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VINYL SULFONE-MODIFIED CARBOHYDRATES: SYNTHESIS AND REACTIONS WITH NUCLEOPHILES

ADITYA KUMAR SANKI# AND TANMAYA PATHAK*

Department of Chemistry, Indian Institute of Technology, Kharagpur – 721 302 (India)

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1 Introduction

Amongst various functionalized sulfones, α,β-unsaturated- or vinyl sulfones have now become generally accepted as useful intermediates in organic synthesis. The vinyl sulfones serve efficiently as both Michael acceptors and a 2π-partner in cycloaddition reactions.[1,2] Carbohydrates, on the other hand, are used extensively as chiral building blocks for the synthesis of various complex molecules.[3-6] The preliminary requirement of such a synthesis is the functionalization of the sugar molecules at the monosaccharide level. Carbohydrates are normally modified *via* their sulfonates, epoxides, olefins, ketones or olefinic derivatives.[7] Due to the high reactivities of vinyl sulfones towards an array of nucleophiles,[1] vinyl sulfone-modified carbohydrates could be used to generate a wide variety of modified monosaccharides.

Vinyl sulfone-modified carbohydrates have the potential for utilization in organic synthesis because (a) almost all carbohydrates, either in pyranose or furanose forms, could be converted to their vinyl sulfone derivatives very easily -the first step being the simple nucleophilic displacements of sulfonates or regioselective (*trans*-diaxial) opening of epoxides by alkyl or aryl mercaptans at various positions,[7] (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] and (c) after using the vinyl sulfone moiety as a tool for functionalization, whenever necessary, the sulfone group could be removed using different reaction conditions so as to functionalize the carbon attached to the sulfone group.[2]

Although vinyl sulfones have been used extensively in synthetic transformations, vinyl sulfone-modified carbohydrates are yet to be used effectively in synthetic organic chemistry. The methodologies discussed above are also applicable to the modification of the carbohydrate moieties of nucleosides. However, vinyl sulfone group may have the additional potential to be used for biological reactions. These aspects have been discussed separately immediate before describing the chemistry of the relevant nucleosides.

2 Background

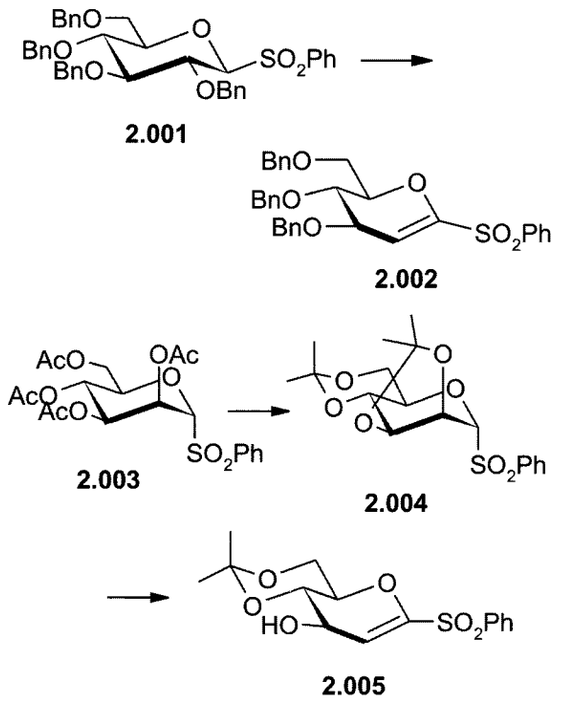
2.1 Vinyl Sulfone-modified Pyranoses

2.1.1 Sulfone Group Attached to C- 1 of Pyranose Ring

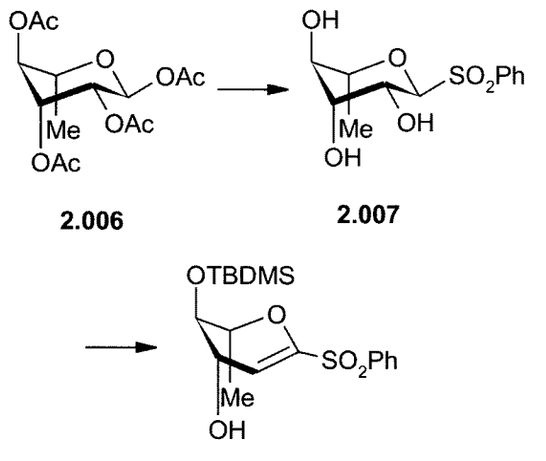
Ferrier and co-workers reported a vinyl sulfone-modified carbohydrate for the first time in 1977 when the attempted displacement of the phenylsulfonyl group from 2,3,4,6-tetra-*O*-benzyl-β-D-*gluco*pyranosyl sulfone **2.001** produced the unwanted vinyl sulfone-modified carbohydrate **2.002**.[8]

Later, in order to access 1-sulfonyl glycals, D-mannosyl sulfone **2.003** was prepared from the corresponding thioglycoside by oxidation. The sulfone tetra-*O*-acetate **2.003** was deacetylated and the tetrol was converted to bisisopropylidene derivative **2.004**. The bisacetal **2.004** was subjected

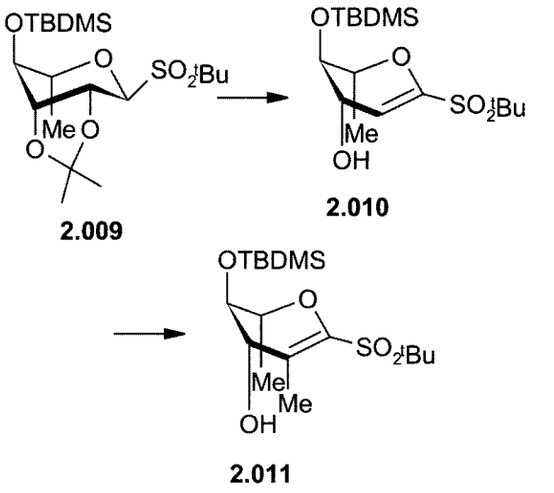
#Present address: Department of Chemistry and Biochemistry, The University of Texas at Austin, 1 University Station, A5300, Austin, Texas 78712-0165, USA.
*Corresponding author
Tel.: (03222)-283342/282251
Fax: (03222)-282252
email: tpathak@chem.iitkgp.ernet.in



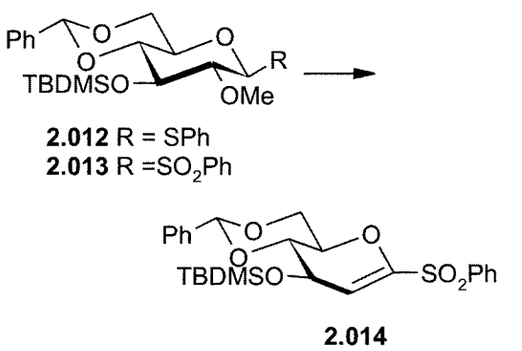
to base-promoted elimination to form the vinyl sulfone derivative **2.005**.[9] L-Rhamnopyranose tetra-*O*-acetate **2.006** was similarly converted to the corresponding vinyl sulfone **2.008** *via* phenyl sufonylglycoside **2.007**. However, vinyl sulfones like **2.005** and **2.008** did not undergo Michael addition reactions with methyl lithium or any other nucleophile.[9] A vinyl sulfone **2.010** carrying a bulky *tert*-butyl group was synthesized from **2.009** and reacted with methyl lithium. No Michael addition occurred and lithiation at C-2 occurred instead. Subsequent reaction of the lithiated species with iodomethane produced 2-methyl vinyl sulfone



2.011. The presence of the ring oxygen α to the sulfone group deactivated the double bond through delocalization of lone pair of electrons and made these vinyl sulfone-modified carbohydrates too unreactive to undergo Michael addition.[9]

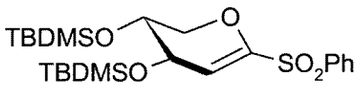


Although 1-sulfonyl glycals did not undergo Michael addition reactions, 1-phenylsulfonyl glucal **2.014** was synthesized from **2.012** and used as a precursor for stannyl-D-glucals because 1-tributylstannyl-D-glycals in general are valuable intermediates for *C*-glycosylation reactions.[10] Recently, 1-phenylsulfonyl glycals **2.015-2.017** as well as **2.014** have been synthesized through modified routes.[11] These glycals undergo an easy Ni(0)-catalyzed coupling with tributylstannyl-magnesium bromide to give the corresponding 1-tributylstannyl glycals.[10,11]

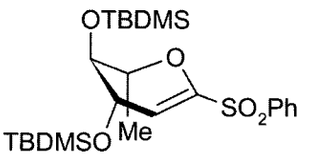


2.1.2 Sulfone Group Attached to C-2 of Pyranose Ring

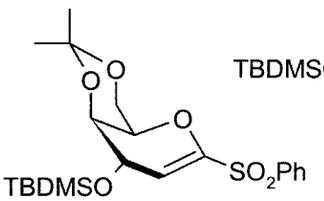
Sugar derivatives having an α-sulfonylalkene moiety constructed on a pyranose ring, hex-2-enopyranoside **2.020** was synthesized by reacting



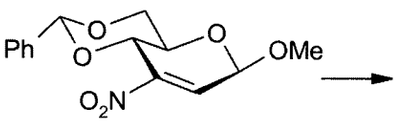
2.015



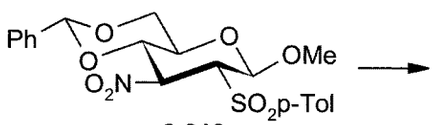
2.017



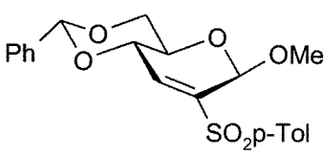
2.016



2.018

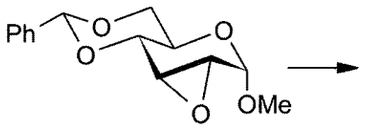


2.019

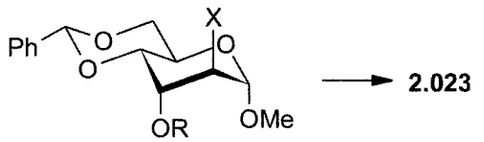


2.020

2.018 with sodium *p*- toluenesulfinate in the presence of acetic acid followed by the treatment of the *gluco*-derivative **2.019** with triethylamine.[12] The α-anomer **2.023** was synthesized in very poor yield from the 3-nitro-hex-2-enopyranoside **2.021** *via* *manno*pyranoside derivative **2.022**. The *galacto*-isomer **2.024** produced the corresponding sulfonyl alkene **2.026** in a similar fashion *via* **2.025**.[12] Due to the difficulties in obtaining compound **2.023** through this route an alternative method for its preparation was developed. Thus, 2,3-anhydro-α-D-*allo*pyranoside **2.027** was treated with sodium *p*-thiocresolate and the product **2.028** was oxidized to **2.029**. Compound **2.029** on mesylation in the presence of triethylamine afforded the vinyl sulfone **2.023** *via* mesylated derivative **2.030**.[12]

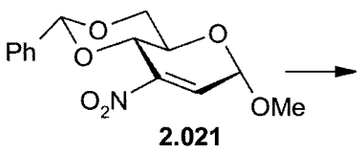


2.027

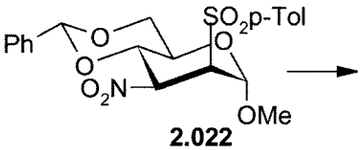


2.028 X = Sp-Tol; R = H
2.029 X = SO_2p-Tol; R = H
2.030 X = SO_2p-Tol; R = Ms

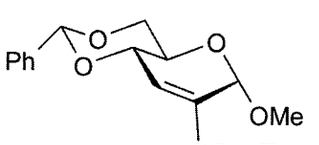
Vinyl sulfone **2.020**, on treatment with methanol, nitromethane, 2,4-pentanedione and ammonia produced the corresponding β-D-*gluco*-adducts **2.031-2.034**, respectively in high yields with high stereoselectivities.[12] Interestingly, the α-anomeric vinyl sulfone **2.023** on treatment with sodium methoxide in methanol underwent elimination instead of addition to afford **2.035**.[13] Treatment of the phenyl analog **2.036** with nitromethane led



