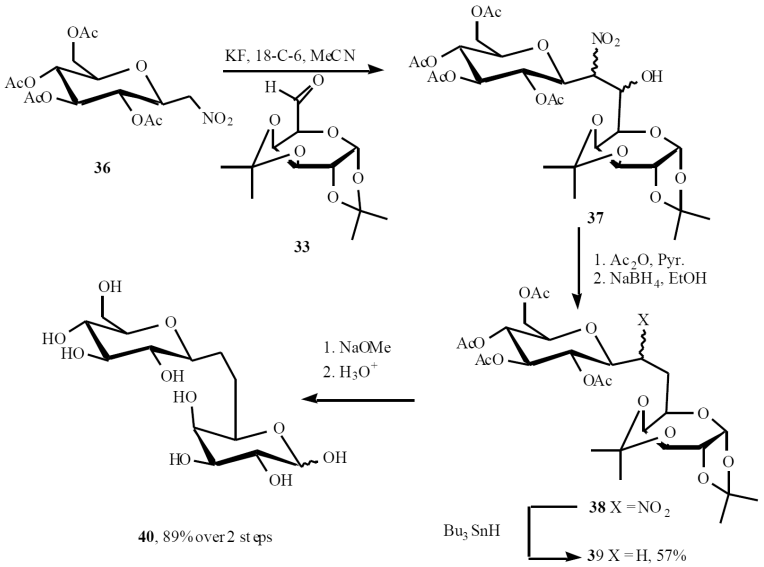

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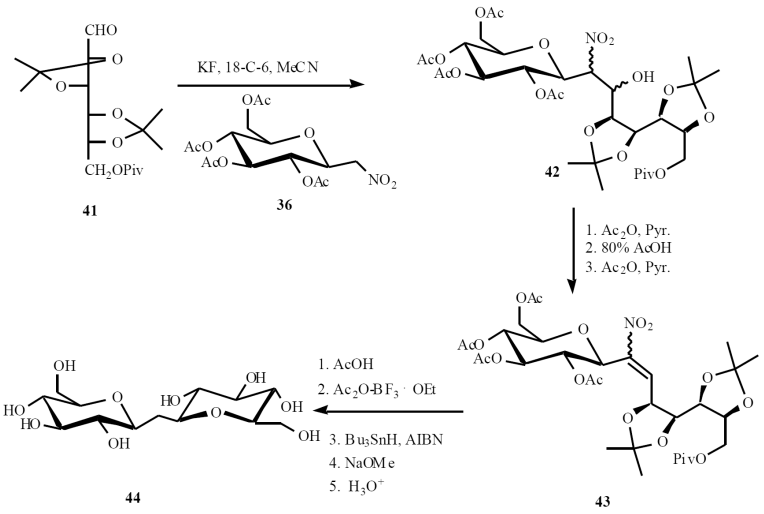

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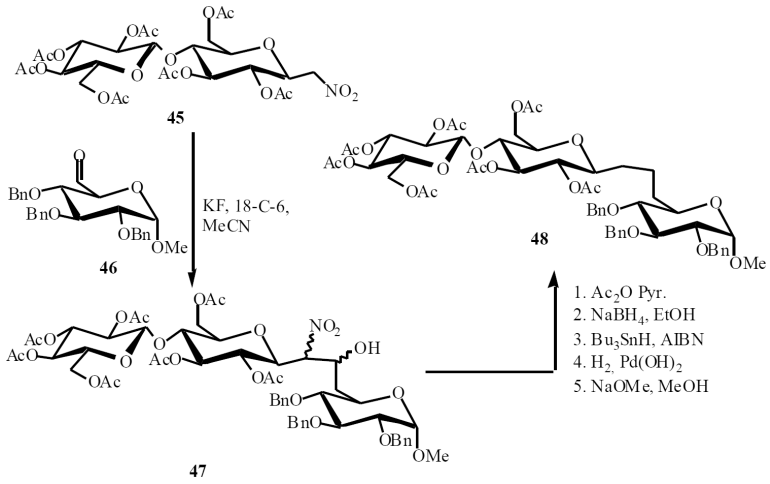

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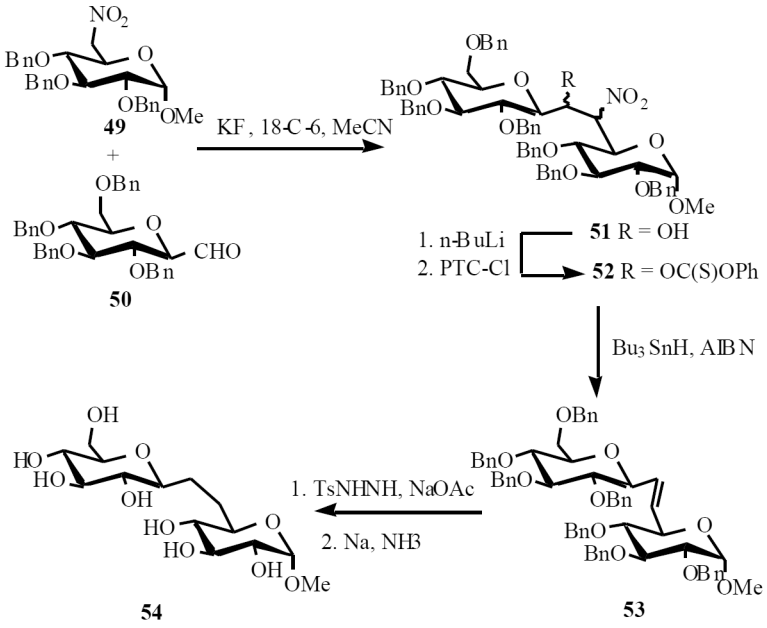

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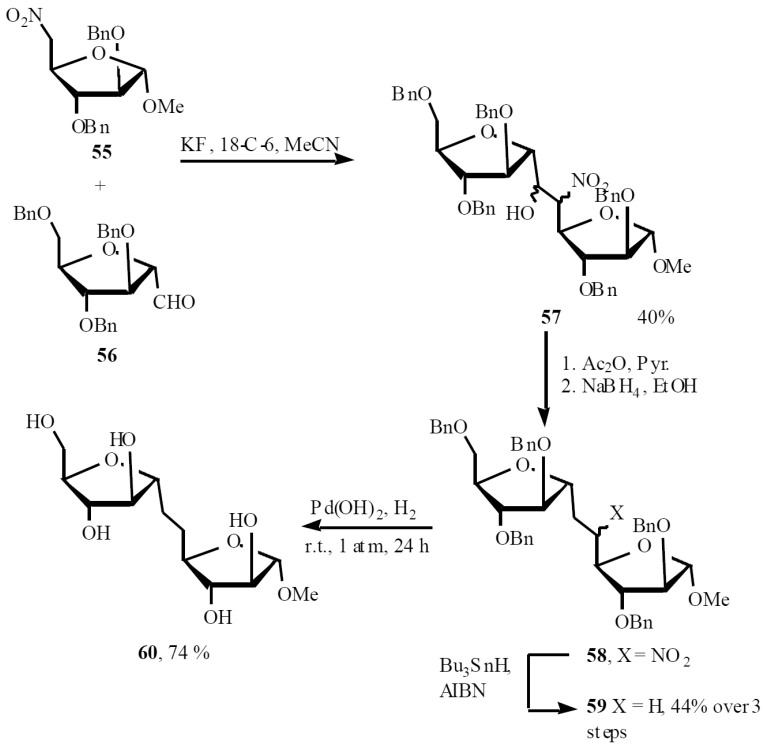

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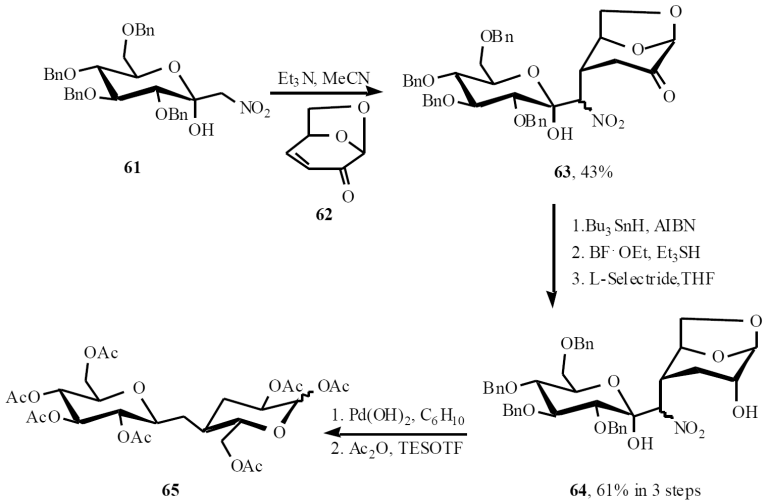

