JOC Article
pubs.acs.org/joc

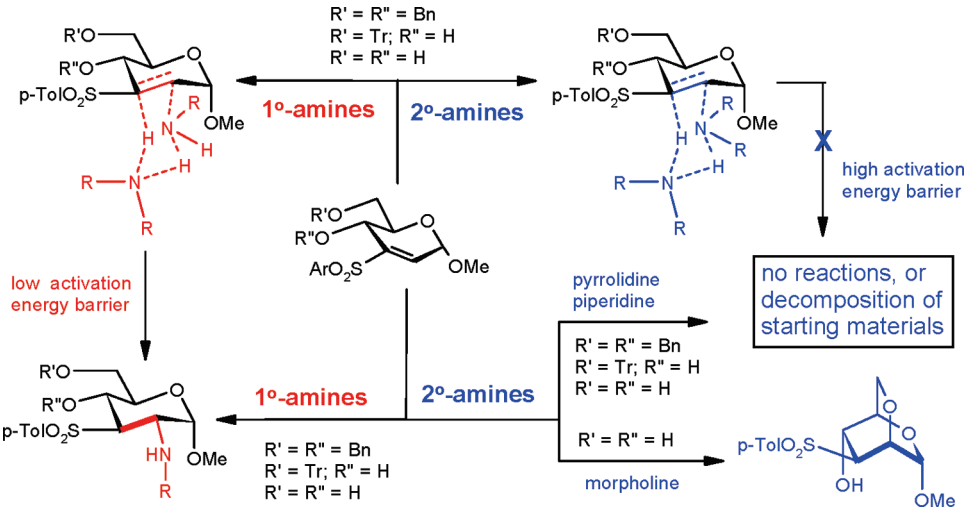
An Experimental and Theoretical Study on the Remarkable Influence of Protecting Groups on the Selectivity of Addition of Amines to Vinyl Sulfone-Modified Hex-2-enopyranosides

Rahul Bhattacharya,[†] Manoj K. Kesharwani,[‡] Chinmoy Manna,[†] Bishwajit Ganguly,*[,‡] Cheravakattu G. Suresh,[§] and Tanmaya Pathak*[,†]

[†]*Department of Chemistry, Indian Institute of Technology, Kharagpur 721 302, India,* [‡]*Analytical Science Discipline, Central Salt & Marine Chemicals Research Institute (CSIR), Bhavnagar 364 002, Gujarat, India, and* [§]*Division of Biochemical Sciences, National Chemical Laboratory, Pune 411 008, India*

tpathak@chem.iitkgp.ernet.in; ganguly@csmcri.org

Received September 26, 2008



Although phenylmethylene-protected vinyl sulfone-modified carbohydrate **2α** reacts with both primary and secondary amines in Michael fashion to afford aminated products, only primary amines react with the dibenzyl-protected **3α**, 6-*O*-trityl-protected **4α**, and unprotected **5α**, highlighting for the first time the remarkable influence of protecting groups on the reaction patterns of vinyl sulfone-modified carbohydrates. The quantum chemical calculations suggest that the Michael addition of amines and proton transfer to vinyl sulfone-modified carbohydrates **2α** and **5α** are possible via relay process in a concerted mechanism. These calculations reveal that the addition of primary amines to vinyl sulfone-modified carbohydrate is preferential due to the low activation energy barriers, whereas the addition of secondary amines has relatively higher activation energy barriers. The theoretical conclusions are in line with the experimental observations.

Introduction

Aminosugars, in general, are one of the most important classes of modified carbohydrates.[1] A large number of 2-amino-2-deoxysugars are the components of various aminoglycoside antibiotics.[2] The most common methods for the

(1) (a) Ferrier, R. J. *Carbohydrate Chemistry*; The Royal Society of Chemistry: Cambridge, 1968−2003; Vols. 1−35. (b) Collins, P. M.; Ferrier, R. J. *Monosaccharides: Their Chemistry and Their Roles in Natural Products*; John Wiley & Sons: Chichester, UK, 1996.