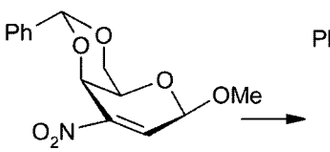
2.021



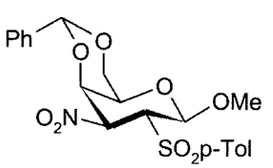
2.022



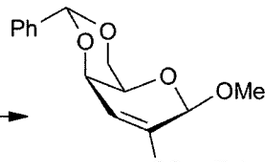
2.023



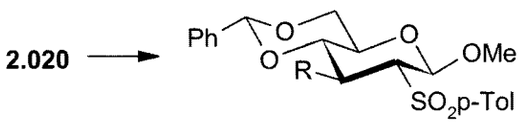
2.024



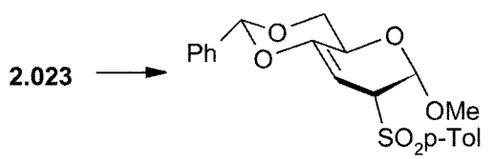
2.025



2.026

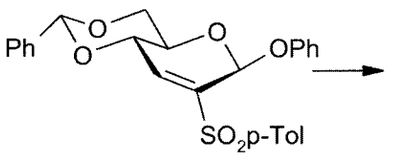


2.031 R = OMe
2.032 R = CH_2NO_2
2.033 R = $CHAc_2$
2.034 R = NHAc

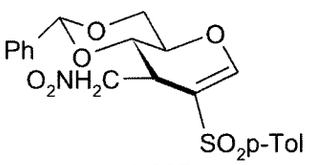


2.035

mainly to an S_N2' process to give 1-enitol derivative **2.037** having the *arabino-* configuration.[13]

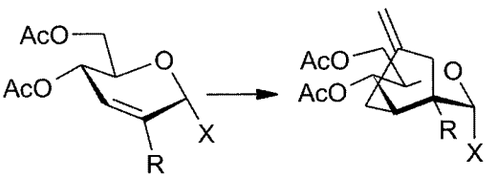


2.036



2.037

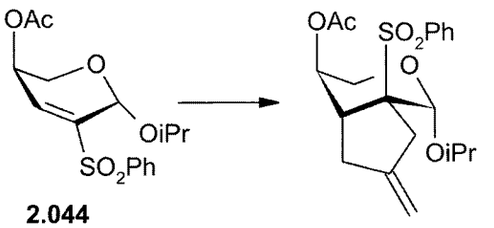
Substrates like **2.038** underwent (3+2) cylcoaddition with a trimethylmethylene zwitterion (precursor **2.039**) in the presence of an *in situ*-generated Pd (0) catalyst to afford an inseparable mixture of two isomers **2.040** and **2.041**.[14] Related vinyl sulfones **2.042** and **2.044**, on the other hand, produced the corresponding 5,6-bicycles **2.043** and **2.045**, respectively possessing *exo*-cyclic unsaturation. These reactions are thought to follow a two-step sequence involving an initial Michael-



2.042 **2.043**

X = O^{i}Pr; R = SO_2Ph

type addition to the electron deficient double bond followed by an attack of the resultant stabilized anion on the palladium complex.[14]

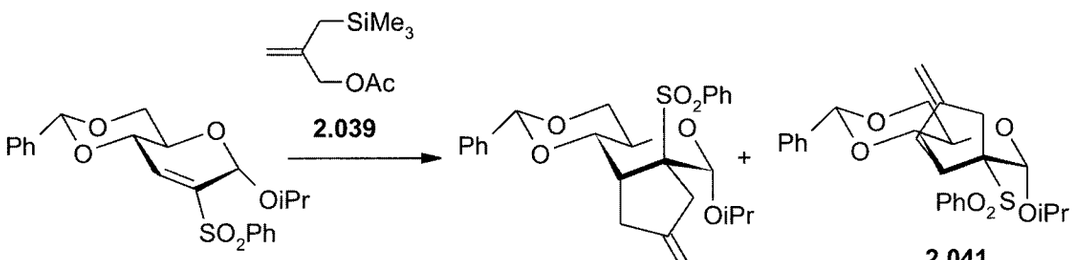


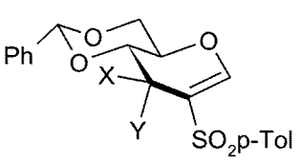
2.044 **2.045**

Compound **2.020** on irradiation with high-pressure mercury lamp in methanol generated a mixture of **2.046** (4%), **2.050** (9%), **2.049** and **2.052** (55% together). The phenyl analog **2.036** also generated a mixture of **2.047** (37%), **2.048**(24%) and **2.051**(11%). In all these cases, equatorial attack by hydroxymethyl radical is slightly predominated over the axial attack. However, due to uncontrolled mixture formation, this particular photoreaction using vinyl sulfone-modified carbohydrates has very little synthetic utility.[15]

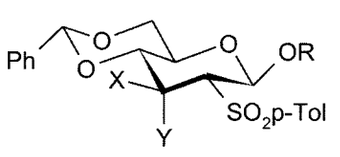
2.1.3 Sulfone Group Attached to C-3 of Pyranose Ring

As has been the case for the conversion of **2.021** to **2.023**, 3-(*p*)-tolylsulfonyl-hex-2-enopyranoside **2.055** was also obtained in poor yield when synthesized from 2-nitrohex-2-enopyranoside **2.053** *via* **2.054**. Therefore, an alternative route for the

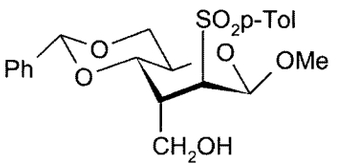




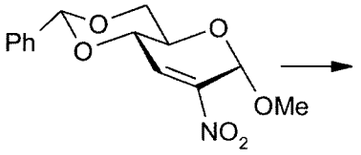
2.046 X = CH_2OH; Y = H
2.047 X = CH_2OAc; Y = H
2.048 X = H; Y = CH_2OAc



2.049 R = Me; X = CH_2OH; Y = H
2.050 R = Me; X = H; Y = CH_2OH
2.051 R = Ph; X = CH_2OAc; Y = H



2.052



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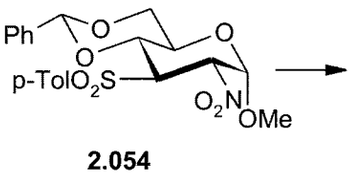
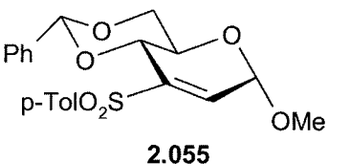


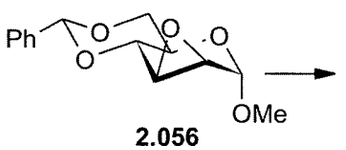
2.054



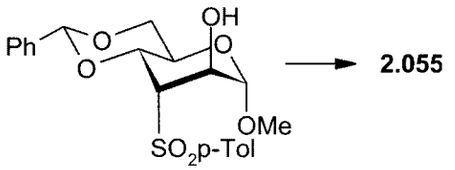
2.055

synthesis of **2.055** was devised from 2,3-*O*-anhydro-α-D-*manno*pyranoside **2.056** *via* **2.057**.[12]

In continuation with the studies on the cycloaddition reactions of vinyl sulfone-modified carbohydrates, the 3,4-unsaturated sulfonyl derivative **2.058** was prepared from L-rhamnose and was treated with acetate **2.039** as previously described.[14] The minor product **2.059** was obtained due to β-attack on the more hindered face of the sulfone and the major product **2.060** was a result of a α-attack on the less hindered face.[14]



2.056



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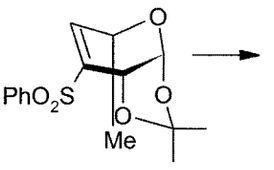
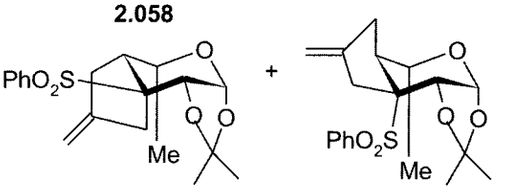
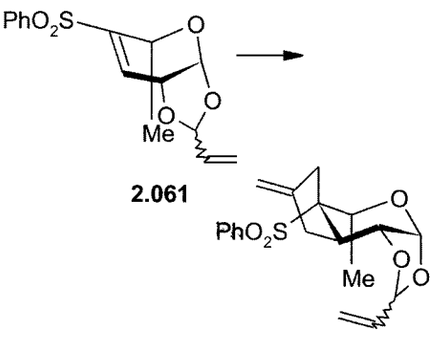


2.058



2.059 (1:2) **2.060**



2.061

2.062

2.1.4 Sulfone Group Attached to C-4 of Pyranose Ring

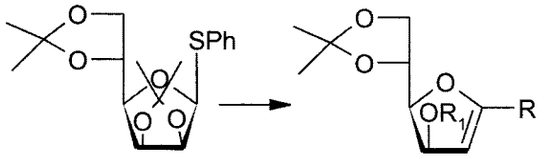
In order to obtain a single product instead of a mixture (e.g. **2.059** and **2.060**), it was possible to design a preferential α-attack by synthesizing a regioisomer of **2.058**. Thus, compound **2.061**, possessing a phenylsufonyl group at C-4 instead of C-3, underwent an α-attack *via* a chair-like transition state to afford only one product **2.062**. This methodology has been put to use in the synthesis of predecessors of the alkaloid ajmalicine and tetrahydroalstonine.[14]

2.2 Vinyl Sufone-modified Furanoses

2.2.1 Sulfone Group Attached to C-1 of Furanose Ring

A furanosyl 1-phenylsulfonyl glycal **2.064** has been synthesized from the thioglycoside **2.063** in

two steps. Like its pyranosyl counterparts **2.014-2.017**, vinyl sulfone **2.064** has been converted to the corresponding 1-tributylstannyl glycal **2.065**.[11]

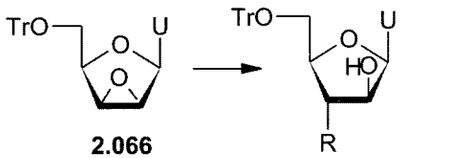


2.063 **2.064** R = SO_2Ph; R_1 = TBDMS
2.065 R = $SnBu_3$; R_1 = TBDMS

2.2.2 Sulfone Group Attached to C-3 of Furanose Ring

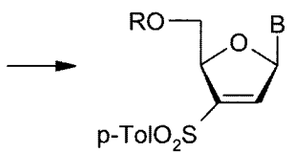
Since 2′,3′-dideoxynucleosides have received increased attention due to their activity against human immunodeficiency virus (HIV),[16] new methods are developed for the functionalization of the sugar moiety of a nucleoside. The methodology of addition across the double bond was not successful with nucleosides partly due to the inert nature of the *endo*-cyclic double bond. Vinyl sulfone, was therefore selected as a tool for the functionalization of the sugar moiety of nucleosides.[17]