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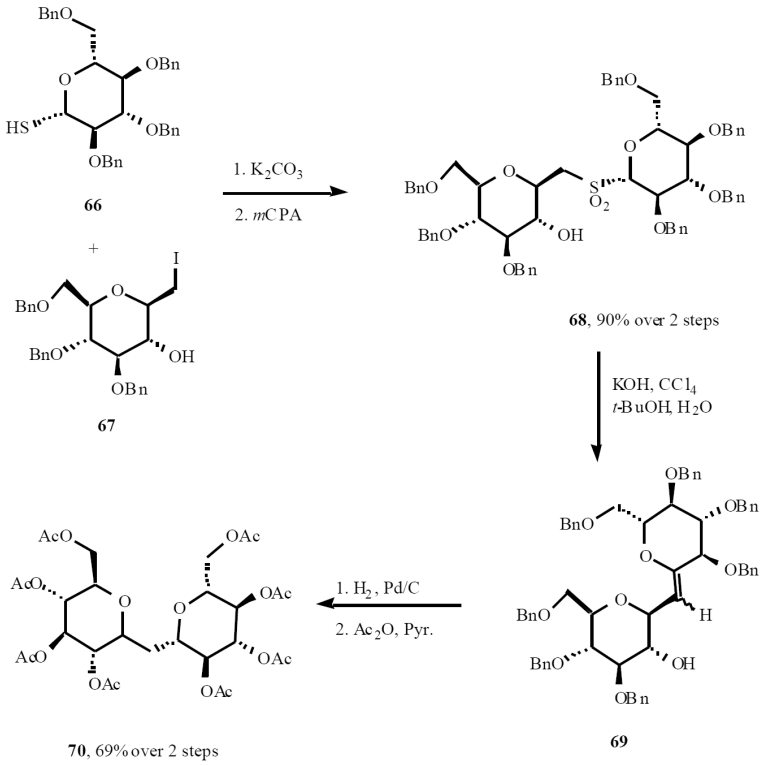

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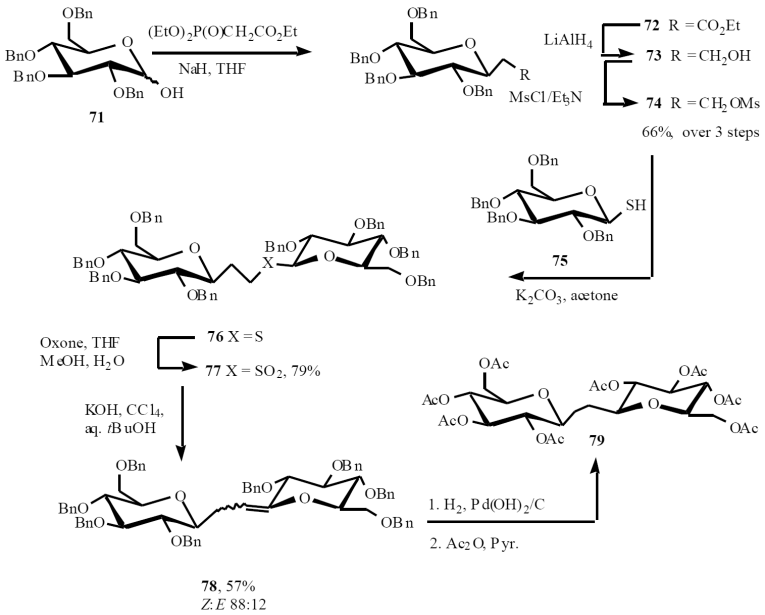

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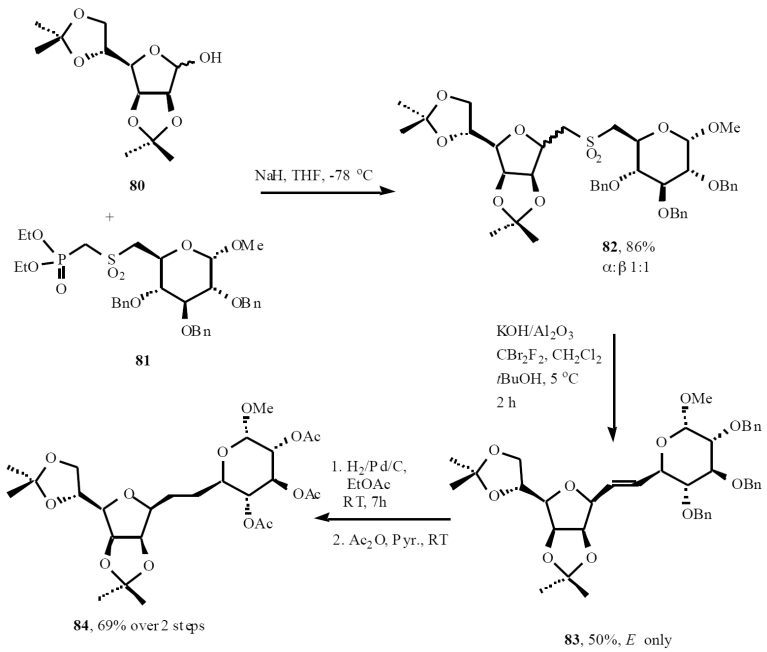

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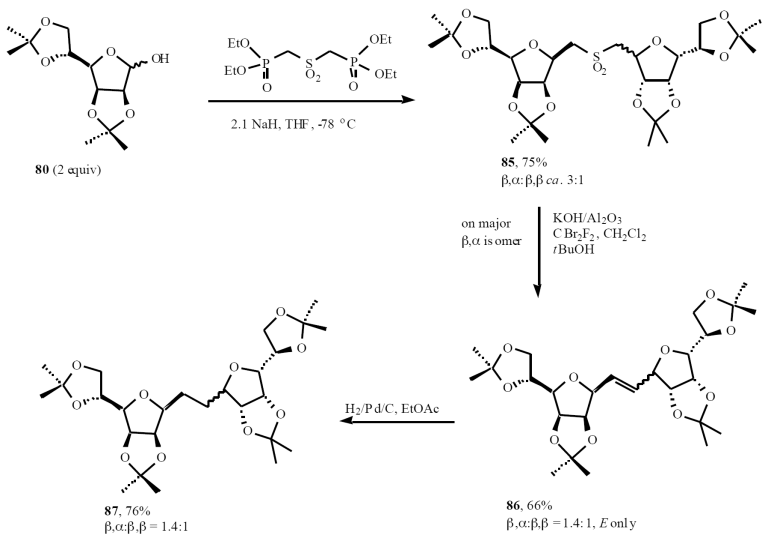

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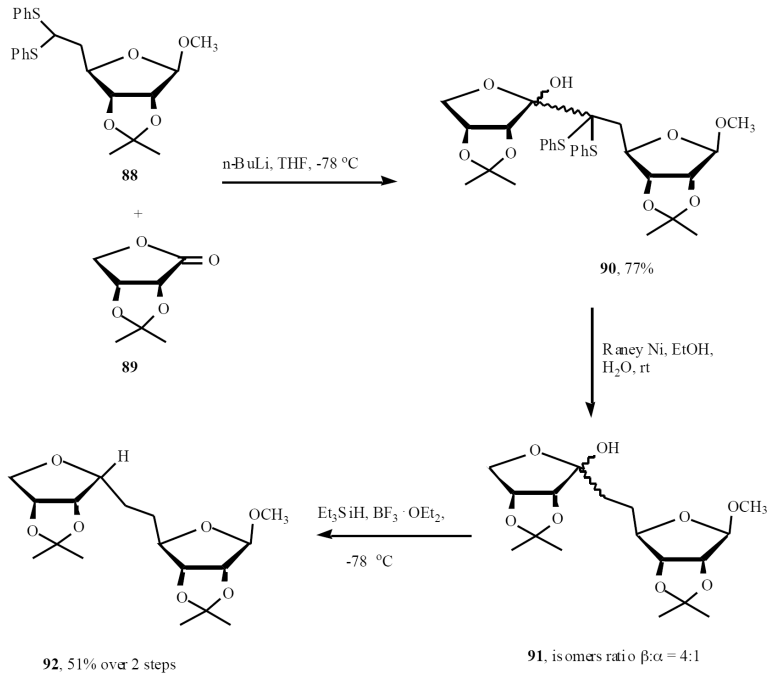

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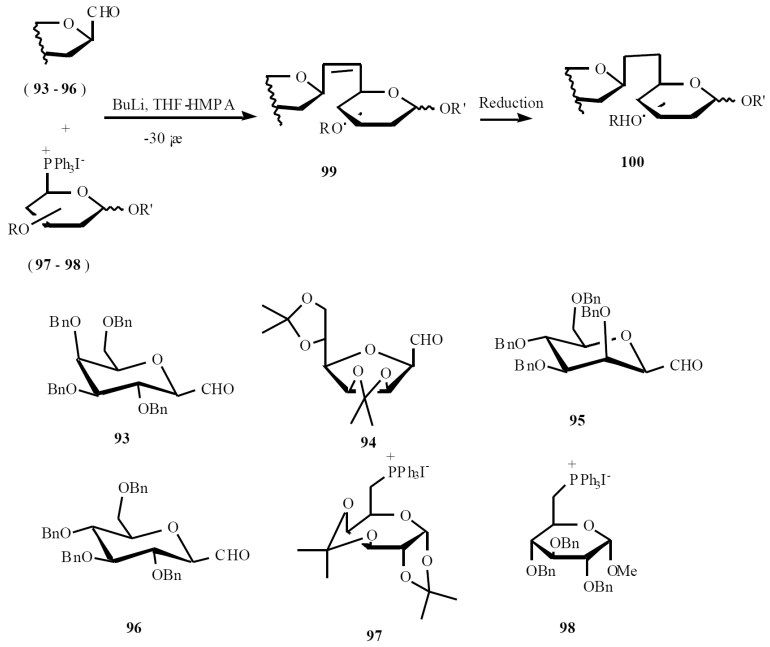

