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An insight into our research on vinyl sulfone-modified pyranosides and furanosides

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ABSTRACT

This review describes the research by the authors on the synthesis of vinyl sulfone-modified carbohydrates and the application of this new class of Michael acceptors in the generation of a wide range of aminosugars, branched-chain sugars, cyclopropanted carbohydrates, densely functionalized cyclopropanes, isonucleosides and pyrroles.

1. Introduction

Application of vinyl sulfones or α,β-unsaturated sulfones in organic synthesis has increased dramatically, and to a limited extent, in biology. Vinyl sulfones are now widely used as useful intermediates in organic synthesis because vinyl sulfones serve efficiently as Michael acceptors as well as 2π-partners in cycloaddition reactions [1–16]. Carbohydrates, on the other hand, are used extensively as chiral building blocks for the synthesis of various complex molecules [17–24]. The preliminary requirement of such a synthesis is the functionalization of the sugar molecules at the monosaccharide level. It is therefore logical to argue that vinyl sulfone-modified (VSM) carbohydrates have the potential for utilization in organic synthesis because after using the vinyl sulfone moiety as a tool for functionalization, desulfonylation under strategically selected conditions [25] would easily generate an array of modified carbohydrates. It is expected that the "in-built" chiralities in sugar molecules would contribute significantly in determining the stereochemical outcome of reactions of VSM carbohydrates.

As part of a research program dealing with the modification of carbohydrates, we intended to investigate a vinyl sulfone-based strategy for the functionalization of carbohydrates for primarily accessing amino- and branched-chain sugars. Limited contributions of other groups in this area have been discussed in detail elsewhere [26–28]. This review attempts to highlight the strategies used by us in combining the vinyl sulfone functional group and carbohydrates as extensively as possible and studying their properties as reactive intermediates.

2. Background

To develop methodologies for the synthesis of new aminosugars, a VSM hex-2-enopyranoside **1**α was treated with various primary and secondary amines [29]. Primary amines, such as isobutylamine, benzylamine and cyclohexylamine were found to add diastereoselectively to produce single isomers **2a–c** with the D-*gluco*- configuration (Scheme 1). 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*- **2d–g** as the major isomers, respectively. The major isomers **2d–g** were separated by crystallization. One of the minor

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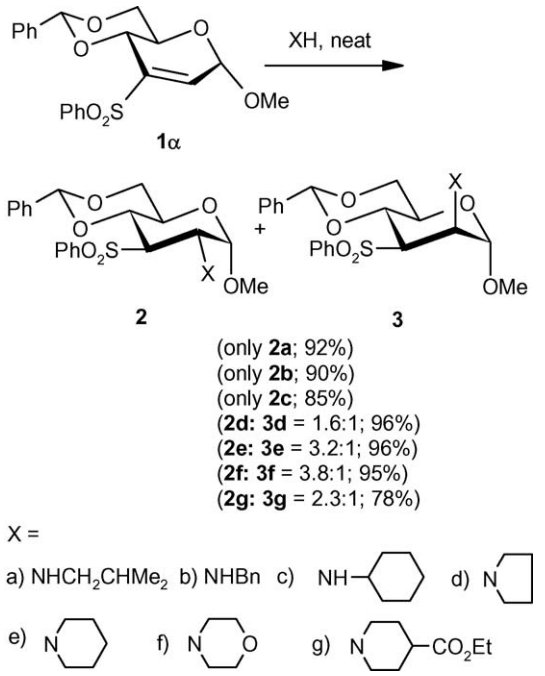
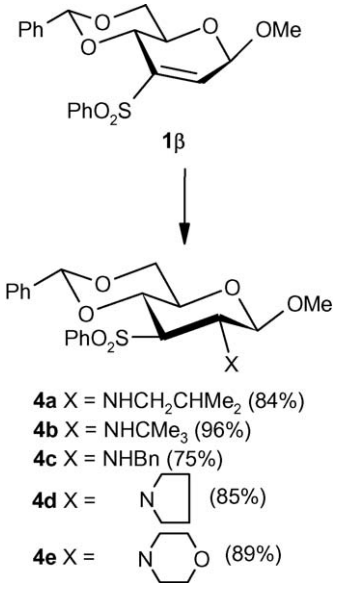


Scheme 1.

manno-isomers **3d** was isolated and unambiguously characterized (Scheme 1) [29].

To examine whether the anomeric configuration influenced the diastereoselectivity of the addition of various nucleophiles to 3- sulfonyl-2-enopyranoside systems, the β-anomeric vinyl sulfone **1**β 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 **4a–e**, respectively (Scheme 2) [29]. It should be noted that **1**α did not react with sterically



Scheme 2.

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 **1**β, on the other hand, reacted smoothly with the same amine at elevated temperature to produce a single isomer **4b** in excellent yield (Scheme 2) [30].

From the above observations, we concluded that the anomeric configuration was playing a crucial role in determining the stereochemical outcome of this type of addition reaction. We therefore decided to expand the scope of this study to other pyranosides as well as furanosides. However, a thorough study on the diastereoselectivity of the addition of a range of nucleophiles to vinyl-sulfone modified carbohydrates required an easy access to a relatively large amount of a wide variety of VSM carbohydrates including anomerically pure analogues **1**α/**1**β, **5**α/**5**β, **6**α/ **6**β, **7**α/**7**β, and **8–13** (Fig. 1).

3. Vinyl sulfone-modified pyranosides and furanosides

3.1. Synthesis

The requirement of anomeric purity of compounds 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 **1**α/**1**β, **5**α/**5**β, **6**α/ **6**β and **7**α/**7**β necessitated the introduction of an arylthio group at the C-3 position of pentose or hexose sugars. One of the easiest ways of forming a C–S bond is 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 [31,32]. Similar strategies would also lead to C–S bond formation at C-4 and C-5 leading to the synthesis of **8** [33], **9** [34] and **10–12** [35] respectively. Vinyl sulfones **13–17** constitute a special class of Michael acceptors used for specific transformations (Sections 3.5–3.7).

VSM pent-2-enofuranosides **5**α and **5**β were first synthesized from easily accessible precursors **18** and **21**. The known lyxo-epoxide **18**, synthesized from D-xylose, was converted to the vinyl sulfone **5**α following thiation (**18** → **19**), oxidation by magnesium monoperoxyphthalate hexahydrate (MMPP) (**19** → **20**), and mesylation followed by elimination (Scheme 3). The known ribo-epoxide **21** was converted into the corresponding vinyl sulfone **5**β following similar sequence of reactions (Scheme 4).

The separate synthetic routes for the starting epoxides **18** and **21**, however, increased the number of steps and reduced the overall yield of the final products. Therefore, it was necessary to devise different approaches towards the synthesis of VSM pent-2-enofuranosides [31,32].

An examination of the percentage 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 α-isomer, respectively [31,32]. Thus, the pattern of glycosylation of various pentose sugars led to the selection of a D-xylo derivative-based strategy for the synthesis of an

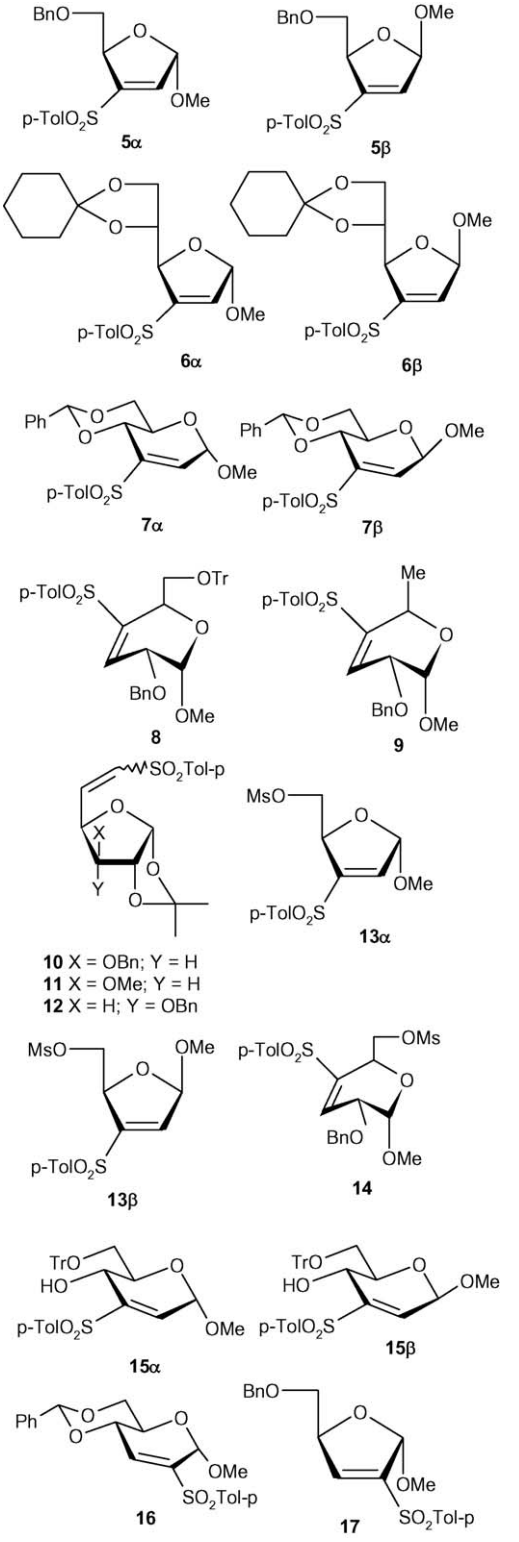
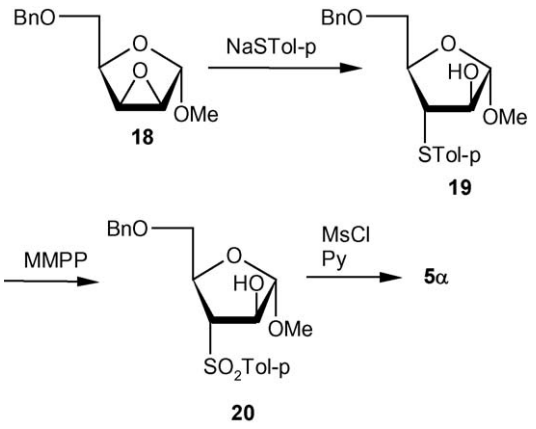
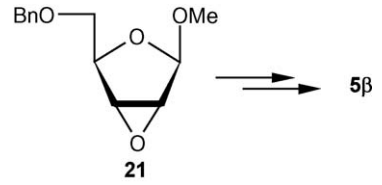


Fig. 1. VSM carbohydrates.

anomeric mixture close to the ideal ratio of 1:1. Therefore, methanolysis of **22** produced an anomeric mixture of **23** and **24** in 1:1.3 (α/β) ratio. Nucleophilic displacement of the tosyl group in the mixture of **23** and **24** by *p*-thiocresolate proceeded smoothly at an elevated temperature to afford a mixture of ribofuranosides **25** and **26**. Compounds **25** and **26** were separated and converted via **27** and **28** into the desired VSM carbohydrates **5**α and **5**β (Scheme 5) [31,32].