2′,3′-*O*-Anhydro-*lyxo*uridine **2.066** was reacted with *p*-toluenethiolate to generate a mixture of regioisomers from which the 3′-functionalized derivative **2.067** was isolated. Compound **2.067** was oxidized to **2.068**, which on reaction with mesyl chloride in pyridine produced **2.069**. N^6,N^6-Dibenzoyl-5′-*O*-(4-methoxytrityl)-3′-enesulfone derivative of adenosine **2.070** was also synthesized



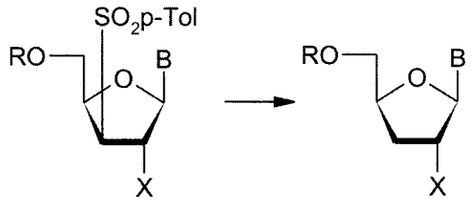
2.066

2.067 R = Sp-Tol
2.068 R = SO_2p-Tol



2.069 B = U; R = Tr
2.070 B = $A^{(Bz)}_2$; R = MMTr

in a similar fashion. Uridine derivative **2.069**, on Michael addition of various nucleophiles produced **2.071**. Desulfonation of **2.071** generated 2′,3′-dideoxy analogues **2.073**. Adenine derivative **2.070** also underwent similar addition reactions to generate **2.072** but the desulfonation step caused extensive glycosidic bond cleavage resulting in very poor yield of **2.074**. It is highly probable that the



2.071 B = U; R = Tr
2.072 B =A or A^{Bz}; R = MMTr

2.073 B = U; R = Tr
2.074 B =A or A^{Bz}; R = MMTr

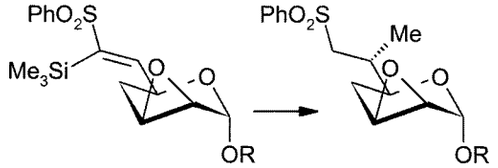
XH =
ammonia; methylamine; benzylamine; glycine methyl ester; dimethylamine; pyrrolidine; piperidine; morpholine; dimethylmalonate; nitromethane

β-configuration of the nucleobases in **2.069** and **2.070** played a decisive role in determining the configuration at C-2′-position of the products (either *xylo*- or *ribo*-) of Michael addition reactions.[17]

2.3 Sulfone Group Attached to an Exocyclic Carbon

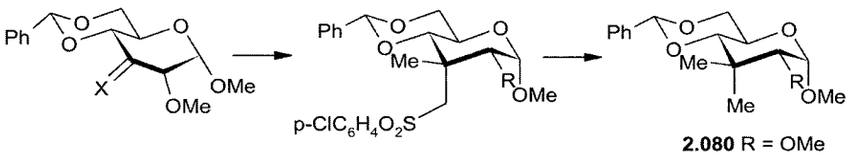
2.3.1 Pyranosyl Exocyclic Vinyl Sulfones

A pyranose derivative **2.075** having a 2-phenylsulfonyl-2-trimethylsilyl vinyl group has been used for the synthesis of (±)-maytansinol; the synthesis initiated by the heteroconjugate addition of MeLi to **2.075** to obtain **2.076**. The addition of MeLi accomplished the complete acyclic stereoselection in the pyranosyl hetero-olefin **2.075**.[18]



2.075 **2.076**

R = CH_2CH_2OMe



2.077 X = O
2.078 X = $CHSO_2p\text{-}ClC_6H_4$

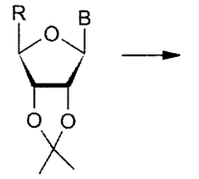
2.079 R = OMe

2.080 R = OMe

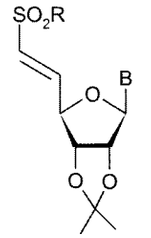
In order to synthesize C-3 geminal di-*C*-methyl pyranoside, ulose **2.077** was converted to sulfonyl olefin **2.078** by Horner-Wittig reaction. Michael addition of dimethyl cuprouslithium to **2.078** produced **2.079**, which was desulfonated by Ra-Ni in refluxing ethanol to produce **2.080**.[19]

2.3.2 Furanosyl Exocyclic Vinyl Sulfones

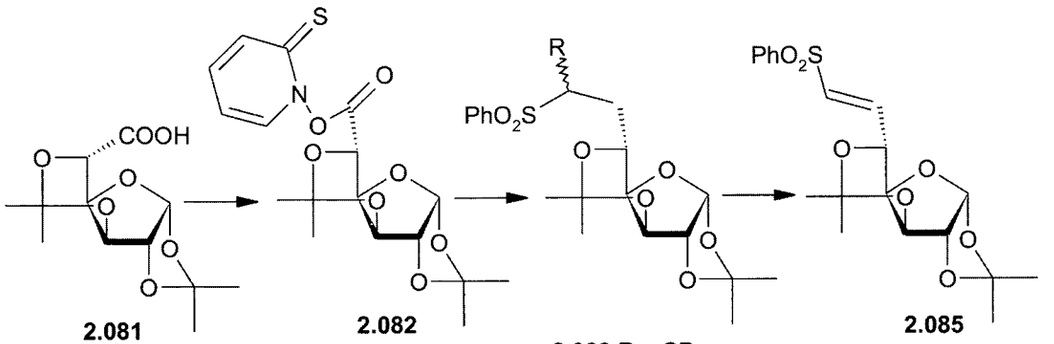
Vinyl sulfone-modified carbohydrates has been synthesized using radical chemistry for the chain elongation at C-5 of pentose sugars. Thus, the bisisopropylidene derivative of glucouronic acid **2.081** on conversion to its 2-thiopyridone derivative **2.082** and irradiation with tungstane lamp in the presence of phenyl vinyl sulfone as a radical trap afforded a mixture of isomers **2.083**. Oxidation to sulfoxide **2.084** followed by the elimination afforded pure alkene **2.085**.[20] The carboxylic acid derivative of isopropylidene uridine **2.086** was also subjected



2.086 R = CO_2Me; B = uracilyl
2.087 R = CO_2Me; B = N^6-benzoyladeninyl
2.088 R = CHO; B = N^6-benzoyladeninyl



2.089 R = Ph; B = uracilyl
2.090 R = Ph; B = N^6-benzoyladeninyl
2.091 R = Et; B = N^6-benzoyladeninyl

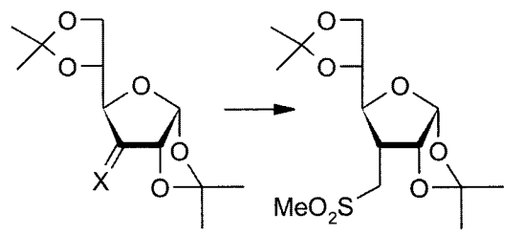


2.081 **2.082** **2.085**

2.083 R = SPyr
2.084 R = S(O)Pyr

to radical reaction in the presence of phenyl vinyl sulfone. Synthetic manipulation afforded the vinyl sulfone **2.089** as a single compound. Similarly, the adenine derivative **2.087** has also been converted to **2.090**.[20] However, a related nucleoside **2.091** was obtained through a much shorter route by reacting aldehyde **2.088** with a sulfone stabilized Horner-Emmons reagent.[21]

1,2:5,6-Diacetone ulose **2.092**, on reaction with a $[(MeO)_2P(O)CH(Li)SO_2Me]$ generated an *exo*-



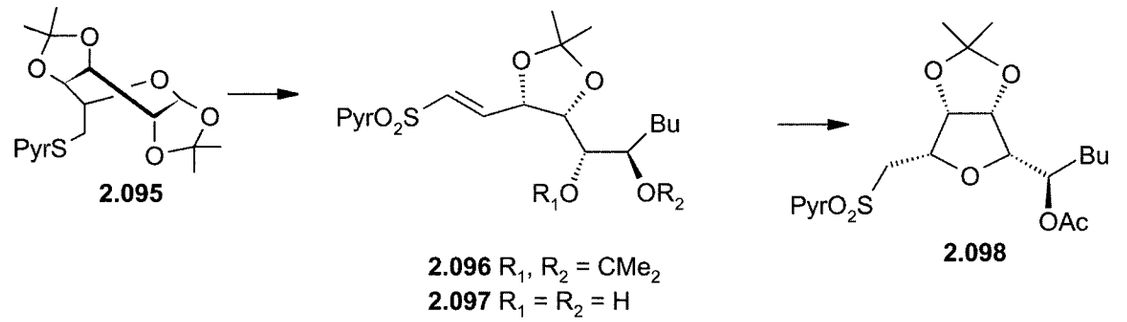
2.092 X = O
2.093 X = $CHSO_2Me$

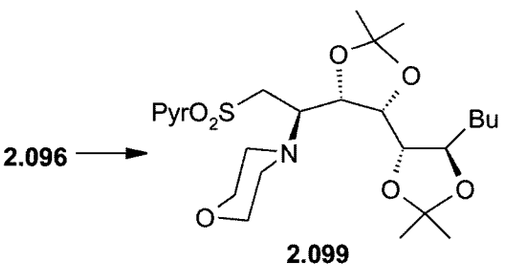
2.094

cyclic α,β-unsaturated sulfone **2.093**, which could be reduced to **2.094** with $[(Ph_3P)CuH]_6$.[21]

2.4 Vinyl Sulfone Group Attached to Open Chain Sugar Derivatives

Sugar derived vinyl sulfone like **2.096** has been synthesized from aza-heterocycle/thiosugar hybrid **2.095** using a Grob-type heterocyclic process followed by the oxidation of the product. Compound **2.097** underwent Michael-initiated ring closure process to build up a chiral polysubstituted oxolan system such as **2.098** with high stereoselectivity. Compound **2.096** was reacted with morpholine to produce adduct **2.099** in 80% yield with *de* exceeding 94%.[22,23]





3 Our Work

As discussed above, nucleophilic addition to double bonds activated by electron withdrawing groups as part of carbohydrates would serve as a useful methodology for the functionalization of monosaccharides. However, a thorough study on the diastereoselectivity of addition of nucleophiles to vinyl-sulfone modified carbohydrates was necessary for the generation of pure diastereomers. At first, we decided to initiate a systematic study of the addition pattern of nucleophiles to vinyl sulfone-modified pent-2-enofuranosides and hex-2-enopyranosides. It is well documented that the stereochemical outcome of the nucleophilic attack at the planar carbonyl group at C-2 position of *threo*-hexopyranosid-2-ulose is controlled by the anomeric configuration.[24] Moreover, it has been mentioned above that nucleophiles attacked the C-2' position of the 2'-enesulfone nucleosides **2.069** and **2.070** exclusively from the α-face of the pent-2'-enofuranosyl moiety of a β-nucleoside.[17] It was, therefore logical to presume that the anomeric configuration would stereoelectronically influence the addition pattern of nucleophiles to *endo*-cyclic monovinyl sulfones derived from carbohydrates (Fig. 1).

