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Vinyl sulfone-modified carbohydrates: an inconspicuous group of chiral building blocks

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Contents

Abbreviations: AIBN, 2,2′-azobisisobutyronitrile; DBU, 1,8-diazabicyclo[5.5.0]undec-5-ene; de, diastereomeric excess; DET, diethyl tartrate; DME, 1,2-dimethoxyethane; DMF, *N*,*N*-dimethylformamide; ee, enantiomeric excess; LAH, lithium aluminium hydride; LDA, lithium diisopropylamide; HMDS, hexamethyldisilazide; *m*-CPBA, *m*-chloroperbenzoic acid; Me, methyl; MMPP, magnesium monoperoxyphthalate hexahydrate; MMTr, monomethoxytrityl; Ms, methanesulfonyl (mesyl); Ph, phenyl; PMB, *p*-methoxybenzyl; Py, pyridine; Pyr, pyridyl; TBAF, tetrabutylammonium fluoride; TBDMS, *tert*-butyldimethylsilyl; THF, tetrahydrofuran; TMG, 1,1,4,4-tetramethylguanidine; Tol, toluoyl; Tr, trityl; Ts, *p*-tolylsulfonyl (tosyl).

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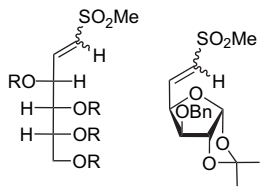
1. Introduction

Since the publication of the review article entitled ''Multiply convergent syntheses via conjugate-addition reactions to cycloalkenyl sulfones'' about two decades ago,[1] α,β-unsaturated sulfones or vinyl sulfones have now become generally accepted as useful intermediates in organic synthesis because vinyl sulfones serve efficiently as Michael acceptors as well as 2π-partners in cycloaddition reactions.[1–4] Although some of the review articles on this topic are general in nature,[1–4] various special aspects of vinyl sulfones such as new synthetic methods using heteroconjugate addition to vinyl sulfones,[5] cycloaddition and cyclisation of unsaturated sufones,[6,7] applications of vinyl sulfones in asymmetric synthesis,[8] vinyl sulfones as ketene equivalents,[9] vinyl sulfones leading to carbasugars,[10] application of Wittig and Horner–Wittig reactions to the synthesis of vinyl sulfones,[11] synthesis of unsaturated sulfones,[12] vinyl sulfones as radical traps,[13] radical conjugate addition to vinyl sulfones,[14] synthetic preparations of vinyl sulfones and their medicinal chemistry applications[15] have been highlighted. The list of reviews cited in this article is by no means comprehensive, but is an indication of the usefulness of the vinyl sulfone group and its popularity with the practising organic chemists. A recently published review[16] on the removal of sulfone group under different reaction conditions for the functionalisation of the carbon attached to the sulfone groups has enriched the arsenals of synthetic chemists who are interested in using vinyl sulfone groups in synthetic transformations.

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 functionalisation of the sugar molecule at the monosaccharide level. Carbohydrates are normally modified via their sulfonates, epoxides, olefins, ketones or olefinic derivatives.[21] It may be argued that vinyl sulfone-modified carbohydrates have the potential for utilisation in organic synthesis because (a) almost all carbohydrates, either in the pyranose or in the furanose forms, can be converted into their 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[1–15] and (c) after using the vinyl sulfone moiety as a tool for functionalisation, desulfonylation under strategically selected conditions[16] would easily generate an array of modified carbohydrates. More importantly, the 'in-built' chiralities in sugar molecules should contribute significantly in determining the stereochemical outcome of the reactions of vinyl sulfone-modified carbohydrates. Considering the importance of the functionalised monosaccharides as 'chiral pools',[17–24] it is surprising that except for a few papers published to date[1–16] not much emphasis has been placed on the importance of vinyl sulfone-modified carbohydrates, although some of these references have casually mentioned selected reactions of vinyl sulfone-modified carbohydrates. In only three articles, the authors have briefly mentioned their own work on vinyl sulfone-modified carbohydrates.[25–27]

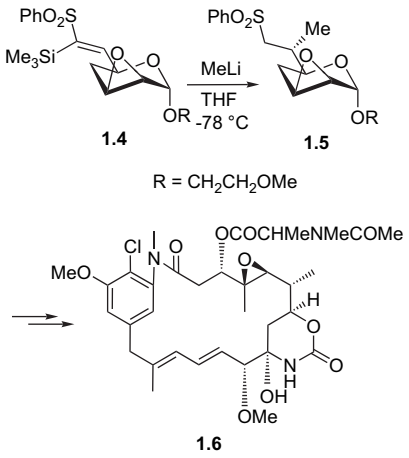
Synthetic and physical studies of vinyl sulfone-modified carbohydrates such as **1.1**–**1.3** were reported as early as 1971.[28–30]



1.1 R = OAc
1.2 R,R = CMe_2
1.3

Interestingly, not until the passing of a decade a pyranose derivative **1.4** having a 2-phenylsulfonyl-2-trimethylsilyl vinyl

group was used for the synthesis of (±)-maytansinol **1.6**,[31] the synthesis being initiated by the heteroconjugate addition of MeLi to **1.4** to obtain **1.5**. The addition of MeLi accomplished the complete acyclic stereoselection in the pyranosyl heteroolefin **1.3**.[31,32] From a historical perspective, this particular synthetic strategy highlighted for the first time the potential of vinyl sulfone-modified carbohydrates as useful chiral building blocks. At the same time, this very reaction highlighted an obvious, but 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.



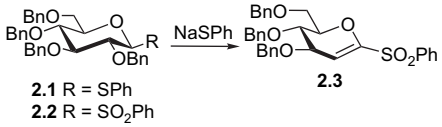
The present author was exposed to the diastereoselective nature of the addition of nucleophiles to vinyl sulfone-modified pent-2′-enofuranosyl nucleosides while developing methodologies for the synthesis of modified nucleosides (see Section 6).[33] Later, this observation led to the initiation of a research program on the stereoselective addition of nucleophiles to vinyl sulfone-modified carbohydrates and the use of this strategy as a methodology for accessing new modified carbohydrates.[34–48] Because of the scattered and inconspicuous nature of the literature on this topic, it was imperative to compile information on the synthesis and chemistry of vinyl sulfone-modified carbohydrates. This exercise has resulted in current report, which has also been extended to cover molecules related to carbohydrates. Thus, vinyl sulfone-modified nucleosides, 'carbohydrate-like' acyclic molecules and carbasugars have been included in the discussion.

2. Vinyl sulfone-modified pyranoses

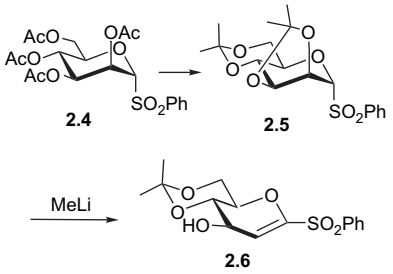
2.1. Sulfone group attached to C-1 of pyranose ring

2.1.1. Synthesis of 1-sulfonyl glycals

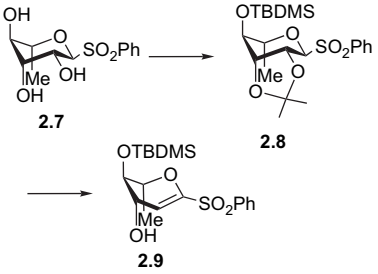
Ferrier and co-workers have reported a cyclic vinyl sulfone-modified carbohydrate in 1977, when attempted displacement of the phenylsulfonyl group from 2,3,4,6-tetra-*O*-benzyl-β-D-*gluco*-pyranosyl sulfone **2.2**, obtained from **2.1** by oxidation, produced the unwanted vinyl sulfone-modified carbohydrate **2.3**.[49]



With the accidental discovery of the vinyl sulfone-modified carbohydrate **2.3**, attempts were made to make use of this class of compounds as Michael acceptors. Thus, 1-sulfonyl glycal **2.6** was synthesised from D-mannosyl sulfone **2.4** via the bisisopropylidene derivative **2.5**. Bisacetal **2.5** was subjected to base-promoted elimination to form the vinyl sulfone derivative **2.6**.[50]

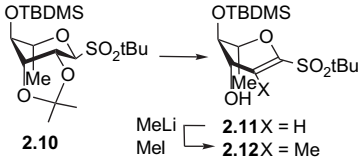


L-Rhamnopyranose tetra-*O*-acetate was similarly converted into the corresponding vinyl sulfone **2.9** via phenyl sulfonyl-glycosides **2.7** and **2.8**.[50]



2.1.2. Reactions of 1-sulfonyl glycals

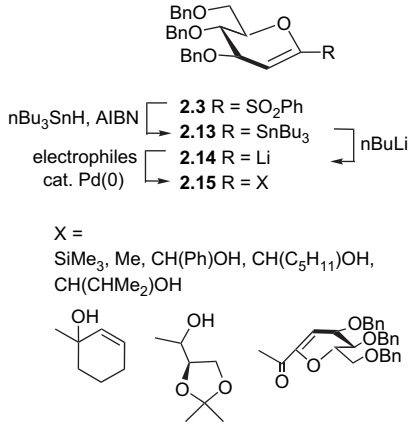
Vinyl sulfones **2.6** and **2.9** did not undergo Michael addition reactions with methyllithium or with any other nucleophiles.[50] Another vinyl sulfone **2.11** carrying a bulky *tert*-butyl group was synthesised from **2.10** and then reacted with methyllithium. No Michael addition occurred and lithiation at C-2 took place instead. Subsequent reaction of the lithiated species with iodomethane produced 2-methyl vinyl sulfone **2.12**.



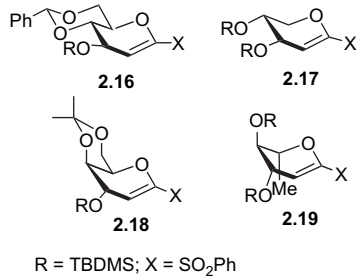
The presence of the ring oxygen α to the sulfone group deactivated the double bond through delocalisation of the lone pair of electrons and rendered these vinyl sulfone-modified carbohydrates too unreactive to undergo Michael addition.[50]

Although 1-sulfonyl glycals did not undergo Michael addition reactions, 1-phenylsulfonyl glucal **2.3** was found to be a useful starting material for the preparation of 1-tri-*n*-butylstannyl-D-glucal **2.13**. Tin–lithium exchange and treatment of the lithium

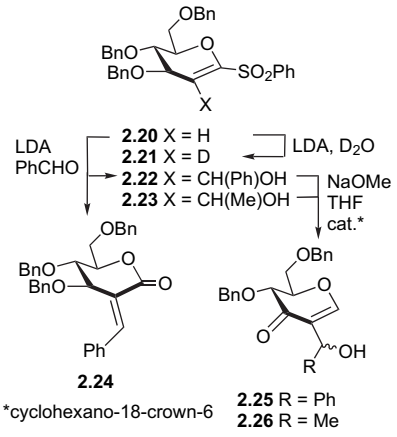
species **2.14** with electrophiles in the presence of a Pd(0) catalyst afforded a range of *C*-glycosylated products **2.15**.[51,52]



Recently, 1-phenylsulfonyl glycals **2.16**–**2.19** have been synthesised through modified routes[53] and these glycals were shown to undergo an easy Ni(0)-catalysed coupling with tributylstannylmagnesium bromide to give the corresponding 1-tributylstannyl glycals.[53]



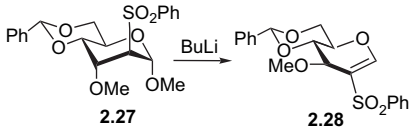
The 2-lithio derivative generated from 1-phenylsulfonyl glycal **2.20** was quenched with D_2O to yield the deuteriated analogue **2.21**. The 2-lithio derivative was reacted with benzaldehyde to generate a 1:3 mixture of diastereomers **2.22**. Compound **2.22** was converted into 2-benzylidene-D-gluconolactone **2.24** with the loss of phenylsulfinic acid. Compound **2.22** and the corresponding analogue **2.23** generated from acetaldehyde were reacted with NaOMe in the presence of dicyclohexano-18-crown-6 to produce the desulfonylated pyranosyl enelactones **2.25** and **2.26**.[54,55]



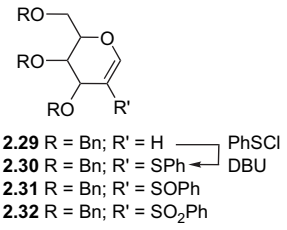
2.2. Sulfone group attached to C-2 of pyranose ring

2.2.1. Synthesis of 2-sulfonyl glycals

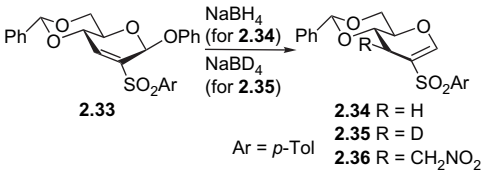
2-Sulfonyl glycal **2.28** was initially synthesised by treating a fully protected 2-sulfonylated *gluco* derivative **2.27** with BuLi.[56]



2-Phenylsulfonyl-substituted glycal derivatives, represented by the general structure **2.32**, were efficiently synthesised from 3,4,6-tri-*O*-benzyl-D-glycals **2.29**. Thus, perbenzylated D-glycals **2.29** were treated with PhSCl in the presence of DBU to afford **2.30**. These thio derivatives were oxidised to sulfoxides **2.31** or further oxidised to 2-sulfonyl glycals **2.32**.[57,58]