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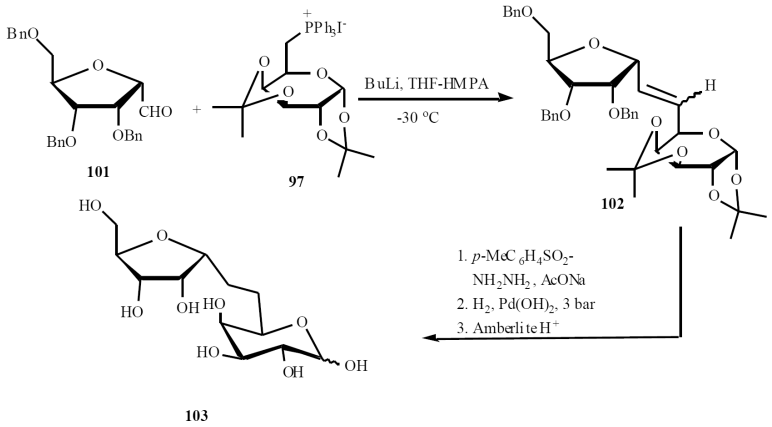

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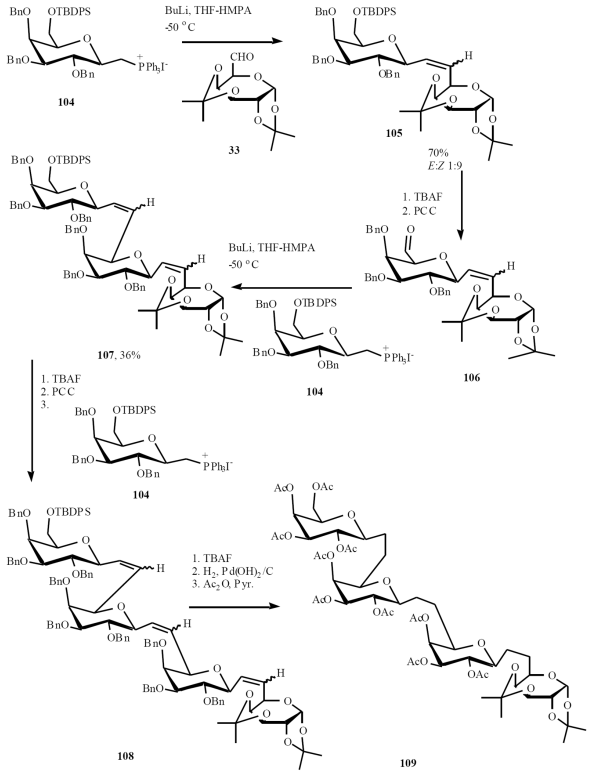

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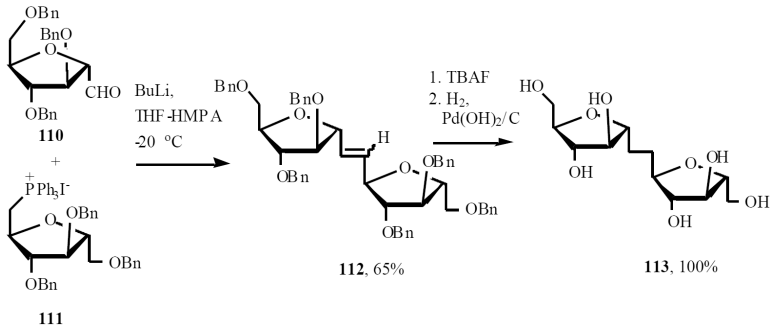

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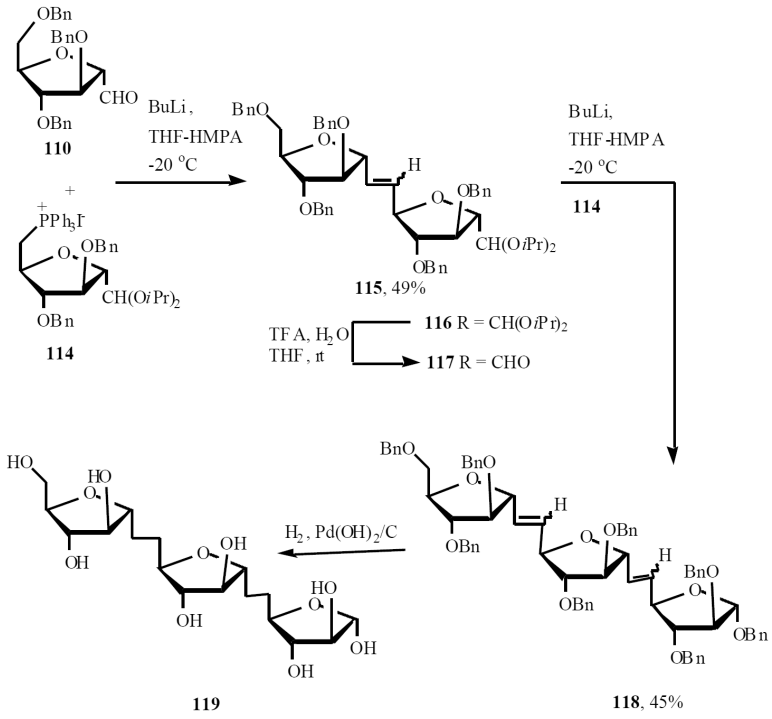

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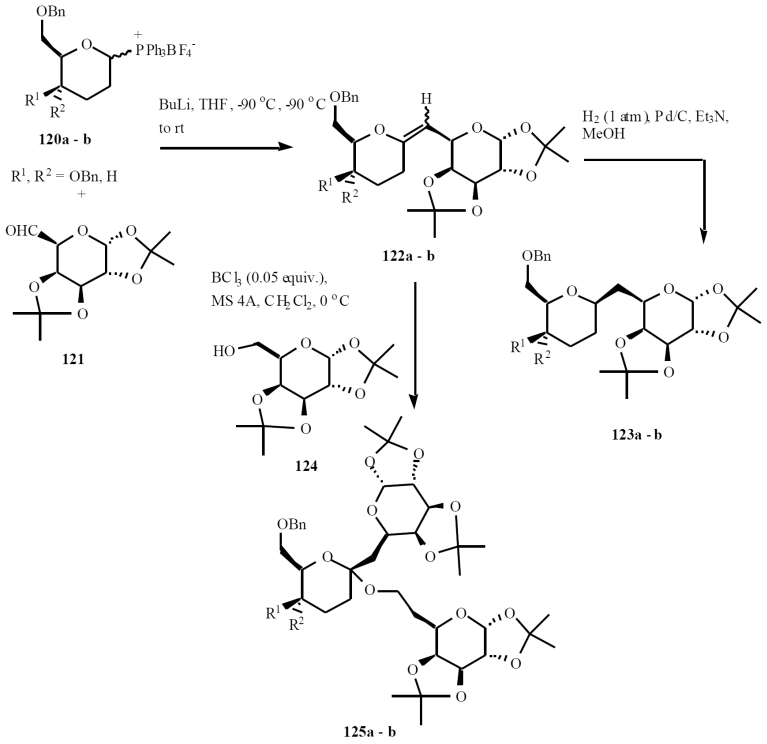

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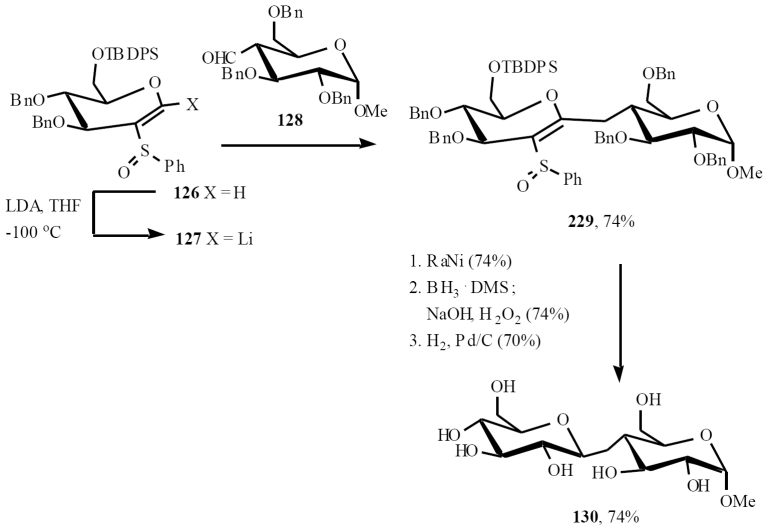

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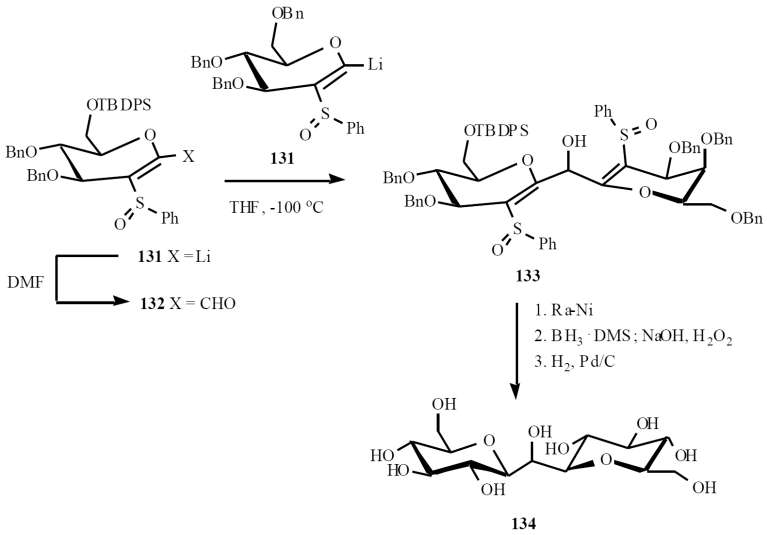