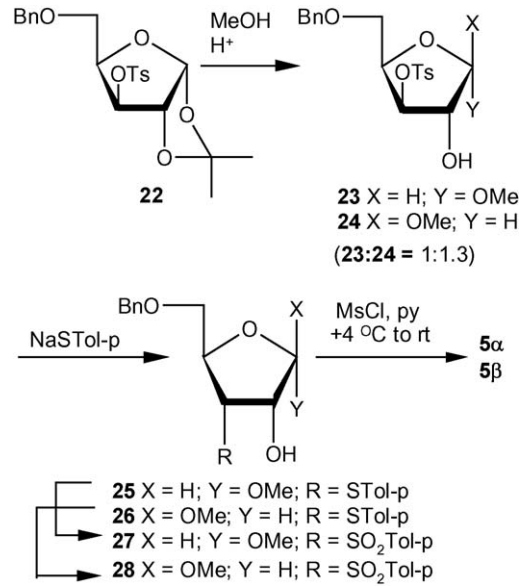


Scheme 3.

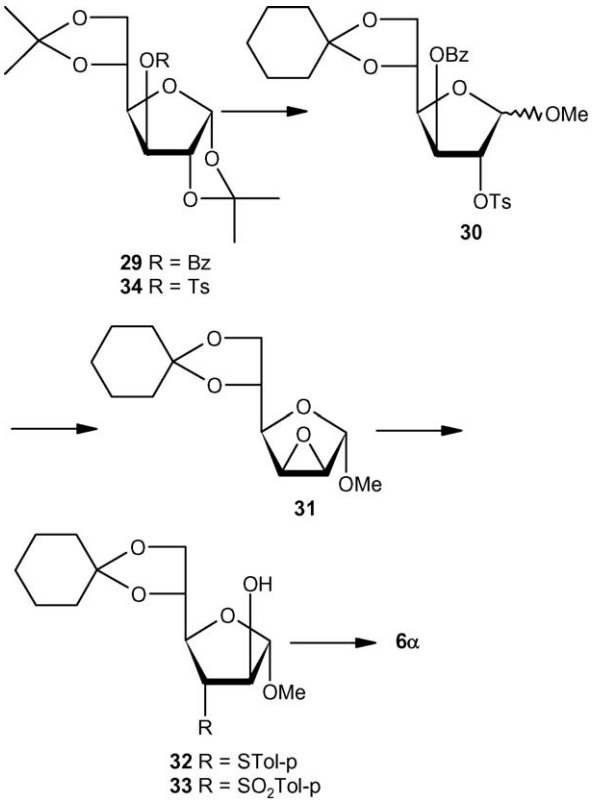


Scheme 4.

Compared to pent-2-enofuranosides **5**α and **5**β, the synthesis of hex-2-enofuranosides **6**α and **6**β was far more complicated because the anomeric ratio of methyl glycosides obtained from **29** (Scheme 6) or **34** (Scheme 7) was



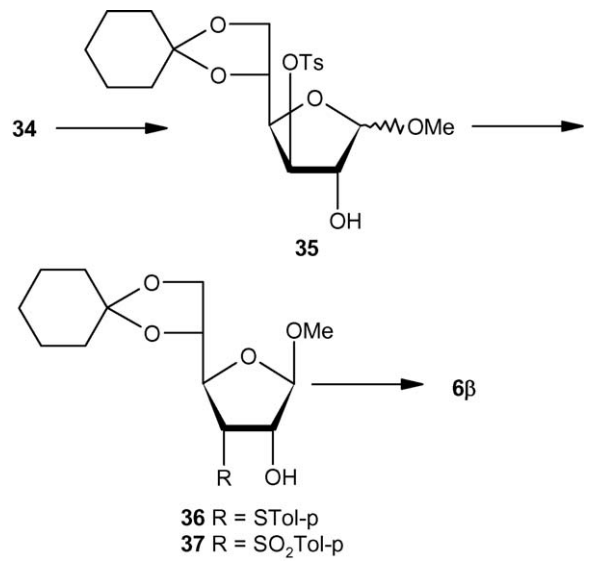
Scheme 5.



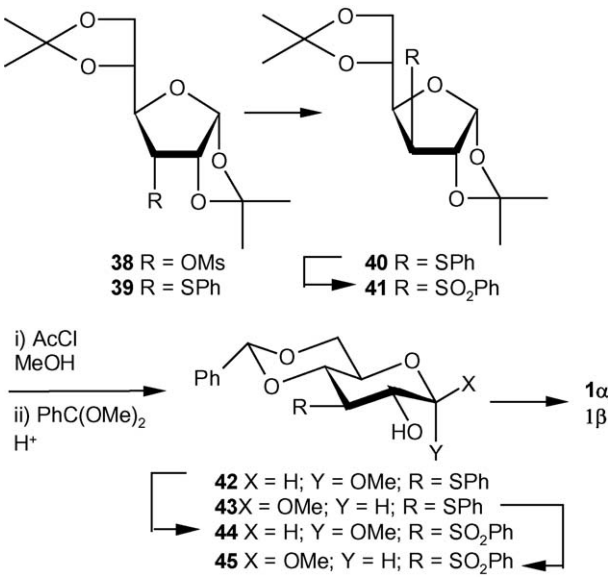
Scheme 6.

far from the ideal value of 1:1 [36]. It was therefore necessary to have two different approaches from the most easily accessible glucofuranose intermediates like **29** or **34**. Thus, benzoate **29** on one-pot methanolysis and cyclohexylidenation produced a mixture, which contained the α-anomer in a major amount. Tosylation of the mixture produced **30**, which on treatment with base produced an anomeric mixture of epoxides. The α-anomeric epoxide **31** was separated from the anomeric mixture and converted into the desired α-anomeric vinyl sulfone **6**α via sulfide **32** and sulfone **33** in the usual way (Scheme 6) [36]. For accessing the β-anomer **6**β, the tosylate **34** was converted into a mixture of methyl glycosides **35** in which the β-anomer was predominant. Displacement of the tosyl group by thiolate produced **36**, which on oxidation produced **37**. Mesylation of **37** led to the formation of β-anomeric vinyl sulfone **6**β (Scheme 7) [36].

VSM hex-2-enopyranoside, **1**α/**1**β and **7**α/**7**β were initially synthesized from sugar epoxides by modifying the method reported by Sakakibara and coworkers [26–28]. However, this strategy turned out to be too long to be useful for accessing relatively large amounts of the anomerically pure compounds. Because of the fact that the arylthio group at the C-3 position of a hexose sugar could be introduced by displacing the leaving groups at the C-3 position as well, materials like **39** and **40** (Scheme 8) [32] were considered as starting sulfide derivatives for providing an easy access to both **1**α and **1**β from a single synthetic intermediate. It was known that the equilibrium mixture of methyl D-allosides in MeOH contained > 30% of furanosides, whereas D-glucose produced methyl D-pyranosides almost exclusively. Although the reported ratio of α- and β-anomers was not close to the ideal value of 1:1 needed for the synthetic strategy, in this case it was more important to obtain the methyl pyranosides without any contamination of the corresponding furanosides. In fact, methanolysis of the allo derivative **39** generated more than six products. Therefore, the gluco derivative **40**, obtained from the mesylated allo derivative **38**, was deprotected and glycosylated in a single operation by using acetyl chloride and MeOH to afford a mixture of 3-deoxy-3-phenylsulfide hexopyranosides; the diols, thus formed were collected as the benzylidene derivatives **42** and **43** in



Scheme 7.

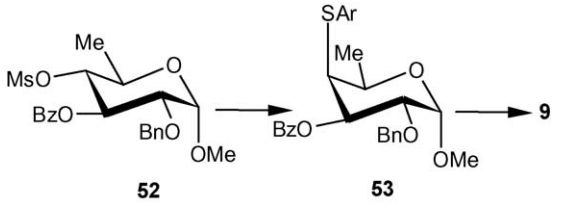


Scheme 8.

2.2:1 ratio and in good yields [31,32]. The anomers were separated by chromatography and were converted separately into the corresponding sulfones **44** and **45** in excellent yields using MMPP in MeOH. In an alternative approach, compound **40** was oxidized to the corresponding sulfone **41**. Compound **41** was deprotected and glycosylated to generate a mixture of anomeric sulfones, which were collected as the benzylidene gluco derivatives **44** and **45**, respectively, in good yields in 1:1.8 ratio. After separation, the sulfones were converted into the desired VSM hex-2-enopyranosides **1**α and **1**β in the usual way (Scheme 8) [31,32].