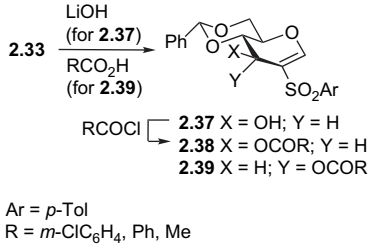


The phenyl-2-enopyranoside analogue **2.33** (see also Section 2.2.4) was expected to produce the 1-enitol derivative easily because the aglyconic phenoxyl group was an efficient leaving group. Thus, **2.33** on treatment with $NaBH_4$ led to an S_N2' reaction to give the 3-deoxy-1-enitol derivative **2.34**. The use of $NaBD_4$ afforded **2.35**, which established that the hydride ion was delivered from the upper side of the pyranose ring.[59]



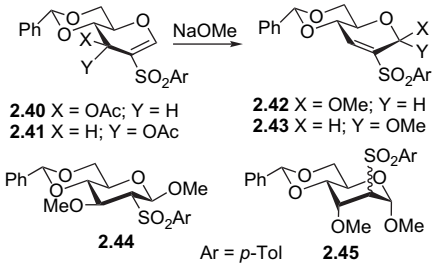
On the other hand, enopyranoside **2.33**, on treatment with LiOH in THF afforded the D-*arabino*-hex-1-enitol derivative **2.37**. Reactions of **2.37** with *m*-chlorobenzoic acid in pyridine afforded the 3-*O*-*m*-chlorobenzoyl-2-deoxy-D-*ribo*-hex-1-enitol derivative **2.39** and other acids were also added in a similar fashion. *m*-Chlorobenzoylation of **2.37** afforded **2.38**, which was the C-3 epimer of **2.39**. Interestingly, the hydride or the hydroxyl nucleophiles were incorporated almost exclusively at the equatorial or quasi-equatorial positions of **2.33** to afford **2.34**, **2.35** and **2.37**. In contrast, carboxylic acids (in the presence of pyridine) exceptionally added from the axial side of **2.33** to afford **2.39**. It is probable that hydrogen bonding

between O-4 and the N–H atom of the pyridinium salt of the acid directed the counter anion to attack C-3 from the bottom of the ring.[59]

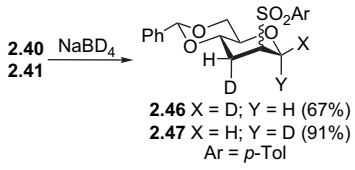


2.2.2. Reactions of 2-sulfonyl glycals

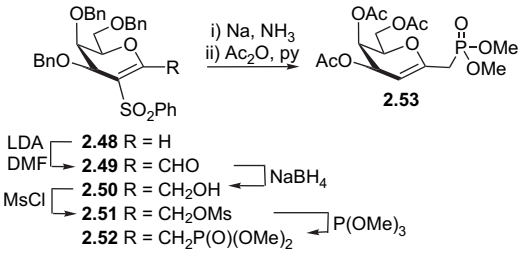
In order to establish the stereoselectivity of nucleophilic addition reactions to 2-sulfonyl glycal derivatives, compounds **2.40** and **2.41** were treated with NaOMe and $NaBD_4$. Thus, compound **2.40** on treatment with NaOMe afforded the β-methoxy derivatives **2.42** and **2.44** as the major compounds in 80% yield. On the other hand, **2.41** produced the α-methoxy analogue **2.43** in 60% yield along with a mixture of **2.44** and **2.45**.



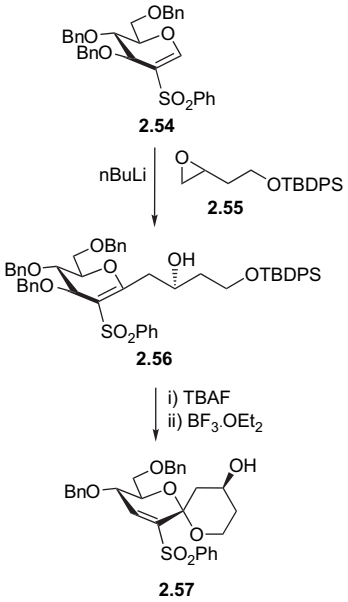
Similarly, **2.40** and **2.41**, on treatment with $NaBD_4$, produced the α- and β-deuteriated derivatives **2.46** and **2.47**, respectively. These observations established that the stereoselectivity of addition of nucleophiles at C-1 of 2-sulfonyl glycals **2.40** and **2.41** was controlled by the configurations of the leaving groups at C-3.[60]



Direct lithiation of 2-phenylsulfonyl-substituted galactal **2.48** and subsequent reaction with DMF yielded 1-*C*-formyl derivative **2.49**. Reduction of **2.49** gave the alcohol **2.50**. On treatment with trimethyl phosphite, mesylate **2.51** of the alcohol **2.50** produced phosphonate **2.52**. Desulfonylation and debenzylation with Na–liq. NH_3 and subsequent acetylation furnished dimethyl phosphonate **2.53**. Glycal-1-ylmethylphosphonates are considered to be useful as precursors of certain glycosyltransferase inhibitors.[57]

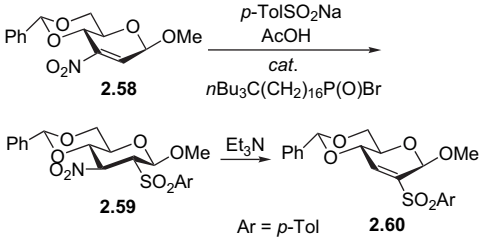


The presence of spiroketals in macrocycles like milbemycins and avermectins has led to the synthesis of spiroketals from 2-sulfonyl glycals. Thus, glucal derivative **2.54** was treated with 1.2 equiv of *n*-BuLi at −78 °C followed by the consecutive addition of epoxide **2.55** and $BF_3 \cdot OEt_2$. The product **2.56** was obtained in a diastereoselective fashion. Treatment of **2.56** with TBAF and $BF_3 \cdot OEt_2$ led to the isolation of the spiroketal **2.57**, which resulted from an apparent Ferrier rearrangement. Once again, the major product formation was a result of thermodynamic control.[61]

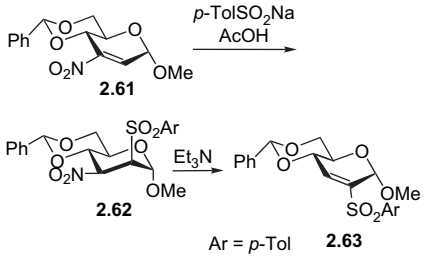


2.2.3. Synthesis of 2-sulfonyl hex-2-enopyranosides

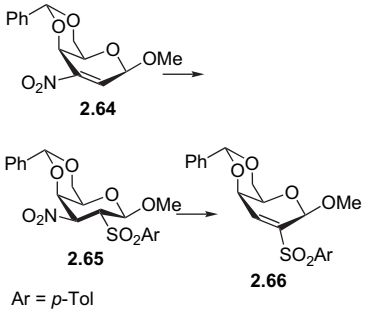
While studying the reactivities of nitro vinyl sugars, Sakakibara and co-workers reported the following synthesis of vinyl sulfone-modified hex-2-enopyranosides. A sugar derivative having an α-sulfonylalkene moiety constructed on a pyranose ring, hex-2-enopyranoside **2.60**, was synthesised by reacting **2.58** with sodium *p*-toluenesulfinate in the presence of acetic acid followed by treatment of the *gluco* derivative **2.59** with triethylamine.[62,63]



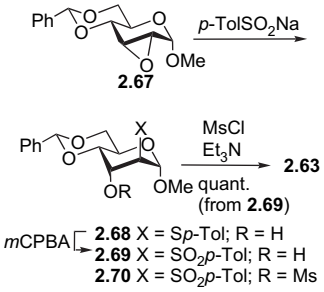
The α-anomer **2.63** was synthesised in very poor yield from 3-nitro-hex-2-enopyranoside **2.61** via the mannopyranoside derivative **2.62**.



The galacto isomer **2.64** produced the corresponding sulfonylalkene **2.66** in a similar fashion via **2.65**.[62,63]

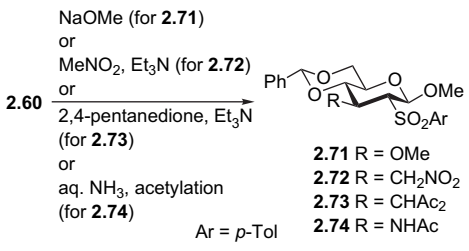


An alternative method for the preparation of **2.63** was developed, because of the difficulties in obtaining the compound through this inefficient route. Thus, the epoxy ring of 2,3-*O*-anhydro-α-D-allopyranoside **2.67** was opened with sodium *p*-thiocresolate and the product **2.68** was oxidised to **2.69**. Compound **2.69**, on mesylation in the presence of triethylamine, underwent a concomitant elimination to afford the vinyl sulfone **2.63** through the intermediacy of the mesylated derivative **2.70**.[62,63]

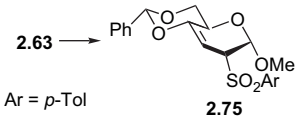


2.2.4. Reactions of 2-sulfonyl hex-2-enopyranosides

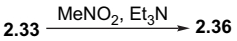
Conjugate additions. Vinyl sulfone **2.60**, on treatment with methanol, nitromethane, 2,4-pentanedione and ammonia, produced the corresponding β-D-*gluco* adducts **2.71**–**2.74**, respectively, in high yields with high stereoselectivities.[59,62]



Interestingly, the α-anomeric vinyl sulfone **2.63**, on treatment with sodium methoxide in methanol, underwent elimination instead of addition to afford **2.75**.[59]

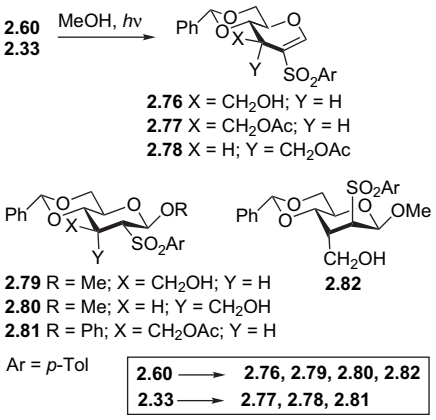


Treatment of the phenyl analogue **2.33** with nitromethane led mainly to an S_N2' process to give the 1-enitol derivative **2.36** (Section 2.2.1) having the *arabino* configuration.[59]

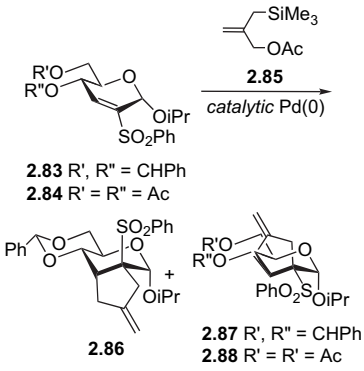


It should be noted that the configuration of the C-4 site influenced the diastereoselectivity of addition of nucleophiles to C-3 of **2.63**. On the other hand, it is probable that a change in the anomeric configuration of the otherwise similar vinyl sulfones **2.60** and **2.63** led to the elimination instead of addition in the case of the latter compound.

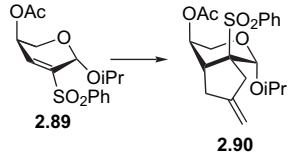
Radical reactions. Compound **2.60** on irradiation with a high-pressure mercury lamp in methanol generated a mixture of **2.76** (4%), **2.79** (9%), **2.80** and **2.82** (55% together). The phenyl analogue **2.33** after photoreaction followed by acetylation generated a mixture of **2.77** (37%), **2.78** (24%) and **2.81**(11%). In all these cases, equatorial attack by a hydroxymethyl radical slightly predominated over the axial attack. This particular photoreaction using vinyl sulfone-modified carbohydrates has very little synthetic utility, however, due to uncontrolled mixture formation.[64]



Cycloaddition reactions. A cycloaddition reaction of a vinyl sulfone-modified carbohydrate was first reported by Trost and co-workers (see Section 4.2.2).[65] This strategy was extended using a different substrate **2.83**, which underwent (3+2) cycloaddition with a trimethylmethylene zwitterion (precursor **2.85**) in the presence of an in situ-generated Pd(0) catalyst to afford an inseparable mixture of two isomers **2.86** and **2.87**.[66] Interestingly, a related vinyl sulfone **2.84** with non-rigid protecting groups like acetyl produced a single isomer **2.88**.[66]



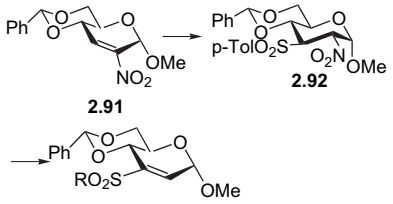
Another vinyl sulfone-modified carbohydrate **2.89** produced the corresponding 5,6-bicycle **2.90** possessing exocyclic unsaturation. These reactions are thought to follow a two-step sequence involving an initial Michael-type addition to the electron-deficient double bond followed by an attack of the resultant stabilised anion on the palladium complex.[66]