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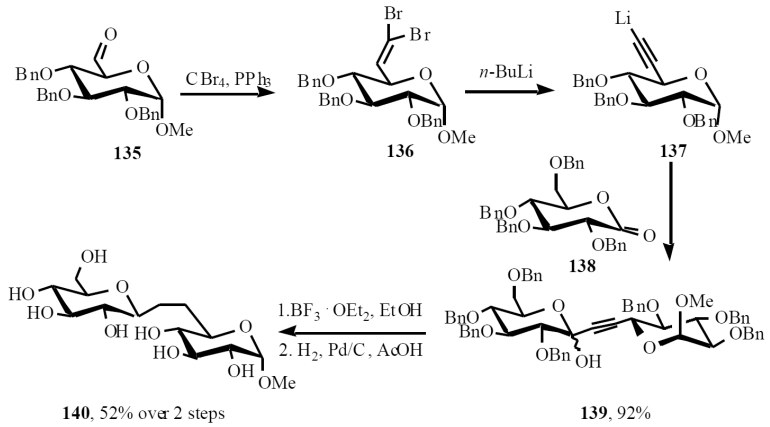

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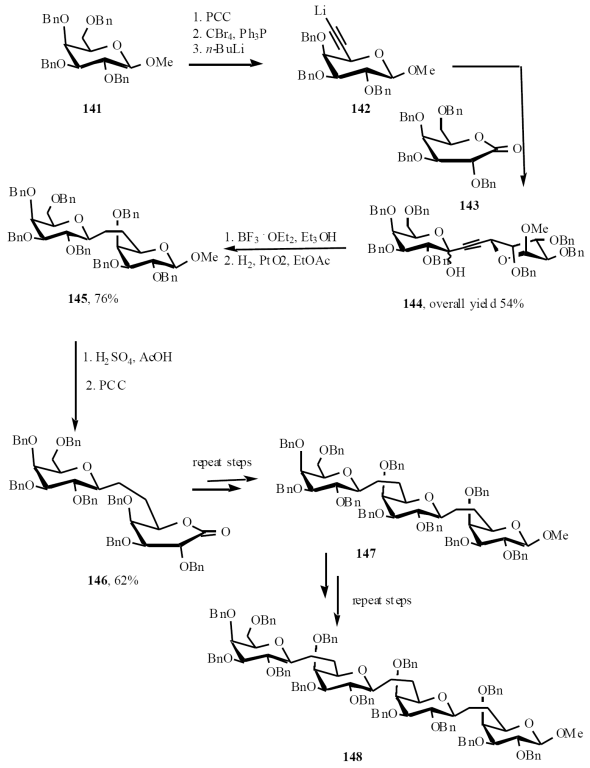

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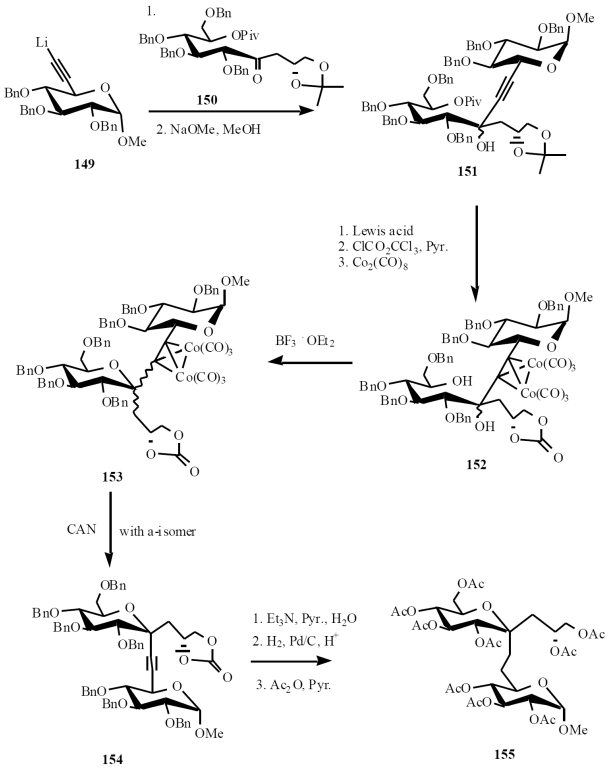

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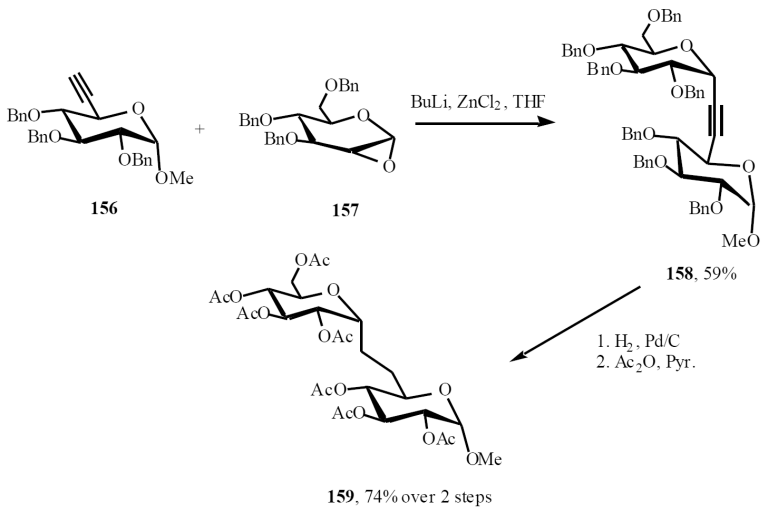

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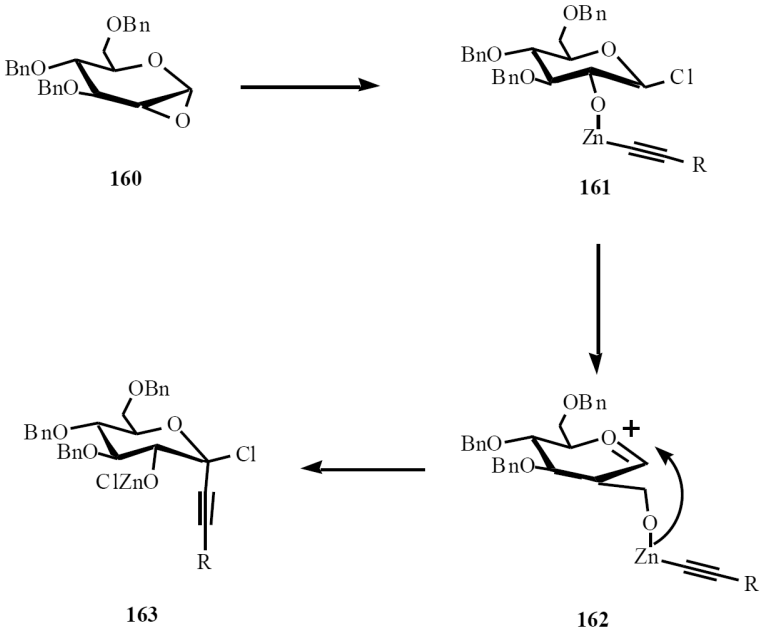

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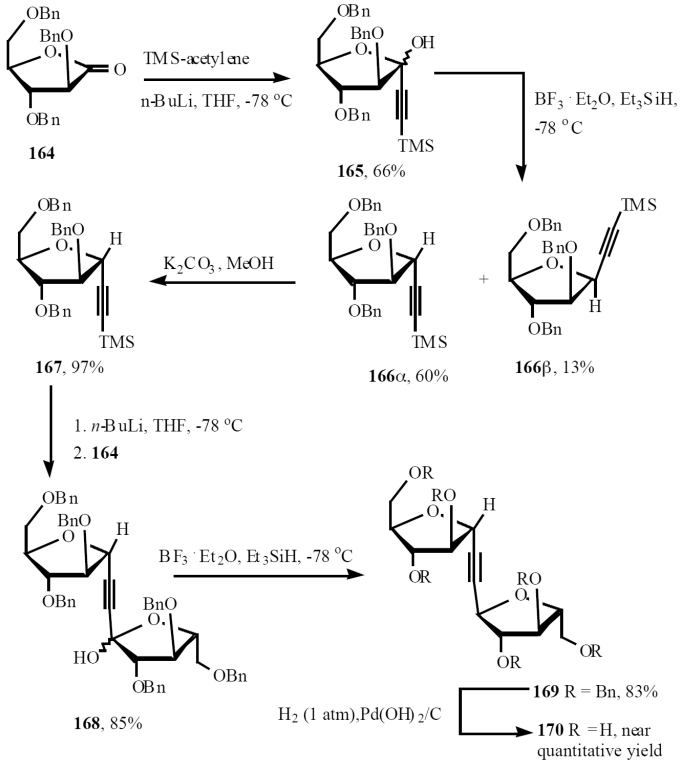