Since we wanted to use the anomeric configuration as a tool to direct the diastereoselectivity of addition of nucleophiles to the 2-position of these enofuranoses, relatively large amount of anomerically pure, vinyl sulfone-modified pent-2-

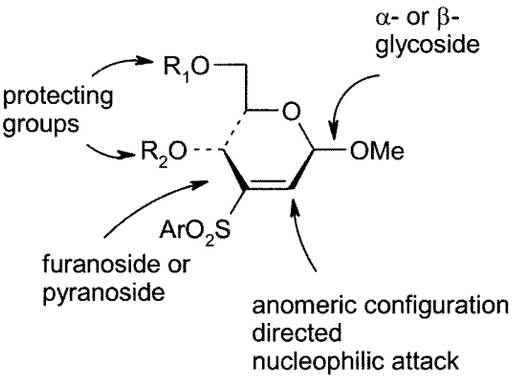
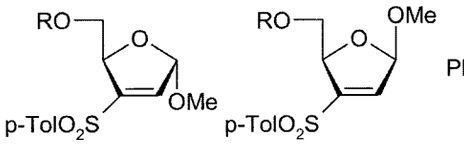


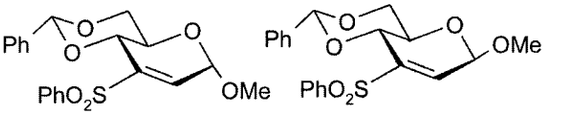
Fig. 1

and hex-2-enofuranoses were needed for studying the reaction patterns with various nucleophiles. However, the requirement of anomeric purity of compounds **3.001-3.004**, **3.005** and **3.006** 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 **3.007** or methyl 2,3-dideoxy-D-pent-2-enofuranoside



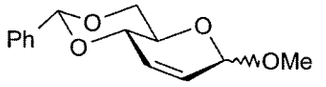
3.001 R = Bn
3.002 R = Tr

3.003 R = Bn
3.004 R = Tr

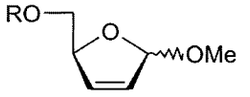


3.005 **3.006**

3.008 as a method was ruled out because such an addition to the corresponding olefinic nucleoside derivatives produced a mixture of at least three diastereomers.[25]



3.007



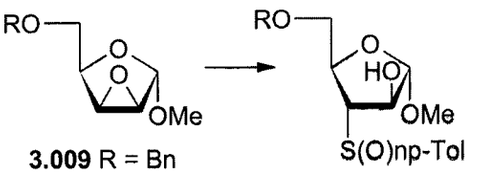
3.008

A retrosynthetic analysis of the route to **3.001-3.004**, **3.005/3.006** necessitated the introduction of an arylthio group at the C-3 position of a pentose or a hexose sugar, respectively. One of the easiest ways of forming a C-S bond would be the regioselective opening of epoxides derived from carbohydrates.[26] Alternatively the arylthio group at the C-3 position of a hexose or a pentose sugar could be introduced by displacing the leaving groups at the C-3 position of the easily accessible starting materials.[7]

3.1 Synthesis of Vinyl Sulfone-modified Pent-2-enofuranosides[27,28]

Synthesis of 3.001-3.004 from Epoxides Derived from Carbohydrates

The known *lyxo*-epoxides **3.009** and **3.010**, synthesized from D-xylose, were treated separately with sodium *p*-thiocresolate in DMF at 80-90 °C to furnish sulfide derivatives **3.011** and **3.012**, respectively in good to excellent yields. Compounds **3.011** and **3.012**, when oxidized separately with magnesium mono-peroxyperphthalate (MMPP) in MeOH generated the corresponding sulfone derivatives **3.013** and **3.014**, respectively in high yields. Compounds **3.013** and **3.014**, on treatment with mesyl chloride in pyridine separately, afforded smoothly the desired vinyl sulfone-modified carbohydrates **3.001** and **3.002**, respectively in

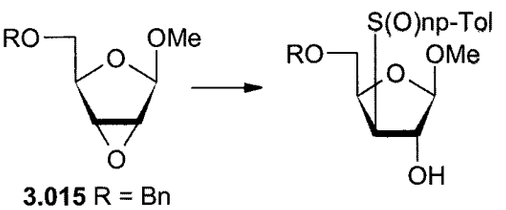


3.009 R = Bn
3.010 R = Tr

3.011 R = Bn, n = 0
3.012 R = Tr, n = 0
3.013 R = Bn, n = 2
3.014 R = Tr, n = 2

3.001 R = Bn
3.002 R = Tr

82% and 84% yields. Similarly, the known *ribo*-epoxides **3.015** and **3.016** were converted to sulfides **3.017** and **3.018**, respectively with *xylo*-configuration in high yields. Compounds **3.017** and **3.018** were converted to the corresponding vinyl sulfones **3.003** and **3.004** *via* sulfone derivatives **3.019** and **3.020** respectively in the usual manner as described above.[27,28]



3.015 R = Bn
3.016 R = Tr

3.017 R = Bn, n = 0
3.018 R = Tr, n = 0
3.019 R = Bn, n = 2
3.020 R = Tr, n = 2

3.003 R = Bn
3.004 R = Tr

It should be noted that this route allows the synthesis of vinyl sulfone-modified pentofuranoses having the C-5 hydroxyl function masked with benzyl as well as an acid labile trityl protecting group because the trityl group is introduced after the acid catalyzed methyl glycoside formation. However, separate synthesis of epoxides **3.009**/**3.010** and **3.015/3.016** increases the number of

steps. Therefore, it was necessary to devise different approaches towards the synthesis of vinyl sulfone-modified pent-2-enofuranosides.[27,28]

*Synthesis of **3.001** and **3.003** from 3-O-tosylated D-xylofuranose*

Compound **3.021** was reacted with sodium *p*-thiocresolate in DMF at 120 °C to produce sulfide derivative **3.022** with *ribo*-configuration in 59% yield. Compound **3.022** was deprotected and glycosylated in one step in the presence of conc. H_2SO_4 in MeOH to generate a mixture of anomers **3.023** and **3.024** (1:10) in 78% yield. The anomers **3.023** and **3.024** were separated at this stage by chromatography and oxidized separately with MMPP in MeOH to the corresponding sulfones **3.025** and **3.026**, respectively in excellent yields. The sulfones **3.025** and **3.026** were converted to vinyl sulfone-modified carbohydrates **3.001** and **3.003** respectively in high yields in the usual way.[27,28]

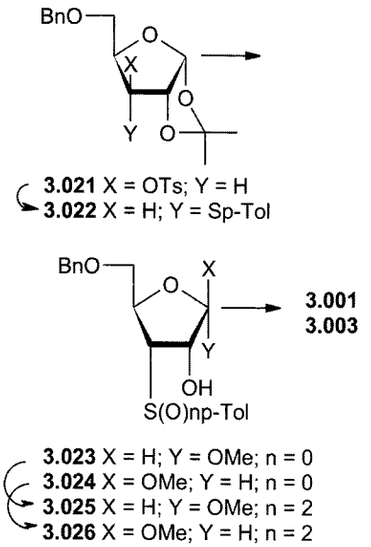
The moderate yield (59%) of the *ribo*-product **3.022** can be partly explained on the basis of the repulsion caused by the 1,2-*O*-isopropylidene group to the incoming nucleophile. Although at this stage the less efficient conversion of **3.021** to **3.022** was acceptable, the major drawback of this methodology was the unacceptable ratio of **3.023** and **3.024** (1:10) in the mixture. The lower ratio of α-anomer **3.023** in the mixture contributed to the poor overall yield of the vinyl sulfone derivative **3.001**.[27,28]

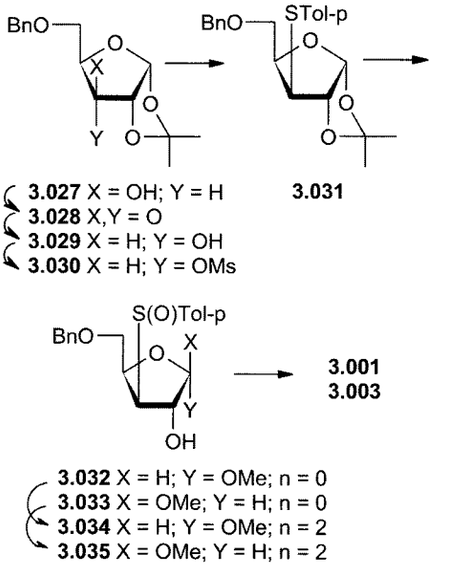
*Synthesis of **3.001** and **3.003** from 3-O-mesylated D-ribofuranose*

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 us to select a D-*xylo*-derivative based strategy for the synthesis of an anomeric mixture close to the ideal ratio of 1:1.[27,28]

5-*O*-Benzyl-1,2-*O*-isopropylidene-3-*O*-mesyl-α-D-*ribo*furanose **3.030**, which had been synthesized from a known compound **3.027** *via* oxidation-reduction followed by mesylation. Compound **3.030** was subjected to nucleophilic displacement by sodium *p*-thiocresolate to generate a sulfide derivative **3.031** with *xylo*-configuration in 79% yield. Compound **3.031** was deprotected and glycosylated to afford a mixture of both α- and β-anomers **3.032** and **3.033** (1.5:1) in excellent yields. The anomers were separated at this stage by flash chromatography. On treatment with MMPP in MeOH, compounds **3.032** and **3.033** produced the corresponding sulfones **3.034** and **3.035**, respectively in excellent yields. Sulfones **3.034** and **3.035** were converted to the desired vinyl sulfones **3.001** and **3.003** in high yields.[27,28]

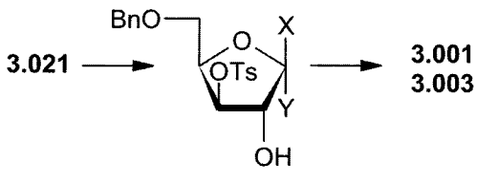
Although the ratio of **3.032** and **3.033** (1.5:1) was acceptable for the synthesis of both the anomers **3.001 and 3.003**, the overall yield again dropped due to the addition of two synthetic steps for converting *xylo*-derivative **3.027** to *ribo*-derivative **3.029** *via* a two-step oxidation-reduction process. We therefore, looked for yet another route for the synthesis of **3.001** and **3.003**.[27,28]





Synthesis of **3.001** and **3.003** from *3-O-tosylated methyl* D-*xylofuranosides*

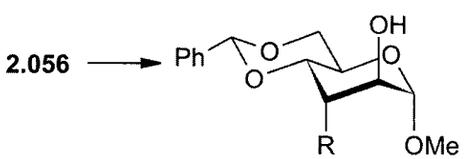
Methanolysis of **3.021** produced an anomeric mixture of **3.036** and **3.037** in a ratio of 1:1.3 (α:β) in 89% yield. In the absence of any steric hindrance, the nucleophilic displacement of the tosyl group of the mixture of **3.036** and **3.037** by *p*-thiocresol proceeded smoothly at elevated temperature to afford a mixture of *ribo*furanosides **3.023** and **3.024** in 94% yield. Compounds **3.023** and **3.024** were separated and converted to the desired vinyl sulfone-modified carbohydrates **3.001** and **3.003**, respectively in the usual manner described above. This synthetic strategy turned out to be the best for the synthesis of **3.001** and **3.003** starting from a single carbohydrate derivative.[27,28]



3.036 X = H; Y = OMe
3.037 X = OMe; Y = H

3.2 Reinvestigation into the Synthesis of Vinyl Sulfone-modified Hex-2-enopyranosides[27,28]

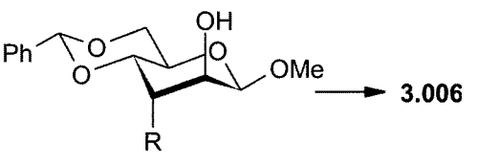
Initially, we synthesized the thiophenyl derivative **3.005** using a modification of the method described earlier (Sec 2.1.3). Thus, epoxide **2.056** was reacted with thiophenol in the presence of 1,1,3,3-tetramethylguanidine (TMG) to afford **3.038**. The corresponding sulfone derivative **3.039** was generated in quantitative yield by oxidizing **3.038** with MMPP. Compound **3.039** was mesylated and the crude mesylated product was subjected to an elimination reaction with DBU in dichloromethane to produce **3.005** in 88% overall yield (4 steps from **2.056**). Similarly, thiophenol in the presence of TMG opened epoxide **3.040** at the 3-position to generate **3.041**. Oxidation of **3.041** to **3.042**,