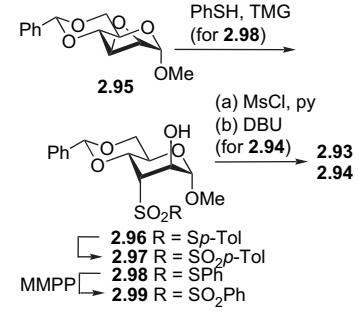


2.3. Sulfone group attached to C-3 of pyranose ring

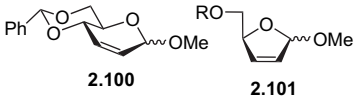
2.3.1. Reinvestigation into the synthesis

As was found for the conversion of **2.61** into **2.63** (Section 2.2.3), 3-*p*-tolylsulfonyl-hex-2-enopyranoside **2.93** was also obtained in poor yield when synthesised from 2-nitrohex-2-enopyranoside **2.91** via **2.92**. Therefore, an alternative route for the synthesis of **2.93** was devised from 2,3-*O*-anhydro-α-D-mannopyranoside **2.95** via **2.96** and **2.97**.[56]

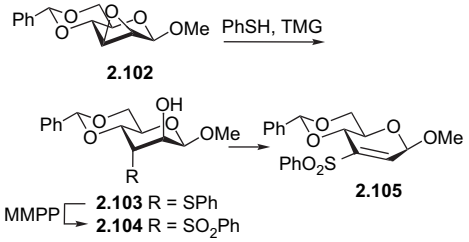




Since Pathak and co-workers[36] initiated a systematic study on the effect of the anomeric configuration on the diastereoselectivity of the addition of nucleophiles to the 2-position of these enopyranoses (Fig. 1), a relatively large amount of anomerically pure, vinyl sulfone-modified hex-2-enopyranoses were found to be needed. The requirement of the anomeric purity of these vinyl sulfone-modified carbohydrates, however, 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. Synthesis of these compounds via the addition of arylsulfenyl chloride to suitably protected methyl 2,3-dideoxy-D-hex-2-enopyranosides **2.100** and the corresponding enofuranosides **2.101** as a method was ruled out, because such an addition to the corresponding olefinic nucleoside derivatives produced a mixture of at least three diastereomers (see Section 6.1.1).[67]



Since one of the easiest methods of forming a C–S bond would be the regioselective opening of epoxides derived from carbohydrates,[68] initially, Pathak and co-workers[36] also synthesised the thiophenyl derivative **2.94** using a modification of the method of Sakakibara and co-workers.[62,63] Thus, epoxide **2.95** was reacted with thiophenol in the presence of TMG to afford **2.98**. The corresponding sulfone derivative **2.99** was generated in quantitative yield by oxidising **2.98** with MMPP. Compound **2.99** was mesylated and the crude mesylated product was subjected to an elimination reaction with DBU in dichloromethane to produce **2.94**. Similarly, thiophenol in the presence of TMG opened epoxide **2.102** at the 3-position to generate **2.103**. Oxidation of **2.103** to **2.104**, followed by mesylation and DBU treatment generated the desired compound **2.105**.[36] The synthetic routes to **2.94** and **2.105** from epoxides **2.95** and **2.102**, however, turned out to be too long to be useful for accessing relatively large amounts of the anomerically pure compounds.



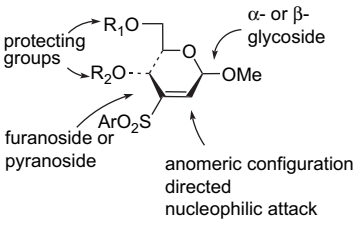
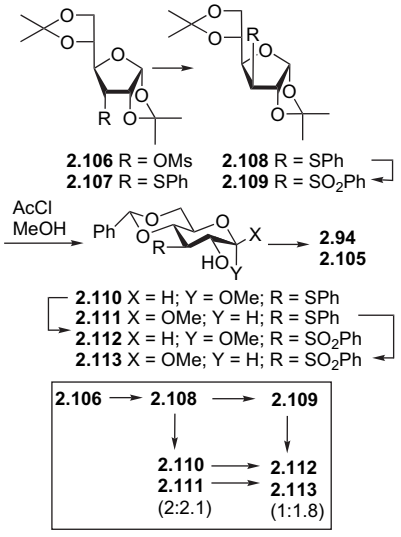


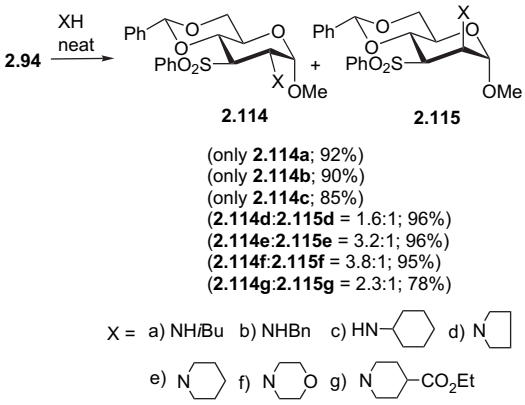
Figure 1.

Because 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 **2.107** and **2.108** were considered as starting sulfide derivatives for providing an easy access to both **2.94** and **2.105** 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 of Pathak and Sanki,[41,42] 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 **2.107** generated more than six products. Therefore, the *gluco* derivative **2.108**, obtained from the mesylated allo derivative **2.106**, was deprotected and glycosylated in a single operation by using acetyl chloride and MeOH to afford a mixture of 3-deoxy-3-phenylsulfide hexopyranosides, which were collected as the benzylidene derivatives **2.110** and **2.111** in a ratio of 2.2:1 in good yields. The anomers were separated by chromatography and were converted separately into the corresponding sulfones **2.112** and **2.113** in excellent yields using MMPP in MeOH. In an alternative approach, compound **2.108** was oxidised to the corresponding sulfone **2.109**. Compound **2.109** was deprotected and glycosylated to generate a mixture of anomeric sulfones, which were collected as the benzylidene *gluco* derivatives **2.112** and **2.113**, respectively, in good yields in a ratio of 1:1.8. After separation, the sulfones were converted into the desired vinyl sulfone-modified hex-2-enopyranosides **2.94** and **2.105** in the usual way.[41,42]

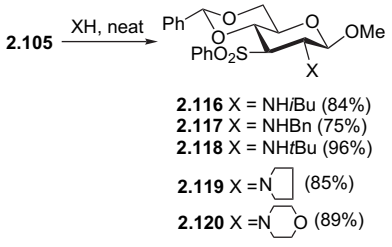


2.3.2. Conjugate addition of amines

In order to study the influence of the anomeric configuration on the diastereoselectivity of the addition of nucleophiles to enopyranoside systems, vinyl sulfone **2.94** was reacted with various primary and secondary amines. Primary amines such as isobutylamine, benzylamine and cyclohexylamine were found to add diastereoselectively to produce single isomers **2.114a**, **2.114b** and **2.114c**, respectively. The secondary amines, pyrrolidine, piperidine, morpholine and ethyl isonipecotate, on the other hand, generated a mixture (isomeric at C-2) having **2.114d–g** as the major isomers and **2.115d–g** as the minor isomers, respectively. The major isomers **2.114d–g** were separated by crystallisation. One of the minor *manno* isomers **2.115d** was isolated to unambiguously establish its structure.



Similarly, the β-anomer **2.105** 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 isomers **2.116–2.120**, respectively.[36] It should be noted that the α-anomer **2.94** did not react with sterically bulky *tert*-butylamine and unreacted starting material was recovered from the reaction mixture. Attempted reactions under forced conditions or prolonged reaction times caused extensive degradation of the starting material.[40] The β-anomer **2.105**, on the other hand, reacted smoothly with the same amine at elevated temperatures to produce a single isomer **2.118** in excellent yield.[40]



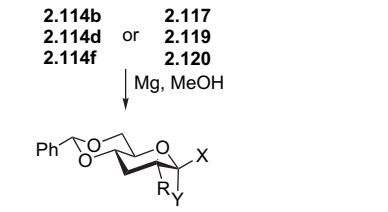
The X-ray analysis of a single crystal of **2.118** revealed that the pyranose ring assumed a boat conformation to facilitate the positioning of the methoxy group of C-1 away from the group at C-2. It was observed that the magnitude of the conformational angle O1–C1–C2–N1 increased in the order **2.116**→**2.117**→**2.118**, confirming this argument. In the case

of the α-methoxy series (compounds **2.114**), however, any increase in this particular conformational angle is prohibited, because of the axial disposition of the 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.[40] The X-ray analysis-based structural study also highlighted the problem of using NMR alone as a tool for identification of the configurations of newly generated centres of carbohydrates.[69]

Although amines added in a diastereoselective fashion to **2.94** and **2.105**, the directive effect of the anomeric configuration on the stereochemical outcome of the reactions was not obvious, because the addition of primary amines to **2.94** exclusively produced C-2 equatorial (*gluco*) products; secondary amines, on reactions with **2.105** produced only the *gluco* derivative, but with **2.94** produced a mixture in which the *gluco* derivative was still the predominant isomer.[36] On the other hand, sterically bulky *tert*-butylamine reacted only with **2.105** (and not with **2.94**) at elevated temperature to produce the *gluco* derivative in high yield.[40]

2.3.3. Desulfonylation of aminosugars

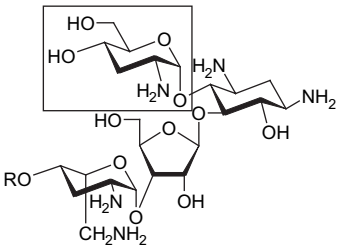
The usefulness of vinyl sulfone-modified carbohydrates as chiral intermediates in synthetic chemistry would depend to a greater extent upon the successful removal of the sulfone group from the body of the carbohydrates after the reaction of the vinyl sulfone group. Thus, compound **2.114b** obtained from **2.94** was desulfonylated by magnesium in methanol in 90% yield to generate the 2-*N*-benzylamino-2,3-dideoxy derivative **2.121**. The related compounds **2.122** and **2.123** were also obtained in high yields. In the β-series, **2.117**, **2.119** and **2.120** were also desulfonylated to **2.124**, **2.125** and **2.126** in 76, 42 and 47% yield, respectively.[38]



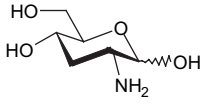
2.121 X = H; Y = OMe; R = NHBn (90%)
2.122 X = H; Y = OMe; R = pyrrolidinyl (91%)
2.123 X = H; Y = OMe; R = morpholinyl (85%)
or
2.124 X = OMe; Y = H; R = NHBn (76%)
2.125 X = OMe; Y = H; R = pyrrolidinyl (42%)
2.126 X = OMe; Y = H; R = morpholinyl (47%)

2.3.4. Synthesis of D-lividosamine and polyaminosugars

The diastereoselective addition of primary amines to **2.94** has been applied to the synthesis of a naturally occurring aminosugar, D-lividosamine, and its analogues.[38] D-Lividosamine (2-amino-2,3-dideoxy-D-glucose) **2.128**, isolated from *Streptomyces lividus*, is present in aminoglycoside antibiotics such as lividomycin B **2.127**.



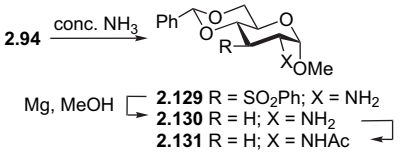
2.127



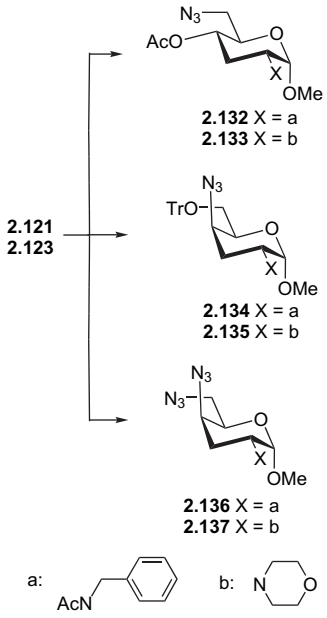
2.128

There is also a need for the development of methodologies for introducing *N*-alkyl and *N*,*N*-dialkyl amino functions at the C-2 equatorial position of carbohydrates, because studies on aminoglycoside antibiotics have shown that the steric bulk and/or varying basicities of amino groups as well as the number of deoxygenated centres in aminosugars plays an important role in determining the antibacterial properties of the aminoglycosides.[38]

The essence of the synthetic strategy leading to the preparation of D-lividosamine **2.128** 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 the C-2 position of pyranosides could have been used as a general route for the synthesis of D-lividosamine and its analogues because of either the undesired configuration or the position of the C–N bond and/or the additional functionalisation of the C-3 hydroxyl group required for the deoxygenation of the C-3 centre. Thus, **2.94** was reacted with concd aq ammonia in dioxane to produce a mixture containing **2.129** in a major amount. The mixture was desulfonylated and the free amino compound **2.130** was acylated. Pure **2.131** crystallised from a benzene–petroleum ether mixture in 65% overall yield.[38] Compound **2.131** was a known intermediate for the synthesis of D-lividosamine **2.128**. It should be noted that **2.121**–**2.123** or **2.124**–**2.126** are the *N*-monoalkylated or *N*,*N*-dialkylated analogues of D-lividosamine reported for the first time in the literature.[38]

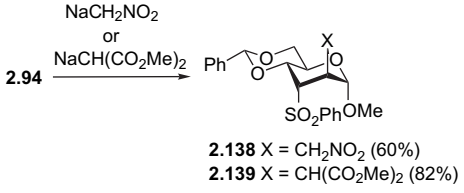


It was possible to widen the application of the above sequence of methodology for the synthesis of several C-3 deoxy polyaminosugars and their analogues. Thus, synthetic manipulations of the desulfonylated compounds **2.121** and **2.123** generated the intermediates **2.132** and **2.133**, respectively, for accessing 2,3,6-trideoxy-2,6-diaminosugars. Similarly, the azido derivatives **2.134/2.135** and **2.136/2.137** are potential intermediates for generating 2,3,4-trideoxy-2,4-diaminosugars and 2,3,4,6-tetradeoxy-2,4,6-triaminosugars, respectively.[39]

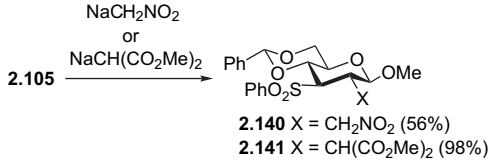


2.3.5. Conjugate addition of carbon nucleophiles

Since the pattern of amine addition to **2.94** and **2.105** was not well defined, it was necessary to study independently the reaction pattern of carbon nucleophiles to these vinyl sulfone-modified carbohydrates. Thus, $NaCH_2NO_2$ reacted with **2.94** to produce a single isomer **2.138** in 60% yield. Similarly, the nucleophile generated from dimethyl malonate and NaH produced exclusively **2.139** in 82% yield.