In line with the synthetic routes discussed above, one of the easiest ways of forming a C–S bond at C-4 is the regioselective displacement of suitably oriented and protected sulfonates or regioselective ring opening of epoxides derived from the corresponding pyranosides. However, it is reported that ring-opening reactions at C3–C4 of epoxy sugars is not strictly regioselective. Moreover, the retrosynthetic analysis revealed that 4-thiopyranosides would be more easily accessible from 4-*O*-mesylates. Therefore, 4-*O*-mesylate **48** (Scheme 9) [33] was used as a common starting material for the synthesis of both **8** and **9**. Thus, the known diol **46** was tritylated at room temperature by using trityl chloride and pyridine to afford **47** within 48 h. Mesylation of **47** afforded the required mesylate derivative **48** in 81% overall yield. Fully protected α-glucomesylate **48** was treated with *p*-thiocresol in DMF in the presence of 1,1,3,3-tetramethylguanidine (TMG) at 150–160 °C to afford galacto-derivative **49**, as expected in good yield within 5 h. Treatment of compound **49** with methanolic NaOMe at reflux temperature for 7 h afforded compound **50** in 97% yield. The corresponding sulfone derivative **51** was generated in quantitative yield within 6 h at room temperature by oxidizing **50** with (MMPP) in MeOH. Compound **51** was subjected to an elimination reaction by using MsCl in pyridine at 0 to +4 °C to afford **8** in 88% yield (Scheme 9) [33].

For the synthesis of 6-deoxy analogue of **8**, the sugar derived mesylate **52** was reacted with *p*-tolylthiol in *N,N*-dimethyl formamide (DMF) in the presence of TMG at about 150–160 °C to afford **53** in 89% yield within 5 h. Compound **53** was finally converted to the required vinyl sulfone **9** (Scheme 10) [34].

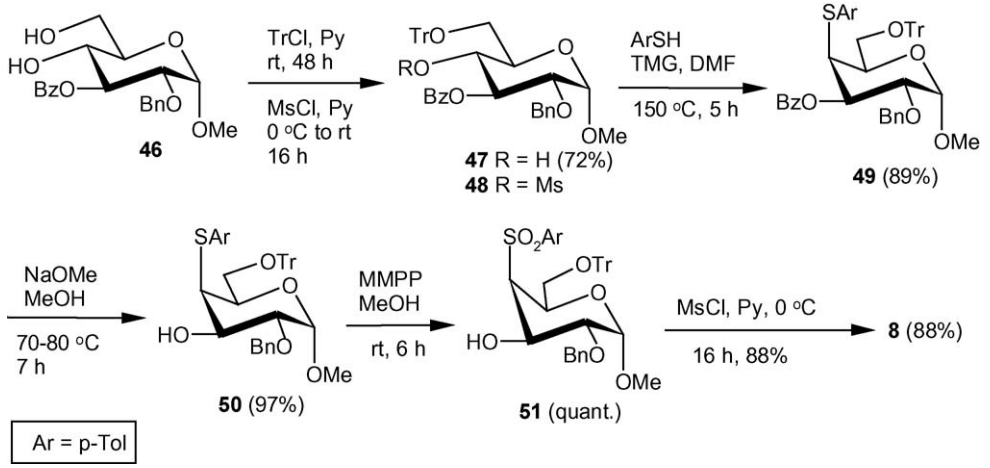


Scheme 10.

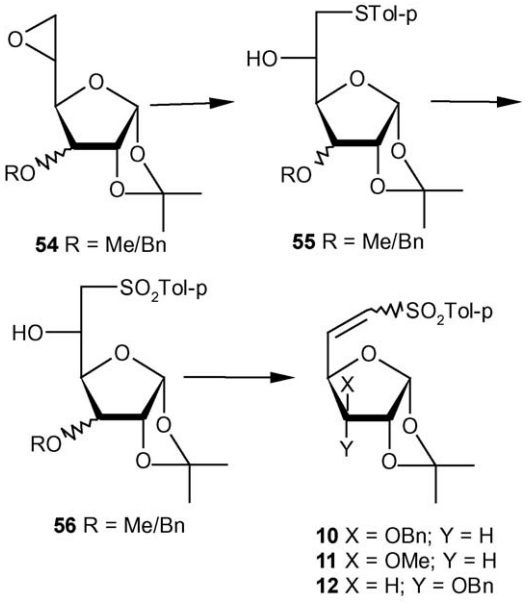
VSM hex-5-enofuranoside **10** and its analogues **11–12** were prepared from the easily accessible epoxides, represented by the general structure **54.** Thus, epoxides **54** were reacted with sodium tolylthiolate to obtain **55** in high yields. Oxidation to **56** followed by mesylation and elimination afforded the desired vinyl sulfones **10–12** (Scheme 11) [35]. Vinyl sulfone **10** was obtained as a mixture of *E* and *Z* isomers in 3:1. Interestingly, the variation of the group at C-3 affected the E/Z ratios to some extent. Thus, by changing from OBn in **10** to OMe in **11**, the E/Z ratio changed from 3:1 to 3:2; in the case of **12**, however, only *E* isomer could be detected. Since the presence of OBn in **10** or OMe in **11** at C-3 caused the formation of *Z* isomer (alongside *E* isomer) as opposed to the exclusive formation of *E* isomer in the case of **12**, it may be argued that the stereoselectivity of abstraction of protons from C-6 of **56** during the elimination reactions of the mesylated products was dictated by the stereoelectronic properties of the group present at C-3 on the β-face of furanosides [35].

3.2. Functionalization at C-2

As mentioned earlier, the addition of primary amines to C-2 of both **1**α and **1**β exclusively produced C-2 equatorial (gluco) products. Secondary amines on reactions with **1**β produced only gluco derivatives but with **1**α produced mixtures containing the gluco derivative as the major



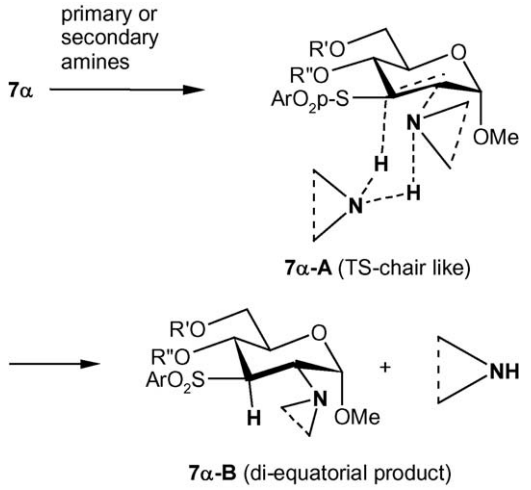
Scheme 9.



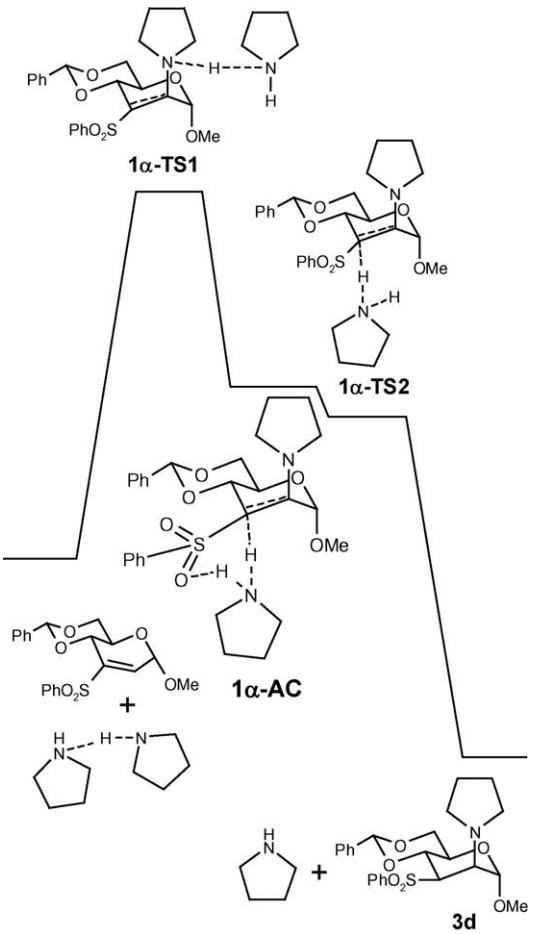
Scheme 11.

component [29]. Reactions of tert-butylamine with **1**α and **1**β indeed exemplified an extreme case of anomeric configuration influencing the addition of nucleophiles to enopyranoside systems **1**α/**1**β. The X-ray analysis of the single crystal of **4b** 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 **4a**, **4b** and **4c** (Scheme 2) that the magnitude of the conformational angles O1-C1-C2-N1 increased in the order **4a** → **4c** → **4b** confirming this argument [30,37]. However, in the case of α-methoxy series (compounds **2;** Scheme 1), 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]. However, all our efforts to deliver primary amines effectively and exclusively from the β-face of the pyranose ring failed.

Although the diastereoselectivity of formation of products **3d–g** may be explained to some extent on the basis of the stereoelectronic repulsion of amines by the anomeric configuration of **1**α, an in-depth analysis was necessary to explain the pattern of addition of amines. Quantum chemical ab initio and DFT calculations performed on these systems established that neutral nucleophiles like amines add onto the Michael acceptors via a concerted mechanism; the transfer of proton to the α-position of the sulfonyl group involves a proton relay process thereby lowering the activation energy for this type of reactions to produce diequatorial compound like **7**α**-B** (**7**α → **7**α**-A** → **7**α**-B**; Scheme 12) [38]. The explanation is applicable to the reaction patterns of both **1**α/**1**β and **7**α/**7**β. The formation of minor product **3d** from **1**α, however, seems to be a stepwise process (Scheme 13) [38]. The transition state **1**α**-Ts1**, formed via the abstraction of pyrrolidine proton by the second pyrrolidine ring transforms into an activated

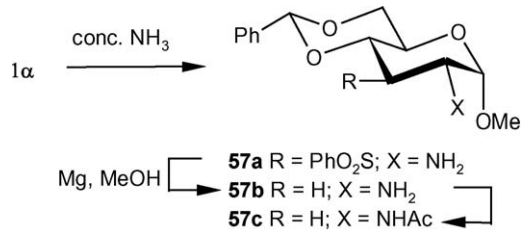


Scheme 12.