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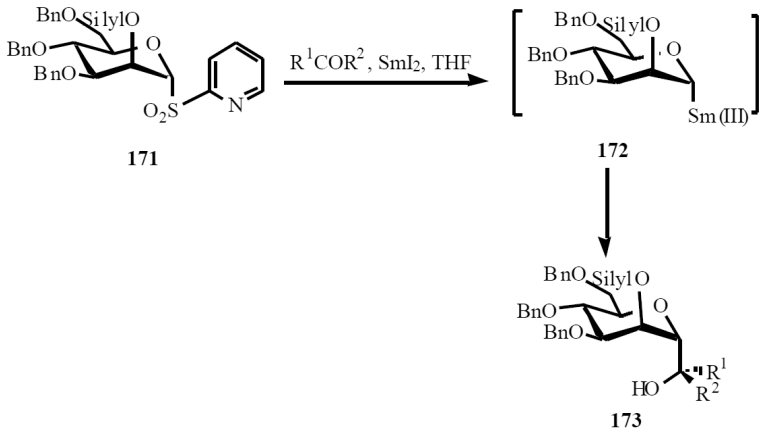

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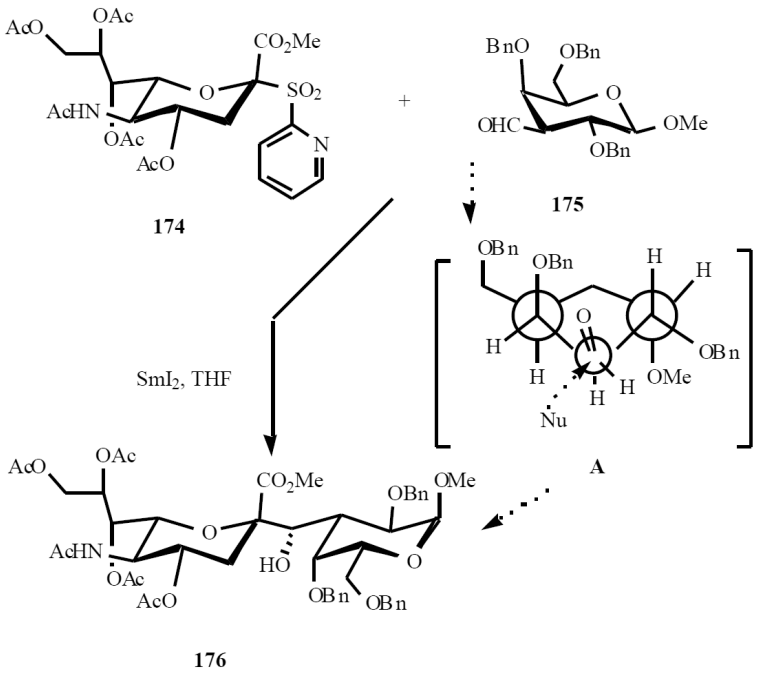

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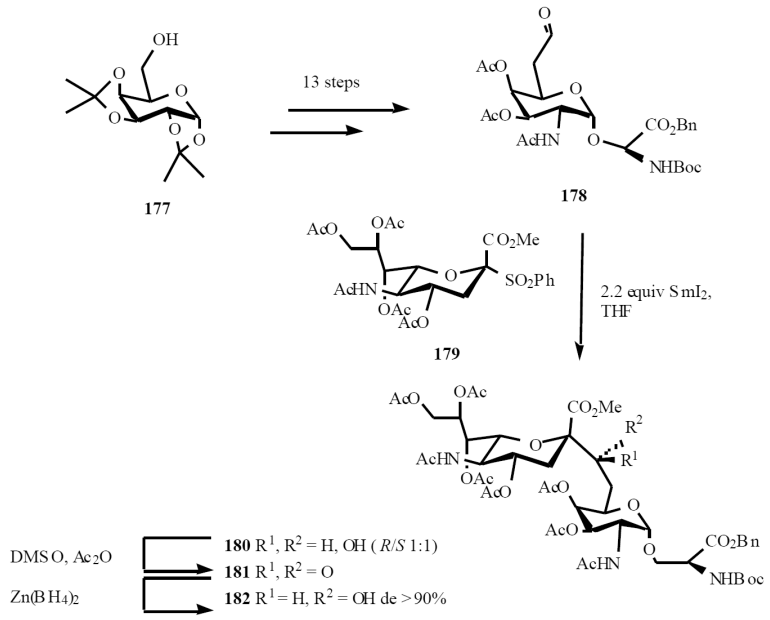

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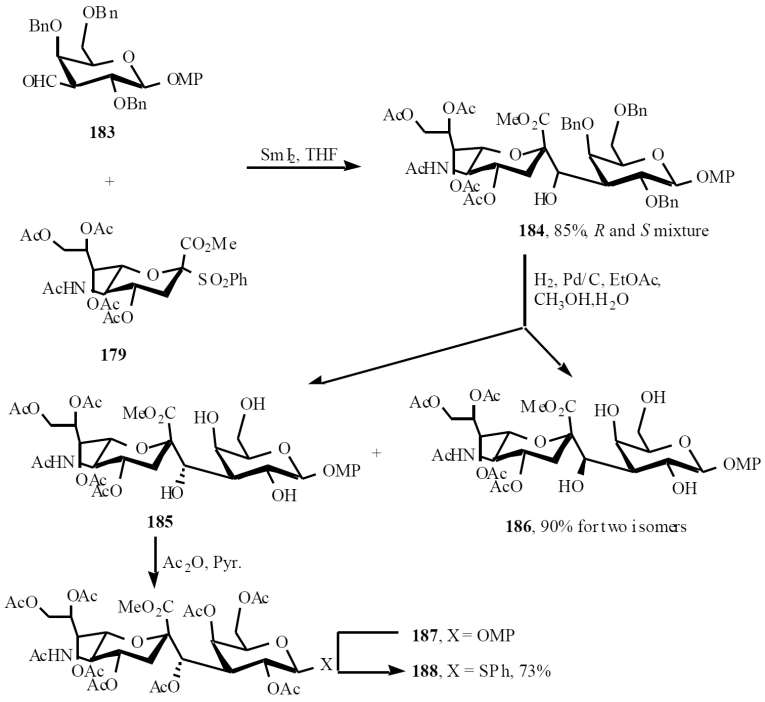

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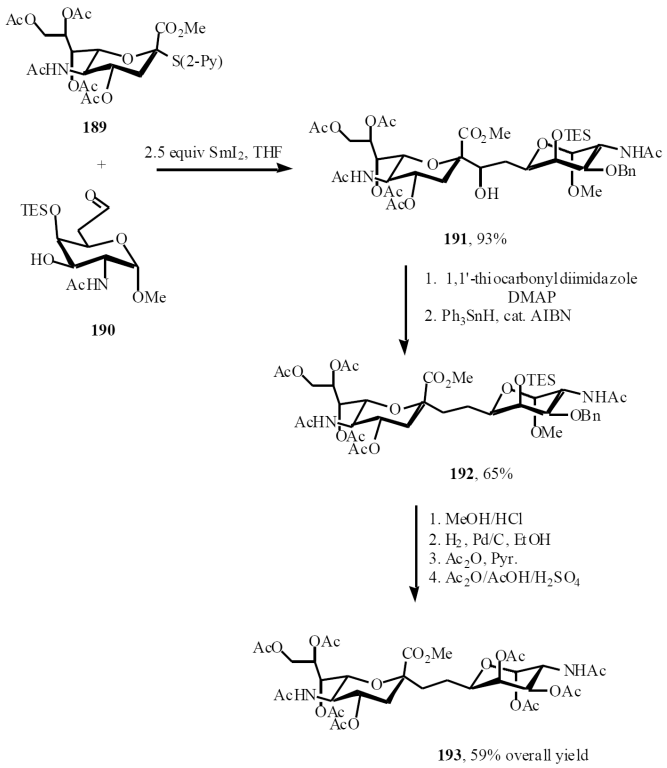

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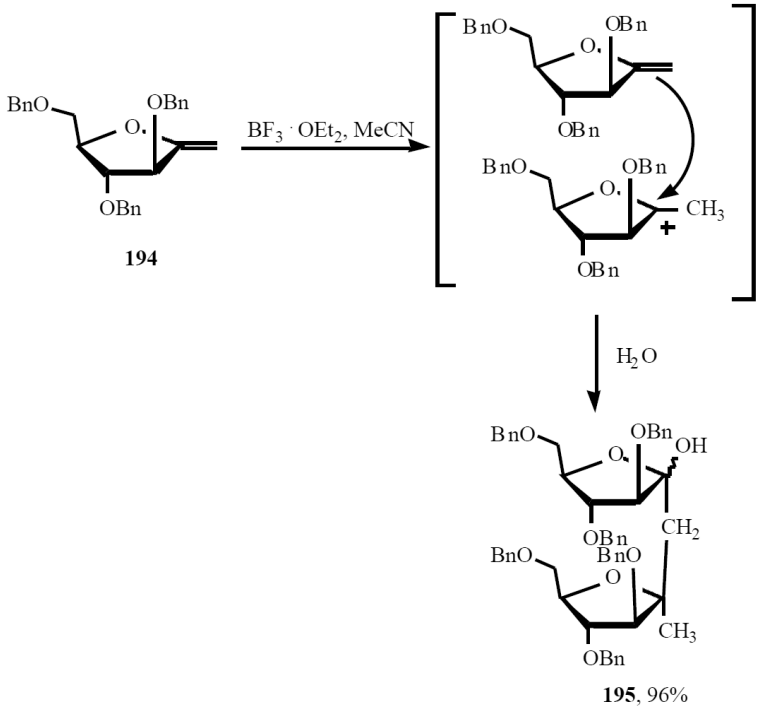