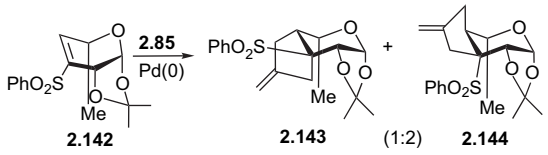


On the other hand, $NaCH_2NO_2$ and $NaCH(CO_2Me)_2$ reacted with **2.105** to produce the single isomers **2.140** (56%) and **2.141** (98%), respectively.[43] It should be noted that, in contrast to the addition pattern of amines to **2.94**, carbon nucleophiles exclusively added to C-2 from a direction opposite to that of the disposition of the anomeric methoxy group.



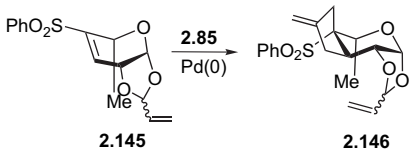
2.3.6. Cycloaddition reactions

In a continuation of the studies on the cycloaddition reactions of vinyl sulfone-modified carbohydrates, the 3,4-unsaturated sulfonyl derivative **2.142** was prepared from L-rhamnose and was treated with the acetate **2.85**, as previously described (Section 2.2.4). The minor product **2.143** was obtained due to β-attack on the more hindered face of the sulfone and the major product **2.144** was a result of an α-attack on the less hindered face.[66]



2.4. Sulfone group attached to C-4 of pyranose ring

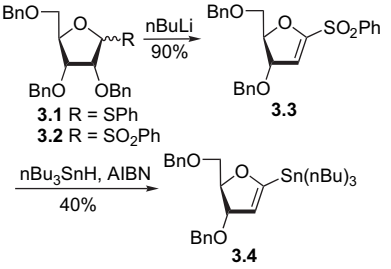
So far, this class of compounds has been mentioned only once in the literature in connection with the work of Holzapfel and van der Merwe.[66] In order to obtain a single product instead of a mixture (e.g., **2.143** and **2.144**), it was possible to design a preferential β-attack by synthesising a regioisomer of **2.142**. Thus, compound **2.145**, possessing a phenylsufonyl group at C-4 instead of C-3, underwent an α-attack via a chair-like transition state to afford only one product **2.146**. This methodology has been put to use in the synthesis of predecessors of the alkaloids, ajmalicine and tetrahydroalstonine.[66]



3. Vinyl sulfone-modified furanoses

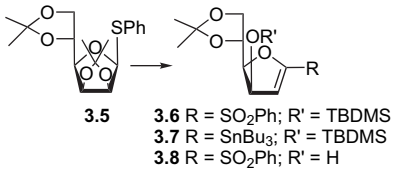
3.1. Sulfone group attached to C-1 of furanose ring

Like their pyranosyl counterparts, most of the furanosyl 1-sulfonyl glycals have been converted into1-tributylstannyl glycals for further synthetic uses. The stannylated 3,5-di-*O*-benzyl furanoid glycal was synthesised by the route previously employed for the preparation of stannylated pyranoid glycals (Section 2.1.2).[51–53] Thus, a phenylthioglycoside **3.1** was oxidised to the corresponding sulfone. Treatment of the sulfone **3.2** with *n*-BuLi resulted in the formation of the unsaturated sulfone **3.3**. 1-Tributylstannyl glycal **3.4** was synthesised by treating the vinyl sulfone **3.3** with *n*-Bu_3SnH–AIBN.[70]

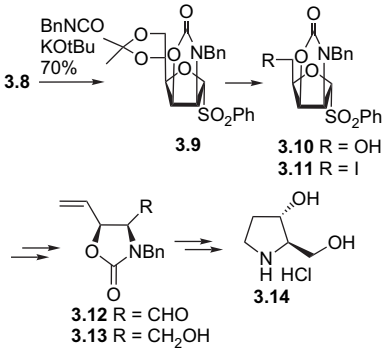


This strategy was broadened further by synthesising a furanosyl 1-phenylsulfonyl glycal **3.6** from the thioglycoside **3.5** in two steps. Like its pyranosyl counterparts **2.16**–**2.19**, the

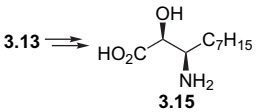
vinyl sulfone **3.6** has been converted into the corresponding 1-tributylstannyl glycal **3.7**.[53]



An interesting application of the furanosyl 1-phenylsulfonyl glycal **3.8** has demonstrated further the utility of this type of building block. Benzyl isocyanate, in the presence of KO*t*-Bu, reacted with the free hydroxyl group of **3.8** and the nitrogen nucleophile of the intermediate intramolecularly attacked the vinyl sulfone group to yield the *cis*-bicyclic oxazolidinone **3.9**. Hydrolysis of **3.9** followed by standard synthetic manipulations afforded the alcohol **3.10**. The alcohol was iodinated to **3.11** and the latter compound was subsequently converted into a 5-vinyl-2-oxazolidone derivative **3.13** via **3.12**. Compound **3.13** was the precursor for the synthesis of the hydrochloride salt of the naturally occurring alkaloid, (2*R*,3*S*)-2-hydroxymethyl-3-hydroxypyrrolidine **3.14**.[71]



The readily accessible 2-oxazolidinone-4-carbaldehyde **3.12** has also proved to be an excellent and practical building block for the synthesis of (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid **3.15**.[72]

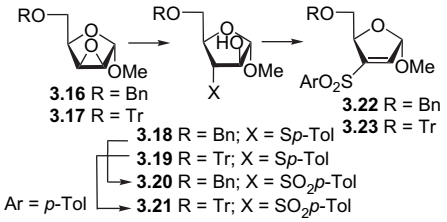


3.2. Sulfone group attached to C-3 of furanose ring

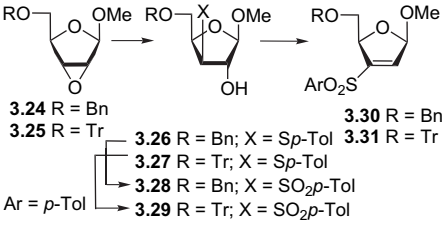
3.2.1. Synthesis of pent-2-enofuranosides

As mentioned in the case of the pyranose derivatives (Section 2.3.1), Pathak and co-workers[41,43,47] were also interested in studying the effect of the anomeric configuration on the diastereoselectivity of the addition of nucleophiles to the 2-position of enofuranoses (see Fig. 1). Therefore, it was necessary to devise a methodology for the synthesis of a relatively large amount of anomerically pure, vinyl sulfone-modified pent-2- and hex-2-enofuranose. In this case, the synthesis of these compounds via the addition of an arylsulfenyl chloride to a suitably protected methyl 2,3-dideoxy-D-pent-2-enofuranoside **2.101** as a method was also ruled out for the reasons discussed in Section 2.3.1.

Vinyl sulfone-modified pent-2-enofuranosides were first synthesised from easily accessible precursors like epoxides. The known *lyxo*-epoxides **3.16** and **3.17**, synthesised from D-xylose, were converted into the vinyl sulfones **3.22** and **3.23** following the reaction sequences of thiation (**3.18/3.19**), oxidation (**3.20/3.21**), and mesylation followed by elimination.



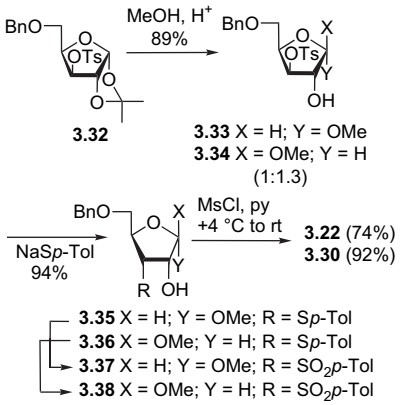
Similarly, the known *ribo*-epoxides **3.24** and **3.25** were converted into the corresponding vinyl sulfones **3.30** and **3.31** via sulfides **3.26/3.27** and sulfones **3.28/3.29**.



It should be noted that these routes allowed the synthesis of vinyl sulfone-modified pentofuranoses having the C-5 hydroxyl function masked with a benzyl as well as an acid-labile trityl protecting group. The separate synthetic routes for the epoxides **3.16/3.17** and **3.24/3.25**, 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 vinyl sulfone-modified pent-2-enofuranosides.[41,42]

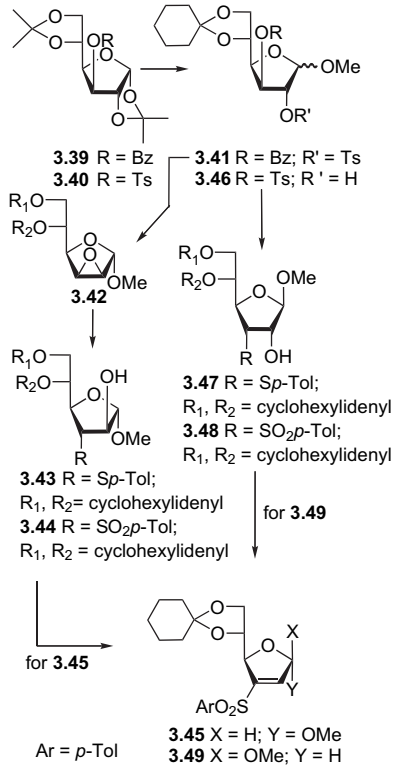
An examination of the percentage compositions of methyl furanosides of D-ribose, D-arabinose, D-xylose and D-lyxose revealed that the ratios of α- and β-furanosides present in equilibrium were 1:3.4, 3.1:1, 1:1.5 and only α-isomer, respectively. Thus, the pattern of glycosylation of various pentose sugars dictated that Pathak and Sanki should select a D-*xylo* derivative-based strategy for the synthesis of an anomeric mixture close to the ideal ratio of 1:1. After several experiments, the following strategy, starting from a single intermediate, was found to be the most suitable. Thus, methanolysis of **3.32** produced an anomeric mixture of **3.33** and **3.34** in a ratio of 1:1.3 (α/β). Nucleophilic displacement of the tosyl group in the mixture of **3.33** and **3.34** by *p*-thiocresolate proceeded smoothly at an elevated temperature to afford a mixture of ribofuranosides **3.35** and **3.36**. Compounds **3.35** and **3.36** were separated and converted via **3.37** and **3.38** into the desired vinyl sulfone-modified carbohydrates **3.22** and **3.30**,

respectively, in the usual manner (described earlier). This synthetic strategy turned out to be the best for the synthesis of **3.22** and **3.30**, starting from a single carbohydrate derivative.[41,42]



3.2.2. Synthesis of hex-2-enofuranosides

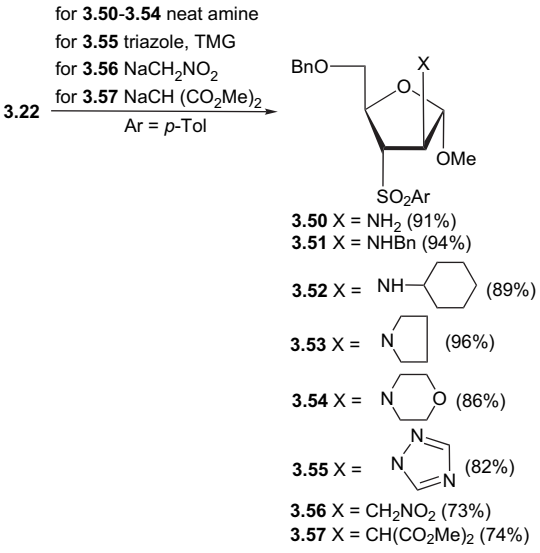
Compared to pent-2-enofuranosides **3.22** and **3.30**, the synthesis of hex-2-enofuranosides was far more complicated because the anomeric ratio of methyl glycosides obtained from **3.39** or **3.40** was far from the ideal value of 1:1. It was therefore necessary to have two different approaches from the most easily accessible glucofuranose intermediates like **3.39** or **3.40**. Thus, benzoate **3.39** on one-pot methanolysis and cyclohexylidenation[73] produced a mixture, which contained the α-anomer in a major amount. Tosylation of the mixture produced **3.41**, which on treatment with base produced an anomeric mixture of epoxides. The α-anomeric epoxide **3.42** was separated from the anomeric mixture and converted into the



