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Minireview

A vinyl sulfone-modified carbohydrate mediated new route to aminosugars and branched-chain sugars

Tanmaya Pathak* and Rahul Bhattacharya

Department of Chemistry, Indian Institute of Technology, Kharagpur 721 302, India

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Abstract—This minireview describes syntheses of various vinyl sulfone-modified carbohydrates and their reactions with nitrogen and carbon nucleophiles for accessing a wide range of aminosugars and branched-chain sugars.

Keywords: Vinyl sulfone; Carbohydrates; Michael addition; Aminosugars; Branched-chain sugars

Contents

1. Introduction

The amino groups present in the aminoglycoside antibiotics and polysaccharides play an important role in

* Corresponding author. Tel.: +91 03222 283342/282251; fax: +91 03222 282252; e-mail: tpathak@chem.iitkgp.ernet.in

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their biological activities.[1] The most important mechanism of resistance to aminoglycoside antibiotics among resistant bacteria arises from enzymatic *N*-acetylation, *O*-phosphorylation, and *O*-nucleotidylation of specific sites in the antibiotics. To avoid such deactivation processes, several semisynthetic aminoglycoside antibiotics have been designed in which either the hydroxyl groups undergoing enzymatic phosphorylation have been removed and/or the amino groups susceptible to acetylation have been masked by acylation or alkylation. The interest in this class of compounds has been renewed with the discovery that aminoglycoside antibiotics interact with a variety of RNA molecules.[1] Chart 1 illustrates some of the naturally occurring aminodeoxysugars which are devoid of one or more hydroxyl groups. For example, lividosamine **1** and purpurosamine C **2** belong to the group of 2-aminodeoxysugars, and acosamine **3** and daunosamine **4** constitute a group of 3-aminodeoxysugars (Chart 1). These compounds are obtained mainly from microbial sources.[2]

On the other hand, several 5-amino-5-deoxysugars have been reported to be useful compounds. For example, 5-deoxy-6-*O*-dodecyl-1,2-*O*-isopropylidene-5-pyrrolidinyl-α-D-glucofuranose and various β-L-*ido* derivatives **5** and **6** have been identified as having antiproliferative and immunomodulatory activities.[3a,b] 5-Aminodeoxyhexoses such as **7** are the key building blocks for the synthesis of a wide variety of polyhydroxylated piperidines which are glycosidase inhibitors[4–6] and the stereoselective synthesis of 5-amino-5-deoxy compound **8**[3c] has been reported (Chart 2).

Although C-2/C-3 positions of pyranoses and furanoses have been aminated extensively, mainly via the reduction of the azido derivative, the direct introduction of primary or secondary amine functions has remained problematic. The azide nucleophile is efficient enough to displace various sulfonyl ester groups from the C-2/C-3 position.[7] Both azide and selected alkylamines are able to open the epoxide ring; however, the regioselectivity of opening of the epoxide ring is controlled by the anomeric configuration as well as the configurations of the C-2/C-3 positions involving epoxide rings.[8]

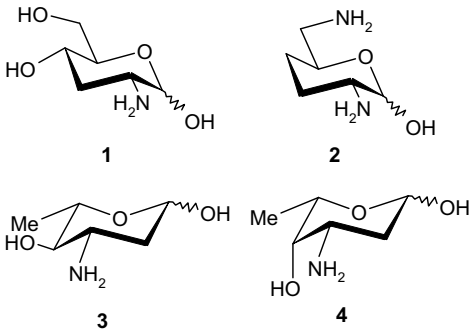


Chart 1.

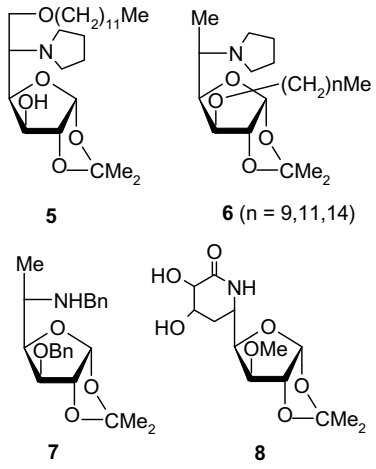


Chart 2.

Branched-chain sugars, having carbon substituents at the non-terminal carbon atoms of the chains, are components of many natural products, especially antibiotics such as eremomycin, vancomycin,[9a] amipurimycin,[9b] etc.[9c] Branched-chain sugars also constitute an important class of functionalized chirons, useful for further transformations.[7b,10] C-5 branched-chain sugars derived from hexofuranosyl carbohydrates have also generated considerable interest as starting materials for the synthesis of natural and non-natural products.[7b,10]

The C–C bond formation at the C-2 or C-3 carbons of carbohydrates has been studied thoroughly, and the addition of nucleophiles to suitable glycosiduloses has been extensively used for the synthesis of branched-chain sugars having polar substituents at the branching carbon atom.[7,9c,10] Reduction of alkylidene glycosides generates another class of branched-chain sugars. The reaction of sugar-derived oxiranes with carbon nucleophiles also provides a general but less efficient method for the synthesis of branched-chain sugars having no substituent at the branching carbon atom.[7,9c,10] The sulfonylated derivatives, are resistant to carbon nucleophiles and there is a limited use of the sugar-derived 2,3-epoxides in C–C bond formation at C-2.[7] However, ketones derived from furanoses or pyranoses remain the most useful functionalized sugars for C–C bond formation at the C-2 position.[7,9c,10]

Several examples of Michael addition of nitrogen nucleophiles including amines to hex-2-en-4-uloses,[11] 2-nitro-hex-2-enopyranosides,[12] and 3-nitro-hex-2-enopyranosides[13,12d] have been reported. 2,3-Dideoxy-hex-2-en-4-ulopyranosides, for example, have been reacted with azide,[11a] partially protected amino acids and benzylamine[11b] to generate several new classes of aminosugars. The major drawbacks of using 4-uloses as starting materials are that (a) the products are always 2,3-dideoxy derivatives and (b) the stereochemical outcome of the reduction of the carbonyl group (C-4) is dependent

on the orientation of the C-2 substituent;[11] such limitations make this route less attractive for synthetic work. Studies on the addition of nucleophiles to C-2 and C-3 vinyl nitro-modified carbohydrates, however, have remained limited to pyranosides.[12,13]

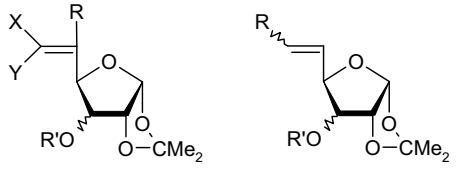
A perusal of the literature on the synthesis of 5-amino-5-deoxysugars reveals that methods for the functionalization of the C-5 position of hexose sugars in general are limited in number mainly because the 5-*O*-sulfonylated hexoses are reluctant to undergo nucleophilic displacement reactions. The use of low-boiling amines for such transformations is problematic, because the reaction has to be carried out at temperatures beyond the boiling points of amines.[3,14] On the other hand, amines regioselectively attack the C-6 position of sugar-derived terminal epoxides.[7,8]

The most common methods for the synthesis of C-5 branched-chain sugars from carbohydrate precursors generally involve either direct attack of carbon nucleophiles at C-5 of 5-ulose derivatives (e.g., **9**–**11**) or the reduction of C-5 alkylidene glycosides **12** generated from sugar aldehydes or ketones (Chart 3).[7b] On the other hand, Michael addition of carbon nucleophiles to electron-deficient sites on hex-5-enofuranosyl carbohydrates, for example, **13**–**16** has been used to a limited extent for the functionalization of the C-5 of carbohydrates, compound **16** being the most widely used Michael acceptor.[7b,9c] Compounds represented by the general structure **17** have been briefly mentioned in the literature (Chart 3).[15]

2. Background

Since vinyl sulfones in general serve efficiently as both Michael acceptors and 2π-partners in cycloaddition reactions,[16] it is logical to envisage that the high reactivities of vinyl sulfones may be combined with the inbuilt chiral structural features[10] of carbohydrates. It may be argued that vinyl sulfone-modified carbohydrates have the potential for utilization in organic synthesis because (a) almost all carbohydrates, either in pyranose or furanose forms, could be converted to vinyl sulfone derivatives very easily, (b) sulfone chemistry has been exploited extensively over decades and its compatibility with a wide variety of simple and complex molecules is well established,[16] and (c) after using the vinyl sulfone moiety as a tool for functionalization, desulfonylation under strategically selected conditions[17] would easily generate an array of modified carbohydrates.[18]

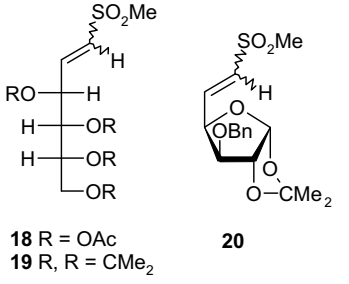
Synthesis and physical studies of vinyl sulfone-modified carbohydrates, **18**–**20**, were reported as early as in 1971 (Chart 4).[15a,19] Although several groups reported the synthesis of glycal derivatives **21**,[20a] **22**,[20b] **23** (Chart 5), and **24**,[20b] attempted Michael addition of methyl lithium to **24** lithiated the C-2 position; subsequent reaction of the lithiated species with iodomethane produced 2-methyl vinyl sulfone **25** (Scheme 1). The presence of the ring oxygen α to the sulfone group deactivated the double bonds of these compounds and made them too unreactive to undergo Michael addition.[20b]



9 R = H; X,Y = O
10 R = Me; X,Y = O
11 R = CH_2OR''; X, Y = O
12 R = Me/CH_2OR''; X, Y = H, alkyl
13 R = CHO
14 R = CO_2R''
15 R = CN
16 R = NO_2
17 R = SO_2R

R' = protecting groups

Chart 3.