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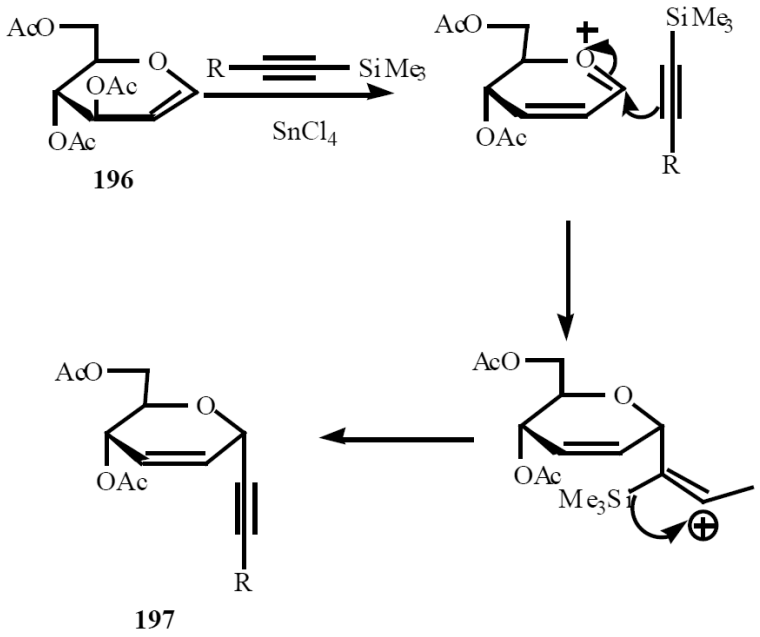

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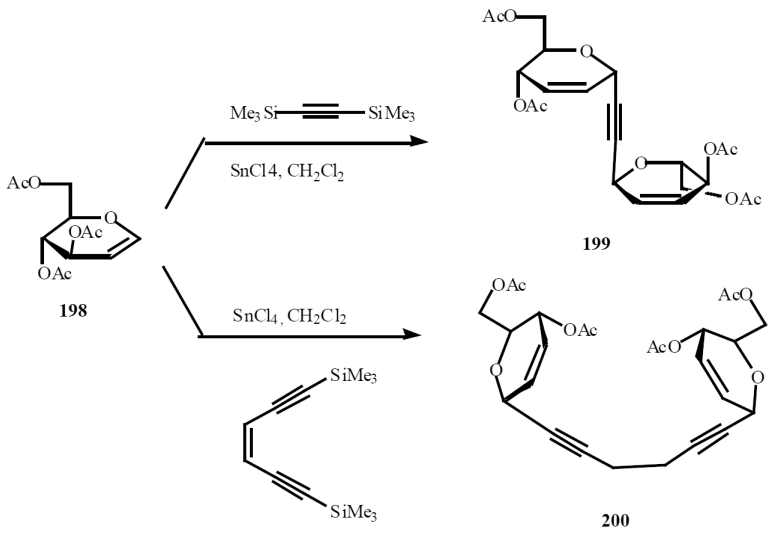

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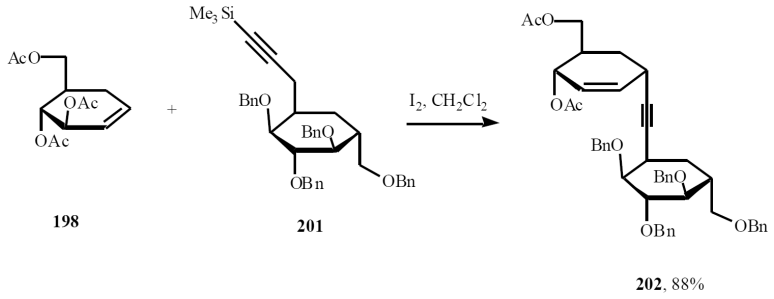

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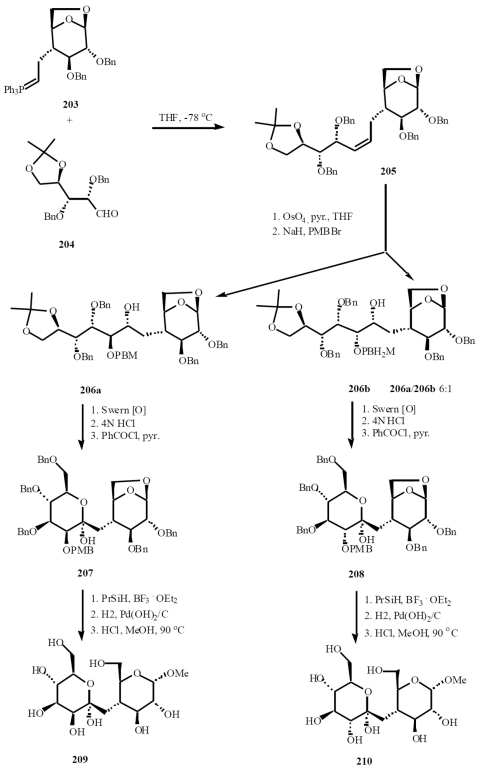

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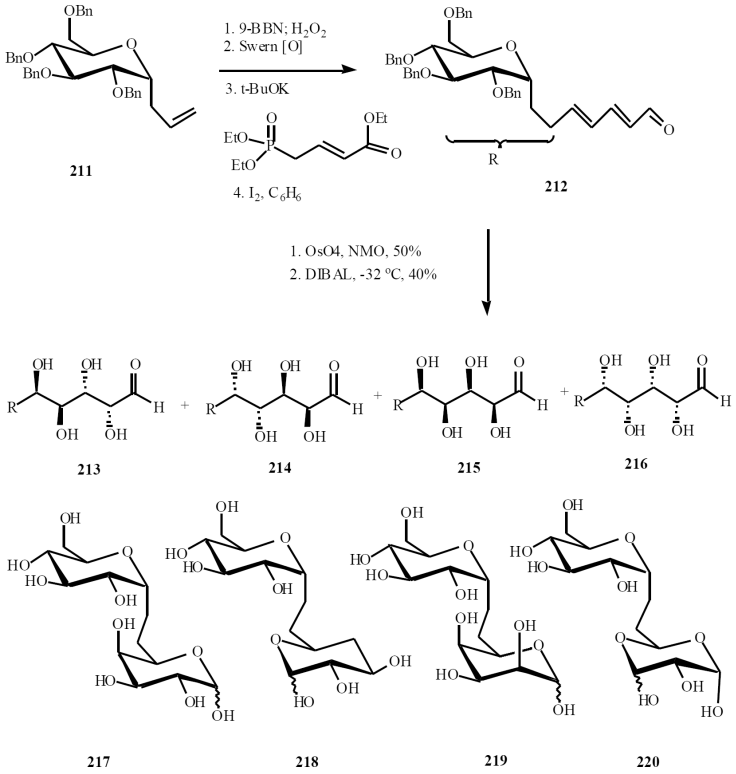

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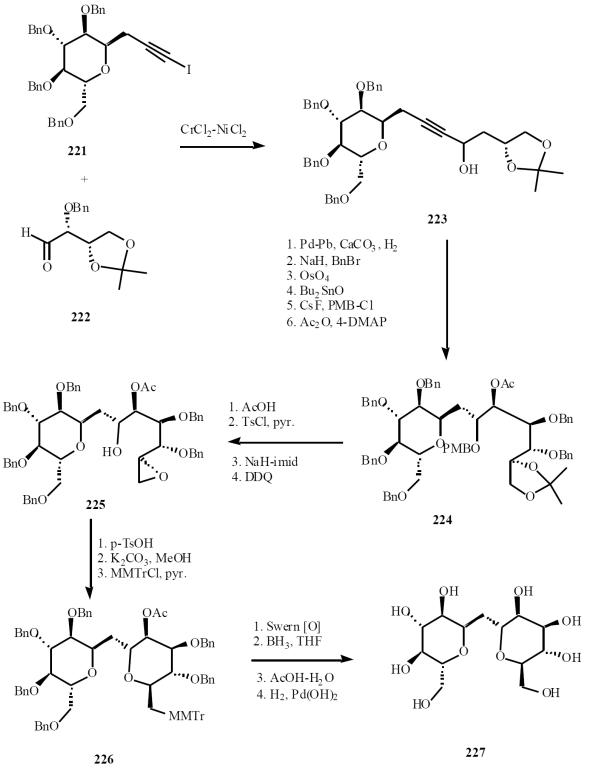