(2) Selected reviews: (a) Banoub, J.; Boullanger, P.; Lafont, D. *Chem. Rev.* **1992**, *92*, 1167–1195. (b) Debenham, J.; Rodebaugh, R.; Fraser-Reid, B. *Ann.* **1997**, 791–802. (c) Lee, S. H.; Cheong, C. S. *Tetrahedron* **2001**, *57*, 4801–4815. (d) Busscher, G. F.; Rutjes, F. P. J. T.; Van Delft, F. L. *Chem. Rev.* **2005**, *105*, 775–791. (e) Magnet, S.; Blanchard, J. S. *Chem. Rev.* **2005**, *105*, 477–497. (f) Hermann, T. *Cell. Mol. Life Sci.* **2007**, *64*, 1841–1852. (g) Zhou, J.; Wang, G.; Zhang, L.-H.; Ye, X.-S. *Med. Res. Rev.* **2007**, *27*, 279–316.

DOI: 10.1021/jo902046g Published on Web 12/17/2009
© 2009 American Chemical Society

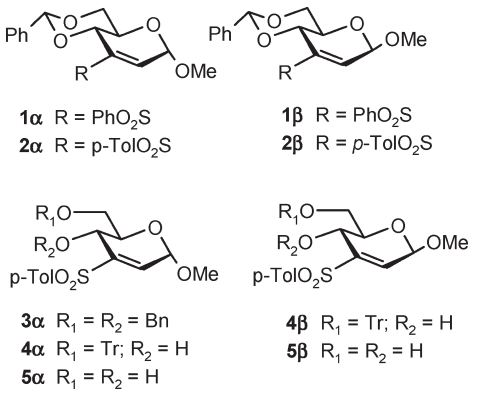
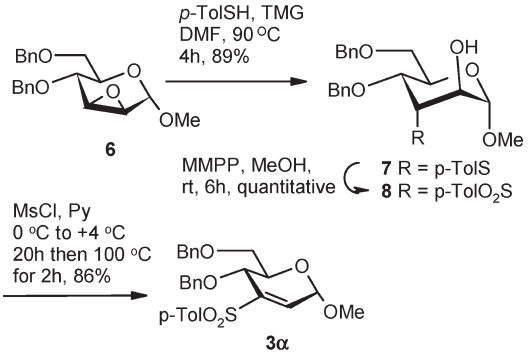


FIGURE 1. Sugar-derived Michael acceptors.

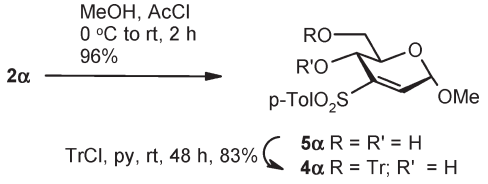
synthesis of aminosugars involve the reactions of amines with sugar-derived epoxides, tosylates, and ketones.[1] Our interest in the area of aminosugars[3] including aminonucleosides[4] led to the designing of an alternative route based on the diastereoselective addition of amines to vinyl sulfone-modified (VSM) carbohydrates **1α** and **1*β*** (Figure 1).[3a] The strategy, followed by desulfonylation of the Michael adducts, led to the synthesis of D-lividosamine (2-amino-2,3-dideoxyglucose) and its analogues.[3b]

Since protection and demasking of functional groups in a synthetic strategy increase the number of steps, thereby decreasing the overall yield of the final products, it was necessary to acquire information on the efficiency of addition of nucleophiles to VSM carbohydrates in the presence of protecting groups other than the phenylmethylene group routinely used so far.[3] More importantly, it was clear from our earlier studies that the directing effects of anomeric configurations were not sufficient criteria to explain the pattern of addition of nucleophiles to compounds like **1** and **2**.[3a,c,g,5,6] We therefore initiated a search for additional factors contributing to the reaction patterns of VSM carbohydrates. It should be noted that the biological importance[7a,d] and synthetic utility of vinyl sulfones triggered studies of "other factors" controlling their reactivities.[7b,c]

SCHEME 1. Synthesis of 3α



SCHEME 2. Synthesis of 4α and 5α



For example, the dependence of the reactivity of a vinyl sulfone as a Michael acceptor on the nature of the group attached to the sulfur atom was determined in order to evaluate the effect of these substituents on the inactivation kinetics of vinyl-sulfone-based cysteine protease inhibitors.[7b] On the other hand, it has been reported recently that the rate of Michael-type addition reactions to conjugated ethylenic sulfones and sulfoxides is influenced by the size of the alkyl group attached to the sulfur atom.[7c] We recently reported that the diastereoselectivity of addition to vinyl sulfone-modified 4-sulfonylhex-3-enopyranoside was nucleophile-dependent.[3g]