18 R = OAc
19 R, R = CMe_2
20

Chart 4.

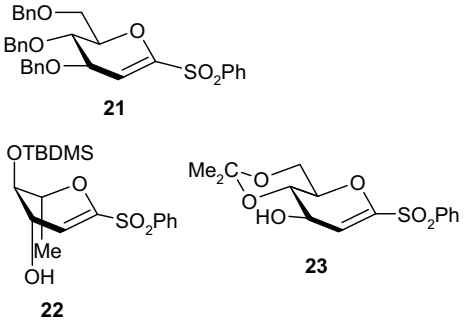
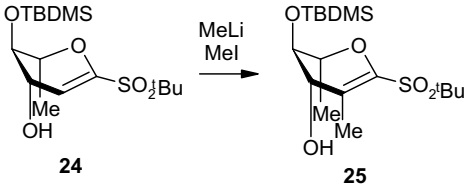
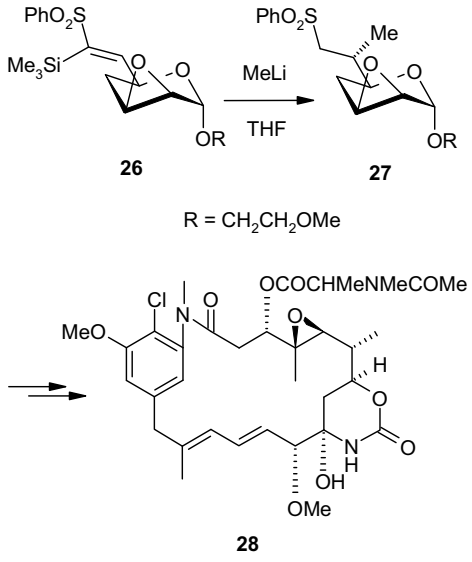


Chart 5.



Scheme 1.



Scheme 2.

Much later, the pyranose derivative **26** containing a 2-phenylsulfonyl-2-trimethylsilylvinyl group was used for the synthesis of (±)-maytansinol **28**;[21] the step was initiated by the heteroconjugate addition of MeLi to **26** to obtain **27** and introduced the methyl group stereospecifically at C-6 (Scheme 2). From a historical perspective, this particular synthetic strategy highlighted for the first time the potential of vinyl sulfone-modified carbohydrates as useful chiral synthons. At the same time, this reaction emphasized the most important property of vinyl sulfone-modified carbohydrates, namely the influence of the carbohydrate moiety on the diastereoselectivity of the addition of nucleophiles to the electron-deficient double bond.[21]

Although vinyl sulfones have been used extensively in synthetic transformations,[16] vinyl sulfone-modified carbohydrates are yet to be used effectively[18] in synthetic organic chemistry. As part of a research program dealing with the modification of carbohydrates, the authors of this article intended to investigate a vinyl sulfone-based strategy for the functionalization of the C-2 and C-5 positions of carbohydrates en route to amino- and branched-chain sugars. This review attempts to highlight the strategies for the synthesis of vinyl sulfone-modified carbohydrates and the importance of these compounds as intermediates for the preparation of aminosugars and branched-chain sugars.[18]

3. Vinyl sulfone-modified pent-2-enofuranosides and hex-2-enofuranosides

3.1. Synthesis

A thorough study on the diastereoselectivity of addition of nitrogen and carbon nucleophiles to vinyl sulfone-modified carbohydrates was necessary to enable the assessment of specific routes to pure diastereomers. Since it was reported that nucleophiles attack the C-2′ position of the 2′-ene-3′-sulfonyl-β-nucleosides exclusively from the α-face,[22] it was logical to presume that the anomeric configuration would stereoelectronically influence the addition pattern of nucleophiles to *endo*-cyclic monovinyl 3-sulfones derived from carbohydrates (Chart 6). Therefore, Pathak and co-workers directed their attention to study the addition pattern of amines and carbon nucleophiles to the α- and β-anomeric pairs of 3-*C*-sulfonyl pent-2-enofuranosides and hex-2-enofuranosides **29/30** and **31/32** (Chart 7). Thus, relatively large quantities of anomerically pure, vinyl sulfone-modified pent-2- and hex-2-enofuranoses **29/30** and **31/32** were needed, and the requirement of anomeric purity of compounds **29**–**32** (Chart 7) imposed greater restrictions on the choice of methodologies for the synthesis of a particular pair of anomers starting from a single and easily accessible starting material.

A retrosynthetic analysis of the route to **29**–**32** necessitated the introduction of an arylthio group at the C-3 position of a pentose or a hexose sugar. One of the easiest ways of forming a C–S bond would be the regioselective opening of epoxides derived from carbohydrates. Alternatively, the arylthio group at the C-3 position of a hexose or a pentose sugar could be introduced by displacing leaving groups at C-3 position of easily accessible starting materials.[23,24]

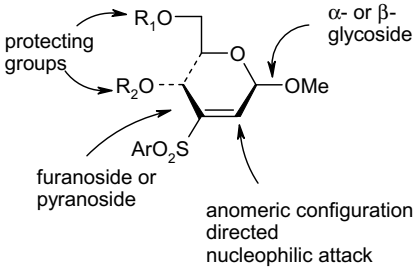


Chart 6.

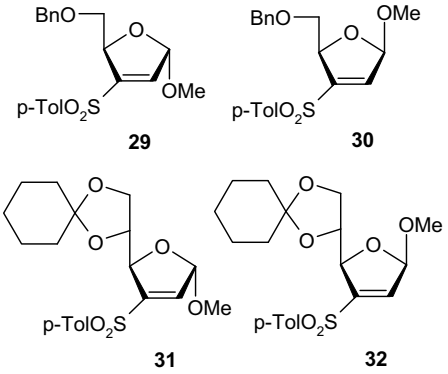
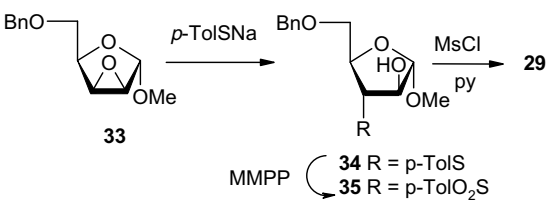


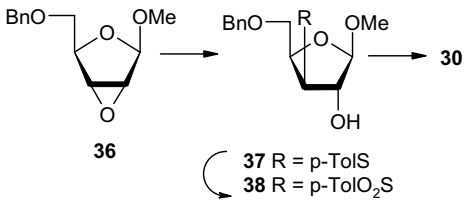
Chart 7.

3.1.1. Syntheses of 3-*C*-sulfonyl pent-2-enofuranosides. The known D-*lyxo*-epoxide **33**, synthesized from D-xylose, was treated with sodium *p*-thiocresolate in DMF at 80–90 °C to furnish sulfide derivative **34** in good yield. Compound **34**, when oxidized with magnesium monoperoxyperphthalate (MMPP) in MeOH, generated the corresponding sulfone **35** in high yields. Compound **35**, on treatment with mesyl chloride in pyridine, smoothly afforded the desired vinyl sulfone-modified carbohydrate **29** in 82% yield (Scheme 3). Similarly, the known D-*ribo*-epoxide **36** was converted to sulfide **37** with the D-*xylo*-configuration in high yield. Compound **37** was converted to the corresponding vinyl sulfone **30** via sulfone **38** in the manner described above (Scheme 4). However, separate synthesis of epoxides **33** and **36** increases the overall number of steps. Therefore, it was necessary to devise different approaches toward the synthesis of vinyl sulfone-modified pent-2-enofuranosides.[23]

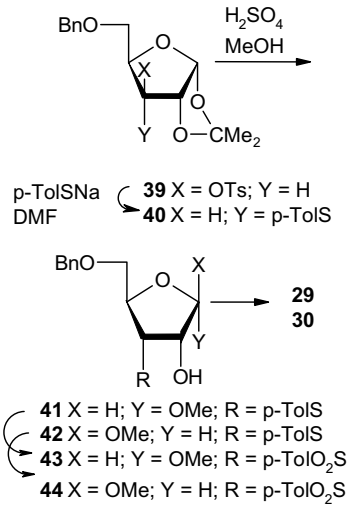
In search of an alternative approach, tosyl derivative **39** was treated with 4-methylbenzenethiol sodium salt in DMF at 120 °C to produce sulfide derivative **40** with the D-*ribo*-configuration in 59% yield. Compound **40** was methanolyzed in one step in the presence of concd H_2SO_4 in MeOH to generate a mixture of anomers **41** and **42** (1:10) in 78% yield. These anomers were separated at this stage by chromatography and oxidized separately with MMPP in MeOH to the corresponding sulfones **43** and **44**, respectively, in excellent yields. Sulfones **43** and **44** were converted to vinyl sulfone-modified carbohydrates **29** and **30**, respectively, in high yields in the usual way (Scheme 5).[23] The moderate yield (59%) of the D-*ribo*-product **40** can be partly explained on the basis of the repulsion caused by the 1,2-*O*-isopropylidene group to the incoming nucleophile. Although at this stage the less efficient conversion of **39** to **40** was acceptable, the major drawback of this methodology



Scheme 3.



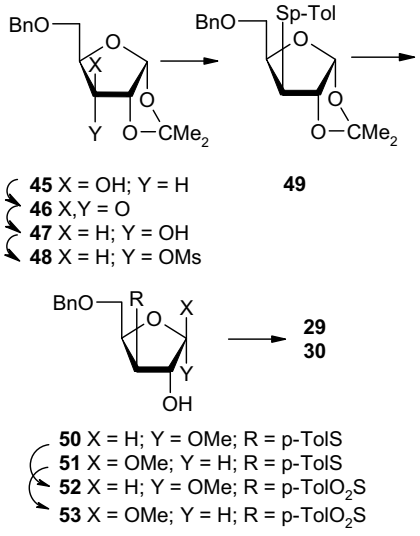
Scheme 4.