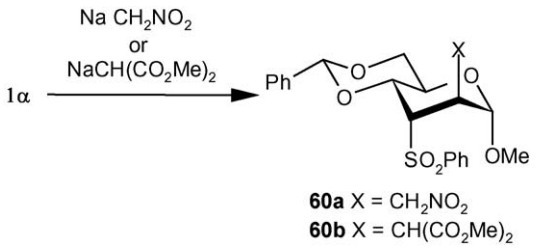


Scheme 13.

complex **1**α**-AC** for the anti-face proton transfer to the olefinic double bond. The protonated pyrrolidine in **1**α**-AC** interacts with sulfone oxygen near the newly formed carbanion, which eventually leads to the formation of the second transition state **1**α**-TS2** with the final transfer of



Scheme 14.



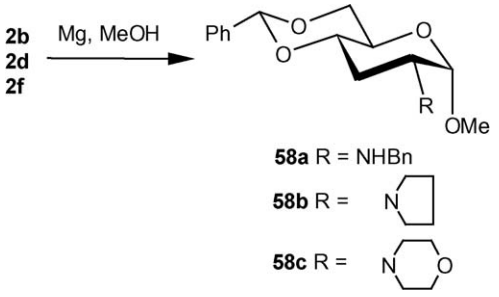
Scheme 17.

proton from the amine to generate the **3d** (Scheme 13). **1α-TS2** is slightly lower in energy compared to the complex, which suggests that the proton transfer process from the protonated pyrrolidine could take place instantaneously without involving these steps [38].

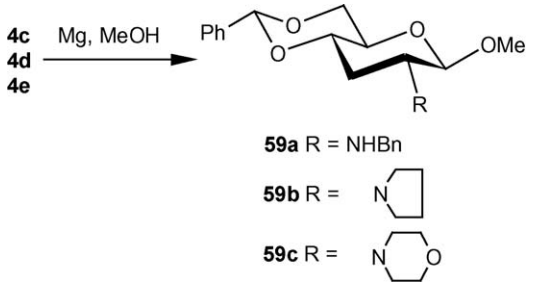
The diastereoselective addition of primary amines to **1α/1β** has been applied to the synthesis of a naturally occurring aminosugar D-lividosamine and its analogues [39]. D-lividosamine (2-amino-2,3-dideoxy-D-glucose) was isolated from *Streptomyces lividus*, and it is present in aminoglycoside antibiotics such as lividomycin-A/lividomycin-B. Thus, compound **1α** was treated directly with conc. aq. ammonia in dioxane to produce a mixture containing mainly compound **57a**. The mixture was desulfonylated and the free amino product **57b** was acylated. Pure aminodeoxysugar **57c,** a known intermediate for the synthesis of D-livodosamine, was crystallized from benzene-pet. ether mixture in 65% overall yield (Scheme 14) [39]. Analogues of **57b** were easily obtained by desulfonylating **2b, 2d** and **2f** to **58a–c** in high yields, respectively (Scheme 15) [39]. In the β-series, **4c–e** were also desulfonylated to **59a–c**, respectively (Scheme 16) [39]. 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 [39,40].

The importance of branched chain sugars led us to study independently the reaction pattern of carbon nucleophiles to **1α/1β**. Thus, the nucleophiles generated from nitromethane and dimethylmalonate, reacted with **1α** to produce single isomers **60a** and **60b** respectively (Scheme 17) [41]. On the other hand, $NaCH_2NO_2$ and $NaCH(CO_2Me)_2$ reacted with **1β** to produce the single isomers **61a** (56%) and **61b** (98%), respectively (Scheme 18) [41]. It should be noted that, in contrast to the addition pattern of amines to **1α**, carbon nucleophiles exclusively added to C-2 from a direction opposite to that of the disposition of the anomeric methoxy group [41].

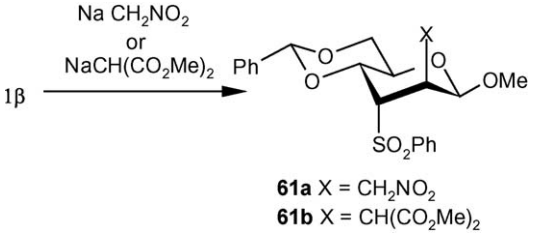
VSM pent-2-enofuranosides **5α/5β** also reacted with a wide range of nitrogen [36,42] and carbon nucleophiles [41]. Thus, the reaction of **5α** with 30% aqueous ammonia and a series of neat amines produced exclusively compounds **62a–e** in high yields (Scheme 19) [42]. The



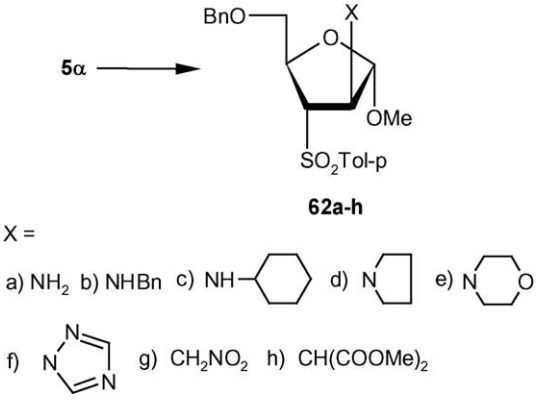
Scheme 15.



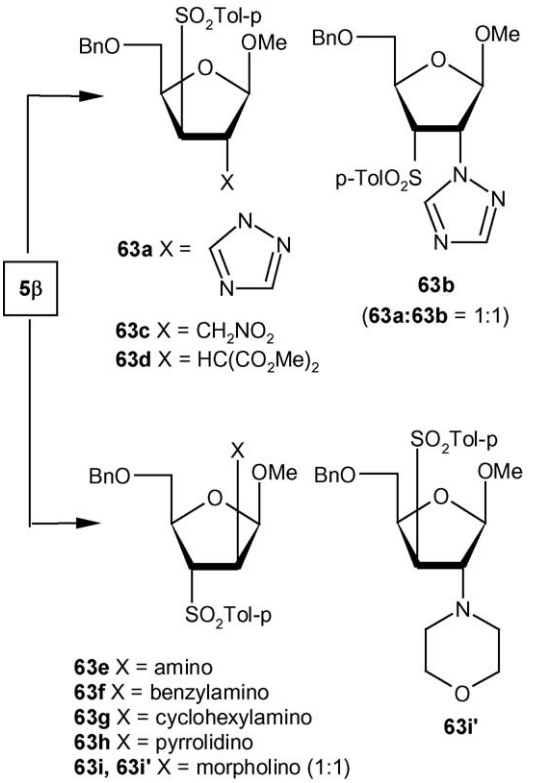
Scheme 16.



Scheme 18.

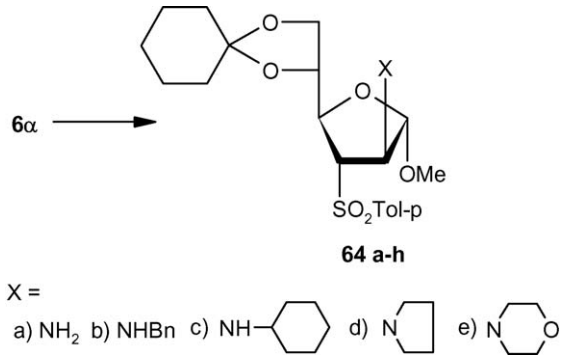


Scheme 19.



Scheme 20.

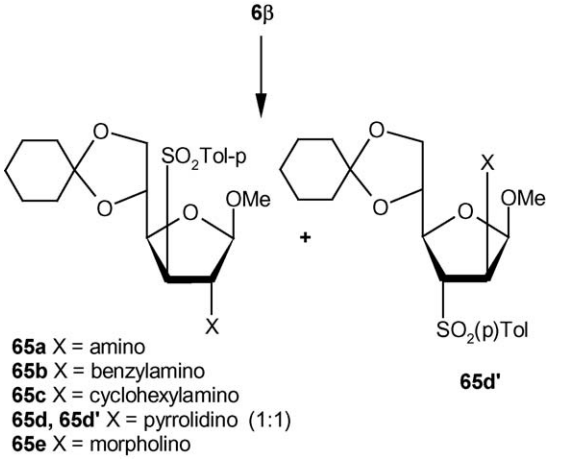
reaction of 1,2,4-triazole with **5**α in the presence of TMG in DMF at ambient temperature produced a single isomer **62f** in high yield [31]. Compound **5**α on reactions with carbanions generated from $NaCH_2NO_2$ and $NaCH(CO_2Me)_2$ produced branched-chain sugars **62 g** and **62 h**, respectively [41]. The β-anomer **5**β, on the other hand reacted with imidazolyl ion to produce a separable mixture of a xylo- and a ribo- analogue **63a** and **63b** respectively in 1:1 ratio (Scheme 20) [31]. Although in this case a mixture was generated, both **63a** and **63b** resulted from the attack of the imidazolyl ion from a direction opposite to the disposition of the anomeric methoxy group. However, **5**β on reactions with $NaCH_2NO_2$ and $NaCH(CO_2Me)_2$ produced branched-chain sugars **63c** and **63d** respectively [41]. Interestingly, vinyl sulfone **5**β on reactions with 30% aqueous ammonia, neat benzylamine, cyclohexylamine, and pyrrolidine at ambient temperature, produced single isomers **63e–i** in high yields (Scheme 20) [36]. In all these cases, the arabino derivatives were the sole products. Only morpholine produced an inseparable mixture of **63i/63i'** in 1:1 ratio (Scheme 20) [36]. It should be noted that **5**α produced the expected D-arabino derivatives **62a–h** (Scheme 19) where the nucleophiles were delivered from a direction opposite to the disposition of the anomeric configuration; [42] **5**β with three nucleophiles also produced the expected D-xylo- and D-ribo-products **63a–d** (Scheme 20) [31,41]. However, in contrary to our expectations, **5**β on reactions with another set of nucleophiles (amines) produced aminosugars **63e–i** with the D-arabino configuration [36].



Scheme 21.