Results and Discussion

Synthesis of Vinyl Sulfones 3α−5α: As a first step, we decided to look into the Michael addition reactions of VSM hex-2-enopyranosyl carbohydrates protected with noncyclic protecting groups such as a benzyl or trityl group or not having any protecting group at all. For the preparation of the dibenzylated VSM carbohydrate **3α**, we started the synthesis from the easily accessible fully protected epoxide **6**. Thus, compound **6**[8] was reacted with *p*-thiocresol and TMG in DMF. The sulfide derivative obtained was oxidized using magnesium bis(monoperoxyphthalate) (MMPP) in methanol to the corresponding sulfone derivative **8** in 89% yield. Compound **8** was mesylated within 20 h at 0 to +4 °C using methanesulfonyl chloride (MsCl) in pyridine. The crude mesylated product was subjected to an elimination reaction in refluxing pyridine to afforded **3α** in 86% overall yield within 2 h (Scheme 1). For the synthesis of 6-*O*-trityl-protected VSM carbohydrate **4α**, and the fully unprotected VSM carbohydrate **5α**, the phenylmethylene-protected compound **2α** was deprotected under acidic conditions to generate the diol **5α** in 96% yield. Tritylation of **5α** under standard conditions produced the monoprotected vinyl sulfone **4α** (Scheme 2).[6] The appearance of peaks at δ 6.94 (**3α**),

(3) (a) Ravindran, B.; Sakthivel, K.; Suresh, C. G.; Pathak, T. *J. Org. Chem.* **2000**, *65*, 2637–2641. (b) Ravindran, B.; Deshpande, S. G.; Pathak, T. *Tetrahedron* **2001**, *57*, 1093–1098. (c) Suresh, C. G.; Ravindran, B.; Pathak, T.; Narasimha Rao, K.; Sasidhar Prasad, J. S.; Lokanath, N. K. *Carbohydr. Res.* **2002**, *337*, 1507–1512. (d) Das, I.; Suresh, C. G.; Pathak, T. *J. Org. Chem.* **2005**, *70*, 8047–8054. (e) Das, I.; Pathak, T. *Org. Lett.* **2006**, *8*, 1303–1306. (f) Das, I.; Pal, T. K.; Suresh, C. G.; Pathak, T. *J. Org. Chem.* **2007**, *72*, 5523–5533. (g) Bhattacharya, R.; Pathak, T. *Carbohydr. Res.* **2009**, *344*, 2336–2341.

(4) (a) Pathak, T. *Chem. Rev.* **2002**, *102*, 1623−1667 and references cited therein. (b) Deshpande, S. G.; Pathak, T. *Tetrahedron Lett.* **2004**, *45*, 2255–2258. (c) Maiti, T. K.; De, S.; Dasgupta, S.; Pathak, T. *Bioorg. Med. Chem.* **2006**, *14*, 1221–1228. (d) Leonidas, D. D.; Maiti, T. K.; Samanta, A.; Dasgupta, S.; Pathak, T.; Zographos, S. E.; Oikonomakos, N. G. *Bioorg. Med. Chem.* **2006**, *14*, 6055–6064. (e) Deshpande, S. G.; Pathak, T. *Tetrahedron.* **2007**, *63*, 602–608. (f) Samanta, A.; Leonidas, D. D.; Dasgupta, S.; Pathak, T.; Zographo, S. E.; Oikonomakos, N. G. *J. Med. Chem.* **2009**, *52*, 932–942.

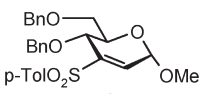
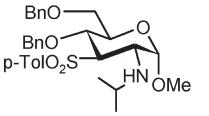
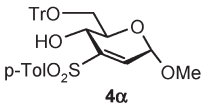
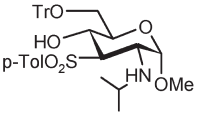
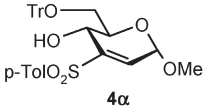
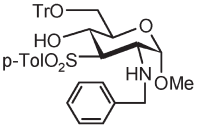
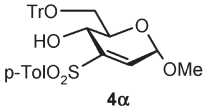
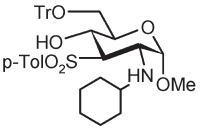
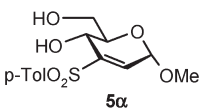
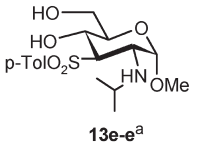
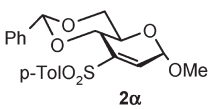
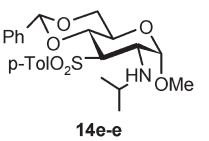
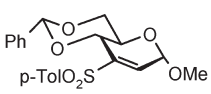
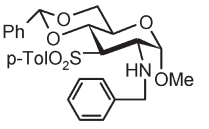
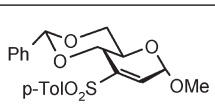
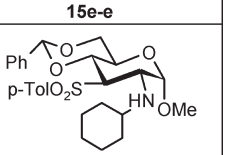
(5) Sanki, A. K.; Suresh, C. G.; Falgune, U. D.; Pathak, T. *Org. Lett.* **2003**, *5*, 1285–1288.