Scheme 5.

was the unacceptable ratio of **41** and **42** (1:10) in the mixture. The lower ratio of α-anomer **41** in the mixture contributed to the poor overall yield of the vinyl sulfone derivative **29** (Scheme 5).[23]

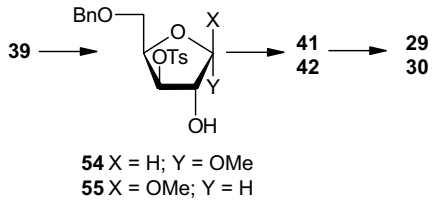
An examination of the anomeric compositions of methyl furanosides of D-ribose, D-arabinose, D-xylose and D-lyxose revealed that the ratios of α- and β-furanosides present in equilibrium were 1:3.4, 3.1:1, 1:1.5 and only the α-*lyxo*-isomer respectively.[7a] Thus, the pattern of glycosylation of various pentose sugars directed Pathak and co-workers to select a D-*xylo*-derivative-based strategy for the synthesis of an anomeric mixture close to the ideal ratio of 1:1. Thus, 5-*O*-benzyl-1,2-*O*-isopropylidene-3-*O*-mesyl-α-D-*ribo*furanose **48** was synthesized from the known compound **45** via oxidation–reduction followed by mesylation (Scheme 6). Compound



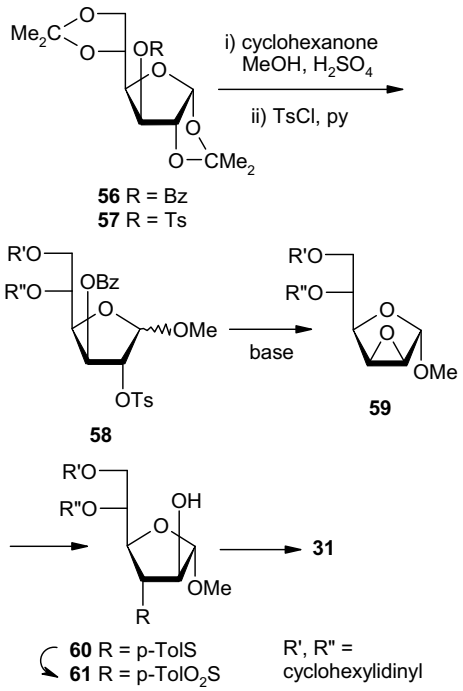
Scheme 6.

48 was subjected to nucleophilic displacement by 4-methylbenzenethiol sodium salt to generate the D-*xylo*-sulfide derivative **49** in 79% yield. Compound **49** was deacetalated and methanolyzed to afford a mixture of α- and β-anomers **50** and **51** (1.5:1) in excellent yields. The anomers were separated by flash chromatography and treated with MMPP in MeOH to yield sulfones **52** and **53**, respectively, in excellent yields. Sulfones **52** and **53** were converted to the desired vinyl sulfones **29** and **30** in high yields.[23] Although the ratio of **50** and **51** (1.5:1) was acceptable for the synthesis of both anomers **29** and **30**, the overall yields were diminished by the need to convert *xylo*-derivative **45** to *ribo*-derivative **47** (Scheme 6). We therefore looked for yet another route for the synthesis of **29** and **30**.[23] Methanolysis of the *xylo*-tosylate **39** (Scheme 5) produced an anomeric mixture of **54** and **55** in the ratio 1:1.3 (α:β) in 89% yield (Scheme 7). The nucleophilic displacement of the tosyl groups of the mixture of **54** and **55** by 4-methylbenzenethiol proceeded smoothly at elevated temperature to afford a mixture of *ribo* furanosides **41** and **42** in 94% yield. Compounds **41** and **42** were separated and converted to the desired vinyl sulfone-modified carbohydrates **29** and **30**, respectively, in the manner described above. This synthetic strategy was the best for the preparation of the vinyl sulfones **29** and **30** starting from a single carbohydrate derivative (Scheme 7).[23]

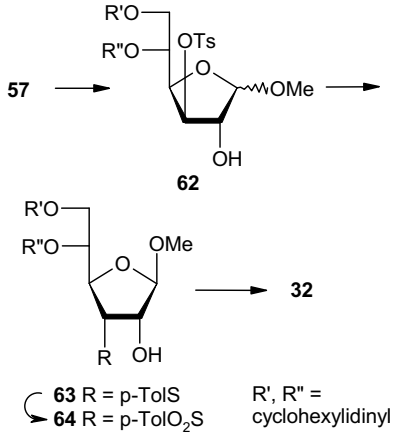
3.1.2. Synthesis of 3-*C*-sulfonyl hex-2-enofuranosides. Compared to pent-2-enofuranosides **29** and **30**, the synthesis of hex-2-enofuranosides **31** and **32** (Chart 7) was more complicated because the anomeric ratio of methyl glycosides obtained from **56** or **57** was far from the ideal value of 1:1. It was therefore necessary to have two different approaches from the most easily accessible glucofuranose intermediates like **56** or **57**. Thus, benzoate **56** on one-pot methanolysis and cyclohexylidenation[24,25] produced a mixture, which contained the α-furanoside in major proportions. Tosylation of the mixture produced **58**, which on treatment with base gave an anomeric mixture of epoxides. The α-anomer **59** was separated from the mixture and converted to the desired α-anomeric vinyl sulfone **31** via sulfide **60** and sulfone **61** in the usual way (Scheme 8). For accessing β-anomer **32**, tosylate **57** was converted to the mixture of methyl glycosides **62** in which the β-anomer was predominant. Displacement of the tosyl group by thiolate produced



Scheme 7.



Scheme 8.

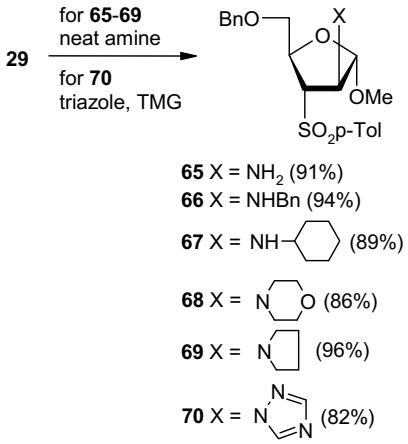


Scheme 9.

63, which on oxidation gave **64**. Mesylation of **64** led to the β-anomeric vinyl sulfone **32** (Scheme 9).[24]

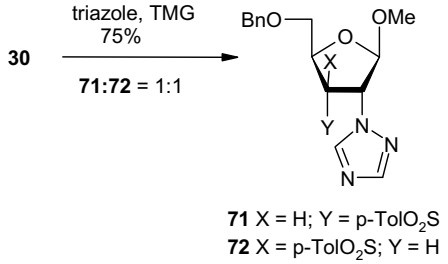
3.2. Aminosugars

To establish the influence of anomeric configuration on the diastereoselectivity of addition of various nucleophiles to the highly reactive vinyl sulfone-modified pent-2-enofuranosides **29/30** and hex-2-enofuranosides **31/32**, these compounds were treated with various nitrogen nucleophiles. Thus, the reaction of **29** with a series of amines exclusively produced compounds **65–69** in high yields.[26] The reaction of 1,2,4-triazole with **29** in

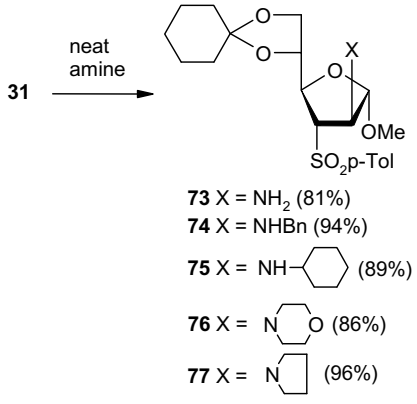


Scheme 10.

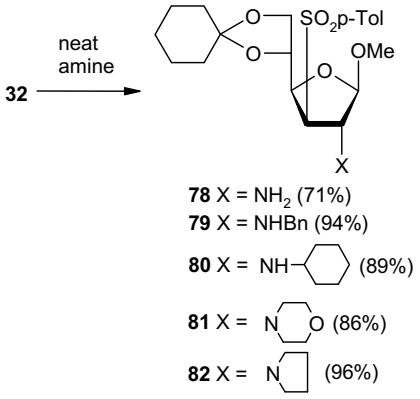
the presence of 1,1,3,3-tetramethylguanidine (TMG) in DMF at room temperature produced the single isomer **70** in high yield (Scheme 10).[23a] The β-anomer **30**, on the other hand, reacted with 1,2,4-triazole to produce a separable mixture (1:1) of the β-*ribo* derivative **71** and a β-*xylo* derivative **72** (Scheme 11).[23a] Ammonia, benzylamine, cyclohexylamine, morpholine, and pyrrolidine added equally efficiently to **31** and **32** in a diastereoselective fashion to produce α-methoxy amino sugars **73**–**77** (Scheme 12) and β-methoxy amino sugars **78**–**82**, respectively, in high yields (Scheme 13).[24,26]



Scheme 11.

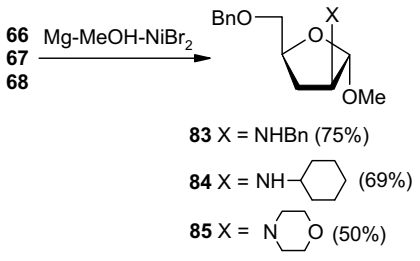


Scheme 12.