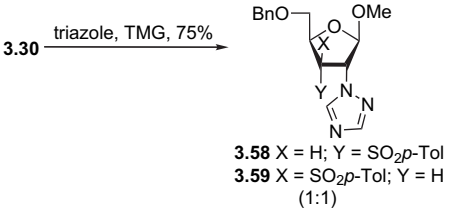
desired α-anomeric vinyl sulfone **3.45** via the sulfide **3.43** and sulfone **3.44** in the usual way. For accessing the β-anomer **3.49**, tosylate **3.40** was converted into a mixture of methyl glycosides **3.46** in which the β-anomer was predominant. Displacement of the tosyl group by thiolate produced **3.47**, which on oxidation produced **3.48**. Mesylation of **3.48** led to the β-anomeric vinyl sulfone **3.49**.[47b]

3.2.3. Conjugate addition of nucleophiles

In order to establish the influence of the anomeric configuration on the diastereoselectivity of the addition of various nucleophiles to the highly reactive, benzyl-protected Michael acceptors **3.22** and **3.30**, these compounds were reacted with various nitrogen nucleophiles. Thus, the reaction of **3.22** with a series of amines produced exclusively compounds **3.50**–**3.54** in high yields.[47a] The reaction of 1,2,4-triazole with **3.22** in the presence of TMG in DMF at ambient temperature produced a single isomer **3.55** in high yield.[41]

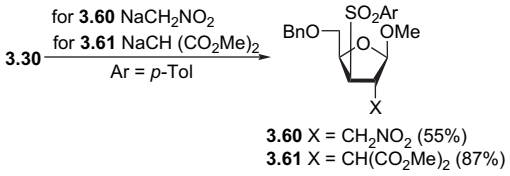


The β-anomer **3.30**, on the other hand, reacted with imidazole to produce a separable mixture (1:1) of a *ribo* derivative **3.58** and a *xylo* derivative **3.59**.[41]



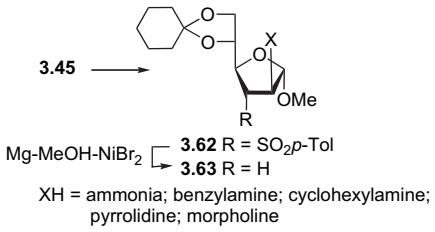
Considering the importance of branched-chain sugars as components of natural products and of functionalised carbohydrates as important intermediates, it was also necessary to study the addition pattern of carbon nucleophiles to vinyl sulfone-modified carbohydrates. Thus, **3.22** on reaction with carbanions generated from $NaCH_2NO_2$ and $NaCH(CO_2Me)_2$ produced the branched-chain sugars **3.56** and **3.57**, respectively.[43] The same carbon nucleophiles, $NaCH_2NO_2$ and

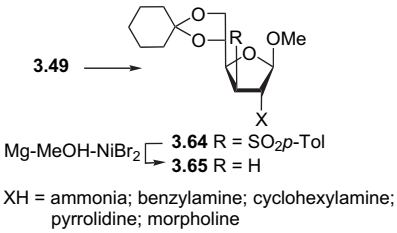
$NaCH(CO_2Me)_2$ produced the desired branched-chain sugars **3.60** and **3.61**, respectively, in a diastereoselective fashion.



It was clear that all the nucleophiles approached the C-2 position from the β-face of the α-anomer **3.22**. For the formation of **3.58**–**3.61**, the nucleophiles attacked the C-2 position of **3.30** exclusively from the α-face.[41,47]

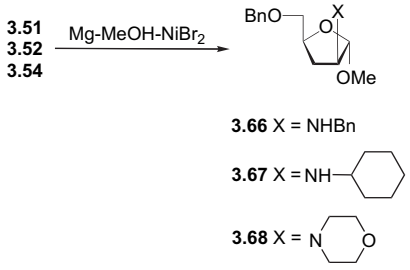
Ammonia, benzylamine, cyclohexylamine, pyrrolidine and morpholine added equally efficiently to **3.45** and **3.49** in a diastereoselective fashion to produce the aminosugars **3.62** and **3.64** in high yields.[47]





3.2.4. Desulfonylation of aminosugars

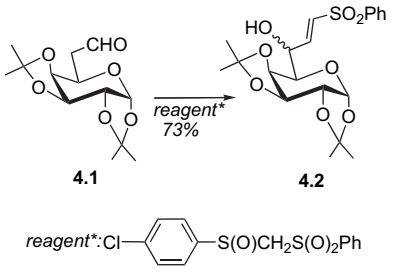
Although pyranosyl aminosugars could be desulfonylated with Mg in MeOH (Section 2.3.3), attempted desulfonylation of a selected group of compounds from the furanosyl series produced inseparable mixtures of compounds. Since the success of a scheme for the synthesis of deoxyaminosugars using vinyl sulfone-modified carbohydrates would depend crucially upon the desulfonylation step, Pathak and Das experimented with a large variety of desulfonylating agents available in the literature. Thus, all of the 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.[47a] It was reported[47a] 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 nickel. This observation prompted Pathak and Das[47] to subject the benzylamino, cyclohexylamino and morpholino derivatives represented by the general structures **3.62** and **3.64** to desulfonylation by the Mg–MeOH–NiX_2 system. All these compounds were desulfonylated to the benzylamino, cyclohexylamino and morpholino derivatives represented by the general structures **3.63** and **3.65**, respectively. Similarly, **3.51**, **3.52** and **3.54** were also converted into the dideoxyaminosugars **3.66**–**3.68**, respectively. Three nickel salts, namely $NiCl_2$, $NiBr_2$ and NiI_2, were employed and $NiBr_2$ was found to be the most efficient for the desulfonylation reaction. Mg–MeOH–$NiBr_2$-based reductive desulfonylation allowed the synthesis of an array of hitherto inaccessible 2-amino-2,3-dideoxypentofuranosides **3.66**–**3.68** and 2-amino-2,3-dideoxyhexofuranosides **3.63** and **3.65**. The yields of the desulfonylation step improved dramatically from 0% with the known reagents to 44–75% with Mg–MeOH–$NiBr_2$.[47]



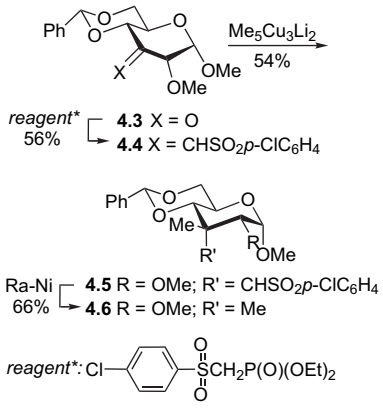
4. Sulfone group attached to an exocyclic carbon

4.1. Pyranosyl exocyclic vinyl sulfones

The first report on the use of a pyranosyl exocyclic vinyl sulfone **1.4** has already been mentioned in Section 1.[31,32] γ-Hydroxy-α,β-unsaturated sulfones have been established as useful acceptors in [3+2] cycloaddition reactions. These compounds were synthesised easily by reacting the corresponding aldehydes with [(4-chlorophenyl)sulfonyl](phenylsulfonyl)-methane. This method has been extended to convert a galactose-derived aldehyde **4.1** into a diastereomeric mixture of γ-hydroxy-α,β-unsaturated sulfones **4.2** as a 7.6:1 mixture of diastereomers.[74] It was expected that the rapid construction of γ-hydroxy-α,β-unsaturated sulfones should greatly enhance their viability as reaction partners for stereoselective organic synthesis.[74]



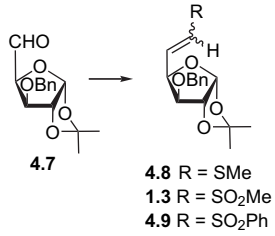
In order to synthesise C-3 geminal di-*C*-methyl pyranoside, ulose **4.3** was converted into the sulfonyl olefin **4.4** by a Horner–Wittig reaction. Michael addition of dilithium pentamethyltricuprate to **4.4** stereoselectively produced **4.5**, which was desulfonylated by Ra–Ni in refluxing ethanol to afford **4.6**.[75]



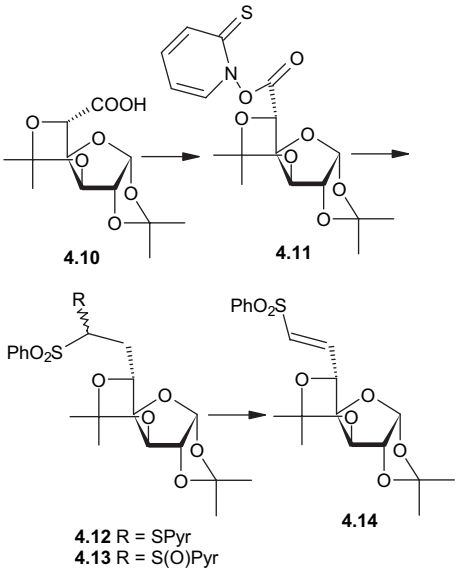
4.2. Furanosyl exocyclic vinyl sulfones

4.2.1. Synthesis

One of the earliest known vinyl sulfone-modified carbohydrates **1.3**, mentioned in Section 1, was synthesised as follows. The sugar-derived aldehyde **4.7** was treated with methylthiomethylene-triphenylphosphorane to obtain **4.8** in 71% yield. The sulfide **4.8** was then oxidised to the desired vinyl sulfone **1.3**.[30]

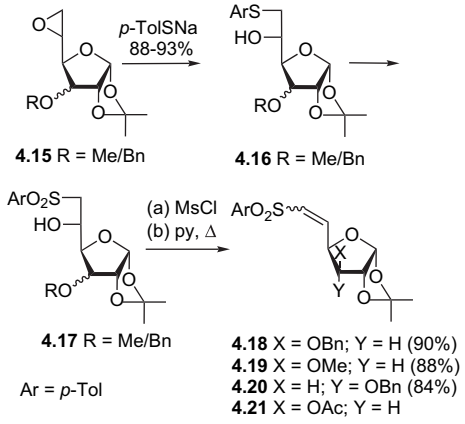


An exocyclic vinyl sulfone-modified carbohydrate has also been synthesised using radical chemistry for the chain elongation at C-5 of pentose sugars. Thus, the bisisopropylidene



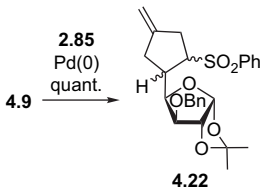
derivative of glucouronic acid **4.10** on conversion into its 2-thiopyridone derivative **4.11** and irradiation with a tungsten lamp in the presence of phenyl vinyl sulfone as a radical trap afforded a mixture of isomers **4.12**. Oxidation to the sulfoxide **4.13** followed by the elimination of pyridyl sulfoxide group afforded the vinyl sulfone-modified carbohydrate **4.14**.[76]

The requirement of relatively large amounts of vinyl sulfone-modified hex-5-enofuranosides again led Pathak and co-workers to devise a simple and general methodology suitable for the large-scale preparation of **4.18** and its analogues such as **4.19/4.20** having various alkyl and aryl groups attached to sulfur. The easily accessible epoxides **4.15** were reacted with sodium tolylthiolate to obtain **4.16** in high yield. Oxidation to **4.17** followed by mesylation and elimination afforded the desired vinyl sulfones **4.18**–**4.20**. Additional experiments established that variation of the group at C-3 affected the *E*/*Z* ratios of the vinyl sulfones.[46]



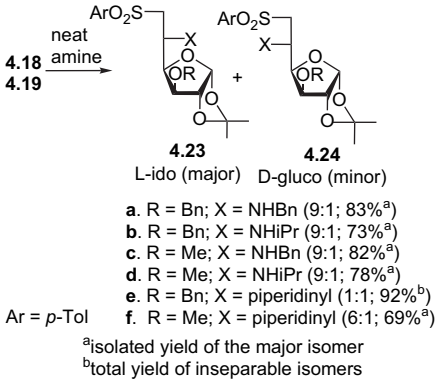
4.2.2. Reactions

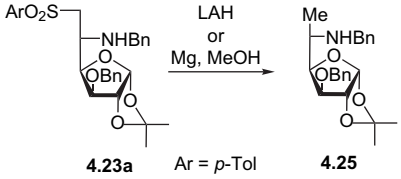
Trost and co-workers introduced γ-alkoxy-α,β-unsaturated sulfones as partners in (3+2) cycloadditions involving the intermediacy of trimethylenemethane–palladium complexes. Thus, the *E*-isomer obtained from a mixture of the glucose-derived vinyl sulfones **4.9** reacted quantitatively with **2.85** to give a 7.5:1 ratio of the two cycloadducts **4.22**.[65]