To establish the fact that the formation of **63e–i** was indeed the result of an "unusual" addition reaction, we intended to examine the similar addition reaction patterns of related VSM hex-2-enofuranosides **6**α and **6**β. Hexofuranoside **6**α on reactions with 30% aqueous ammonia, neat benzylamine, cyclohexylamine, pyrrolidine, and morpholine at ambient temperature, generated single isomers **64a–e** in high yields (Scheme 21) [36]. Similarly, vinyl sulfone **6**β on reaction with the same group of amines generated single isomers **65a–c** and **65e** in high yields. Only pyrrolidine afforded an inseparable mixture of compounds **65d/65d′** in a ratio 1:1 (Scheme 22) [36]. It was therefore clear from these experiments that, except for the formation of **65d′**, amino nucleophiles were always delivered to C2 of **5**α, **6**α, and **6**β from a direction opposite to that of the disposition of the anomeric methoxy group. It may therefore be emphasized that the addition pattern of amines to **5**β was unusual in nature (Scheme 20) [36]. Interestingly, in the case of another β-anomeric VSM carbohydrate **5**β, at least one nucleophile (pyrrolidine) showed the tendency of attacking C2 in the unusual way [36].

Successful synthesis of deoxyaminosugars using carbohydrate vinyl-sulfones would depend on the critical desulfonylation step. Although sulfonyl groups were successfully removed from pyranosyl derivatives (Schemes 15 and 16), all attempts to desulfonylate



Scheme 22.

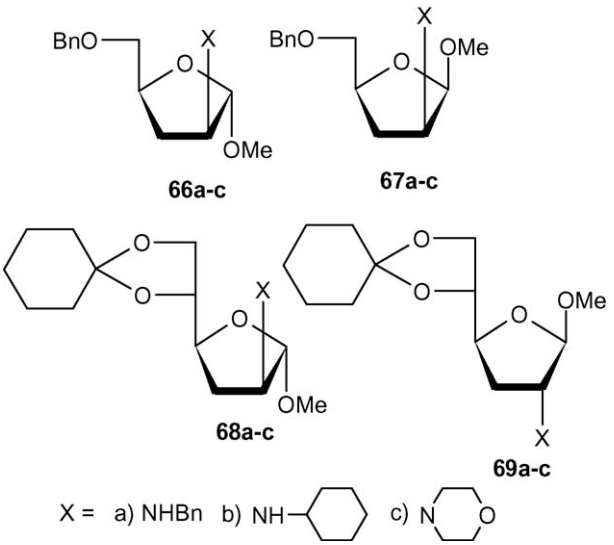
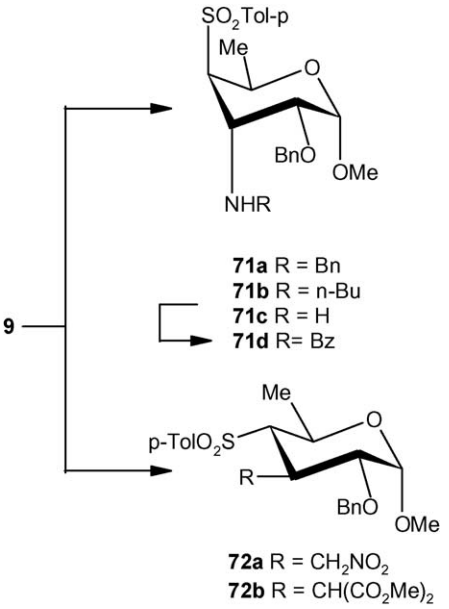


Fig. 2. The desulfonylation of a wide range of furanosides with the Mg-MeOH-$NiBr_2$ system.



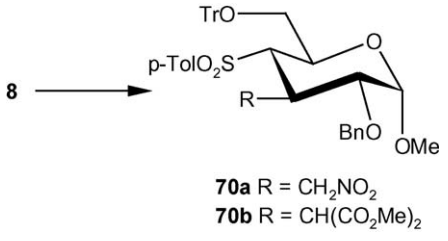
Scheme 24.

furanosyl derivatives with conventional reagents failed. After several experiments, we could desulfonylate a wide range of furanosides with Mg-MeOH-$NiBr_2$ system to produce dideoxyaminosugars **66a–c**, **67a–c**, **68a–c** and **69a–c** (Fig. 2) [42].

3.3. Functionalization at C-3

Barring only two reports on the use of systems like 2-sulfonyl-hex-2-enopyranoside as a Michael acceptor and 4-sulfonyl-hex-3-enopyranoside as a partner in a cycloaddition reaction [28], the strategy for the functionalization of the C-3 carbon of a VSM carbohydrate largely remains unexplored. We therefore, intended to synthesize and study the reaction patterns of a 4-sulfonyl-hex-3-enopyranoside **8** derived from D-glucose. Although, compound **8** on reactions with primary amines produced inseparable mixture of adducts, carbon nucleophiles generated from nitromethane and dimethylmalonate afforded single D-*gluco* adducts **70a** and **70b**, respectively (Scheme 23) [33].

The 6-deoxy analogue **9** on reactions with neat benzylamine at 80–90 °C generated a mixture from which the major product **71a** was isolated in 79% yield (Scheme 24) [34]. Similarly, reactions of **9** with neat *n*-butylamine at elevated temperature afforded **71b** in 83% yield. Aq. ammonia (30%) at room temperature produced a mixture

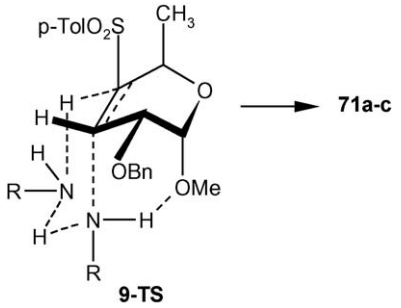


Scheme 23.

from which the major product **71c** was isolated in 81% yield; the product was however characterized as the *N*-benzoyl derivative **71d**. Compound **9** on the other hand, on reactions with carbon nucleophiles generated from nitromethane or dimethylmalonate in the presence of $^{t-}$BuOK in THF at reflux temperature, generated single compounds **72a** and **72b** in 73 and 78% yields respectively (Scheme 24) [34].

Although it is difficult to pinpoint the exact reasons for the diastereoselectivity of addition of nucleophiles to **8–9**, it may be argued that for the formation of branched chain derivatives **70a–b** (Scheme 23) and **72a–b** (Scheme 24), the incoming nucleophile added to C-3 from a direction opposite to the disposition of C-2 OBn group; additionally the bulky substituent at C-3 preferred to orient itself at the equatorial position and thus among all other possibilities, the most stable products were formed. It should be noted that compounds **70a–b** and **72a–b** represent a special class of branched-chain sugars reported for the first time [33,34].

Since amines were expected to add to the C-3 position of **9** from a direction opposite to that of the disposition of the C-2 benzyloxy group to afford a D-*gluco* derivative having four (C2, C3, C4 and C5) equatorial bonds, the formation of products **71a–c** with C–N axial bond at C-3 and C–S axial bond at C-4 was surprising. However, we have mentioned earlier that the addition of neutral species like amines to a Michael acceptor may take place through concerted mechanism involving a proton relay process (Scheme 12) [34]. Considering the same mechanistic pathway, we argued that the *cis*- addition of amines to compound **9** generated the *trans*- product **71a–c**. It is highly probable that the preferential formation of *trans*-diaxial geometry in the transition state over the *trans*-diequatorial geometry resulted from the positioning of amines via six-membered transition states as depicted in Scheme 25. It is also probable that an additional H-bonding such as R–N—H—OMe stabilized the transition state **9-TS** further to such an extent that the formation of tetra-



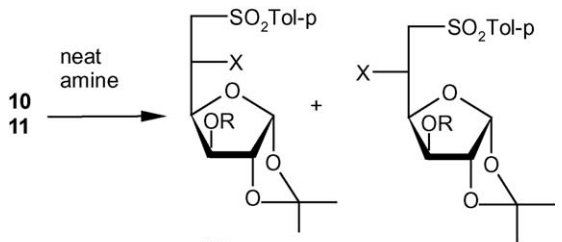
Scheme 25.

equatorial products (like **72a–b**) was overruled in favor of the formation of C3-C4 diaxial products **71a–c** (Scheme 25) [34].

3.4. Functionalization at C-5

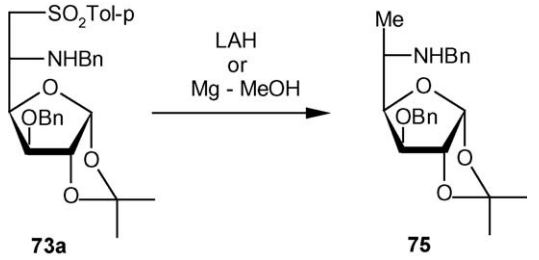
Methods for the functionalization of the C-5 position of hexose sugars are limited in number because the 5-*O*-sulfonylated hexoses are reluctant partners in nucleophilic displacement reactions and 5,6-epoxides (e.g. **54**; Scheme 11) are regioselectively opened at C-6 when reacted with nucleophiles [35,43]. Therefore, the 3-*O*-benzylated gluco derivative **10** was reacted with neat benzylamine and isopropylamine to produce **73a/74a** (9:1) and **73b/74b** (9:1), respectively. In both cases, the L-ido derivatives **73a** and **73b** were the major products (Scheme 26) [35]. It should be noted that all addition reactions were performed using the inseparable E/Z mixtures of **10** and **11**. It is therefore not possible to comment on the influence of these geometrical isomers, if any, on the stereochemical outcome of these reactions.