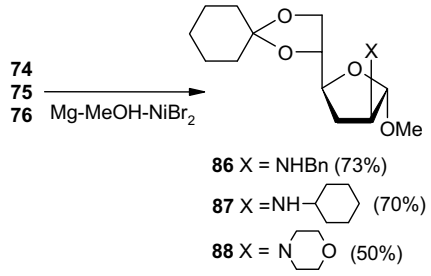


Scheme 13.

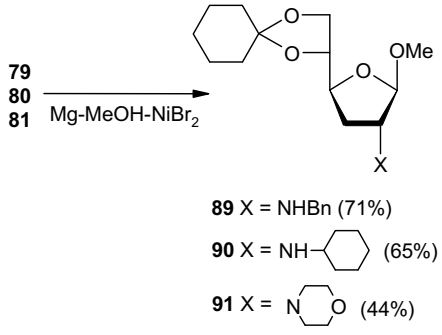
3.2.1. Desulfonylation of the sulfonyl aminofuranosides. Attempted desulfonylation of a selected group of the sulfonyl aminofuranoses from the furanosyl series generated inseparable mixtures of products. Since the success of a method for making deoxyaminosugars using the vinyl sulfone adducts would depend crucially on the desulfonylation step, Pathak and co-workers experimented a large variety of desulfonylating agents available from the literature. Almost all reported reagent systems such as Na–Hg, Mg–EtOH–$HgCl_2$, Al–Hg, SmI_2, $NiBr_2$–DME–PPh_3, Raney-Ni, and $LiAlH_4$ failed to yield the desired deoxyaminosugars. It was reported that the reduction of nickel halides with low-oxidation-potential metals such as magnesium produced finely divided Ni(0), which exhibited general catalytic activity greater than commercial Raney-Ni.[26] This observation prompted Pathak and co-workers to subject the benzylamino, cyclohexylamino, and the morpholino derivatives to desulfonylation by the Mg–MeOH–NiX_2 system. Thus com- pounds **66**–**68** were desulfonylated to benzylamino, cyclohexylamino, and the morpholino derivatives **83**–**85**, respectively, (Scheme 14). Similarly, hexofuranosides **74**–**76** and **79**–**81** were also converted to the aminodideoxysugar **86**–**88** (Scheme 15) and **89**–**91** (Scheme 16), respectively. Three nickel salts, namely $NiCl_2$, $NiBr_2$, and NiI_2 were employed and $NiBr_2$ was found to be most efficient for the desulfonylation reaction. Mg–MeOH–$NiBr_2$-based reductive desulfonylation allowed the synthesis of an



Scheme 14.



Scheme 15.

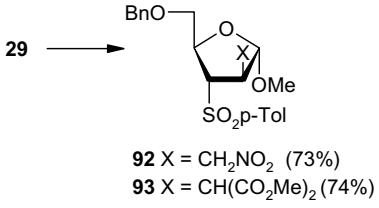


Scheme 16.

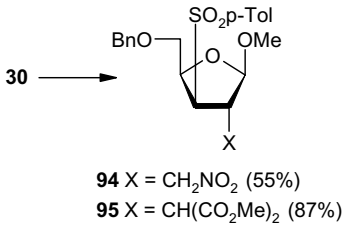
array of hitherto inaccessible 2-amino-2,3-dideoxypentofuranosides **83**–**85** and 2-amino-2,3-dideoxyhexo-furanosides **86**–**91**. The yield of the desulfonylation step dramatically improved from 0% with the known reagents to 44–75% with Mg–MeOH–$NiBr_2$.[26]

3.3. Branched-chain sugars

Considering the importance of branched-chain sugars as components of natural products as well as functionalized intermediates for the synthesis of many natural products,[7,9c,10] it was necessary to study the addition pattern of carbon nucleophiles to **29** and **30**. Thus, **29** on reactions with carbanions generated from $NaCH_2NO_2$ and $NaCH(CO_2Me)_2$ produced branched-chain sugars **92** and **93**, respectively, in good yields (Scheme 17). The β-anomer **30** also produced adducts **94** and **95** in a diastereoselective fashion under similar conditions (Scheme 18).[27]



Scheme 17.



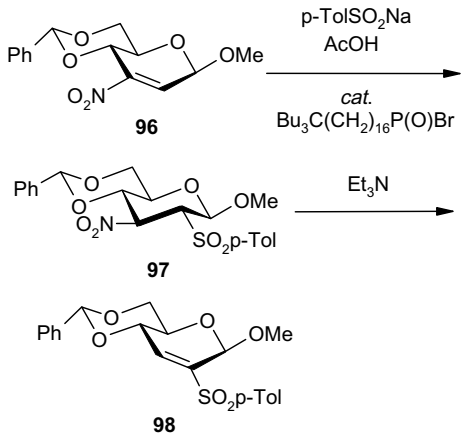
Scheme 18.

4. Vinyl sulfone-modified hex-2-enopyranosides

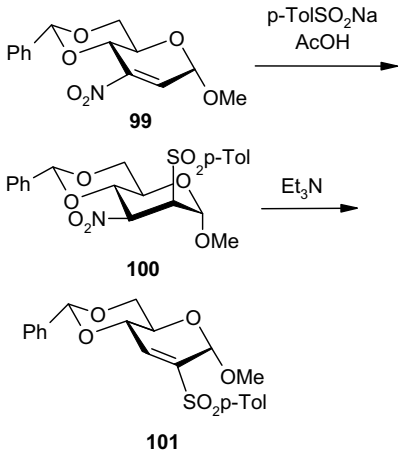
4.1. Synthesis

While studying the reactivities of conjugated nitrovinyl sugars, Sakakibara and co-workers reported the synthesis of 2-*C*-sulfonyl-hex-2-enopyranosides. Thus, the vinyl nitro derivative **96** was treated with sodium 4-tolylsulfinate in the presence of acetic acid to obtain the nitro sulfonyl derivative **97**. The *gluco*-derivative **97** on treatment with triethylamine produced the vinyl sulfone **98** (Scheme 19).[28a,b] The α-anomer **101** was synthesized in very poor yield from the 3-nitro-hex-2-enopyranoside **99** via the mannopyranoside derivative **100** (Scheme 20). Therefore, an alternative method for the preparation of **101** was developed. Thus, the epoxy ring of 2,3-anhydro-α-D-allopyranoside **102** was opened with 4-methylbenzenethiol sodium salt and product **103** was oxidized to sulfone **104**. Compound **104** on mesylation in the presence of triethylamine underwent concomitant elimination to afford the vinyl sulfone **101** through the intermediacy of the mesylated derivative **105** (Scheme 21).[28a,b]

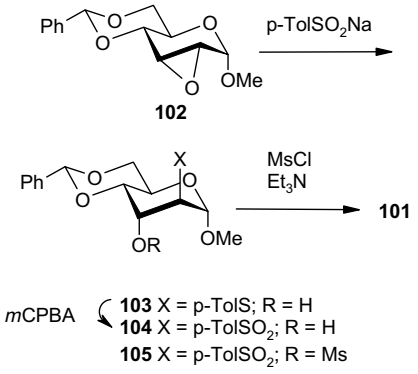
Pathak and co-workers studied the addition pattern of amines and carbon nucleophiles to the α- and β-anomeric pairs of 3-*C*-sulfonyl-hex-2-enopyranosides **106** and **107** (Chart 8).



Scheme 19.



Scheme 20.



Scheme 21.

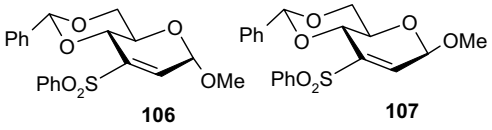
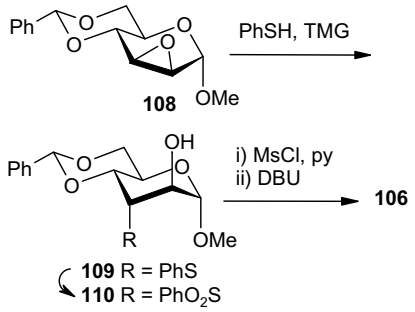
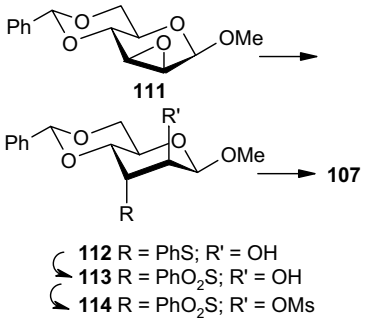


Chart 8.

Initially, 3-*C*-sulfonyl-hex-2-enopyranoside **106** was synthesized by modifying the method reported by Sakakibara and co-workers.[28a,b] Thus, epoxide **108** was treated with thiophenol in the presence of TMG to afford **109**. The corresponding sulfone derivative **110** was generated in quantitative yield by oxidizing **109** with MMPP. Compound **110** was mesylated and the crude mesylated product was subjected to an elimination reaction with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in dichloromethane to produce **106** in 88% overall yield (4 steps from **108**) (Scheme 22). Similarly, thiophenol in the presence of TMG opened epoxide **111** at the 3-position to generate sulfide **112**. Oxidation of **112** to sulfone **113**, followed by mesylation and DBU treatment



Scheme 22.

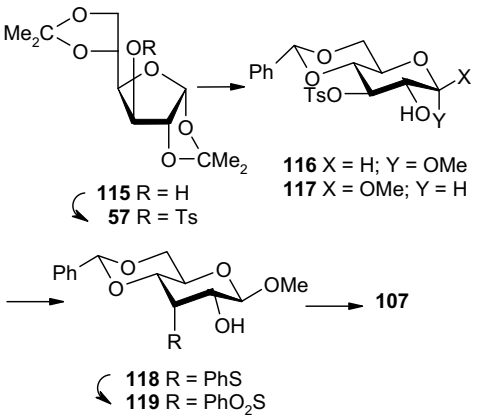


Scheme 23.

