VINYL SULFONE-MODIFIED CARBOHYDRATES: SYNTHESIS AND REACTIONS WITH NUCLEOPHILES

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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. Carbohydrates, on the other hand, are used extensively as chiral building blocks for the synthesis of various complex molecules. 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. Due to the high reactivities of vinyl sulfones towards an array of nucleophiles, 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, (b) sulfone chemistry has been exploited extensively over decades and its compatibility with a wide variety of simple and complex molecules is well established, 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.

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-glucopyranosyl sulfone 2.001 produced the unwanted vinyl sulfone-modified carbohydrate 2.002.

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...
to base-promoted elimination to form the vinyl sultone derivative 2.005.\(^9\) L-Rhamnopyranose tetra-$O$-acetate 2.006 was similarly converted to the corresponding vinyl sulfone 2.008 via phenyl sulfonylglycoside 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 $\alpha$ 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.\(^4\)

Although 1-sulfonyle 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-phenylsulfonyle 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 tributylstannylmagnesium bromide to give the corresponding 1-tributylstannyl glycals.\(^10,11\)

2.1.2 Sultone Group Attached to C-2 of Pyranose Ring

Sugar derivatives having an $\alpha$-sulfonylalkene moiety constructed on a pyranose ring, hex-2-enopyranoside 2.020 was synthesized by reacting.
2.018 with sodium p-toluenesulfinate in the presence of acetic acid followed by the treatment of the gluco-derivative 2.019 with triethylamine.\textsuperscript{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 sulfonyle alkene 2.026 in a similar fashion via 2.025.\textsuperscript{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-allopyranoside 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.\textsuperscript{12}

Vinyl sulfone 2.020, on treatment with methanol, nitromethane, 2,4-pentanediol and ammonia produced the corresponding β-D-gluco-adducts 2.031-2.034, respectively in high yields with high stereoselectivities.\textsuperscript{13} Interestingly, the α-anomeric vinyl sulfone 2.023 on treatment with sodium methoxide in methanol underwent elimination instead of addition to afford 2.035.\textsuperscript{13} Treatment of the phenyl analog 2.036 with nitromethane led
Substrates like 2.038 underwent (3+2) cycloaddition with a trimethylmethylene zwitterion (precursor 2.039) in the presence of an in situ-generated catalyst to afford an inseparable mixture of two isomers 2.040 and 2.041. 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-type addition to the electron deficient double bond followed by an attack of the resultant stabilized anion on the palladium complex.

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 photochemistry using vinyl sulfone-modified carbohydrates has very little synthetic utility.

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)-tolsulfonyl-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
synthesis of 2.055 was devised from 2,3-O-anhydro-\(\alpha\)-D-mannopyranoside 2.056 via 2.057.\textsuperscript{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.\textsuperscript{14} The minor product 2.059 was obtained due to \(\beta\)-attack on the more hindered face of the sulfone and the major product 2.060 was a result of a \(\alpha\)-attack on the less hindered face.\textsuperscript{14}

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 \(\alpha\)-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 \(\alpha\)-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.\textsuperscript{14}

2.2 Vinyl Sulfone-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.  

![Chemical structure](image)

2.063 2.064 R = SO₂Ph; R₁ = TBDMS
2.065 R = SnBu₃; R₁ = 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), 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, then, was therefore selected as a tool for the functionalization of the sugar moiety of nucleosides.

2',3'-O-Anhydro-β-lyouridine 2.066 was reacted with p-toluenesulfochloride 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. N⁶,N⁶-Dibenzoyl-5'-O-(4-methoxytrityl)-3'-enesulfone derivative of adenosine 2.070 was also synthesized 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 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.

2.3 Sulfone Group Attached to an Exocyclic Carbon

2.3.1 Pyranosyl Exocyclic Vinyl Sulfones

A pyranose derivative 2.075 having a 2-phenylsulfonfonyl-2-trimethylsilyl vinyl group has been used for the synthesis of (+)-maytansinol; the synthesis initiated by the heterocoujugate 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.
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 cuprouslium to 2.078 produced 2.079, which was desulfonated by Ran-Ni in refluxing ethanol to produce 2.080.\textsuperscript{19}

### 2.3.2 Furanosyl Exocyclic Vinyl Sulfones

Vinyl sulfone-modified carbohydrates have 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.\textsuperscript{20} The carboxylic acid derivative of isopropylidene uridine 2.086 was also subjected 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.\textsuperscript{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.\textsuperscript{21}

1,2:5,6-Diacetone ulose 2.092, on reaction with a [(MeO)\textsubscript{2}P(O)CH(Li)SO\textsubscript{2}Me] generated an \textit{exo-}
cyclic α,β-unsaturated sulfone 2.093, which could be reduced to 2.094 with \([(\text{Ph}_3\text{P})\text{CuH}]_2\).\(^{21}\)

### 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%.\(^{20,23}\)

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 stereoechemical outcome of the nucleophilic attack at the planar carbonyl group at C-2 position of \textit{threo}-hexopyranosid-2-ulo is controlled by the anomic 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 anomic configuration would stereoelectronically influence the addition pattern of nucleophiles to \textit{endo}-cyclic monovinyl sulfones derived from carbohydrates (Fig. 1).