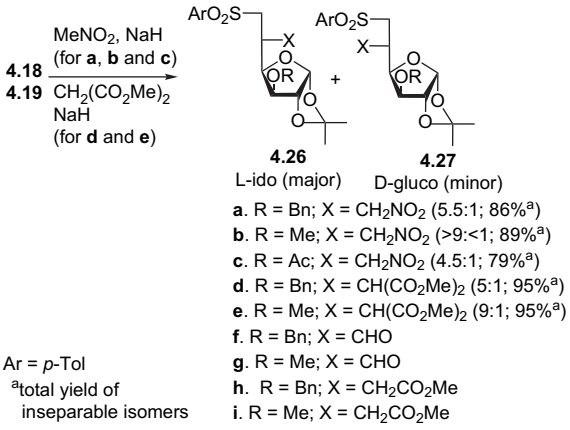
Apart from the above example, the strategy for the functionalisation of a carbon centre away from the pyranose or furanose ring using a vinyl sulfone-modified carbohydrate as a Michael acceptor has never been explored, in spite of the efficient application of the Michael addition reaction to **1.04**.[31] Interestingly, the methods for the functionalisation 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., **4.15**) are regioselectively opened at C-6 when reacted with

nucleophiles. Therefore, the 3-*O*-benzylated *gluco* derivative **4.18** was reacted with neat benzylamine and isopropylamine to produce **4.23a/4.24a** (9:1) and **4.23b/4.24b** (9:1), respectively. In both cases, the *ido* derivatives **4.23a** and **4.23b** were the major products, and these were isolated and identified unambiguously. The 3-*O*-methylated *gluco* derivative **4.19** reacted in a similar fashion with benzylamine and isopropylamine to produce **4.23c/4.24c** (9:1) and **4.23d/4.24d** (9:1), respectively. In this case, the *ido* isomer was also the major product. It is noteworthy that the stereoelectronic effect of OMe at C-3 of compound **4.19** is sufficient to impose diastereoselectivity in favour of the L-*ido* derivative. The influence of C-3 substitution on the diastereoselectivity of addition was established further when the allo derivative **4.20** showed a significant-to-complete lack of diastereoselectivity of addition when reacted with benzylamine and isopropylamine. Compound **4.20**, 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 **4.18** and **4.19** to produce **4.23e/4.24e** (1:1) and **4.23f/4.24f** (6:1), respectively. The allo isomer **4.20** produced the piperidino adduct in a 1:1 ratio. It was possible to desulfonylate **4.23a** to **4.25** using both LAH and Mg in MeOH.[46]

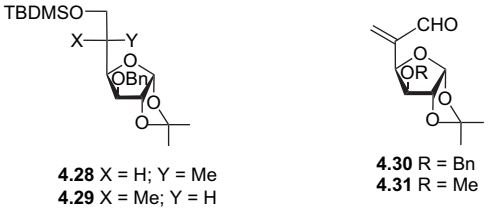




This strategy was exploited further for the diastereoselective C–C bond formation at C-5 of hexofuranosyl carbohydrates using carbon nucleophiles.[48] Thus, vinyl sulfones **4.18** and **4.19** were reacted with $NaCH_2NO_2$ to generate the addition products **4.26a/4.27a** (5.5:1) and **4.26b/4.27b** (>9:<1), respectively, in very good yields. The diastereoselectivity dropped when **4.21** was treated with $NaCH_2NO_2$ to obtain **4.26c/4.27c** (4.5:1). The other nucleophile $NaCH(CO_2Me)_2$ reacted at a much faster rate with **4.18** and **4.19** to generate mixtures of the addition products **4.26d/4.27d** (5:1) and **4.26e/4.27e** (9:1), respectively, in very good yields.

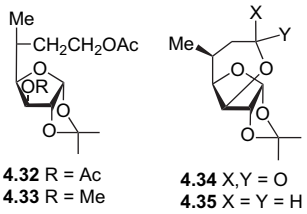


In order to highlight the usefulness of the branched-chain sugars **4.26** and **4.27**, Pathak and co-workers have converted these chirons into important intermediates for further applications in organic synthesis.[48] Thus, the mixtures of **4.26a/4.27a** and **4.26b/4.27b** were subjected separately to a modified Nef carbonyl synthesis to generate **4.26f/4.27f** and **4.26g/4.27g**, respectively. The crude aldehydes **4.26f/4.27f** were reduced to the corresponding alcohols and the latter compounds were protected with a *tert*-butyldimethylsilyl (TBDMS) group; the protected compounds were desulfonylated with Mg in MeOH to generate the branched-chain sugars **4.28** and **4.29**. The debenzylated product obtained from **4.28** has been 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.[48] Alternatively, the sulfonyl group of aldehydes **4.26f/4.27f** and **4.26g/4.27g** was eliminated under basic conditions to yield the single vinyl aldehydes **4.30** and **4.31**, respectively.

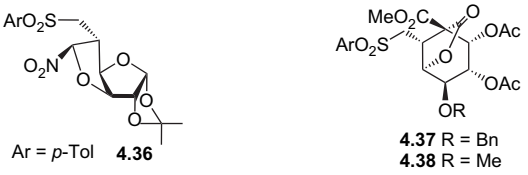


The dimethyl malonate adducts **4.26d/4.27d** and **4.26e/4.27e**, on the other hand, were treated separately with NaCl in a DMSO–H_2O mixture at 130 °C to obtain the corresponding monoesters **4.26h** and **4.26i**. In this case, the minor isomers **4.27h** and **4.27i** could not be isolated. Compounds **4.26h** and **4.26i** after desulfonylation and debenzylation afforded new deoxyheptose sugars, which were isolated, respectively, as the diacetate **4.32** or as the monoacetate **4.33**. Similarly, **4.26h** was easily converted into a bicyclic lactone **4.34** in two steps. Compound **4.34** was shown to be an

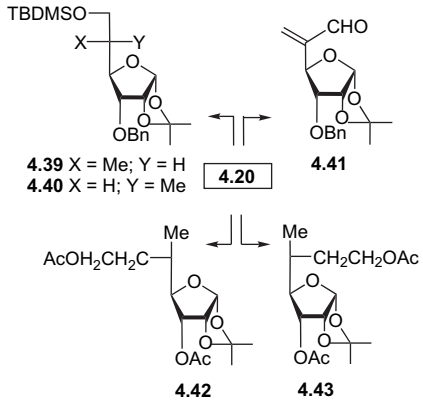
important intermediate, which has been used earlier for the synthesis of (4*R*)-4-[(*E*)-2-butenyl]-4,*N*-dimethyl-L-threonine (MeBmt), a β-hydroxy-α-amino acid.[48] The deoxyheptose sugar obtained from **4.26f** was converted into a structurally related bicyclic derivative **4.35**.



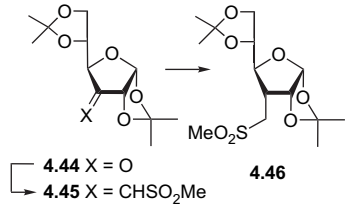
Interestingly, **4.26c/4.27c** on treatment with NaOMe–MeOH followed by Ag_2O–MeI yielded **4.36**. Since one of the most important applications of branched-chain sugars as chirons is in the synthesis of carbocycles, we subjected mixtures of **4.26d/4.26d** and **4.26e/4.26e** separately to deisopropylidenation followed by concomitant cyclisation under acidic conditions. The major products thus obtained were acetylated to furnish the bicyclic lactones **4.37** and **4.38**.[48]



As discussed in the case of the amino compounds above, the diastereoselectivity of the addition of carbon nucleophiles to **4.18** and **4.19** was controlled to a great extent by the configuration and substituents present at C-3. Therefore, as expected, the allo derivative **4.20** showed a complete or significant lack of diastereoselectivity of addition when reacted with carbon nucleophiles. Diastereomers were, however, separated at various stages. The reaction sequences described above generated various chirally pure products **4.39**–**4.43** from **4.20**.

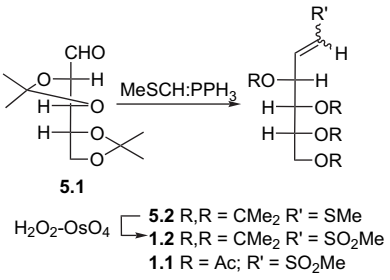


An exocyclic α,β-unsaturated sulfone **4.45**, obtained from 1,2:5,6-diacetone ulose **4.44**, reacted with $[(Ph_3P)CuH]_6$ to generate the reduced product **4.46**.[77]

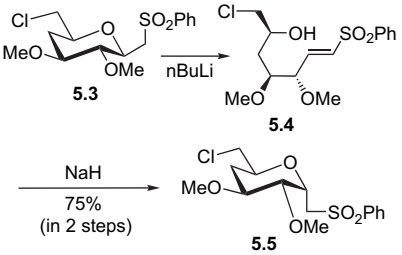


5. Vinyl sulfone group attached to open-chain sugar derivatives

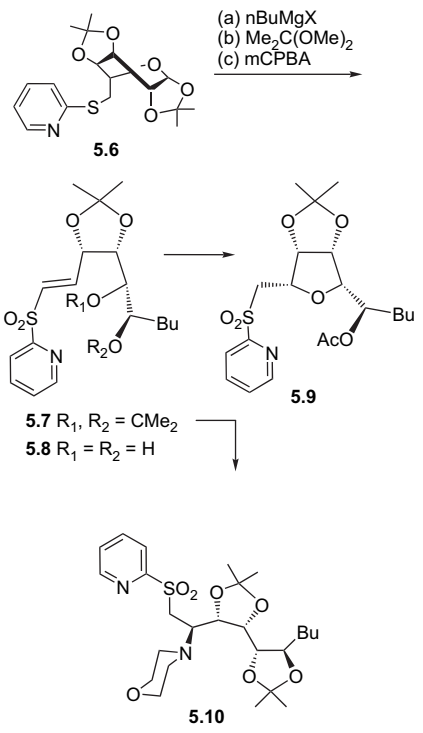
The action of MeSCH:PPh_3 on 2,3-4,5-di-*O*-isopropylidene-aldehydo-D-arabinose **5.1** led with good yields to the corresponding unsaturated sugars **5.2**. Oxidation of **5.2** with H_2O_2–OsO_4 gave the corresponding vinyl sulfones **1.1**. Deprotection of **1.1** followed by acetylation afforded **1.2**.[29]



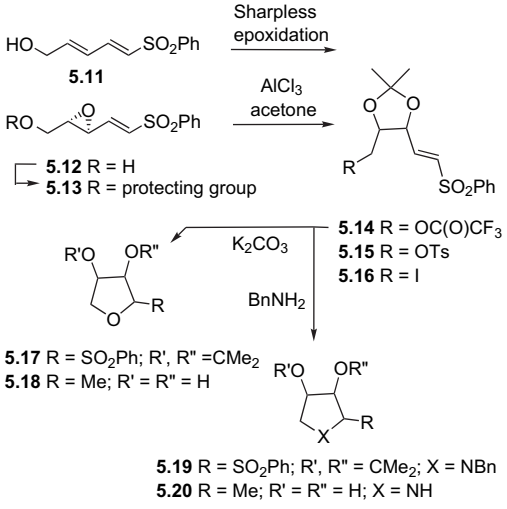
Treatment of **5.3** with *n*-BuLi at −78 °C followed by quenching with HOAc afforded the acyclic vinyl sulfone **5.4**. Treatment of **5.4** with NaH provided a methodology for the synthesis of cyclised products containing the α-isomer **5.5** in a major amount. Compounds **5.3** and **5.5** are potential starting materials for the synthesis of ambruticin.[78]



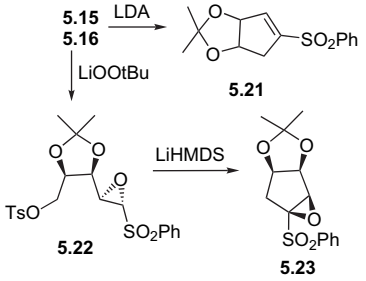
An acyclic vinyl sulfone **5.7** has been synthesised from the aza-heterocycle–thiosugar hybrid **5.6** using a Grob-type heterocyclic process followed by oxidation of the product. Compound **5.8** underwent a Michael-initiated, ring-closure process to build up a chiral polysubstituted oxolan system **5.9** with high stereoselectivity. Compound **5.7** was reacted with morpholine to produce the adduct **5.10** in 80% yield with de >94%.[25,79]



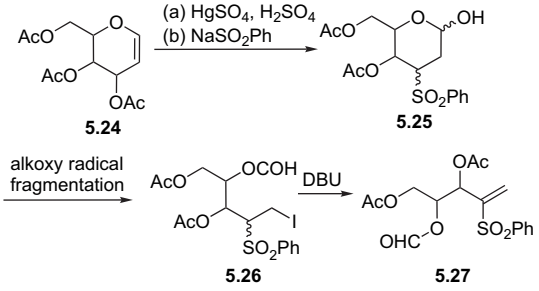
In the recent past, several dihydroxylated acyclic vinyl sulfones, which could be considered as derivatives of pentoses and are somewhat similar to **5.7/5.8**, have been used in the synthesis of diverse groups of heterocyclic and carbocyclic compounds. The synthesis of these vinyl sulfones, however, originated from non-carbohydrate precursors.[80,81] Thus, vinyl sulfone **5.11** was subjected to Sharpless epoxidation with L-(+)-DET to obtain the epoxide **5.12** with an ee of 95%. The regio- and stereoselectivity of the opening of the epoxide leading to diols was controlled by varying the protecting groups on the alcohol **5.13**. Thus, chirally pure and protected diols **5.14** were converted into enantiomeric tetrahydrofurans (+)-**5.17**/(−)-**5.17** and pyrrolidine analogues (+)-**5.19**/(−)-**5.19** by a combination of Michael addition and nucleophilic displacement reactions. These compounds were finally desulfonylated and deprotected to afford (+)-**5.18**/(−)-**5.18** and (+)-**5.20**/(−)-**5.20**.[80]