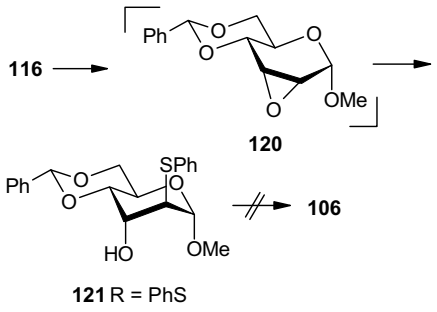
generated the desired compound **107** in 75% overall yield (4 steps from **111**) (Scheme 23).[29]

For accessing relatively large amounts of anomerically pure **106** and **107** through a shorter route, we applied the 'glycosylation driven strategy',[23a] which was successfully utilized in the synthesis of **29** and **30** (Chart 7). It was reported that the equilibrium mixture of methyl D-allosides in MeOH contained more than 30% of furanosides, whereas D-glucose produced methyl D-pyranosides almost exclusively.[7a] Although the reported ratio of α- and β-anomers was not close to the ideal value of 1:1, in this case, it was more important to obtain the methyl pyranosides without any contamination by the corresponding furanosides. This observation prompted us to study the feasibility of using the known tosylate **115** from which compounds **116** and **117** can readily be obtained, as the starting material.[23]

Compound **57** (Scheme 8), easily available from bis-isopropylidene glucose **115**, was converted to pyranosides **116** and **117** by deprotection, methanolysis followed by benzylidenation in the ratio 1:1.5. The anomers were separated by column chromatography. The β-anomer **117** was treated with sodium thiophenolate to afford sulfide derivative **118**. Compound **118** was oxidized to **119** and the latter, under mesylation conditions, smoothly generated the desired vinyl sulfone **107** in overall 79% yield (in 4 steps from **117**) (Scheme 24). The α-anomer **116**, when treated with sodium thiophenolate, produced the unwanted β-sulfide derivative



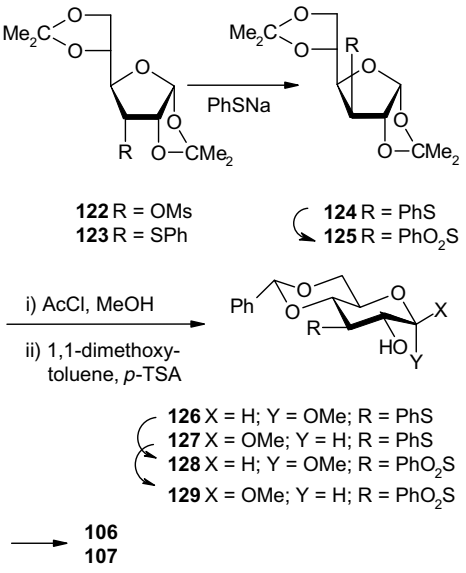
Scheme 24.



Scheme 25.

121. Since it was reported that **116** very easily forms epoxide **120**, it was logical to conclude that under the reaction conditions *altro*-derivative **120** was formed (Scheme 25). No further study was carried out on this reaction sequence because it was not possible to synthesize the desired vinyl sulfone **106** through this route.[23]

To overcome the aforementioned problems and to have easy access to both **106** and **107** through a single intermediate, Pathak and co-workers studied another sequence of reactions using two possible starting materials **123** and **124** (Scheme 26). Here also, for reasons discussed above, the *gluco*-derivative **124** was the starting material of choice over the *allo*-derivative **123** because methanolysis of the latter generated more than six products. Thus, the known mesylated *allo*-derivative **122** was treated with sodium thiophenolate to afford sulfide derivative **124** with the *gluco*-configuration. Compound **124** was deprotected and methanolyzed in a single operation by using acetyl chloride and MeOH to afford a mixture of methyl 3-deoxy-3-phenylthio-glucopyranosides, which were converted to the benzylidene derivatives **126** and **127** in the ratio 2.2:1 in good yields. The anomers were separated by chromatography and were then converted to the corresponding sulfones **128** and **129**, respectively, in excellent yields using MMPP in MeOH. In an alternative approach, compound **124**



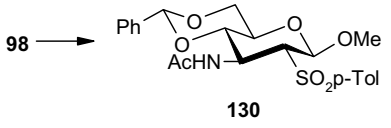
Scheme 26.

was oxidized to the corresponding sulfone **125** in excellent yield. Compound **125** was deprotected and methanolyzed by acetyl chloride and MeOH in one step to generate a mixture of anomeric sulfones, which were collected as the benzylidene *gluco*-derivatives **128** and **129**, respectively, in good yields in a ratio 1:1.8. The anomers were separated by column chromatography and were converted to the desired vinyl sulfone-modified hex-2-enopyranosides **106** and **107**, respectively, in excellent yields (Scheme 26).[23]

By comparison with the lengthy synthesis of **106** and **107** from D-glucose in 14 steps (7 steps for each anomer; Schemes 22 and 23)[28] the route starting from **122**[23] makes use of common intermediates up to compounds **128** and **129**, thereby drastically reducing the overall purification steps (Scheme 26). Although overall yields for both methods are comparable, methyl β-D-*gluco* pyranoside, which has been used in Scheme 23,[28a,b] is far too expensive as a starting material to be used in a large-scale multi-step synthesis.

4.2. Aminosugars

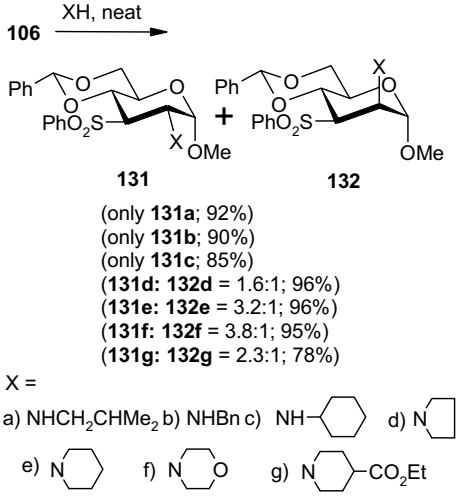
Reaction of the vinyl sulfone **98** with ammonia in THF followed by acetylation afforded a mixture of two products, from which 71% of **130** was isolated (Scheme 27).[28c]



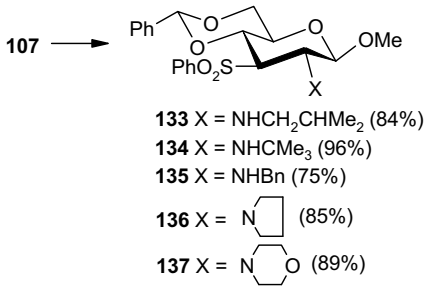
Scheme 27.

In order to study the influence of the anomeric configuration on the diastereoselectivity of the addition of various nucleophiles to 3-sulfonyl-2-enopyranoside systems, anomerically pure α-vinyl sulfone **106** was treated with various primary and secondary amines. Primary amines such as isobutylamine, benzylamine, and cyclohexylamine were found to add diastereoselectively to produce single isomers **131a**, **131b**, and **131c**, respectively, with the D-*gluco* configuration (Scheme 28). The secondary amines, pyrrolidine, piperidine, morpholine, and ethyl isonipecotate, on the other hand, generated a mixture (isomeric at C-2), also having the D-*gluco*-**131d**, **131e**, **131f**, and **131g** as the major isomers, respectively. The major isomers **131d–g** were separated by crystallization. One of the minor *manno*-isomers **132d** was isolated and unambiguously characterized (Scheme 28).[29] Similarly, the β-anomeric vinyl sulfone **107** was treated with isobutylamine, benzylamine, *tert*-butylamine, pyrrolidine, and morpholine. The primary as well as secondary amines were found to add diastereoselectively to produce single β-D-*gluco* isomers **133–137**, respectively (Scheme 29).[29]

It should be noted that **106** did not react with sterically bulky *tert*-butylamine and unreacted starting material was recovered from the reaction mixture. Attempted reactions under forcing conditions or prolonged reaction time caused extensive degradation of the starting material. The β-anomer **107**, on the other hand, reacted smoothly with the same amine at elevated temperature to produce a single isomer **134** in excellent yield. Reactions of *tert*-butylamine exemplified an extreme case of anomeric configuration influencing the addition of nucleophiles to enopyranoside systems **106** and **107**.[30a] The X-ray analysis of the single crystal of **134** revealed that the pyranose ring assumed a boat conformation to facilitate the positioning of the methoxy group of C-1 away from the group at C-2. It was observed from the X-ray analysis of **133**, **134**,[30a] and **135**[30b] that the magnitude of the conformational angles O1–C1–C2–N1 increased in the order **133→135→134** confirming this argument. However, in the case of α-methoxy series (compounds **131**), any increase in this particular conformational angle is prohibited because of the axial disposition of C-1 methoxy group. Thus a bulkier group, greater than a critical size, could not be accommodated at the C-2 position of the α-anomers.[30]

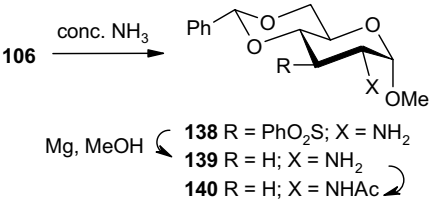


Scheme 28.

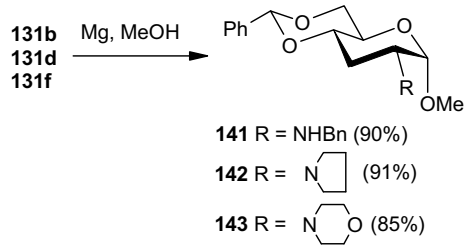


Scheme 29.