The 3-*O*-methylated gluco derivative **11** reacted in a similar fashion with benzylamine and isopropylamine to produce **73c/74c** (9:1) and **73d/74d** (9:1), respectively. In this case too, the L-ido isomer was the major product. It is noteworthy that the stereoelectronic effect of OMe at C-3 of compound **11** is sufficient to impose diastereoselectivity



a. R = Bn; X = NHBn (9:1)
b. R = Bn; X = NHiPr (9:1)
c. R = Me; X = NHBn (9:1)
d. R = Me; X = NHiPr (9:1)
e. R = Bn; X = piperidinyl (1:1)
f. R = Me; X = piperidinyl (6:1)

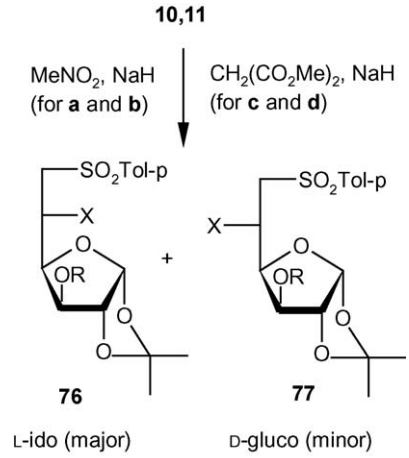
Scheme 26.



Scheme 27.

in favor of the L-ido derivative. The influence of C-3 substitution on the diastereoselectivity of addition was established further when the allo derivative **12** showed a significant to complete lack of diastereoselectivity of addition when reacted with benzylamine and isopropylamine. Compound **12**, with a significantly reduced steric bulk at C-3 because of the presence of a hydrogen atom instead of β-OBn/OMe at C-3, produced inseparable mixtures of benzylamino and isopropylamino adducts in ratios of 1:1 and 3:2, respectively. A secondary amine piperidine reacted with **10** and **11** to produce **73e/74e** (1:1) and **73f/74f** (6:1) respectively (Scheme 26) [35]. The allo isomer **12** produced the piperidino adduct in a 1:1 ratio. It was possible to desulfonylate **73a** to **75** using both LAH and Mg in MeOH (Scheme 27) [35].

This strategy was exploited further for the diastereoselective C–C bond formation at C-5 of hexofuranosyl carbohydrates using carbon nucleophiles [43]. Thus, vinyl sulfones **10** and **11** were reacted with $NaCH_2NO_2$ to generate the addition products **76a/77a** (5.5:1) and **76b/77b** (>9:<1), respectively, in very good yields (Scheme 28)



a R = Bn; X = CH_2NO_2 (5.5:1)
b R = Me; X = CH_2NO_2 (>9:<1)
c R = Bn; X = $CH(CO_2Me)_2$ (5:1)
d R = Me; X = $CH(CO_2Me)_2$ (9:1)
e R = Bn; X = CHO
f R = Me; X = CHO
g R = Bn; X = CH_2CO_2Me
h R = Me; X = CH_2CO_2Me

Scheme 28.

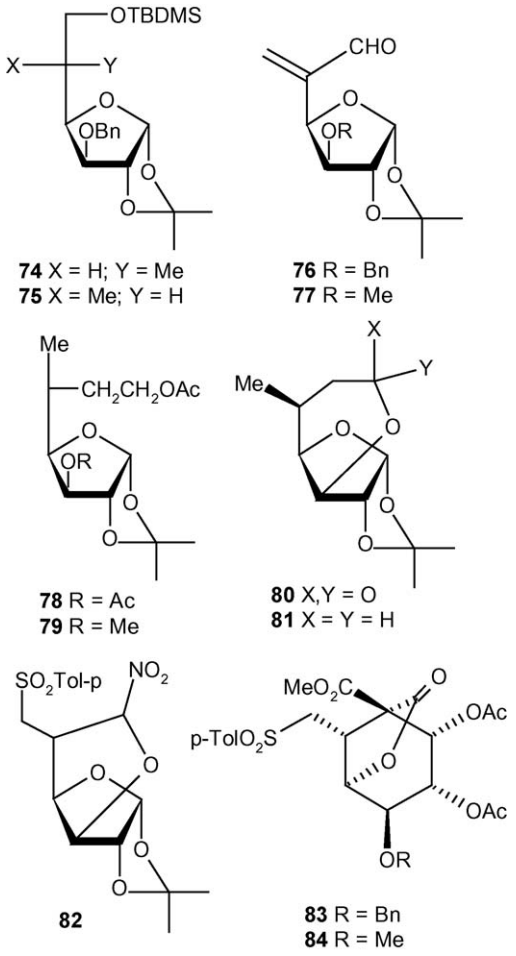


Fig. 3. The synthesis of various modified carbohydrates and carbocycles.

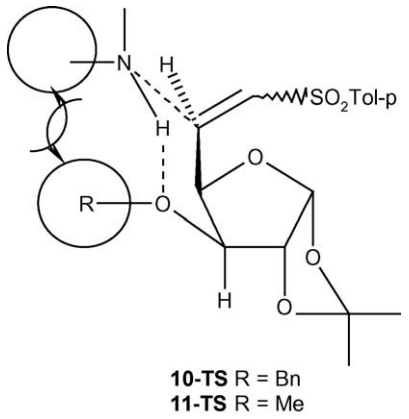


Fig. 4. The formation of an H-bonded transition state **10-TS** or **11-TS**.

[43]. The other nucleophile $NaCH(CO_2Me)_2$, reacted at a much faster rate with **10** and **11** to generate mixtures of the addition products **76c/77c** (5:1) and **76d/77d** (9:1), respectively, in very good yields [43]. The branched-chain sugars **76** and **77** were converted to a wide range of products **76e-h** and **77e-h** (Scheme 28) [43] using a variety of synthetic manipulations. Some of the latter compounds were utilized further for the synthesis of various modified carbohydrates **78–82** as well as carbocycles **83** and **85** (Fig. 3) [43]. As discussed in the case of the amino compounds (Scheme 26), the diastereoselectivity of the addition of carbon nucleophiles to **10** and **11** was controlled to a great extent by the configuration and substituents present at C-3. Therefore, as expected, the allo derivative **12** showed a complete or significant lack of diastereoselectivity of addition when reacted with carbon nucleophiles [43].

To explain the diastereoselectivity of addition of amines to **10–12**, we postulated the formation of an H-bonded transition state **10-TS** or **11-TS** having the geometry of a six membered ring (Fig. 4) [35]. This system fixed the transition state in the L-ido configuration. We argued that the stereoelectronic interactions between the R group (OBn/OMe) would allow the amine nucleophile to take up the position as shown in Fig. 4. Minimum interactions of primary amines with OBn (**10-TS**) or OMe (**11-TS**) allowed the amines to attack C-5 in a diastereoselective fashion via the H-bonded intermediate. A more severe interaction of OBn (**10-TS**) with a bulky secondary amine piperidine did not allow the formation of the hydrogen-bonded intermediate but highly reactive piperidine reacted with **10** anyway without any selectivity. A moderate interaction between OMe (**11-TS**) and piperidine allowed most of the reaction to proceed through a 6-membered intermediate. In the absence of any such intermediates in case of **12**, both primary and secondary amines attacked C-5 from both sides without any diastereoselectivity [35]. However, the same concept is not applicable in the case of carbon nucleophiles because the negatively charged carbon nucleophiles are not capable of forming H- bonds with OMe or OBn groups present at C-3 positions of **10** and **11**. An alternative explanation based on the model reported for the addition of primary amines to *E* (or *Z*)-6-bromo-5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylo-hept-5-eno-l,4-furanurononitriles was invoked to explain the product distribution in this case [43]. Thus, a carbon nucleophile was repelled by the OMe group of **11** and was forced to attack the double bond from the other side resulting in the formation of the L-ido product preferentially (Fig. 5A) [43]. In the case of **12**, however, the carbon nucleophile was weakly repelled by the ring-oxygen and attacked the double bond from both sides resulting into a loss of diastereoselectivity of addition (Fig. 5B) [43].

A critical situation arose in the case of **10**. In theory, reaction of **10** should have resulted into the same diastereoselective product formation as was the case for **11** (Fig. 5). However, we presumed that an additional factor like the equilibrium between two rotamers **10A** and **10B** blocked both sides of C-5 (Fig. 6) resulting into a lower diastereoselectivity still favoring the formation of L-ido isomer **76a** [43].

3.5. Cyclopropanated carbohydrates

Integration of cyclopropanes and carbohydrates has been identified as an important area of research in cyclopropane related synthetic chemistry. This particular combination provides access to a class of strained and

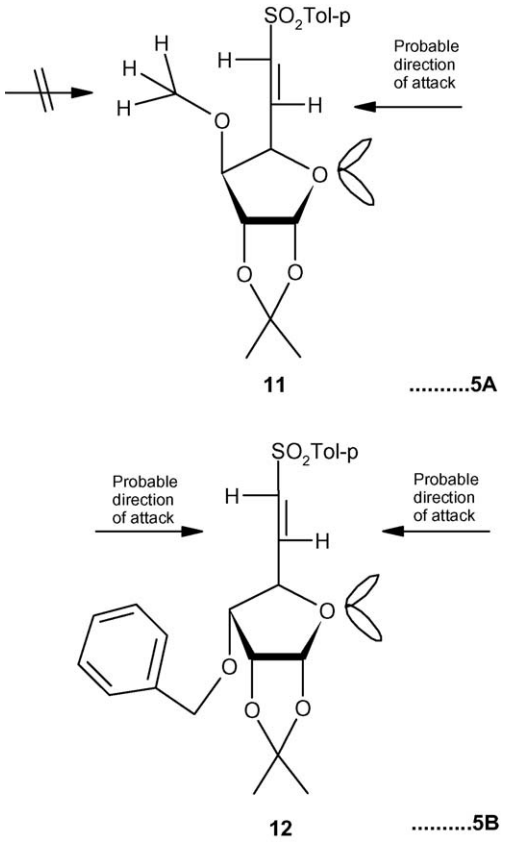


Fig. 5. A: the preferential formation of L-ido product; B: the loss of diastereoselectivity of addition.