3.038 R = SPh
3.039 R = SO_2Ph

→ **3.005**

3.040



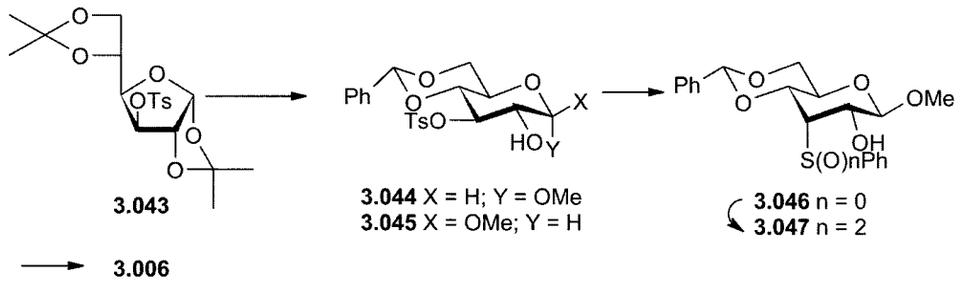
3.041 R = SPh
3.042 R = SO_2Ph

followed by mesylation and DBU treatment generated the desired compound **3.006** in 75% overall yield (4 steps from **3.040**).[27,28]

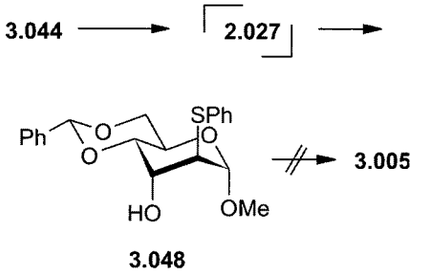
For accessing relatively large amount of anomerically pure **3.005** and **3.006** through a shorter route, we applied the "glycosylation driven strategy",[27] which was successfully utilized in the synthesis of **3.001** and **3.003**. It has been reported that the equilibrium mixture of methyl-D-allosides in MeOH, contained more than 30% of furanosides whereas D-glucose produced methyl-D-pyranosides almost exclusively. Although the reported ratio of α- and β-anomers were not close to the ideal value of 1:1, in this case it was more important to get the methyl pyranosides without any contamination of the corresponding furanosides. This observation prompted us to study the feasibility of using the known tosylate **3.043** as the starting material.[27,28]

Synthesis of 3.005 and 3.006 from 3-O-tosylated D-*glucofuranose*

The known tosylate **3.043** was considered as a suitable starting material because it could be easily converted to a mixture of **3.044** and **3.045** (*via* deprotection, glycosylation followed by benzylidenation) in a ratio 1:1.5. The anomers were separated by column chromatography. The β-anomer **3.045** was reacted with sodium thiophenolate to afford sulfide derivative **3.046**. Compound **3.046** was oxidized to **3.047** and the latter under mesylation conditions generated smoothly the desired vinyl sulfone **3.006** in overall 79% yield (in 3 steps from **3.045**). The α-anomer **3.044**, when treated with sodium thiocresolate, produced an unwanted sulfide derivative **3.048**. Since it was reported that **3.044** very easily formed the epoxide **2.027**, it was logical to conclude that under the reaction conditions *altro*-derivative **3.048**



was formed. No further study was carried out on this reaction sequence because it was not possible to synthesize the desired vinyl sulfone **3.005** through this route.[27,28]



*Synthesis of **3.005** and **3.006** from 3-O-mesylated D-allofuranose*

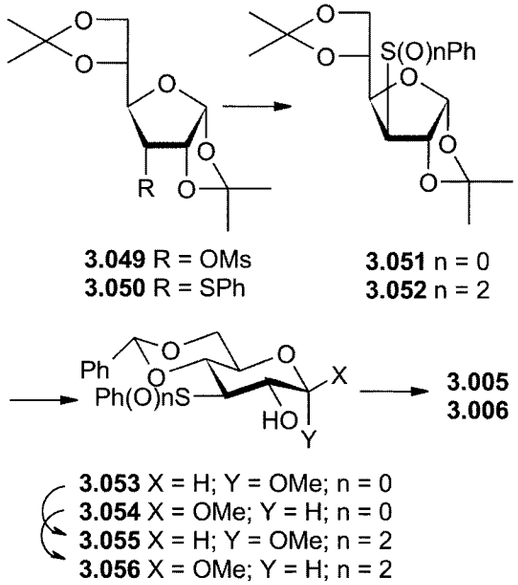
To overcome the aforementioned problems and to have an easy access to both **3.005** and **3.006** through a single intermediate we studied another sequence of reactions using two possible starting materials **3.050** and **3.051** which were obtained by displacing the leaving groups of **3.043** and **3.049**, respectively by sodium thiophenolate. Here also, for reasons discussed above, the *gluco*-derivative **3.051** was the starting material of choice over the *allo*-derivative **3.050** because methanolysis of the latter generated more than six products. The known mesylated *allo*-derivative **3.049** was treated with sodium thiophenolate to afford sulfide derivative **3.051** with *gluco*-configuration.[27,28]

Compound **3.051** 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 **3.053** and **3.054** in a ratio 2.2:1 in good yields. The anomers were separated by chromatography and were converted separately to the corresponding sulfones **3.055** and **3.056** in excellent yields using MMPP in MeOH. In an alternative approach, compound **3.051** was oxidized to the corresponding sulfone **3.052** in excellent yield. Compound **3.052** was deprotected and glycosylated by acetyl chloride and MeOH in one step to generate a mixture of anomeric sulfones, which were collected as the benzylidene *gluco*-derivatives **3.055** and **3.056**, respectively in good yields in a ratio 1:1.8. The anomers were separated by column chromatography. Compounds **3.055** and **3.056** were converted to the desired vinyl sulfone-modified hex-2-enopyranosides **3.005** and **3.006**, respectively in excellent yields.[27,28]

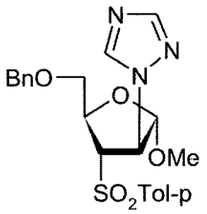
3.3 Vinyl Sulfone-modified Pent-2-enofuranosides as Michael Acceptors

3.3.1 Reactions with Planar Heterocycles[27]

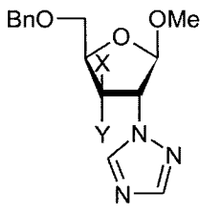
In order to establish the influence of anomeric configuration on the diastereoselectivity of addition of various nucleophiles to the highly reactive Michael acceptors **3.001** and **3.003**, these compounds were reacted separately with 1,2,4-triazole in the presence of TMG in DMF at ambient temperature. Compound **3.001** produced a single isomer **3.057** in 82% yield where the nucleophile approached the C-2 position



from the β-face. Compound **3.003**, on the other hand produced a separable mixture (total yield 75% in a ratio of 1:1) of a *ribo*-derivative **3.058** and a *xylo*-derivative **3.059**. For the formation of both **3.058** and **3.059**, the nucleophile attacked the C-2 position of **3.003** exclusively from the α-face.[27]



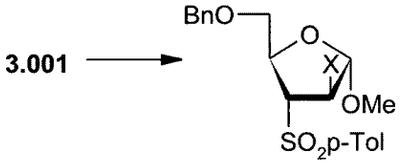
3.057



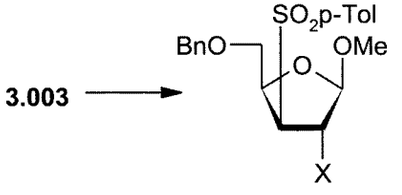
3.058 X = H; Y = SO_2Tol-p
3.059 X = SO_2Tol-p; Y = H

3.3.2 Reactions with Carbon Nucleophile[29]

Considering the importance of branched chain sugars as components of natural products as well as functionalized intermediates for the synthesis of many natural products, it was necessary to study the addition pattern of carbon nucleophiles to **3.001** and **3.003**. Thus, **3.001** and **3.003** on reaction with carbanions generated from CH_3NO_2/NaOMe and CH_3NO_2/$^tBuO^-K^+$ produced branched-chain sugars **3.060** (73%) and **3.062** (55%) respectively. Dimethylmalonate adducts **3.061** (74%) and **3.063** (87%) were also synthesized in a diastereoselective fashion.[29]



3.060 X = CH_2NO_2
3.061 X = $CH(COOMe)_2$



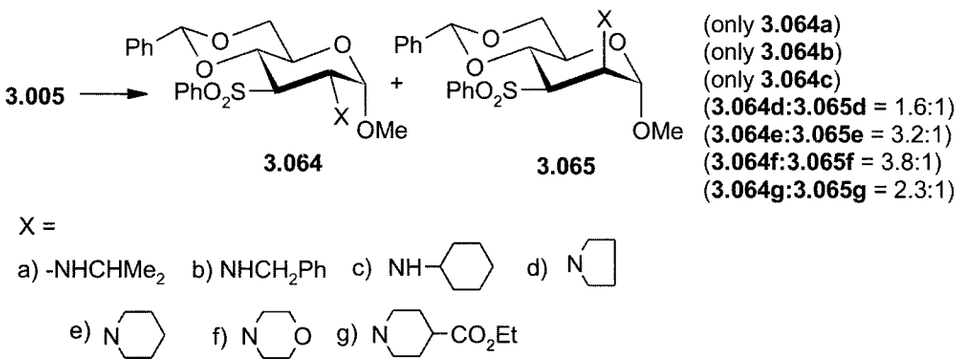
3.062 X = CH_2NO_2
3.063 X = $CH(COOMe)_2$

3.4 Vinyl Sulfone-modified Hex-2-enopyranosides as Michael Acceptors

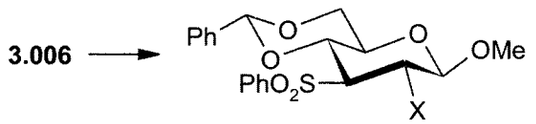
3.4.1 Reactions with Amines[30-33]

In order to study the influence of anomeric configuration on the diastereoselectivity of addition of various nucleophiles to enopyranoside systems, anomerically pure α-vinyl sulfone **3.005** was reacted with various primary and secondary amines. Primary amines, such as isobutyl amine, benzylamine and cyclohexylamine were found to add diastereoselectively to produce single isomers **3.064a**, **3.064b** and **3.064c** respectively. The secondary amines, pyrrolidine, piperidine, morpholine and ethyl isonipecotate, on the other hand, generated a mixture (isomeric at C-2) having **3.064d**, **3.064e**, **3.064f** and **3.064g** as the major isomers, respectively. The major isomers **3.064d-g** were separated by crystallization. One of the minor *manno*-isomers **3.065d** was isolated to unambiguously establish its structure. Similarly, the β-anomer **3.006** 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 **3.066-3.070,** respectively.[30] It should be noted that **3.005** 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 time caused extensive degradation of the starting material. The β-anomer **3.006**, on the other hand, reacted smoothly with the same amine at elevated temperatures to produce a single isomer **3.068** in excellent yield.[31]

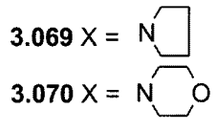
It has been reported that the addition of *p*-toluenethiol to 1-(*p*)-tolylsulfonylcyclohexene produced *cis*-2-(*p*)-tolylmercapto-1-(*p*)-tolylsulfonylcyclohexane because an arylsulfonyl group, which had a much larger steric requirement than an arylmercapto group should tend to occupy an equatorial position. The stereochemistry of nucleophilic addition reactions to more complicated systems like 3-nitro-hex-2-enopyranosides **2.021** and **2.018**, however, has been discussed in terms of electrostatic interactions, stereoelectronic control, steric hindrance, $A^{(1,3)}$ strain and also hydrogen bonding. A generalization that the axial attack predominates over equatorial attack for **2.021** and the converse is true for **2.018** has been arrived at



on the basis of reactions of **2.021** and **2.018** with several nucleophiles although one of the earliest work in this area with amines as nucleophiles contradicted this generalization; sterically demanding purine bases, however, added to **2.021** and **2.018** from the β- and α- sides, respectively.[30]