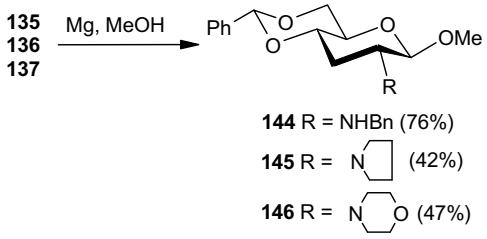
The diastereoselective addition of primary amines to **106** and **107** has been applied to the synthesis of a naturally occurring aminosugar D-lividosamine and its analogues. D-Lividosamine (2-amino-2,3-dideoxy-D-glucose) **1** (Chart 1), isolated from *Streptomyces lividus*, is present in aminoglycoside antibiotics such as lividomycin-A/lividomycin-B.[31] The essence of the synthetic strategy leading to the preparation of D-lividosamine **1** and its alkylated analogues lies in the introduction of amino and *N*-alkyl amino groups at the C-2 carbon of the pyranoses in equatorial configurations followed by (or prior to) deoxygenation at the C-3 site. None of the known methods of amination of pyranosides could have been used as a general route for the synthesis of D-lividosamine and its analogues, either because of the undesired configuration or position of the C–N bond and/or the additional functionalization of the C-3 hydroxyl group required for the deoxygenation of the C-3 center.[32] Thus, compound **106** was directly treated with concd aq ammonia in dioxane to produce a mixture containing mainly compound **138**. The mixture was desulfonylated and the free amino product **139** was acylated. Pure aminodeoxysugar **140**, a known intermediate for the synthesis of D-livodosamine **1**, was crystallized from benzene–pet. ether mixture in 65% overall yield (Scheme 30).[32]



Scheme 30.



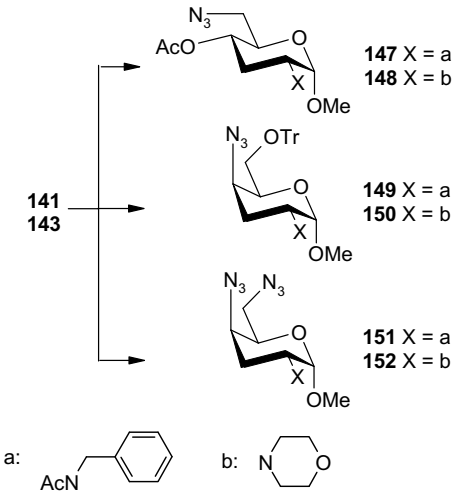
Scheme 31.



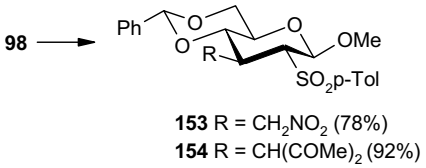
Scheme 32.

Analogues of **139** were easily obtained by desulfonylating **131b**, **131d**, and **131f** to **141**–**143** in high yields, respectively (Scheme 31). In the β-series, **135**–**137** were also desulfonylated to **144**–**146**, respectively (Scheme 32).[32]

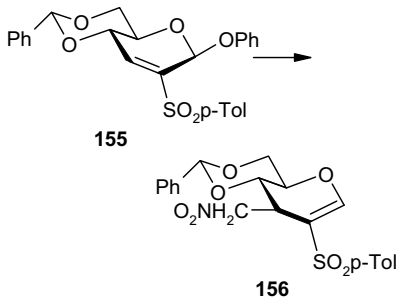
It is possible to widen the application of the above sequence of methodologies for the synthesis of C-3 deoxy polyaminosugars like purpurosamine A (2-amino-2,3,4,6,7-pentadeoxy-6-methylamino-D-*ribo*-heptose), purpurosamine B (2,6-diamino-2,3,4,6,7-pentadeoxy-D-*ribo*-heptose), nebrosamine (2,6-diamino-2,3,6-trideoxy-D-*ribo*-hexose), sisosamine (2,6-diamino-2,3,4,6-tetradeoxy-D-*glycero*-hex-4-enose), kasugamine (2,4-diamino-2,3,4,6-tetradeoxy-D-*arabino*-hexose), 3-deoxyprumycin [4-(D-alanylamino)-2-amino-2,3,4-dideoxy-L-arabinose] and their analogues.[2,32] Thus, synthetic manipulations of the desulfonylated compounds **141** and **143** generated intermediates **147/148** (Scheme 33) for accessing 2,3,6-trideoxy-2,6-diamino sugars, intermediates **149/150** for 2,3,4-trideoxy-2,4-diamino sugars and intermediates **151/152** for 2,3,4,6-tetradeoxy-2,4,6-triamino sugars (Scheme 33).[33]



Scheme 33.



Scheme 34.



Scheme 35.

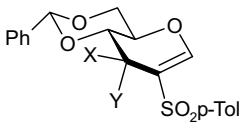
4.3. Branched-chain sugars

Treatment of the vinyl sulfone **98** in refluxing nitromethane containing triethylamine provided the β-nitromethyl derivative **153**. 2,4-Pentanedione similarly produced the corresponding β-D-*gluco* adduct **154** in excellent yield (Scheme 34).[28c]

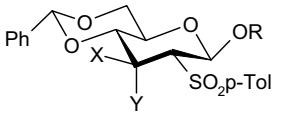
Treatment of the phenyl analogue **155** with nitromethane led mainly to an S_N2' process to give 1-enitol derivative **156** having the D-*arabino* configuration (Scheme 35).[28c]

Compound **98** on irradiation with a high-pressure mercury lamp in methanol generated a mixture of **157** (4%), **161** (9%), **160** and **163** (55% together) (Chart 9). The phenyl analogue **155** after photoreaction followed by the acetylation of the products generated a mixture of **158** (37%), **159** (24%), and **162** (11%). In all these cases, equatorial attack by hydroxymethyl radical slightly predominated over the axial attack. However, due to uncontrolled mixture formation, this particular photoreaction using vinyl sulfone-modified carbohydrates has very little synthetic utility (Chart 9).[34]

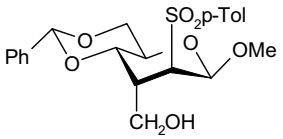
The importance of branched-chain sugars led Pathak and co-workers to independently study the reaction pattern of carbon nucleophiles to **106** and **107**. Thus, the nucleophile generated from CH_3NO_2 and NaOMe reacted with **106** to produce a single isomer **164**. Similarly, the nucleophile generated from dimethylmalonate



157 X = CH_2OH; Y = H
158 X = CH_2OAc; Y = H
159 X = H; Y = CH_2OAc



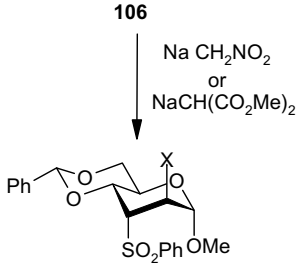
160 R = Me; X = CH_2OH; Y = H
161 R = Me; X = H; Y = CH_2OH
162 R = Ph; X = CH_2OAc; Y = H



163

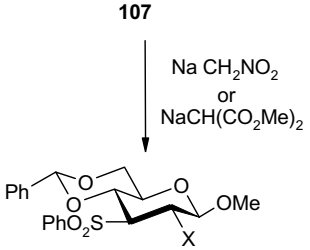
Chart 9.

and NaH exclusively produced **165** in high yield (Scheme 36). On the other hand, $NaCH_2NO_2$ and $NaCH(CO_2Me)_2$ reacted with **107** to produce single isomers **166** and **167**, respectively (Scheme 37).[27]



164 X = CH_2NO_2 (60%)
165 X = $CH(CO_2Me)_2$ (82%)

Scheme 36.



166 X = CH_2NO_2 (56%)
167 X = $CH(CO_2Me)_2$ (98%)

Scheme 37.

5. Vinyl sulfone-modified hex-5-enofuranosides

5.1. Synthesis

Pathak and co-workers also wanted to extend the study on the diastereoselectivity of the addition of amines and carbon nucleophiles to a series of modified hex-5-enofuranoside-6-sulfones. In the absence of any literature data on related vinyl sulfones, it was expected that the functional groups present at C-3 would influence the stereochemical outcome of these reactions (Chart 10) as was reported in the case of the 6-nitro analogues **16** (Chart 3).[7b] The epimeric vinyl sulfonyl hex-5-enofuranosides **168/170** and the analogues **169** and **171** were, therefore, selected for studying the diastereoselectivity of addition of amines and carbon nucleophiles at C-5 (Chart 11). The requirement of relatively large amounts of vinyl sulfone-modified hex-5-enofuranosides again led to the design of a simple and general methodology suitable for the large-scale preparation of **168–171** having various protecting groups at C-3. Thus, easily accessible epoxides **172–174** were treated with sodium tolylthiolate to get **175–177** in high yields. Oxidation to **178–180** followed by mesylation and elimination afforded the desired vinyl sulfones **168–170**. Variation of the group at C-3 affected the *E*:*Z* ratios of the vinyl sulfones (Scheme 38).[35]

5.2. Aminosugars

The 3-*O*-benzylated D-*xylo* derivative **168** was treated separately with neat benzylamine and isopropylamine to produce **181a/182a** (9:1) and **181b/182b** (9:1), respectively.[35] In both cases, the L-*ido* derivatives **181a** and

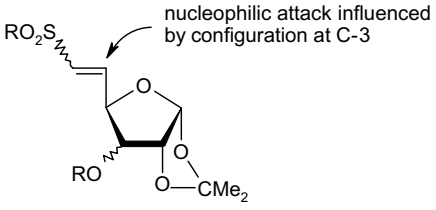
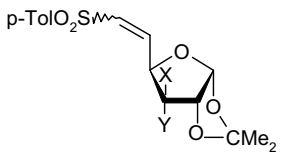
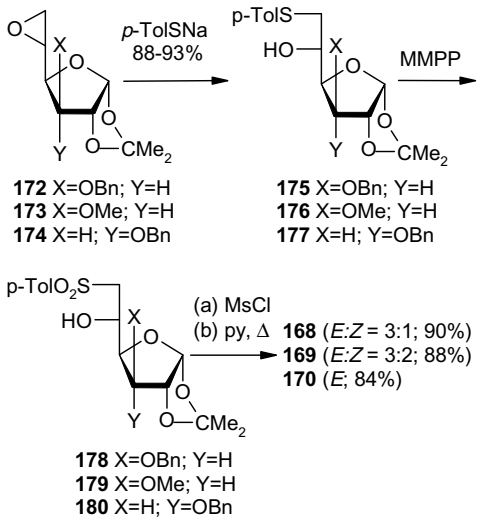


Chart 10.