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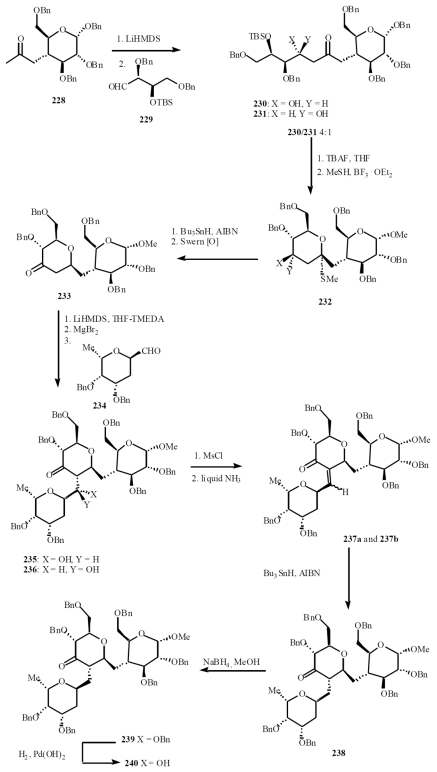

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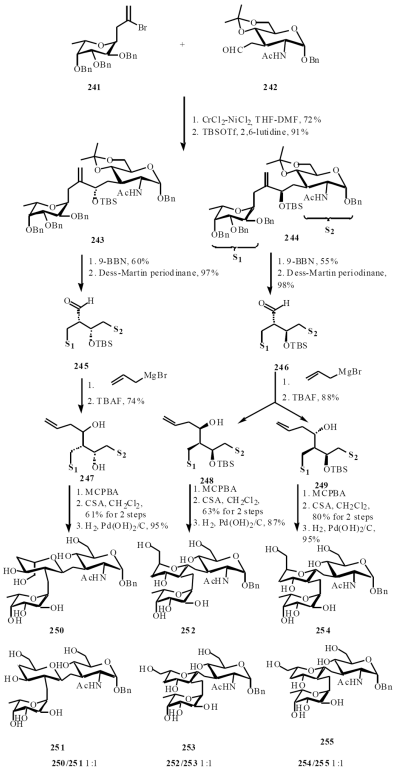

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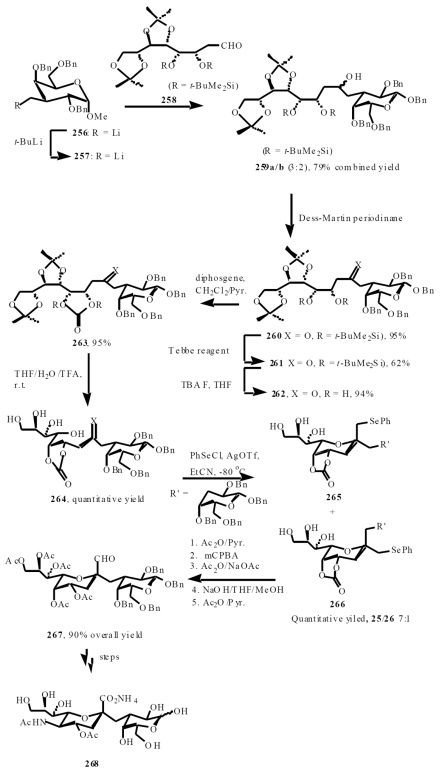

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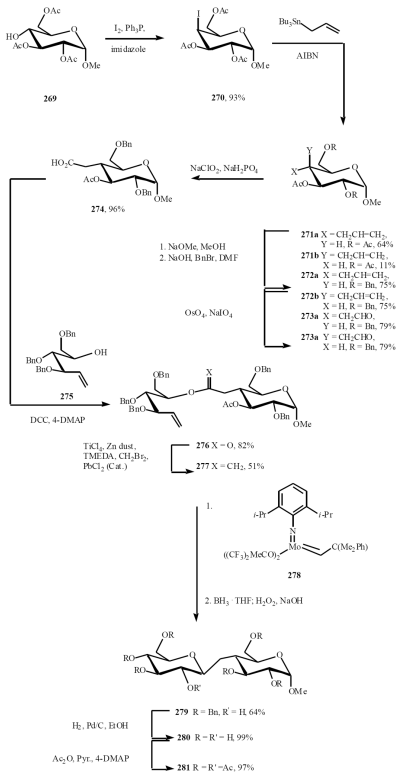

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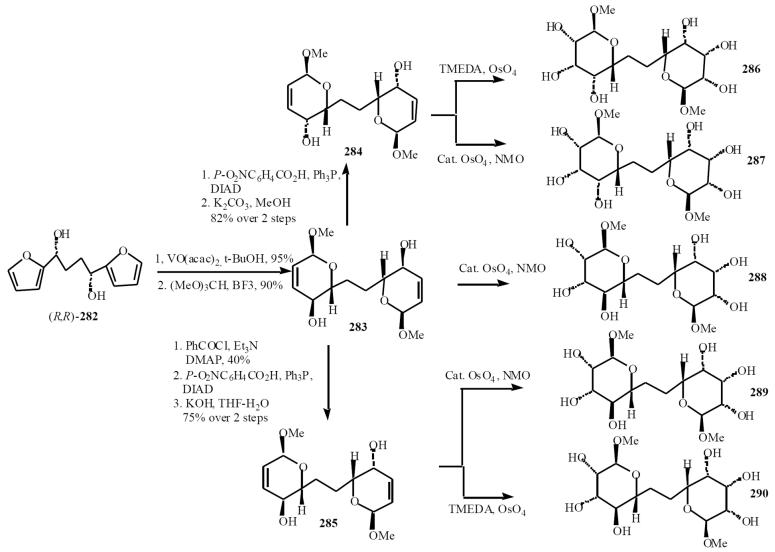

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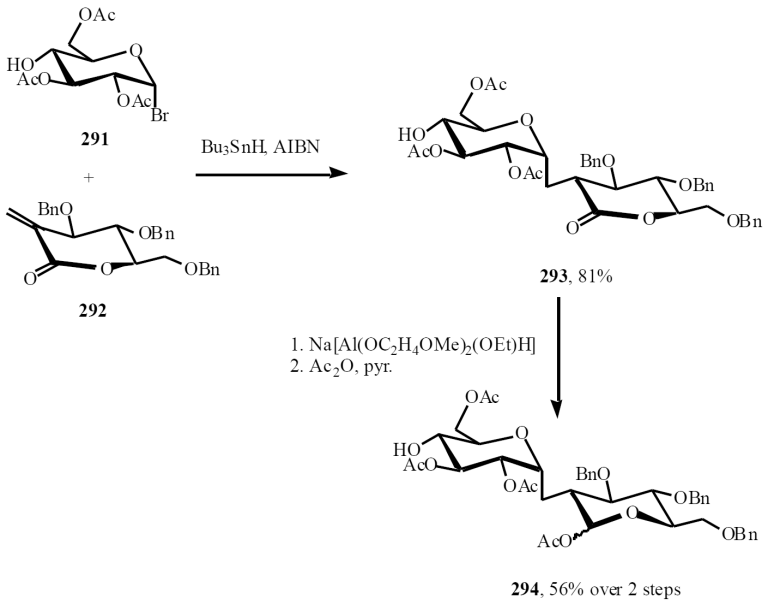
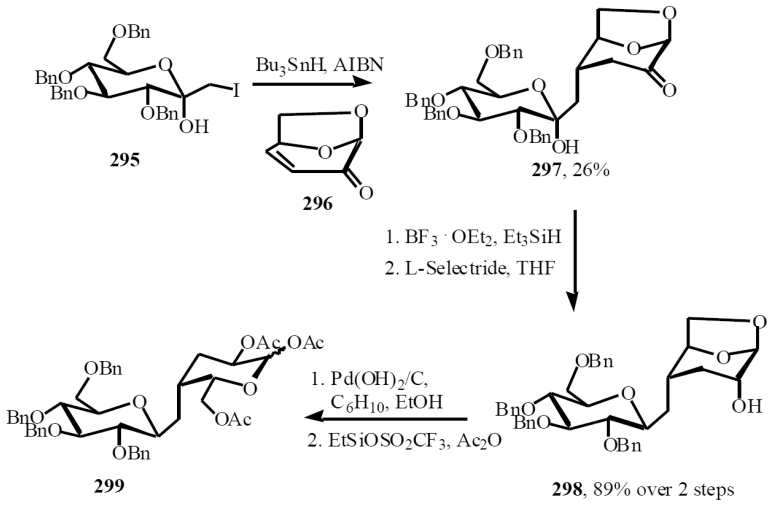
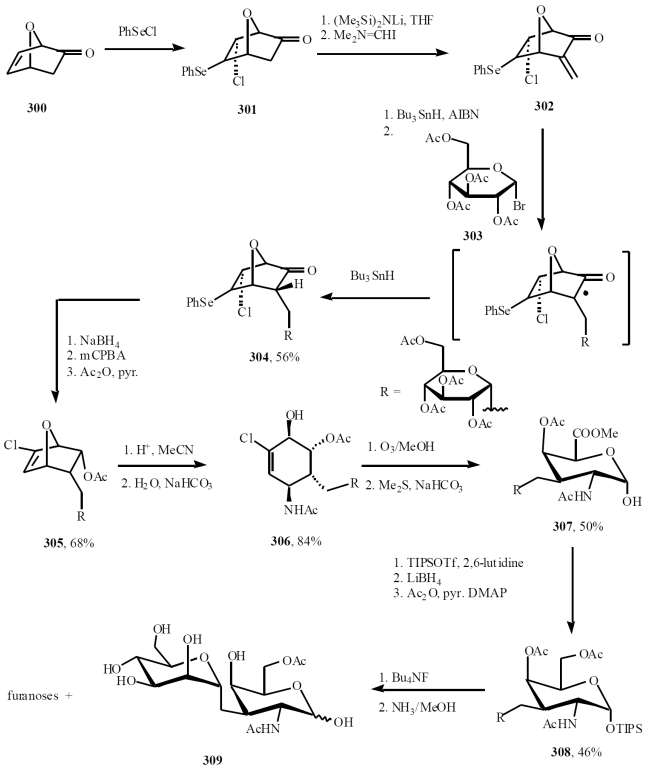