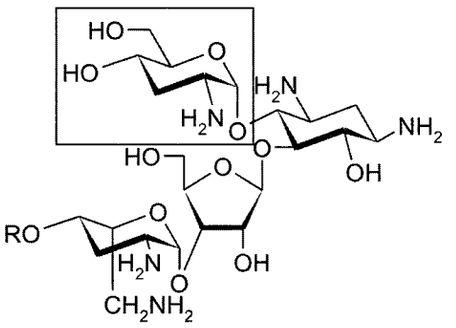
3.066 X = $NHCHMe_2$
3.067 X = $NHCH_2Ph$
3.068 X = $NHC(Me)_3$



In the light of above observations, it can be stated that the stereochemical course of addition of amines to **3.005** and **3.006** does not fully obey any of the precedence. In a partially rigid bicyclic system of **3.005** and **3.006**, the sterically bulky phenylsulfonyl group is expected to occupy the equatorial position. In the case of **3.005**, primary amines always attacked the C-2 center from equatorial direction to produce thermodynamically more stable diequatorial products. Interestingly, however, sterically bulky secondary amines, on reaction with **3.005** produced mixture of products, epimeric at C-2. To explain the formation of mixture of products **3.064d-g** and **3.065d-g**, one has to bear in mind the established conventions that (a) secondary amines carrying nonbonded electron pairs would face electrostatic repulsion by C1-O1 and C1-O5 bonds and (b) thermodynamically more stable diequatorial products should predominate. Nevertheless, to explain the formation of *manno*-isomers (such as **3.065d**), it is necessary to assume the existence of a stereoelectronic factor, responsible for repelling the incoming secondary amines from equatorial direction, although the exact nature of the hindrance cannot be rationalized at this point.[30]

Compound **3.006**, on the other hand, on reaction with both primary and bulky secondary amines produced thermodynamically more stable diequatorial products. In this case, it was difficult to establish conclusively whether the electrostatic repulsion between attacking amines, C1-O1 and C1-O5 bonds directed the nucleophiles to attack the C-2 position of **3.006** from the equatorial direction resulting in the formation of single isomers **3.066-3.070**. This observation, nevertheless, falls more in line with the generalized rule that in the case of a β-anomeric substrate, a nucleophile should approach C-2 site preferably from the equatorial direction.[30] Reactions of *tert*-butylamine exemplified an extreme case of anomeric configuration influencing the addition of nucleophiles to enopyranoside systems **3.005** and **3.006**.[31]

The diastereoselective addition of primary amines to **3.005** and **3.006** has been applied to the synthesis of a naturally occurring aminosugar D-lividosamine and its analogues.[32] D-Lividosamine (2-amino-2,3-dideoxy-D-glucose) **3.078**, isolated from *Streptomyces Lividus*, is present in aminoglycoside antibiotics such as lividomycin-A/ lividomycin–B **3.071**. 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 bulks and/or the varying basicities of amino groups as well as the number of deoxygenated centers in aminosugars play important role in

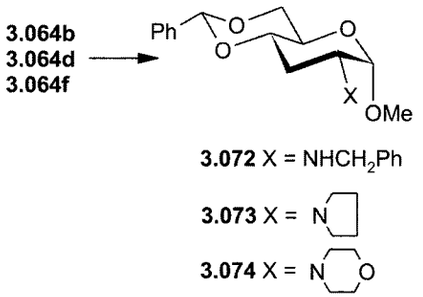


3.071

determining the properties of aminoglycosides.[32]

The essence of the synthetic strategy leading to the preparation of D-lividosamine **3.078** 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 C-3 site. None of the known methods of amination of C-2 position of pyranosides could have been used as a general route for the synthesis of D-lividosamine and its analogues either because of the undesired configuration or position of the C-N bond and/or the additional functionalization of the C-3 hydroxyl group required for the deoxygenation of the C-3 center.[32]

Thus, compound **3.064b** obtaind from **3.005** was desulfonated by magnesium in methanol in 90% yield to generate the 2-*N*-benzylamino-2,3-dideoxy product **3.072**. Compound **3.072** was debenzylated with palladium hydroxide on charcoal to **3.076**. Crude **3.076** was acetylated to **3.077**, which was reported to be an intermediate for accessing **3.078**. However, to reduce the number of steps, **3.005** was reacted directly with conc. aq. ammonia in dioxane to produce a mixture containing **3.075** in major amount (^{1}H NMR). The mixture was desulfonated and the free amino compound **3.076** was acylated. Pure **3.077** was crystallized out from benzene-petroleum ether mixture in 65% overall yield.[32]

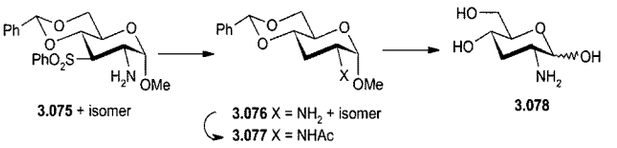


3.064b
3.064d
3.064f

3.072 X = $NHCH_2Ph$

3.073 X = N

3.074 X = N O

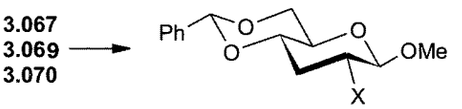


3.075 + isomer

3.076 X = NH_2 + isomer
3.077 X = NHAc

3.078

The analogues of **3.077** could be easily obtained by desulfonating **3.064d** and **3.064f** to **3.073** and **3.074** in 91% and 85% yields, respectively. In the β-series, **3.067**, **3.069** and **3.070** could also be desulfonated to **3.079**, **3.080** and **3.081** in 76%, 42% and 47% yields, respectively.[32]



3.067
3.069
3.070

3.079 X = NHBn

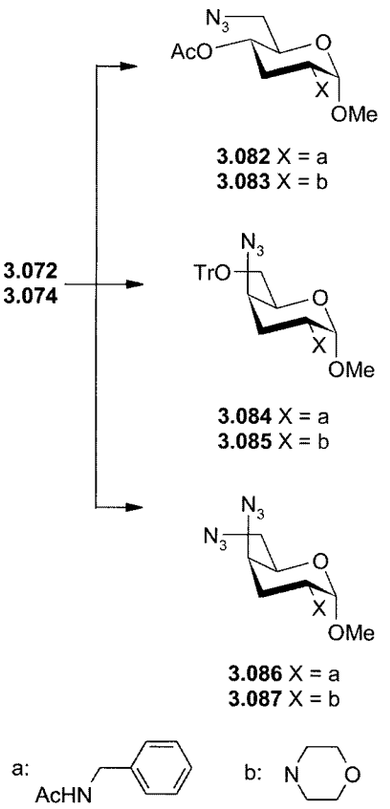
3.080 X = N

3.081 X = N O

It is possible to widen the application of the above sequence of methodology for the synthesis of several C-3 deoxy polyaminosugars such as, tobrosamine (2,6-diamino-2,3,6-trideoxy-D-*ribo*-hexose), purpurosamine A (2-amino-2,3,4,6,7-pentadeoxy-6-methylamino-D-*ribo*-heptose), purpurosamine B (2, 6-diamino-2,3,4,6,7-pentadeoxy-D-*ribo*-heptose), purpurosamine C (2, 6-diamino-2,3,4,6-tetradeoxy-D-*erythro*-hexose), sisosamine (2, 6-diamino-2,3,4,6-tetradeoxy-D-*glycero*-hex-4-enose), kasugamine (2,4-diamino-2,3,4,6-tetradeoxy-D-arabinohexose), 3-Deoxy-prumycin [4-(D-alanylamino)-2-amino-2,3,4-dideoxy-L-arabinose] and their analogues. Thus, synthetic manipulations of the desulfonated compounds **3.072** and **3.074** generated intermediates **3.082/3.083** for accessing 2,3,6-trideoxy-2,6-diamino sugars, intermediates **3.084/3.085** for accessing 2,3,4-trideoxy-2,4-diamino sugars and intermediates **3.086/3.087** for accessing 2,3,4,6-tetradeoxy-2,4,6-triamino sugars.[33]

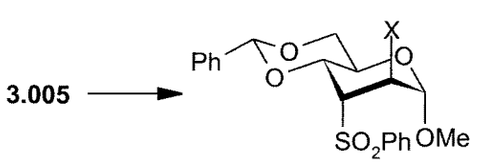
3.4.2 Reactions with Carbon Nucleophiles[29]

Although amines added in diastereoselective fashion to **3.005** and **3.006**, the directive effect of the anomeric configuration on the stereochemical outcome of the reactions was not obvious because the addition of primary amines exclusively produced C-2 equatorial (*gluco*-) products. Secondary amines, on reactions with **3.006** produced only *gluco*-

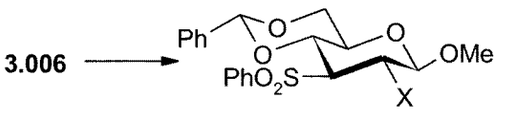


derivative but with **3.005** produced a mixture in which *gluco-* was still the predominant isomer.[30] On the other hand, sterically bulky *tert*-butylamine, reacted only with **3.006** (and not with **3.005**) at elevated temperature to produce the *gluco-* derivative in high yield.[31]

It was therefore necessary to study independently the reaction pattern of carbon nucleophiles to **3.005** and **3.006**. Thus, the nucleophile generated from CH_3NO_2 and NaOMe, reacted with **3.005** to produce a single isomer **3.088** in 60% yield. Similarly, nucleophile generated from dimethylmalonate and NaH produced exclusively **3.089** in 82% yield. On the other hand, $NaCH_2NO_2$ and the sodium salt of dimethylmalonate reacted with **3.006** to produce single isomers **3.090** (56%) and **3.091** (98%) respectively. In order to highlight the usefulness of

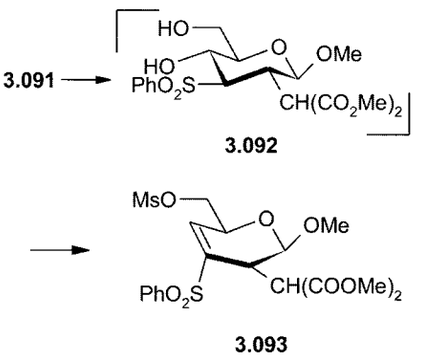


3.088 X = CH_2NO_2
3.089 X = $CH(COOMe)_2$



3.090 X = CH_2NO_2
3.091 X = $CH(COOMe)_2$

the branched-chain sugars generated so far with the help of our method, **3.091** was deprotected under acidic conditions to **3.092** in high yield. Mesylation of the crude dihydroxy compound **3.092** furnished a densely functionalized branched-chain sugar **3.093**. This novel Michael acceptor is a ready intermediate for nucleophilic attack at C-4 as well as C-6 by external nucleophiles for the synthesis of extensively modified carbohydrates.[29]