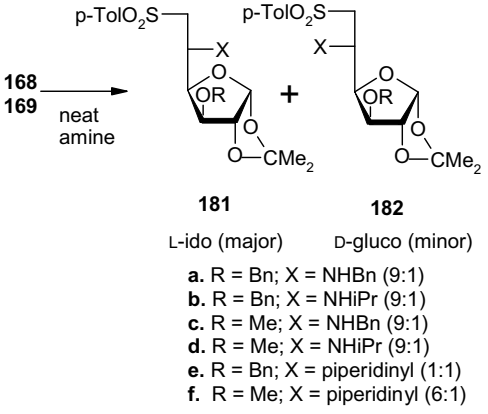


168 X=OBn; Y=H
169 X=OMe; Y=H
170 X=H; Y=OBn
171 X=OAc; Y=H

Chart 11.

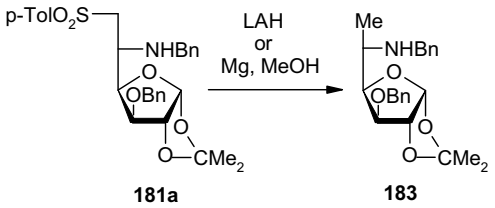


Scheme 38.



Scheme 39.

181b were the major products, which were isolated and identified unambiguously (Scheme 39). The 3-O-methylated D-*xylo* derivative **169** also reacted in a similar fashion with benzylamine and isopropylamine to produce **181c/182c** (9:1) and **181d/182d** (9:1), respectively (Scheme 39). In these cases also, the L-*ido* isomers were again the major products. It is noteworthy that the effect of the OBn and OMe groups at C-3 of compounds **168** and **169** is sufficient to impose diastereoselectivity in favor of the L-*ido* derivative. The influence of C-3 substitution on the diastereoselectivity of addition was established further when the D-*ribo* derivative **170** showed a significant or a complete lack of the diastereoselectivity of addition when treated with benzylamine and isopropylamine. The secondary amine piperidine reacted with **168** and **169** to produce **181e/182e** (1:1) and **181f/182f** (6:1), respectively. The D-*ribo* isomer **170**, with significantly reduced steric bulk at C-3 (because of the presence of a hydrogen atom instead of β-OBn/OMe

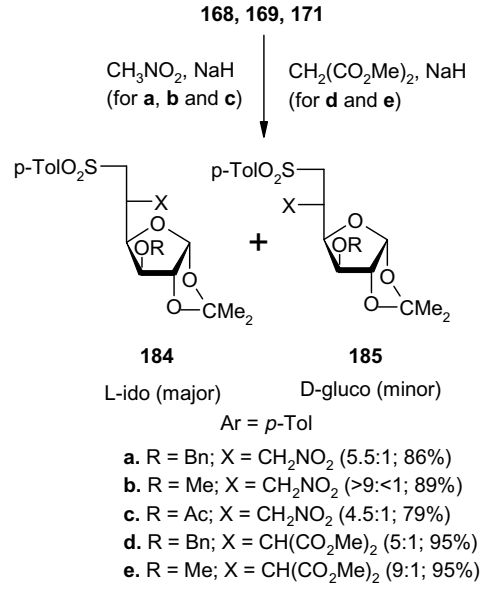


Scheme 40.

groups), produced inseparable mixtures of benzylamino and isopropylamino adducts in the ratios 1:1 and 3:2, respectively; it produced the piperidino adduct in 1:1 ratio. It was possible to desulfonylate **181a** to **183** using either LAH or Mg–MeOH (Scheme 40). The 5-amino-5,6-dideoxy-L-*ido* sugar **183** has the potential to generate nojirimycin analogue.[35]

5.3. Branched-chain sugars

The nucleophilic addition strategy was exploited further for the diastereoselective C–C bond formation at C-5 of hexofuranosyl carbohydrates using carbon nucleophiles.[36] Thus, vinyl sulfones **168** and **169** were treated with $NaCH_2NO_2$ to generate addition products **184a/185a** (5.5:1) and **184b/185b** (>9:<1), respectively, in very good yields. Interestingly, the diastereoselectivity dropped when the acetyl-protected vinyl sulfone **171** was treated with $NaCH_2NO_2$, and **184c/185c** were formed in the ratio 4.5:1 (Scheme 41). The other nucleophile $NaCH(CO_2Me)_2$ reacted at a much faster rate with **168** and **169** to generate mixtures of addition products **184d/185d** (5:1) and **184e/185e** (9:1), respectively, in very good yields (Scheme 41).[36]



Scheme 41.

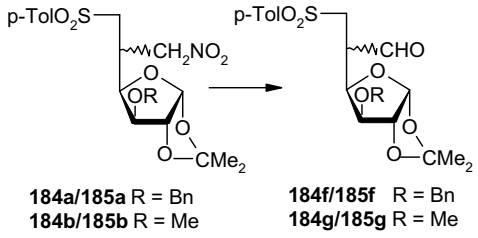
To highlight the usefulness of the branched-chain sugars **184** and **185**, these chirons were converted into important intermediates for further applications in organic synthesis.[36] Thus, the mixtures of **184a/185a** and **184b/185b** were subjected separately to a modified Nef carbonyl synthesis to generate **184f/185f** and **184g/185g**, respectively (Scheme 42). The dimethylmalonate adducts **184d/185d** and **184e/185e**, on the other hand, were treated separately with NaCl in Me_2SO–water at 130 °C to obtain the corresponding monoesters **184h** and **184i**. In this case, minor isomers could not be isolated (Scheme 43).

Interestingly, **184c/185c** on treatment with NaOMe/MeOH followed by Ag_2O/MeI yielded a non-methylated compound **186**. Treatment of **184c/185c** with NaOMe/MeOH followed by Ag_2O/I_2 in THF also afforded the same compound. It may be argued that the 'aci-nitro' group formed in the presence of Ag_2O was iodinated at the α-position. The iodo intermediate underwent cyclization to produce **186** (Chart 12).[36] Since one of the most important applications of branched-chain sugars as chirons is in the synthesis of carbocycles, Pathak and co-workers subjected mixtures of **184d/185d** and **184e/185e** separately to de-isopropylidenation followed by concomitant cyclization under acidic conditions. The major products thus obtained were acetylated to furnish bicyclic lactones **187** and **188** (Chart 12).[36]

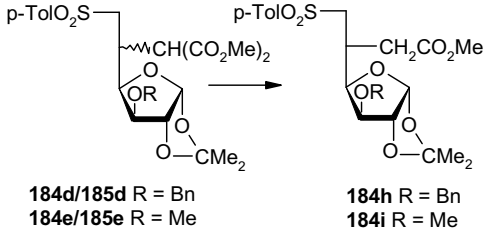
The crude aldehydes **184f/185f** (Scheme 42) were reduced to the corresponding alcohols and the latter compounds were protected with the *tert*-butyldimethylsilyl group; the protected compounds were desulfonylated with Mg in MeOH to generate branched-chain sugars **189** and **190** (Chart 13). The debenzylated product obtained from **189** was used earlier as an intermediate for the synthesis of 1,3,9-trideoxy-3,5-di-*C*-methyl-L-talitol which was a potential chiron for the C33–C37 segment of amphotericin B.[36] Alternatively, the sulfonyl groups of aldehydes **184f/185f** and **184g/185g** (Scheme 42) were eliminated under basic conditions to yield single vinyl aldehydes **191** and **192**, respectively (Chart 13).

Compounds **184h** and **184i** (Scheme 43), after desulfonylation and debenzylation, afforded new deoxyheptose sugars; these sugars were isolated, respectively, as diacetate **193** or monoacetate **194** (Chart 14). Similarly, **184h** was easily converted to a bicyclic lactone **195** in two steps. Compound **195** was shown to be an important intermediate used earlier for the synthesis of (4*R*)-4-[(*E*)-2-butenyl]-4, *N*-dimethyl-L-threonine (MeBmt), a β-hydroxy-α-amino acid. The deoxyheptose sugar obtained from **184f** was converted to a structurally related bicyclic derivative **196** (Chart 14).[36]

As discussed in the case of amino compounds above (Scheme 39), the diastereoselectivity of addition of carbon nucleophiles to **168** and **169** was controlled to a great extent by the configuration and substituents pre-



Scheme 42.



Scheme 43.

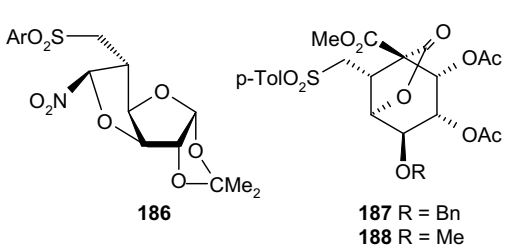


Chart 12.