Vinyl sulfones **5.15** and **5.16** on treatment with LDA gave the cyclopentenone derivative **5.21** in poor yield. Alternatively, treatment of **5.16** with *t*-BuOOLi−K at −78 °C afforded the epoxide **5.22** in excellent yield and with high stereoselectivity. Treatment of the epoxide **5.22** with LiHMDS afforded the cyclised product **5.23** in high yield.[81]



2,3-Dideoxy-3-phenylsulfonyl hexopyranoses **5.25** obtained from the 3-acetylated glycal **5.24** were transformed into β-iodosulfones **5.26** by using (diacetoxyiodo)benzene and iodine via alkoxy radical fragmentation. Dehydroiodination using DBU afforded the acyclic 1,2-dideoxy-4-*O*-formyl-2-(phenylsulfonyl)-pent-1-enitols **5.27**. The configuration of the starting glycal dictated the configurations at the C-3 and C-4 sites of the vinyl sulfones.[82]



6. Monovinyl and acetylenic sulfone-modified pyrimidine nucleosides

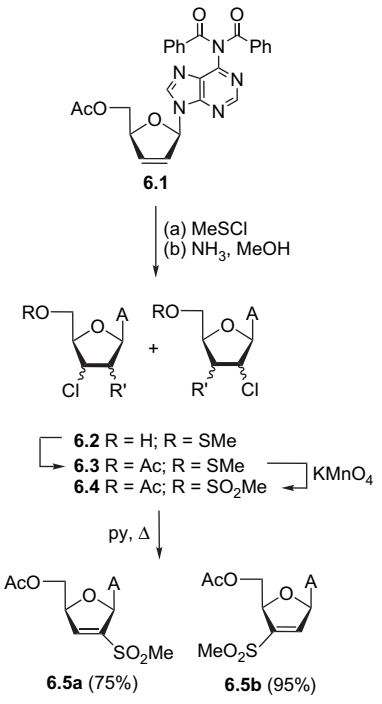
Since 2′,3′-dideoxynucleosides have received increased attention due to their activity against human immunodeficiency virus (HIV), new methods are being developed for the functionalisation of the sugar moiety of a nucleoside.[83] Chattopadhyaya and co-workers introduced vinyl sulfone-modified carbohydrates for the functionalisation of the carbohydrate moieties of the nucleosides.[33] On the other hand, attempts were made to incorporate strongly electrophilic groups in the carbohydrate moieties of nucleosides with the hope that these groups would react with biological nucleophiles such as a non-functionalised thiols or amino groups present in enzymes.[34] Thus, exocyclic vinyl sulfone[34,35] and acetylinic

sulfone[44] were constructed on the carbohydrate moieties of the nucleosides.

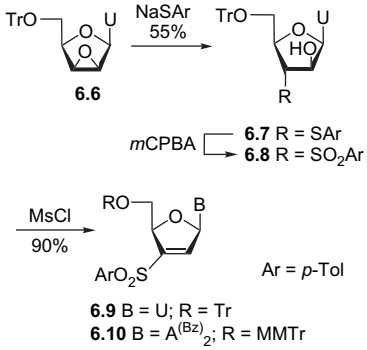
6.1. Endocyclic vinyl sulfone-modified nucleosides

6.1.1. Synthesis

Addition across the double bond was also attempted as a strategy for the functionalisation of the C-2′ and C-3′ positions of nucleosides. This methodology was not completely successful with nucleosides, mainly due to the inert nature of the *endo*-cyclic double bond, as was the case with the carbohydrates **2.100** and **2.101**. Aryl- and alkylsulfenyl chlorides were, however, found to react with olefinic nucleosides. Thus, adenine derivative **6.1** was reacted with PhSCl to obtain all four diastereomers **6.2**. Deprotection followed by selective acetylation of **6.2** afforded **6.3**. Oxidation of **6.3** afforded **6.4**. Treatment of two pairs of diastereomers represented by the general structures **6.4** with pyridine at elevated temperature afforded two isomeric vinyl sulfones **6.5a** and **6.5b**.[67]

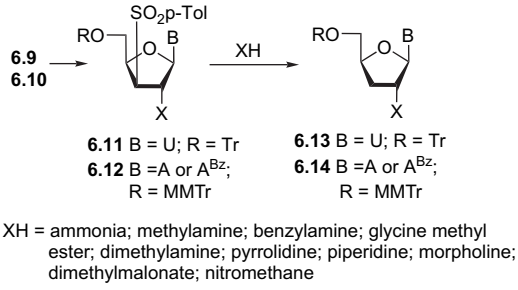


Later, the vinyl sulfone functionality was selected as a tool for the modification of the sugar moiety of nucleosides and a more efficient method for the synthesis of a single regioisomer was devised.[33] Thus, 2′,3′-*O*-anhydro-lyxouridine **6.6** was reacted with *p*-toluenethiolate to generate a mixture of regioisomers from which the 3′-functionalised derivative **6.7** was isolated. Compound **6.7** was oxidised to **6.8**, which on reaction with mesyl chloride in pyridine produced **6.9**. An N^6,N^6-dibenzoyl-5′-*O*-(4-methoxytrityl)-3′-enesulfone derivative of adenosine **6.10** was also synthesised using a similar strategy.[33]

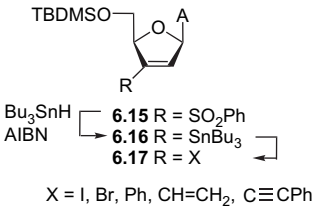


6.1.2. Reactions

Uridine derivative **6.9** on Michael addition of various nucleophiles produced **6.11** in good-to-excellent yields. Desulfonylation of **6.11** with Na-Hg generated 2′,3′-dideoxy analogues **6.13**. Adenine derivative **6.10** also underwent similar addition reactions to generate **6.12**, but the desulfonylation step caused extensive glycosidic bond cleavage resulting in a very poor yield of **6.14**. It is highly probable that the β-configuration of the nucleobases in **6.9** and **6.10** played a decisive role in determining the configuration at the C-2′-position of the products (either *xylo*- or *ribo*-) of the Michael addition reactions.[33]



Vinyl sulfone-modified adenosine **6.15** has been converted into 3′-*C*-tributylstannyl-d_4A **6.16** in the usual way. The latter compound was transformed into a series of olefinic nucleosides **6.17** under different reaction conditions. Vinyl sulfone **6.15** was found to be a better candidate than d_4A for the regiospecific stannylation reaction.[84]

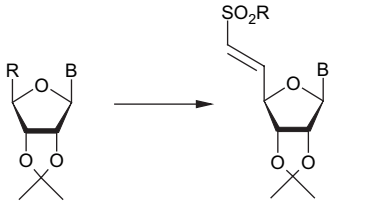


6.2. Exocyclic vinyl sulfone-modified nucleosides

6.2.1. Synthesis

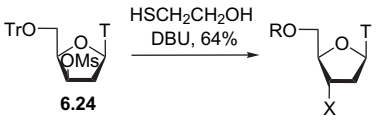
As discussed above (**4.14** from **4.10**), the carboxylic acid derivative of isopropylidene uridine **6.18** was also subjected

to radical reaction in the presence of phenyl vinyl sulfone. Synthetic manipulation afforded the vinyl sulfone **6.21** as a single compound. Similarly, the adenine derivative **6.19** was also converted into **6.22**.[76] A related nucleoside **6.23** was, however, obtained through a much shorter route by reacting aldehyde **6.20** with [(*p*-tolylsulfonyl)methylene]triphenylphosphorane.[85]



6.18 R = CO_2Me; B = U
6.19 R = CO_2Me; B = A^{Bz}
6.20 R = CHO; B = A^{Bz}
6.21 R = Ph; B = U
6.22 R = Ph; B = A^{Bz}
6.23 R = Ph; B = A

1-(2-Deoxy-3-*O*-mesyl-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine **6.24** was treated with 2-mercaptoethanol in the presence of DBU to produce **6.25** in 64% yield. Compound **6.25** was easily oxidised by MMPP to **6.26**. Sulfone **6.26** was converted to the desired vinyl sulfone **6.27** in the usual way. Compound **6.27** could be detritylated, if necessary, to the free hydroxy derivative **6.28** under acidic conditions.[34]



6.24

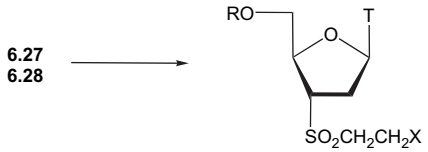
6.25 R = Tr; X = SCH_2CH_2OH
6.26 R = Tr; X = $SO_2CH_2CH_2OH$
6.27 R = Tr; X = $SO_2CH{=}CH_2$
6.28 R = H; X = $SO_2CH{=}CH_2$

(a) MsCl, py
(b) 4 to 60 °C

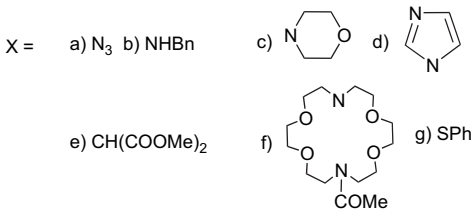
6.2.2. Reactions

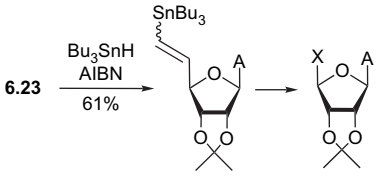
Various nucleophiles such as those derived from hydrazoic acid, benzylamine, morpholine, imidazole, $NaCH(CO_2Me)_2$, 1,4,10,13-tetraoxa-7,6-diazacyclooctadecane and thiophenolate reacted smoothly with either the protected vinyl sulfone **6.27** or the deprotected derivative **6.28** to furnish compounds **6.29a–g** in excellent-to-moderate yields. Selected tritylated products were deprotected using 80% acetic acid at elevated temperature or with ion-exchange resins and collected as the benzoyl derivatives **6.30a**, **6.36e** and **6.39g**.[34]

Compound **6.22** was debenzoylated and the product **6.23** was treated with Bu_3SnH to obtain 6′-vinylstannanes **6.40**. Compound **6.40** was used as a precursor for the synthesis of a wide range of 5′-modified derivatives of adenosine **6.41**.[85]



6.29a R = Tr; X = a
6.30a R = Bz; X = a
6.31b R = H; X = b
6.32c R = Tr; X = c
6.33c R = H; X = c
6.34d R = Bz; X = d
6.35e R = Tr; X = e
6.36e R = Bz; X = e
6.37f R = Tr; X = f
6.38g R = Tr; X = g
6.39g R = Bz; X = g



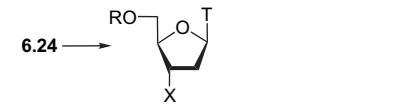


6.40 **6.41**

X =
HC=CH_2, C(Br)=CH_2, HC=CHF/Cl/Br/I, C≡CPh

6.3. Exocyclic acetylenic sulfone-modified nucleosides

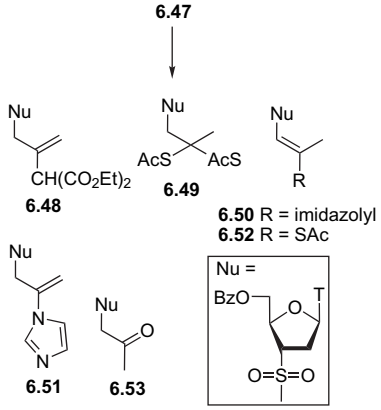
For accessing acetylenic sulfone-modified thymidine, **6.24** was converted into 3′-*S*-(acetylthio)-3′-deoxythymidine **6.42**. Alkaline hydrolysis of **6.42** at low temperature furnished the free thiol derivative **6.43**, which was treated with propargyl bromide in the presence of DBU to furnish the propargylthio derivative **6.44**. Detritylation of **6.44** afforded **6.45**, which was then benzoylated. 5′-*O*-Benzoylated sulfide **6.46** was oxidised to yield the acetylenic sulfone nucleoside **6.47**.[44]



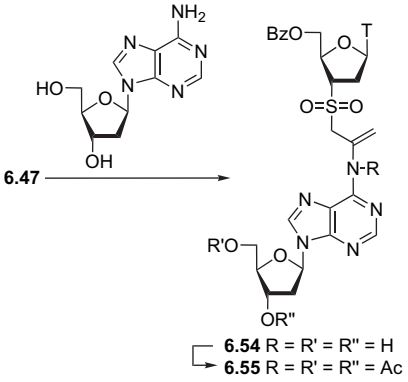
6.42 R = Tr; X = SAc
6.43 R = Tr; X = SH
6.44 R = Tr; X = SCH_2CCH
6.45 R = H; X = SCH_2CCH
6.46 R = Bz; X = SCH_2CCH
6.47 R = Bz; X = SO_2CHCCH_2

Compound **6.47** on reaction with 1 equiv or an excess of $NaCH(CO_2Me)_2$ afforded **6.48**. On the other hand, reaction of **6.47** with 2 equiv of thioacetic acid and DBU produced **6.49**. It is likely that the reaction proceeded through an

intermediate like **6.52**, which underwent further addition of the thioacetate nucleophile to produce **6.49**. Reactions of 2 equiv of imidazole with **6.47** produced a mixture of **6.50** and **6.51** in equal amounts. Interestingly, the reactions of **6.47** with amines produced completely different results. Compound **6.47** on treatment with a strong base and an efficient nucleophile, piperidine, produced a keto derivative **6.53**, whereas a weak base and a lethargic nucleophile, 3-fluoroaniline, also produced the same keto compound **6.53**. It was highly probable that the enamines, which were expected to form, underwent instantaneous hydrolysis to produce **6.53**.