Since we wanted to use the anomic 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 anomic 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 \textit{via} the addition of arylsulfonyl chloride to suitably protected methyl 2,3-dideoxy-\textit{d}-hex-2-enopyranosides 3.007 or methyl 2,3-dideoxy-\textit{d}-pent-2-enofuranoside
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.\(^{25}\)

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-xylene, 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-peroxyphthalate (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 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 xyla-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.\(^{27,28}\)

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.\textsuperscript{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\textsubscript{2}SO\textsubscript{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.\textsuperscript{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.\textsuperscript{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 anemic mixture close to the ideal ratio of 1:1.\textsuperscript{27,28}

5-O-Benzyl-1,2-0-isopropylidene-3-O-mesyl-α-D-ribofuranose 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 (1:1:5) 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.\textsuperscript{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.\textsuperscript{27,28}
Synthesis of 3.001 and 3.003 from 3-O-tosylated methyl D-xylofuranosides

Methanalysis of 3.021 produced an anemic 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 ribofuranosides 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

3.021 → 3.001 3.003
3.036 X = H; Y = OMe
3.037 X = Me; Y = H

3.2 Reinvestigation into the Synthesis of Vinyl Sulfone-modified Hex-2-enopyranosides27,28

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, 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-allopyranosides 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 benzylideneation) 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 altor-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.\textsuperscript{27,28}

![Chemical structures](image)

**Synthesis of 3.005 and 3.006 from 3-O-mesyalted 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 methanalysis 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.\textsuperscript{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.\textsuperscript{27,28}

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

#### 3.3.1 Reactions with Planar Heterocycles

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

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

3.4.1 Reactions with Amines20,33

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 isopectotate, 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-butyramine, 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-butyramine 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-toluene thiol to 1-(p)-tolyisufonylcyclohexene produced cis-2-(p)-tolymercapto-1-(p)-tolyisufonylcyclohexane 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, stereo electronic 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.\textsuperscript{30}

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{31}

The diastereoselective addition of primary amines to 3.005 and 3.006 has been applied to the synthesis of a naturally occurring aminosugar DL-lividosamine and its analogues.\textsuperscript{32} DL-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-diethyl 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
determining the properties of aminoglycosides.\textsuperscript{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.\textsuperscript{32}

Thus, compound 3.064b obtained 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 (\textsuperscript{1}H NMR). The mixture was desulfonated and the free amino compound 3.076 was acetylated. Pure 3.077 was crystallized out from benzene-petroleum ether mixture in 65% overall yield.\textsuperscript{32}

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 \(\beta\)-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.\textsuperscript{32}

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-heptose), purpuroside A (2-amino-2,3,4,6,7-pentideoxy-6-methylamino-D-ribo-heptose), purpuroside B (2, 6-diamino-2,3,4,6,7-pentideoxy-D-ribo-heptose), purpuroside C (2, 6-diamino-2,3,4,6-tetrahydro-D-erythro-hexose), sisosamine (2, 6-diamino-2,3,4,6-tetrahydro-D-glycero-hex-4-enose), kasugamine (2,4-diamino-2,3,4,6-tetrahydro-D-arabinohexose), 3-Deoxyprumycin [(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-tetrahydro-2,4,6-triamino sugars.\textsuperscript{33}

\textbf{3.4.2 Reactions with Carbon Nucleophiles}\textsuperscript{30}

Although amines added in diastereoselective fashion to 3.005 and 3.006, the directive effect of the anomeric configuration on the stereoechemical 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. On the other hand, sterically bulky tert-butyamine, reacted only with 3.006 (and not with 3.005) at elevated temperature to produce the gluco- derivative in high yield.

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$_3$NO$_2$ 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$_3$NO$_2$ 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 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.

3.5 Monovinyl Sulfone-modified Pyrimidine Nucleosides

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.
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 bispropargyl sulfones as well as acyclic monopropargyl sulfones. Since monopropargyl sulfones exhibited much higher potencies than the cyclic bispropargyl 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.15

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 Nucleosides14,15

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.17

For accessing acetylenic sulfone modified thymidine, 3.094 was converted to 3’-S-(acetythio)-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-chloroperoxybenzoic 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 (δCH, 6.26 ppm or 6.07 ppm) and peaks at 211.8 ppm (δC=), 96.3 ppm (δCH) and 84.3 ppm (δCH2) in the 1H and 13C NMR spectra respectively.15

3.5.2 Reactions of Vinyl and Acetylenic Sulfone-modified Nucleosides14,15

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

![Chemical Structure](image)
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 S'-free hydroxy compound 3.110c.24

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.24

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 5 h 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 3.122.25

Taking into consideration the pattern of reactions of amines of two extreme pKa 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 Ac₂O in pyridine at room temperature for 15 h to furnish 3.124 in 88% yield.¹⁵

3.6 Divinyl Sulfone-modified Pyrimidine Nucleoside²⁶,²⁷

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 moiety, would generate bicyclic nucleosides when reacted with appropriate nucleophiles.²⁸

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-xylopyridine 3.126 and 3'-deoxy-3'-S-(2-hydroxyethylthio)-5'-O-trityl-araouridine 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 benzyolated 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'-epithiiranion 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 byaq. 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 3.135.26

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.25 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

demonstrated that the exo-cyclic vinyl sulfone group of 3.134 or 3.135 was more reactive than the endo-cyclic one.26, 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-glucopyranoside, 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 deoxynamnosugars. 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.\(^ {31}\) 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 attached 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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