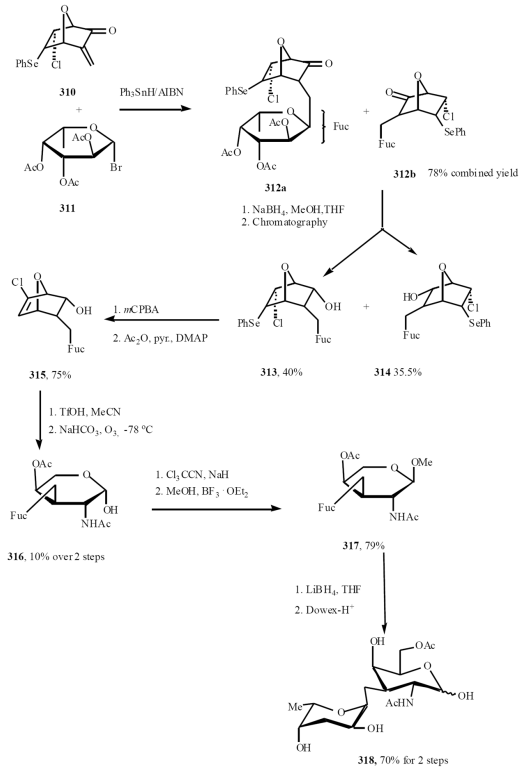
Scheme (51).



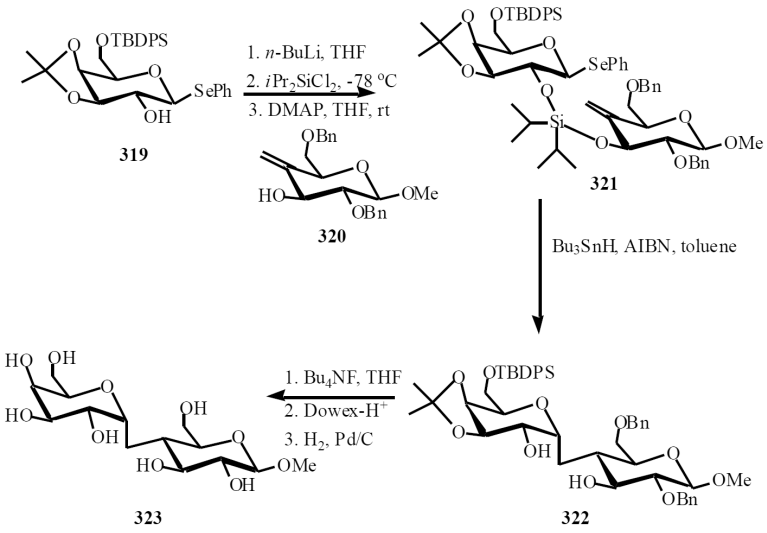
Scheme (52).



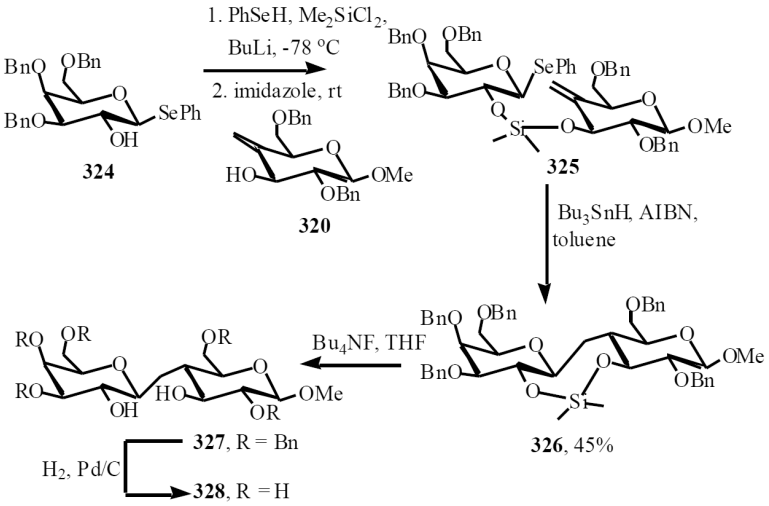
Scheme (53).



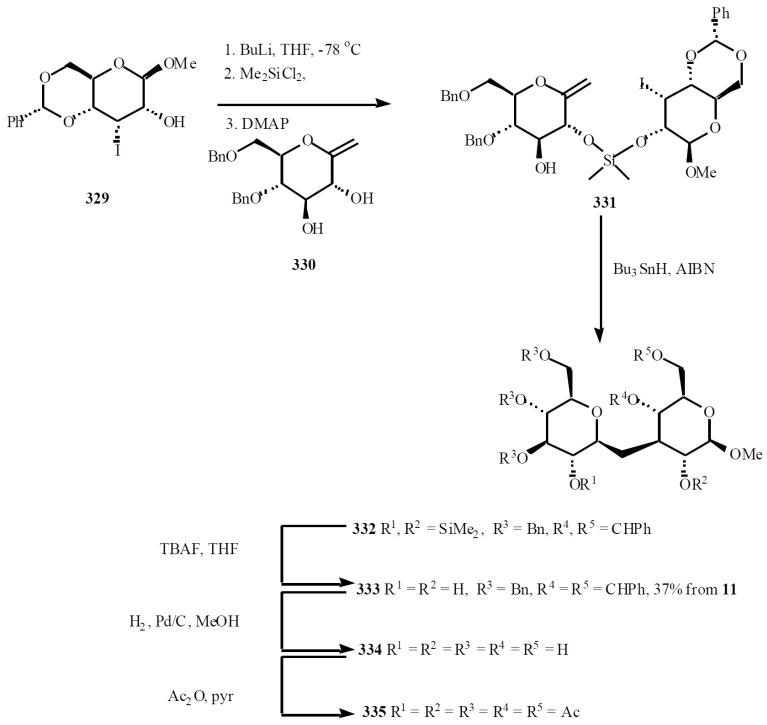
Scheme (54).



Scheme (55).



Scheme (56).



Scheme (57).

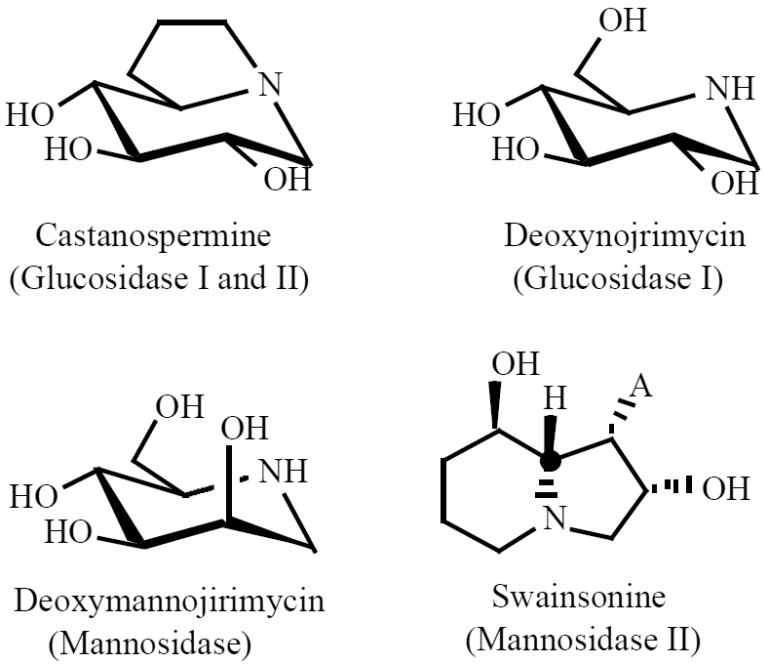


Fig. (1).
Natural inhibitors.

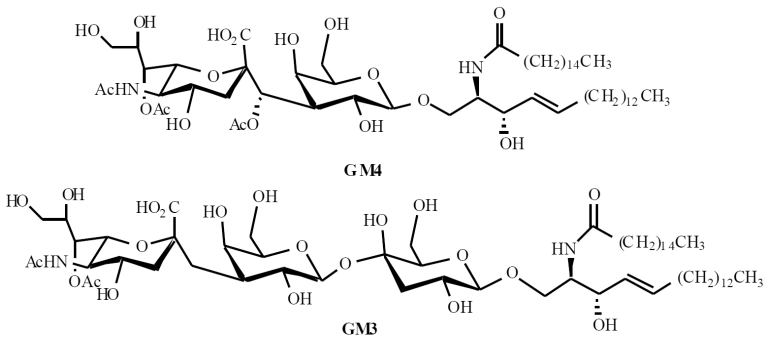


Fig. (2).