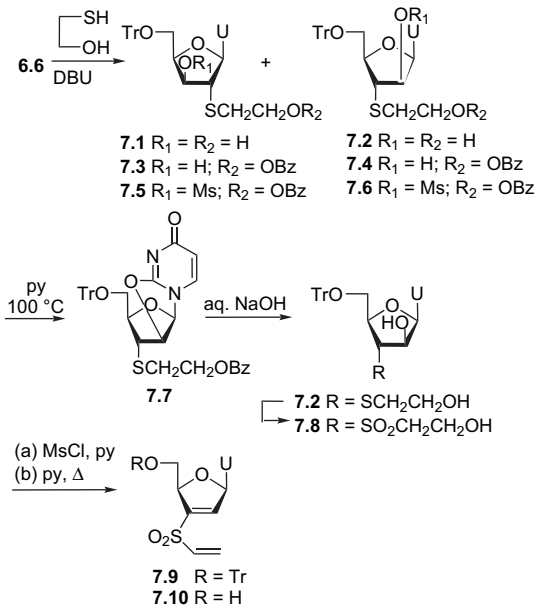
In order to elaborate further on the alkylating properties of **6.47**, 2′-deoxyadenosine was reacted with **6.47**. A stable dimeric product **6.54** was isolated as the triacetate derivative **6.55**, establishing **6.47** as an alkylating agent of a biomolecule like deoxyadenosine.[44]



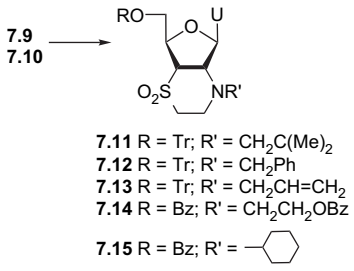
7. Divinyl sulfone-modified pyrimidine nucleosides

Like monovinyl sulfones, the divinyl sulfone group has also been reported to inhibit the action of glyceraldehyde-3-phosphate dehydrogenase. Therefore, as an essential extension of the work reported on the monovinyl sulfone nucleoside **6.28**, Pathak and co-workers decided to incorporate a divinyl sulfone group into the carbohydrate moiety of uridine. It was also envisaged that nucleosides carrying bisvinyl sulfone groups as part of the carbohydrate moieties would generate bicyclic nucleosides when reacted with appropriate nucleophiles.[35]

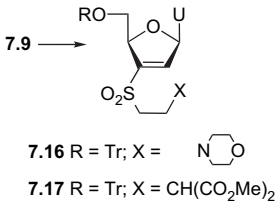
The synthesis of the target bisvinyl sulfone-modified nucleoside started with the epoxide **6.6**, which was reacted with 2-mercaptoethanol in the presence of TMG to generate a mixture of inseparable xylouridine **7.1** and arauridine **7.2** derivatives. The primary hydroxyl groups of the hydroxyethylthio moieties of **7.1** and **7.2** were benzoylated selectively at 0 °C to afford **7.3/7.4**. The secondary hydroxyl groups of **7.3/7.4** were mesylated to produce **7.5/7.6**. The mixture of **7.5/7.6** was heated at 100 °C in pyridine, resulting in the formation of the 2,2′-*O*-anhydro derivative **7.7** via a thiaranium ion intermediate. Debenzoylation and concomitant hydrolysis of the 2,2′-*O*-anhydro bridge of **7.7** produced a single isomer **7.2**. Oxidation of **7.2** and mesylation of the sulfone **7.8** followed by the heating of the product in pyridine produced the desired divinyl sulfonyl uridine **7.9**.



Compound **7.9** on reaction with isobutylamine, benzylamine and allylamine produced the bicyclic derivatives **7.11**–**7.13**, respectively, in high yields and in a stereoselective fashion. The crude divinyl sulfone **7.10**, obtained from **7.9**, was reacted with ethanolamine and cyclohexylamine and the products were isolated as the benzoyl derivatives **7.14** and **7.15**, respectively. All bicyclic products formed in a diastereoselective fashion producing only cis-connectivities at C-2′ and C-3′ of **7.11**–**7.15**; the structures of these compounds were established by an alternative synthesis.



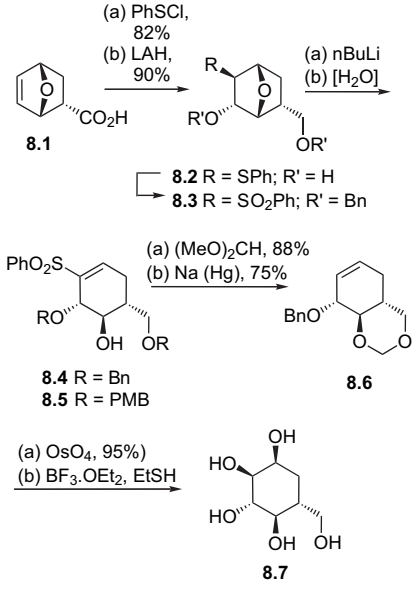
One equivalent of each of morpholine and $NaCH(CO_2Me)_2$ reacted with **7.9** to produce **7.16** and **7.17**, respectively. These reactions demonstrated the higher reactivity of the exocyclic vinyl sulfone group over the *endo*-cyclic moiety.[35,45]



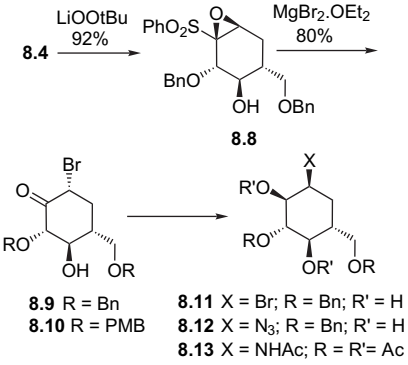
8. Vinyl sulfone-modified carbasugars

Carbasugars are carbocyclic analogues of carbohydrates having a methylene group instead of a ring-oxygen atom. These compounds act as enzyme inhibitors, sweeteners and antibiotics, and are therefore the subject of studies related to new synthetic strategies and structural modifications.[11]

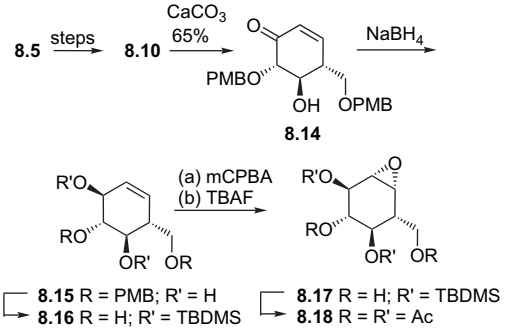
The most widely used intermediates in the synthesis of carbasugars include the 7-oxanorbornenic systems, such as **8.1**. Regio- and stereospecific sulfenolactonization of **8.1** followed by reduction with LAH afforded the diol **8.2**. Benzylation of the hydroxyl groups and oxidation afforded the sulfone **8.3**. Deprotonation with *n*-BuLi followed by hydrolysis resulted in β-elimination of the strained oxygen bridge of **8.3** to provide the vinyl sulfone-modified carbapyranose **8.4**. Compound **8.4** was protected further and the product was desulfonylated to generate the olefin **8.6**. Bis-hydroxylation of **8.6** followed by deprotection produced carba-α-DL-glucopyranose **8.7**.[86]



The diastereoselectivity of the nucleophilic epoxidation of a vinyl sulfone-modified carbasugar like **8.4** depends upon the selection of the protecting groups and the benzyl group of **8.4** that helped in producing a single α,β-epoxy sulfone **8.8**. The stereochemical outcome of the epoxidation of **8.4** was rationalised on the basis of the conformational behaviour of the vinyl sulfone-modified carbasugar, along with the coordinative effects of the homoallylic hydroxyl group. The α-bromo keto derivative **8.9** was obtained as a major compound by epoxide opening with concomitant loss of the phenylsulfonyl group. Compound **8.9** was reduced to the desired alcohol **8.11** as the major component of a diastereomeric 82:13 mixture. Nucleophilic displacement of the bromo group provided the azido alcohol **8.12**, which after reduction followed by acetylation afforded the peracetylated validamine **8.13**. Validamine, an aminocarbasugar is known for its inhibitory activity against various glucose hydrolases. Several diastereomers of validamine have also been synthesised using this strategy.[87]

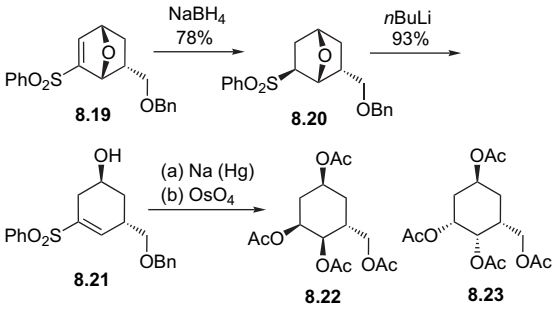


A similar stereodivergent approach has been utilised in the synthesis of a racemic mixture of a naturally occurring carbasugar cyclophellitol, which is a potent β-glucosidase inhibitor. The synthesis started with **8.10**, which was obtained from the vinyl sulfone-modified carbasugar **8.5**. Dehydrobromination afforded the α,β-unsaturated ketone **8.14**. Selective reduction of the ketone to the alcohol **8.15** followed by protection with a TBDMS group and deprotection of the PMB group afforded **8.16**. As mentioned earlier (**8.4** to **8.8**), the epoxidation of the alkene is controlled by the nature of the hydroxyl protecting group; in this case, the epoxidation of **8.16** produced **8.17**. Deprotection followed by acetylation produced peracetylated (±)-cyclophellitol **8.18**.[88]

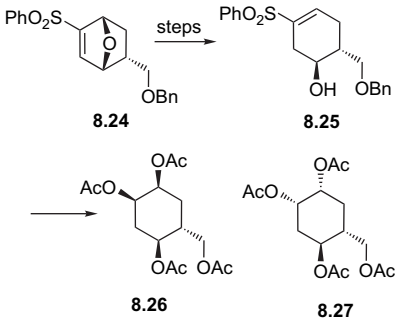


Vinyl sulfone-modified carbapyranoses were used further for the synthesis of several new 2- or 3-deoxy carbapyranoses. Thus, compound **8.20**, obtained by the Michael addition of a hydride ion to **8.19**, was subjected to *n*-BuLi-mediated

cleavage of the ether linkage; the product of this reaction **8.21** was desulfonylated and the olefin was subjected to bis-hydroxylation (see **8.4** to **8.7**). Separation of the isomers and protecting group manipulation produced peracetylated 2-deoxy-5a-carba-α-DL-allopyranose **8.22** and 2-deoxy-5a-carba-α-DL-galactopyranose **8.23**.



Using a similar strategy, **8.24** was converted into the vinyl sulfone-modified carbapyranose **8.25**. Hydride addition to **8.25** followed by synthetic manipulations described earlier generated 3-deoxy-5a-carba-α-DL-glucopyranose **8.26** and 3-deoxy-5a-carba-β-DL-mannopyranose **8.27**.[89]



9. Concluding remarks

With the help of several scattered and rather unrelated examples of vinyl sulfone-modified carbohydrates compiled from literature, an attempt has been made to draw the attention of synthetic chemists to the fact that this class of compounds has the potential to act as an unlimited and versatile source of chiral building blocks. This area remains under-explored and under-utilised as is evident from the limited number of publications. Interestingly, vinyl sulfones were reported to inhibit the action of glyceraldehyde-3-phosphate dehydrogenase and vinyl sulfone containing dipeptides were shown to be efficient cysteine protease inhibitors through covalent bond formation with the enzymes.[15,34,35] The inherent nucleophilic reactivity of the cysteine thiolate moiety, which in part defines the cysteine proteases, has led to the design of irreversible inhibitors based on vinyl sulfones; studies have suggested strongly that an inhibitor of cathepsin K may be an effective therapeutic agent for the prevention and treatment of osteoporosis.[90] Vinyl sulfones have also been shown to be effective inhibitors against cruzain, a cysteine protease that plays a crucial role in the life cycle of *Trypanosoma cruzi*, the aetiologic agent of Chagas′disease.[15] In addition to acting as cysteine protease inhibitors, vinyl sulfones have also recently been shown to inhibit *Staphylococcus aureus* sortase and HIV-1 integrase; vinyl geminal disulfones have been described as potent inhibitors of HIV-1 integrase, which is responsible for inserting double-stranded viral DNA into the host genome where it is then replicated using cellular machinery.[15] Surprisingly, no biological data on any vinyl sulfone-modified carbohydrate are available in the literature to date.[15,90] The vast area of vinyl sulfone-modified carbohydrates or intermediates, which can generate vinyl sulfone-modified carbohydrates in situ, therefore remains essentially untapped.

The results reported in this review are a pointer to the usefulness of the combination of vinyl sulfone groups and carbohydrates in the synthesis of wide-ranging modified carbohydrates—cyclic as well as acyclic, nucleosides and carbasugars. It is clearly evident from the discussions in the preceding sections that two main types of chemical reactions, namely Michael addition and desulfostannylation, have been successfully implemented using vinyl sulfone-modified carbohydrates as substrates. The vast potential of vinyl sulfone-modified carbohydrates and their down-stream products as chirally pure synthetic intermediates and certainly as new chemical entities for targeting biological macromolecules is yet to be unearthed.

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