3.5 Monovinyl Sulfone-modified Pyrimidine Nucleosides[34,35]

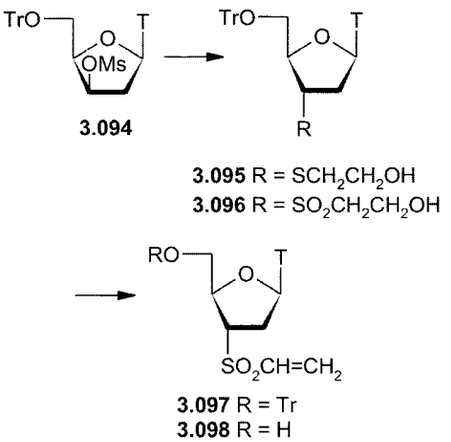
In an attempt to access anti-HIV drug more potent than 3′-azido-3′-deoxythymidine (AZT), it has been proposed to introduce reactive functional groups at the 3′-position of thymidine. It was expected that a strongly electrophilic group would react with biological nucleophiles such as a non-functionalized thiol or an amino group present in an enzyme. Earlier attempts in this area were not successful because the functionalities attached to the 3′-end, namely thiocyanate or isothiocyanate were most probably not reactive enough to form covalent bonds with the enzyme tested. Interestingly, vinyl sulfones were reported to inhibit the action of glyceraldehyde-3-phosphate dehydrogenase and the vinyl sulfone containing dipeptides were shown to be efficient cystein protease inhibitors through covalent bond formation with the enzymes. It was, therefore, decided to incorporate strongly electrophilic vinyl sulfone group into the carbohydrate moieties of nucleosides.[34]

It has also been reported that acetylenic sulfone is a highly reactive group toward conjugate addition reactions although there are only a few reports on the biological properties of compounds functionalized with acetylenic and allenic sulfone groups. Propargyl sulfone- modified steroids and triazoles were shown to inhibit glucose-6-phosphate dehydrogenase and human leukocyte elastase. The usefulness of this functional group was further highlighted by the reports on the DNA-cleaving properties of cyclic bispropargylic sulfones as well as acyclic monopropargylic sulfones. Since monopropargylic sulfones exhibited much higher potencies than the cyclic bispropargylic sulfones as DNA cleaving agents via alkylation mechanism, we envisaged that the incorporation of the allenic sulfone moiety in the sugar part of a nucleoside may generate alkylating agents with novel properties.[35]

It is important to note that vinyl sulfone group has been used earlier as a tool for the functionalization of the carbohydrate moieties of the nucleosides. The sulfone group was removed after the formation of C-N and C-C bonds.[17] We, on the contrary wanted to retain the group in the molecule and study its reactivities with various nucleophiles.

3.5.1 Synthesis of Vinyl and Acetylenic Sulfone-modified Nucleosides[34,35]

Thus, 1-(2-deoxy-3-*O*-mesyl-5-*O*-trityl-β-D-*threo*-pentofuranosyl) thymine **3.094** was treated with mercaptoethanol in the presence of DBU to produce **3.095** in 64% yield. Compound **3.095** was easily oxidized by MMPP to **3.096** in 75% yield. Sulfone **3.096** was converted to the mesylated derivative in pyridine at +4 °C and the same pyridine solution was heated at 60 °C for 0.5 h to produce the desired vinyl sulfone **3.097** in 71% overall yield. Compound **3.097** could be detritylated, if necessary, to the free hydroxy derivative **3.098** under acidic conditions.[34]



3.094

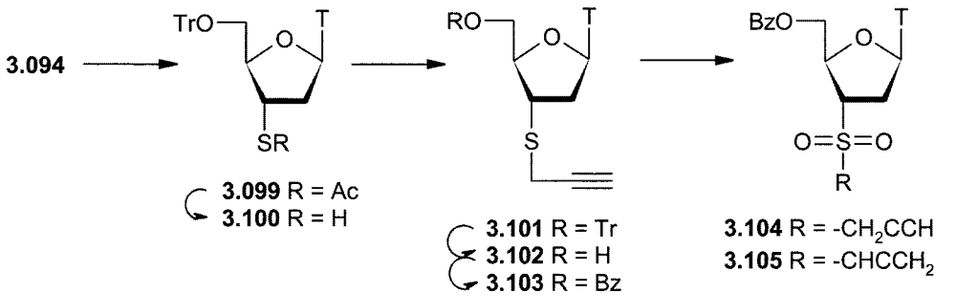
3.095 R = SCH_2CH_2OH
3.096 R = $SO_2CH_2CH_2OH$

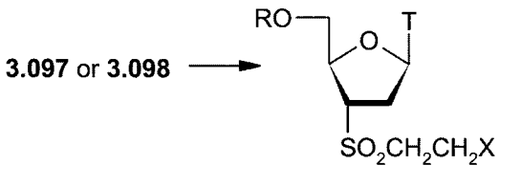
3.097 R = Tr
3.098 R = H

For accessing acetylenic sulfone modified thymidine, **3.094** was converted to 3′-*S*-(acetylthio)-3′-deoxythymidine **3.099** following a literature procedure. Alkaline hydrolysis of **3.099** at low temperature furnished the free thiol derivative **3.100**. A dichloromethane solution of crude **3.100** was treated with propargyl bromide in the presence of DBU at room temperature for 15 h to furnish 3′-*S*-(propargylthio)-5′-*O*-trityl-3′-deoxythymidine **3.101** in 68% yield in two steps. Compound **3.101** could be easily deprotected at this stage to generate a propargylthio analogue of AZT, namely 3′-deoxy-3′-S-(propargylthio) thymidine **3.102**. Although it was possible to convert **3.101** to **3.102**, it was necessary to have a protecting group at the 5′-position for the purification of compounds obtained from addition reactions. Therefore, **3.102** was benzoylated using standard procedure to obtain the 5′-*O*-benzoyl derivative **3.103** in 88% yield. Oxidation of **3.103** with m-chloroperbenzoic acid afforded either **3.104** or **3.105** in 83% yield. However, structure **3.105** was attributed unambiguously to the product because of the presence of a triplet (=CH, 6.26 ppm or 6.07 ppm) and peaks at 211.8 ppm (=C=), 96.3 ppm (=CH) and 84.3 ppm ($=CH_2$) in the ^1H- and ^{13}C NMR spectra respectively.[35]

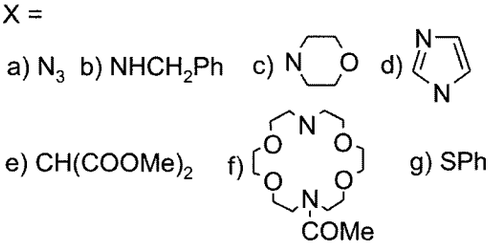
3.5.2 Reactions of Vinyl and Acetylenic Sulfone-modified Nucleosides[34,35]

Either the protected vinyl sulfone **3.097** or the deprotected derivative **3.098** was reacted with various nucleophiles. Nucleophiles such as, hydrazoic acid, morpholine, sodium salt of dimethylmalonate, 1,4,10,13-tetraoxa-7, 6-diazacyclooctadecane and thiophenol reacted smoothly with compound **3.097** to furnish compounds **3.106a**, **3.109c**, **3.112e**, **3.114f** and **3.115g**, respectively in excellent to moderate yields. Similarly, compound **3.098** reacted with benzylamine and imidazole in protic solvents at ambient temperature to produce compounds **3.108b** and **3.110d** (after benzoylation), respectively in high yields. The diaza crown ether product **3.114f** was characterized as *N*-acetyl derivative. Compounds **3.106a**, **3.112e** and **3.115g** were deprotected using





3.106a R = Tr; X = a
3.107a R = Bz; X = a
3.108b R = H; X = b
3.109c R = Tr; X = c
3.110c R = H; X = c
3.111d R = Bz; X = d
3.112e R = Tr; X = e
3.113e R = Bz; X = e
3.114f R = Tr; X = f
3.115g R = Tr; X = g
3.116g R = Bz; X = g

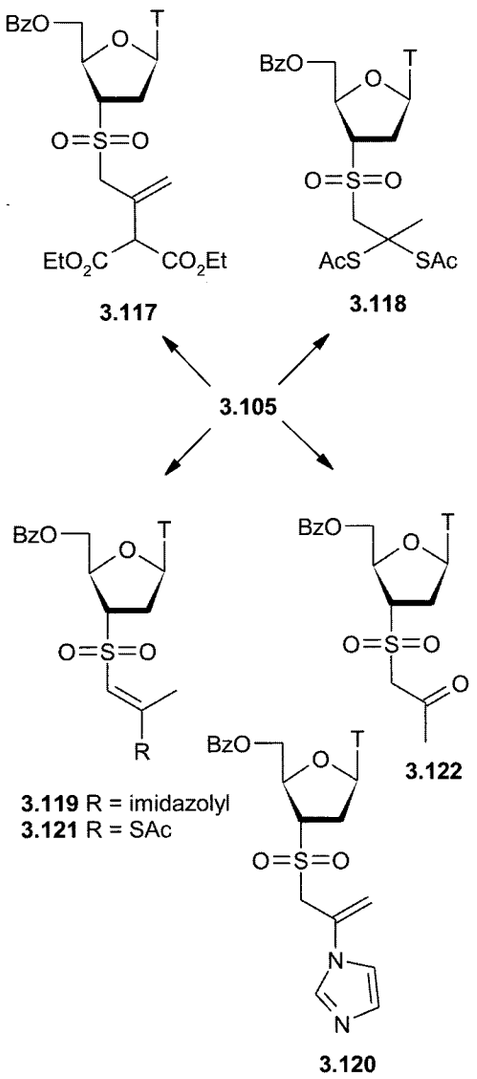


80% acetic acid at elevated temperature or with ion-exchange resins (IR 120H$^+$) and the products were converted to benzoyl derivatives **3.107a**, **3.113e** and **3.116g** respectively in high yields; compound **3.109c** was deprotected and isolated as the 5'-free hydroxy compound **3.110c**.[34]

In order to establish the reaction pattern of the newly synthesized allenic sulfone-modified nucleoside, **3.105** was reacted with different nucleophiles. Thus **3.105** on reaction with seven equivalents of the sodium salt of diethylmalonate in THF at room temperature for 2.5 h afforded **3.117** in 82% yield where one equivalent of carbon nucleophile formed the adduct as expected. On the other hand, reaction of **3.105** at room temperature for 15 h with two equivalents of the sulfur nucleophile generated by a strong organic base DBU from thioacetic acid in dichloromethane produced **3.118** in 44% yield. In this case, however two equivalents of the sulfur nucleophile reacted with the allenic sulfone system. It is likely that the reaction proceeded through an intermediate like **3.131**, which underwent further addition of the thioacetate nucleophile to produce **3.118**. To the best of our knowledge this is one of the rare examples of the double addition of a nucleophile to an allenic sulfone system. Reactions of two equivalents of imidazole with **3.105** in DCM at room temperature produced a mixture of **3.119** and **3.120** within 2 h in 35% and 33% yields respectively.[34]

Interestingly, reactions of **3.105** with amines produced completely different results. Compound **3.105** on treatment with four equivalents of a strong base and an efficient nucleophile, piperidine in DCM at room temperature for 5h did not produce any addition product. Instead a keto derivative **3.122** was isolated in 70% yield. On the other hand a weak base and a lethargic nucleophile, 3-fluoroaniline after 24 h at room temperature also produced the same keto compound **3.122** in 68% yield. Since there were several reports on the isolation of stable enamines from various allenic sulfones, it was surprising that the enamines, which were expected from **3.105** were so highly unstable that they underwent instantaneous hydrolysis to produce **3.122**.[35]