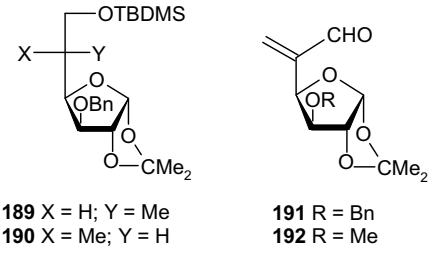


Chart 13.

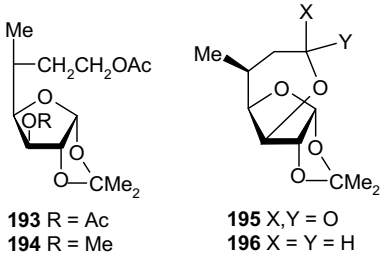
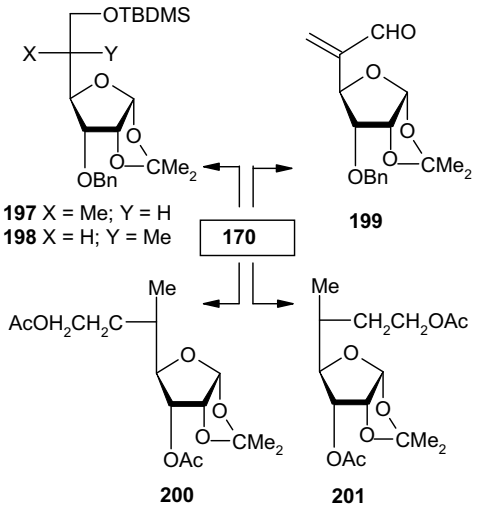


Chart 14.

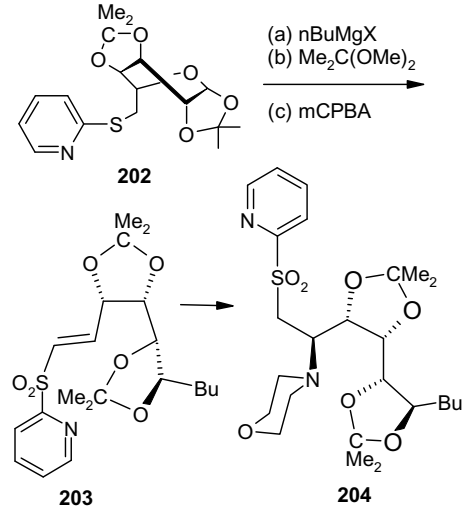


Scheme 44.

sent at C-3. Interestingly, the D-*ribo* derivative **170** showed a complete or significant lack of the diastereoselectivity of addition when treated with carbon nucleophiles. However, diastereomers were separated at various stages. Reaction sequences described above generated various chirally pure products **197**–**201** from **170** (Scheme 44).[36]

6. Miscellaneous examples

Sugar-derived vinyl sulfone **203** has been synthesized from aza-heterocycle/thiosugar hybrid **202** using a Grob-type heterocyclic process followed by the oxidation of the product. Compound **203** was treated with morpholine to obtain an acyclo aminosugar **204** in 80% yield with *de* exceeding 94% (Scheme 45).[18a,37]



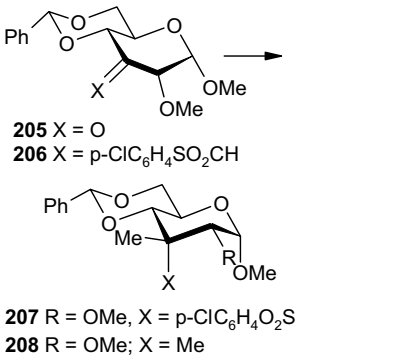
Scheme 45.

To synthesize C-3 geminal di-*C*-methyl pyranoside, ulose **205** was converted to sulfonyl olefin **206** by Horner–Wittig reaction. Michael addition of dimethyl cuprouslithium to **206** produced **207**, which was desulfonylated by Ra–Ni in refluxing ethanol to produce **208** (Scheme 46).[38]

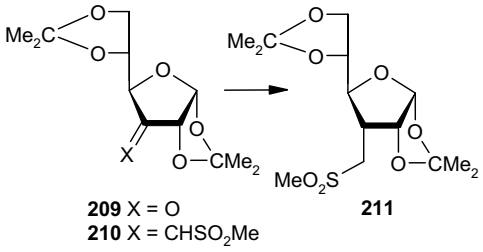
1,2:5,6-Diacetone ulose **209** on reaction with $[(MeO)_2P(O)CH(Li)SO_2Me]$ generated an exocyclic α,β-unsaturated sulfone **210**, which was reduced to **211** with $[(Ph_3P)CuH]_6$ (Scheme 47).[39]

Trost and co-workers introduced γ-alkoxy-α,β-unsaturated sulfones as partners in (3+2) cycloadditions involving the intermediacy of trimethylenemethane–palladium complexes. Thus, the *E*-isomer **212** on treatment with **213** in the presence of Pd(0) afforded a 7.5:1 ratio of two cycloadducts **214** (Scheme 48).[15b]

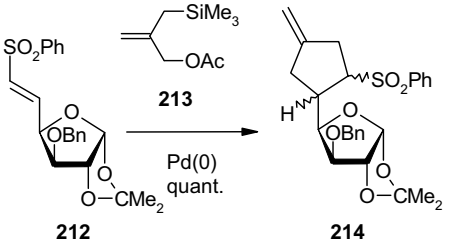
The strategy was extended using a different substrate **215**, which underwent (3+2) cycloaddition to afford an inseparable mixture of two isomers **217** and **218** (Scheme



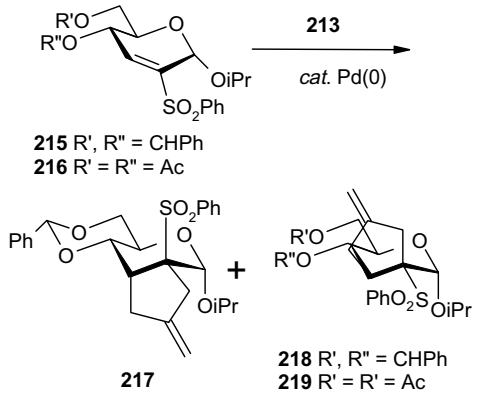
Scheme 46.



Scheme 47.



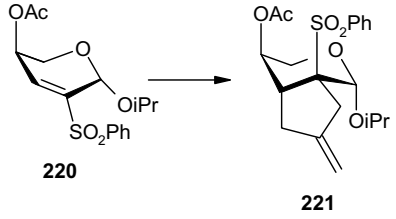
Scheme 48.



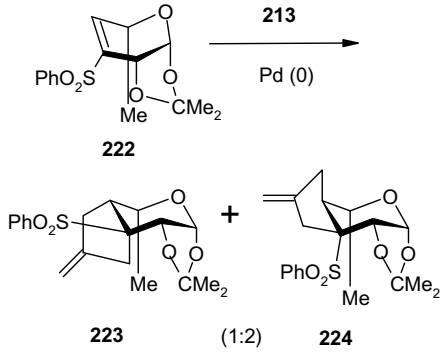
Scheme 49.

49).[40] Interestingly a related vinyl sulfone **216** with non-rigid protecting groups like acetyl produced a single isomer **219** (Scheme 49).[40] Another vinyl sulfone-modified carbohydrate **220** also produced the corresponding 5,6-bicycle **221** possessing exocyclic unsaturation (Scheme 50).

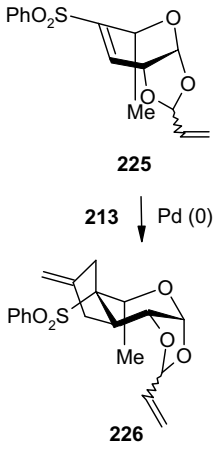
In this connection the 3,4-unsaturated sulfonyl derivative **222** was prepared from L-rhamnose and was treated with acetate **213**. The minor product **223** was obtained due to the β-attack on the more hindered face of the sulfone and the major product **224** was a result of the α-attack on the less hindered face (Scheme 51).[40] To obtain a single product instead of a mixture, the preferential α-attack was obtained by treating compound **225** under similar reaction conditions; compound **225** possessing a phenylsufonyl group at C-4 instead of C-3 underwent an α-attack via a chair-like transition state



Scheme 50.



Scheme 51.



Scheme 52.

to afford only one product **226** (Scheme 52).[40] These reactions are thought to follow a two-step sequence involving an initial Michael-type addition to the electron-deficient double bond followed by an attack of the resultant stabilized anion on the palladium complex.[40]

7. Concluding remarks

Although the functionalization of vinyl sulfone-modified carbohydrates has the potential to be useful as a powerful methodology for accessing interesting modified monosaccharides, the area has remained under-explored and under-utilized. Pathak and co-workers initiated a systematic study on the synthesis and reactions of vinyl sulfone-modified pent-2-enofuranosides, hex-2- enopyranosides, and hex-5-enofuranosides. Results compiled in this report establish the fact that vinyl sulfone-modified carbohydrates are indeed useful intermediates for the synthesis of several new deoxyaminosugars and branched-chain sugars. The present study acquires greater importance in view of the significant role of C–N equatorial bonds at the C-2 positions of naturally occurring aminosugars and the easy construction of C–N bond at the C-2 position. The same set of vinyl sulfone-modified carbohydrates are also equally important for accessing a wide range of molecules starting from branched-chain sugars to carbocycles. It has also been established that the in-built chiralities of carbohydrates play a significant role in deciding the diastereoselectivity of the addition reaction although the exact cause of this effect is yet to be established. It is evident from discussions in the preceding sections that mainly Michael addition reaction has been utilized effectively so far for the synthesis of aminosugars and branched-chain sugars. An in depth study on the scope and limitation of vinyl sulfone-modified carbohydrates will unearth the vast potential of this special class of compounds and their down-stream products.

Acknowledgments

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