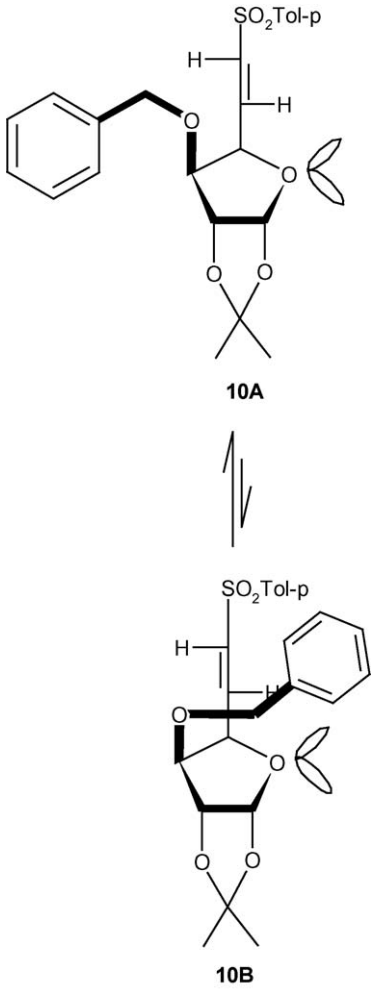


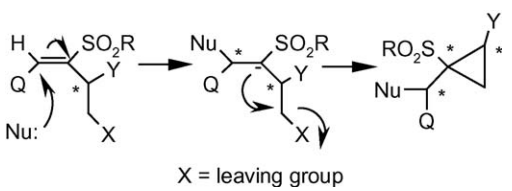
Fig. 6. The equilibrium between two rotamers **10A** and **10B** block both sides of C-5.

reactive cyclopropanes embedded in chiral appendages like carbohydrates. On the basis of the argument developed on Michael Initiated Ring Closure reactions (Scheme 29), we proposed that VSM carbohydrates with suitably positioned leaving groups, such as **13**α, **13**β and **14** should be capable of generating cyclopropanated carbohydrates [44]. Thus the VSM carbohydrate **13**α was reacted with NaOMe or NaOBn, to get the cyclopropanated carbohydrates **85a** and **85b**, respectively in excellent yields (Scheme 30) [44]. A bulky, sugar-derived nucleophile, methyl-2,3-anhydro-lyxofuranoside in the presence of NaH easily produced a disaccharide **85c** in high yield. Interestingly, reactions of benzylamine, and the sodium salt of dimethylmalonate with **13**α did not produce any cyclopropane derivative but generated only addition products instead. However, these intermediates represented by the general structure **84**, on treatment with K_2CO_3/MeOH or NaH yielded cyclopropanes **85d** and **85e** (Scheme 30) [44].

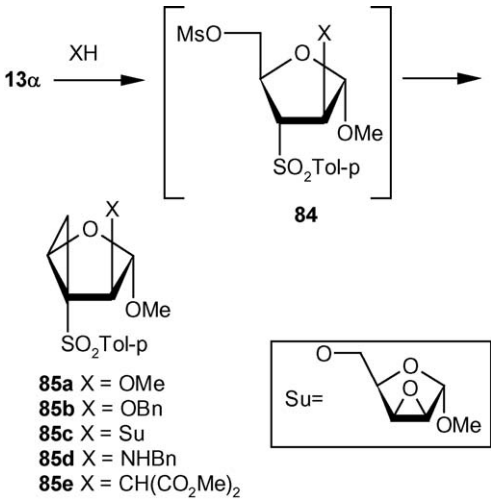
The other vinyl sulfone **13**β, under similar conditions produced cyclopropanated carbohydrates **86a/86b** (1:1), **86c**, and **86d** (Scheme 31). Mg in MeOH desulfonylated **85b** and **86c** to cyclopropane ethers **87** and **89** respectively in high yields. The aminocyclopropane **85c** was desulfonylated to **89** with Mg-$NiBr_2$-MeOH at 60 °C in good yield (Scheme 32) [44].

Further synthetic manipulation of **85e** and **86d** led to the formation of fully protected and enantiomerically pure cyclopropanols **90** and **91** (Fig. 7) [44].

To synthesize C3-C4 cyclopropanated pyranosides from the branched-chain sugar **70a**, it was subjected to a modified Nef- carbonyl synthesis to generate the corresponding aldehyde **92** (Scheme 33) [33]. The aldehyde was then reduced with $NaBH_4$ to the corresponding alcohol and the alcohol was mesylated under standard conditions. The crude mesylate **93** was subjected to the ring closure involving intramolecular alkylation reaction in the presence of *t*BuOK dispersed in THF to afford compound **94** in 65% overall yield (Scheme 33) [33].

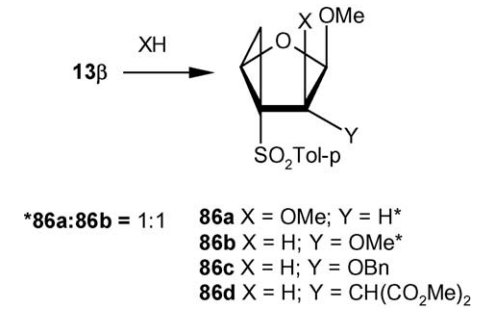


Scheme 29.

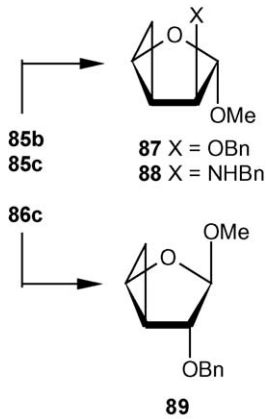


Scheme 30.

Compound **14** on reactions with nitromethane in the presence of tBuOK in THF at reflux temperature, generated a separable mixture of compounds **95a** and **96a** (Scheme 34) [33]. The mixture was separated over silica gel and compound **95a** was treated with a suspension of tBuOK in THF for 2 h at room temperature to afford compound **96a** in 83% combined yield. Similarly, dimethylmalonate in the presence of *t*BuOK in THF afforded compound **95b** and **96b**.



Scheme 31.



Scheme 32.

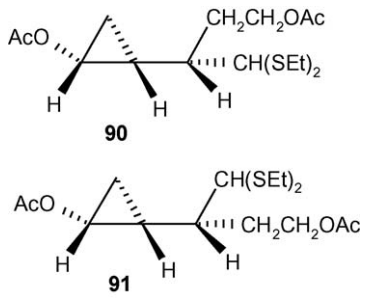
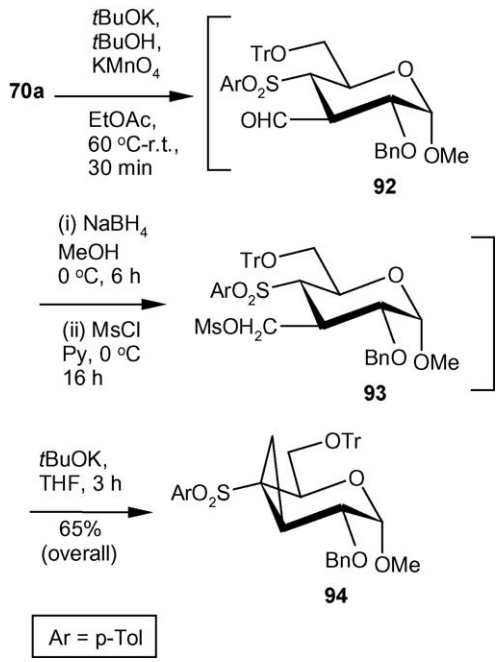


Fig. 7. The formation of fully protected and enantiomerically pure cyclopropanols **90** and **91**.

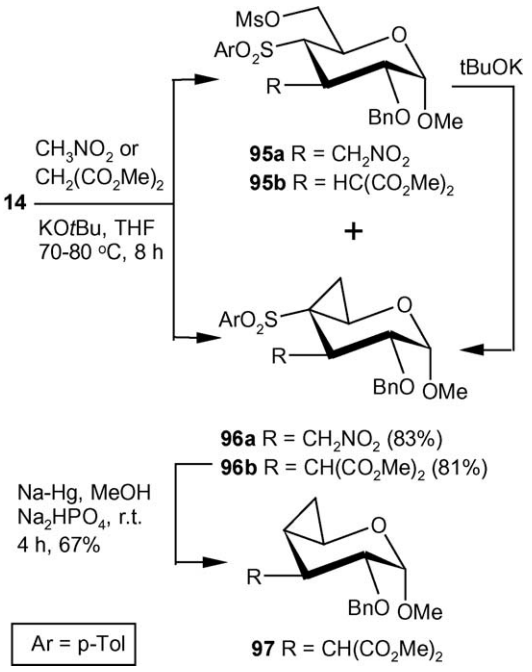
Separation of the mixture over silica gel and treatment of compound **95b** with tBuOK in THF afforded compound **96b** in 81% combined yield. Compound **96b** on treatment with Na-Hg in dry MeOH at room temperature underwent desulfonylation reaction affording compound **97** in 67% yield (Scheme 34). Schemes 33 and 34 represent new strategies for the synthesis of a hitherto unknown C3-C4 cyclopropanated pyranoside and a C3-branched-, C4-C5 cyclopropanated pyranoside [33].

3.6. Isonucleosides

To broaden the scope of nucleoside-based therapeutics, a novel class of modified nucleosides in which nucleobases are linked to the non-aromatic carbons of carbohydrates has been designed. These ‘‘isonucleosides’’ are promising therapeutic agents of apparently very low toxicity and some of them show strong and selective anti-cancer and antiviral activities. The bond connecting the nucleobase and carbohydrate has higher degree of stability towards



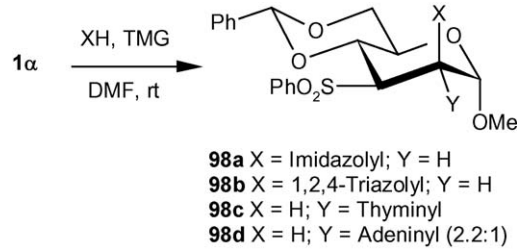
Scheme 33.