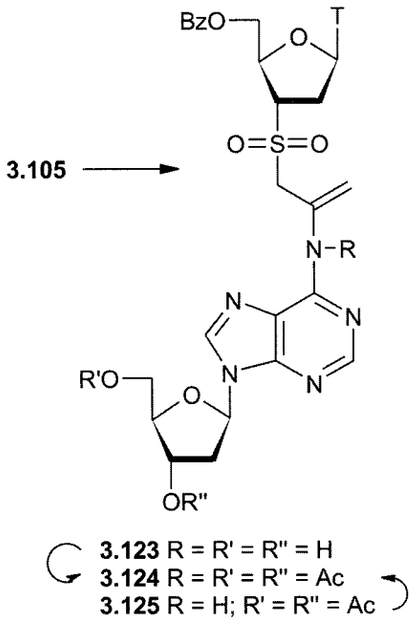
Taking into consideration the pattern of reactions of amines of two extreme p*K*a values with **3.105** mentioned above, **3.105** was not expected to react with nucleobases to form any stable compounds. Moreover, reactions of 4-(naphthalene-1-sulfonyl)-buta-2,3-dien-1-ol with adenine and guanine reportedly produced labile adducts which hydrolyzed to the expected 2-keto derivative. However, when slightly more than one equivalent of 2'-deoxyadenosine was reacted with **3.105** in



dioxane for 2 days a stable dimeric product **3.123** was formed and the product was isolated as the triacetate derivative **3.124** in 46% overall yield. In order to establish the structure of the product **3.124** unambiguously, 1.5 equivalent of 3', 5'-di-O-acetyl-2'-deoxyadenosine was reacted with **3.105** in DCM at room temperature for 28 h to obtain **3.125** in 68% yield. In this case also the product was stable enough to withstand all purification conditions. Compound **3.125** was acetylated with Ac_2O in pyridine at room temperature for 15 h to furnish **3.124** in 88% yield.[35]

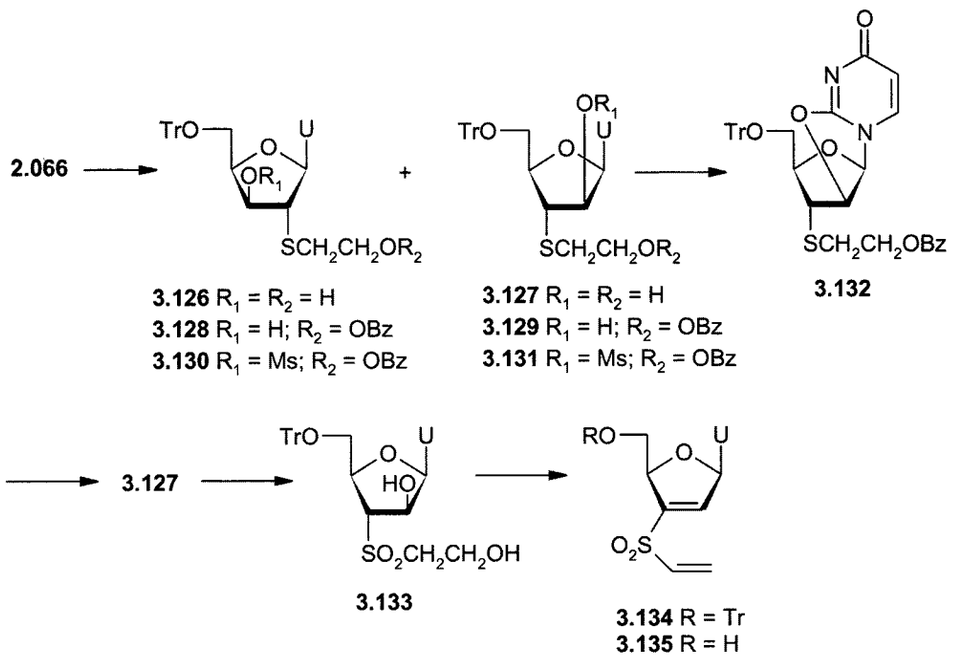
3.6 Divinyl Sulfone-modified Pyrimidine Nucleoside[36,37]

Like monovinylsulfones, bisvinylsulfone group has also been reported to inhibit the action of glyceraldehyde-3-phosphate dehydrogenase.



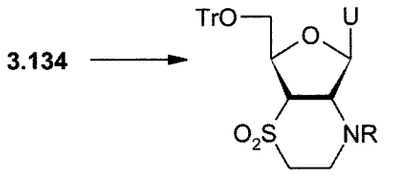
Therefore, as an essential extension of the work reported above, we decided to incorporate a bisvinyl sulfone group into the carbohydrate moiety of uridine. It was also envisaged that nucleosides carrying bisvinyl sulfone group as part of the carbohydrate moieties, would generate bicyclic nucleosides when reacted with appropriate nucleophiles.[36]

The synthesis of the target bisvinyl sulfone-modified nucleoside started with the epoxide **2.066**, which was reacted with mercaptoethanol in the presence of TMG to generate a mixture of 2'-deoxy-2'-*S*-(2-hydroxyethylthio)-5'-*O*-trityl-*xylo*uridine **3.126** and 3'-deoxy-3'-*S*-(2-hydroxyethylthio)-5'-*O*-trityl-*ara*uridine **3.127**. As all efforts to separate the isomers failed, the primary hydroxyl groups of the hydroxyethylthio moieties of **3.126** and **3.127** were benzoylated selectively at 0 °C. After work-up, 2' (3')-hydroxyl groups of the crude benzoylated products **3.128** and **3.129** were mesylated at 0 °C. The resulting mesylated products **3.130** and **3.131** were heated at 100 °C in pyridine; intramolecular 2',3'-epithiiranium ion formation followed by the attack of C-2 oxygen at the C-2' center resulted in the formation of 2,2'-*O*-anhydro derivative **3.132** in 50% overall yield in four steps. Compound **3.132** was debenzoylated and the 2,2'-*O*-anhydro bridge was hydrolyzed by aq. NaOH treatment to produce **3.127** in 96% yield. Oxidation of **3.127** with MMPP produced **3.133** in 86% yield. Both of the hydroxyl groups of **3.133** were mesylated and the crude

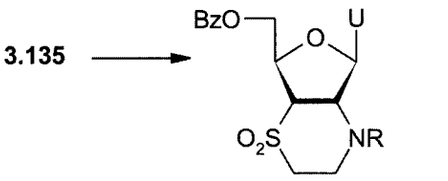


product obtained after work-up was heated at 40 °C in pyridine; elimination of the mesylates produced the desired bisvinyl sulfonyl uridine **3.134** in 86% yield. Detritylation of **3.134** with 80% aq. acetic acid produced **3.135**.[36]

Compound **3.134** was reacted with primary amines, such as isobutyl amine, benzylamine and allylamine in methanol to produce bicyclic derivatives **3.136-3.138**, respectively in high yields and in a stereoselective fashion. Crude bisvinyl sulfone **3.135**, obtained from **3.134** was reacted with ethanolamine and cyclohexylamine and the products were isolated as the benzoyl derivatives **3.139** and **3.140**, respectively. One equivalent of *p*-anisidine reacted with **3.135** to produce a single compound. Attempted cyclization of this compound was unsuccessful even at elevated temperature.[35] The product was isolated as its dibenzoyl derivative **3.141**. Morpholine and dimethylmalonate reacted with **3.134** to produce **3.142** and **3.143** in 92% and 86% yields, respectively. All these reactions

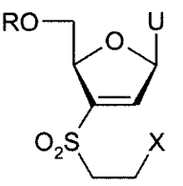


3.136 R = $CH_2C(Me)_2$
3.137 R = CH_2Ph
3.138 R = $CH_2CH{=}CH_2$

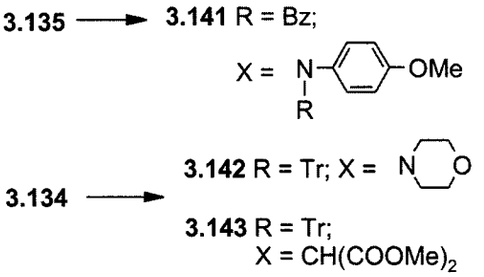


3.139 R = CH_2CH_2OBz

3.140 R =



3.141-3.143



demonstrated that the *exo*-cyclic vinyl sulfone group of **3.134** or **3.135** was more reactive than the *endo*-cyclic one.[36, 37]

4 Conclusion

It has been established from several scattered and rather unrelated examples of vinyl sulfone-modified carbohydrates compiled from literature that the reactions of this class of compounds has the potential to act as a powerful methodology for accessing interesting modified monosaccharides. However, the area remains underexplored and underutilized. Therefore we initiated a systematic study on the synthesis and reactions of vinyl sulfone-modified hex-2-enopyranosides and pent-2-enofuranosides.

Both α- and β-anomers of vinyl sulfone-modified pent-2-enofuranosides **3.001-3.004** have been synthesized for the first time using epoxides derived from carbohydrates as starting materials as well as by taking advantage of the formation of α- and β-methyl glycosides in almost equal ratios only from derivatives of D-xylose.[27,28] In the synthesis of α- and β-anomers of vinyl sulfone-modified hex-2-enopyranosides, a D-glucose derivative was selected over a D-allose compound as the starting material because the former almost exclusively produced the required methyl pyranosides. In comparison to the lengthy synthesis of **3.005** and **3.006** from D-glucose in 14 steps (7 steps for each anomer)[30] the route starting from **3.049**[27,28] makes use of common intermediates up to compounds **3.055** and **3.056**, thereby drastically reducing the overall purification steps. Although overall yields for both the methods are comparable, methyl β-D-*gluco*pyranoside, which has been used in the earlier synthesis,[30] is far too expensive as a starting material to be used in a large-scale multi-step synthesis.

We have established that vinyl sulfone modified carbohydrates are very useful intermediates for the synthesis of several new deoxyaminosugars. The present study acquires greater importance in view of the significant role of C-N equatorial bonds at the C-2 positions of naturally occurring aminosugars, such as D-lividosamine. Syntheses of compounds **3.064** and **3.066-3.070** from **3.005** and **3.006** respectively, therefore, constitute one of the very few examples of the introduction of *N*-monoalkylated and *N,N*-dialkylated amines to the C-2 carbon of pyranoses in equatorial configurations. Efficient addition of 1,2,4-triazole to **3.001** and **3.003**, on the other hand opens up a new route for the synthesis of isonucleosides having nucleobases attached to non-anomeric positions.[30-33]

It should be noted that in contrast to the reactions with amines,[30] **3.005** and **3.006** on reaction with carbon nucleophiles generated products, which manifested fully the directing effect of the anomeric configurations. In both the cases the carbanion added to the planar olefinic systems from a direction opposite to that of the disposition of the anomeric methoxy group. Interestingly, in contrast to the α-D-*manno* configuration of the product obtained from the reaction of carbon nucleophiles with **2.021**, **3.005** produced **3.088** and **3.089** having three axially disposed functional groups on three consecutive carbon atoms (α-D-*altro* configuration) of a six-membered system.[29]

In the area of nucleosides, a reactive triatomic analog of AZT, carrying the vinyl sulfone at the 3′-position has been prepared. This compound has been shown to react very efficiently with a variety of nucleophiles to generate new classes of modified nucleosides where the functional groups are attached to the C-3′ of a nucleoside through a flexible ethyl sulfone spacer.[34] In a related area, we have also reported the first synthesis of an allenic sulfone-modified reactive nucleoside which can alkylate deoxyadenosine.[35] A protocol has also been developed for the synthesis of a nucleoside carrying bisvinyl sulfone group. This is the only example of bisvinyl sulfone group attatched to a chiral appendage. This type of doubly functionalized nucleoside has the potential to generate a wide variety of modified nucleosides including a novel class of bicyclic thiazine S,S-dioxide derivatives.[36,37]

The results reported in this review indicate that it is indeed possible to widen the application of a combination of vinyl sulfone group and carbohydrates in the synthesis of wide ranging modified carbohydrates (and nucleosides) with synthetic and biological utility. The application of nucleophilic addition to vinyl sulfone-modified carbohydrates in the synthesis of higher sugars, unnaturally linked oligosaccharides, sugar based clusters and acyclic synthons are currently in progress in our laboratory.

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