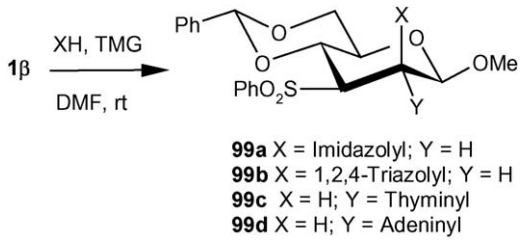
Scheme 34.

acids and enzymatic deamination when compared to those of nucleosides [45].

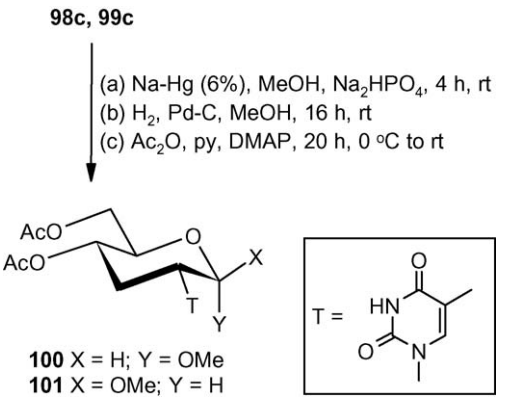
Vinyl sulfone **1**α on treatment with imidazole, 1,2,4-triazole and thymine in the presence of TMG in anhydrous DMF at ambient temperature, generated single isomers **98a–c**, respectively in high yields. Adenine, on the other hand, under similar reaction conditions afforded an inseparable mixture of two compounds **98d** in 2.2:1 ratio (Scheme 35) [46]. β-vinyl sulfone **1**β was also treated with the same set of nucleophiles under similar conditions to afford single isomers **99a–d**, respectively, in moderate to good yields (Scheme 36) [46].



Scheme 35.



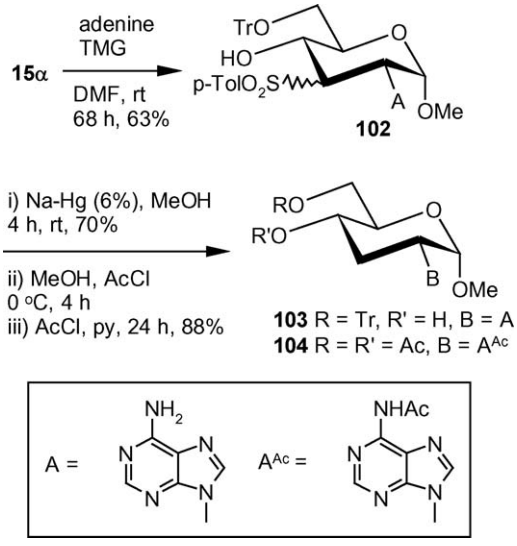
Scheme 36.



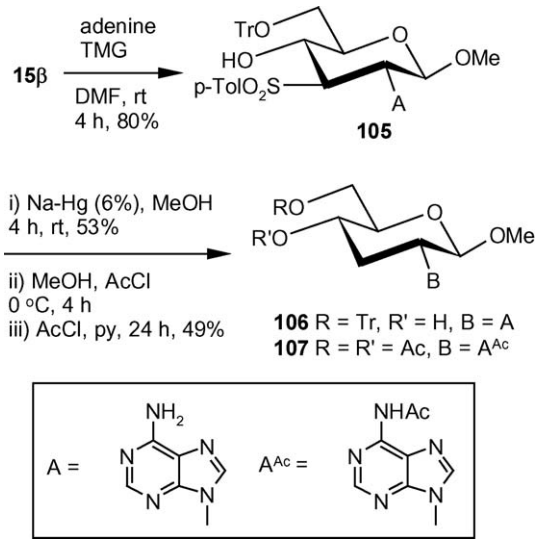
Scheme 37.

Vinyl sulfones **5**α and **5**β also reacted efficiently with these planar heterocycles [46]. However, attempted desulfonylation of furanosides using Na-Hg, MeOH-Mg or even with MeOH-Mg-$NiBr_2$ used successfully in the synthesis of furanosyl deoxyaminosugars **66–69** (Fig. 2) led to extensive degradation of the starting materials [46]. Only the pyranosides were found to be stable towards Na-Hg (6%) mediated desulfonylation reactions. Thus, the thymine derivatives **98c** and **99c** on treatment with Na-Hg (6%) in a buffered system underwent efficient desulfonylation. Products of the desulfonylation reactions were directly deprotected under reductive conditions and finally acetylation produced the desired isonucleosides **100** and **101** in 72 and 64% overall yields, respectively (Scheme 37) [46].

In an alternative approach, tritylated α-methoxy vinyl sulfone **15**α on treatment with adenine in the presence of TMG in anhydrous DMF at ambient temperature, afforded an inseparable mixture of compounds **102** in 1:1 ratio. The mixture was subjected to Na-Hg mediated desulfonylation to afford a single compound **103** proving that the sulfonylated derivatives **102** was a mixture of C-3 epimers.



Scheme 38.



Scheme 39.

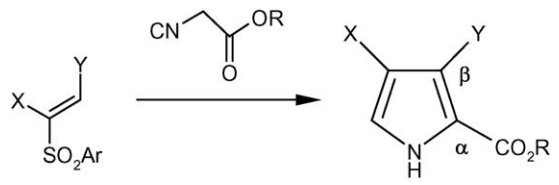
The trityl group of **103** was removed easily under acidic condition and the deprotected product was isolated as the peracetylated derivative **104** in good yield in two steps (Scheme 38) [46].

The β-methoxy vinyl sulfone **15**β under similar reaction conditions reacted with adenine to afford a single isomer **105**. Compound **105** was desulfonylated by Na-Hg to **106** in good yield. Compound **106** was detritylated under acidic condition and the product was isolated as the peracetylated derivative **107** in 49% yield in two steps (Scheme 39) [46].

3.7. Pyrroles

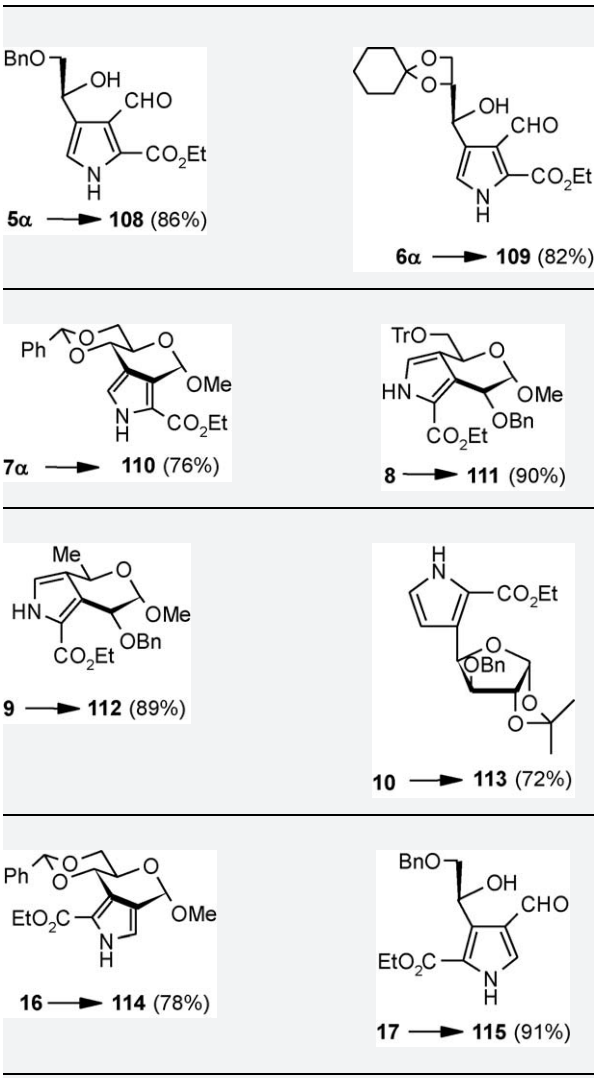
Pyrrole-containing compounds, in general, play crucial roles in nature and substituted pyrroles are important for research in pharmaceutical and material sciences. Although a variety of synthetic approaches for the preparation of pyrroles has been developed over the years, a perusal of the literature reveals that even now the synthesis of highly functionalized pyrroles remains a synthetic challenge in terms of regioselectivity and chemoselectivity [47]. Moreover, synthesis of β-substituted pyrroles was reported to be particularly difficult because the direct alkylation or acylation of pyrroles produced the desired products as minor components.

Conjugate addition of the anion generated from an isocyanoacetate to vinyl sulfones was put forward as a methodology for the synthesis of pyrrole-2-esters (Scheme 40) [47]. However, the strategy stagnated over the years for the non-availability of straightforward and general methodologies for the synthesis of polysubstituted vinyl sulfones. The serious shortcomings of currently available methods for the synthesis of polysubstituted pyrroles were compounded by the fact that strategies for the synthesis of pyrroles attached to chiral moieties are virtually nonexistent. Since we had access to different pyranosyl and furanosyl vinyl sulfones, we reacted vinyl sulfones **5**α**, 6**α**, 7**α**, 8–10, 16** and **17** with ethyl isocyanoacetate using standard protocols to afford a wide variety of densely functionalized pyrroles **108**–**115** (Table 1) [47]. Interestingly, the furanosyl rings of **5**α, **6**α, and **17** opened up during the reaction to directly afford polysubstituted pyrrole aldehydes **108, 109** and **115** respectively [47].



Scheme 40.

Table 1
Chiral pyrroles from vinyl sulfone-modified carbohydrates.



4. Future prospects

Although carbohydrates are primarily modified via their sulfonates, epoxides or ketones [17–24], we have made an attempt to highlight the usefulness of the combination of

vinyl sulfone groups and carbohydrates in the synthesis of wide-ranging modified carbohydrates as well as chirally pure non-carbohydrate molecules. It is clear from the examples cited in this review that this class of compounds, indeed, has the potential to act as an unlimited and versatile source of chiral building blocks. We are in the process of unearthing the vast potential of VSM carbohydrates and their downstream products as chirally pure target molecules as well as new chemical entities capable of eliciting responses in biological systems.

Conflict of interest

No conflict of interest is affecting either of the authors.

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