(6) Sanki, A. K.; Bhattacharya, R.; Atta, A. K.; Suresh, C. G.; Pathak, T. *Tetrahedron* **2008**, *64*, 10406–10416.

(7) (a) For a review, see: Meadows, D. C.; Gervay-Hague, J. *Med. Res. Rev.* **2006**, *26*, 793–814. (b) Reddick, J. J.; Cheng, J.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1967–1970. (c) Usera, A. R.; Posner, G. H. *J. Org. Chem.* **2007**, *72*, 2329–2334. (d) Kerr, I. D.; Lee, J. H.; Farady, C. J.; Marion, R.; Rickert, M.; Sajid, M.; Pandey, K. C.; Caffrey, C. R.; Legac, J.; Hansell, E.; McKerrow, J. H.; Craik, C. S.; Rosenthal, P. J.; Brinen, L. S. *J. Biol. Chem.* **2009**, *284*, 25697–25703.

(8) Wu, X.; Kong, F.; Lu, D.; Li, G. *Carbohydr. Res.* **1992**, *235*, 163–178.

TABLE 1. Comparison of Reaction Patterns of α-Anomeric Vinyl Sulfones 2α−5α with Primary Amines (5 equiv) in THF at Room Temperature

No.	Substrate	Amine Time Yield	Product
1.1	 **3α**	Isopropyl amine 14 h 93%	 **9e-e**
1.2	 **4α**	Isopropyl amine 12 h 91%	 **10e-e**
1.3	 **4α**	Benzyl amine 5 d --[b,c]	 **11e-e**
1.4	 **4α**	Cyclo-hexyl amine 5 d --[b,c]	 **12e-e**
1.5	 **5α**	Isopropyl amine 10 h 53%	 **13e-e**[a]
1.6	 **2α**	Isopropyl amine 8 h 90%	 **14e-e**
1.7	 **2α**	Benzyl amine 26 h 80%	 **15e-e**
1.8	 **2α**	Cyclo-hexyl amine 28 h 78%	 **16e-e**

[a]Identified as the trityl derivative **10e-e**. [b]Reaction incomplete at room temperature. [c] > 90% yield at 90−100 °C.

δ 6.83 (**4α**), and δ 6.88 (**5α**) confirmed the presence of the vinyl group.

Reactions of Vinyl Sulfones 2α−5α with Primary and Secondary Amines: The dibenzylated derivative **3α**, on treatment with isopropylamine (5 equiv in THF), produced a single compound **9e-e** in 93% yield within 14 h at ambient temperature (Table 1, No. 1.1).[9] The tritylated derivative **4α** on reactions with isopropylamine under similar conditions produced a single compound **10e-e** in 91% yield within 12 h (Table 1, No. 1.2). Although reactions of **4α** with benzylamine (5 equiv) and cyclohexylamine (5 equiv) in THF remained incomplete even after 5 days at room temperature, compounds **11e-e** (Table 1, No. 1.3) and **12e-e** (Table 1, No. 1.4) were obtained in 60−70% yields; however, these reactions could be pushed to completion within 12 h only by heating the reaction mixtures at 90−100 °C to produce **11e-e** and **12e-e** in 91 and 93% yields, respectively (Table 1). Compound **5α**, having no protecting group, on treatment with isopropylamine (5 equiv in THF) for 10 h at room temperature, produced a mixture of at least three compounds. It was possible to isolate one of the products **13e-e** in 53% yield (Table 1, No. 1.5), which was identified as the trityl derivative **10e-e** (Table 1). It was necessary to unambiguously establish the configurations of C-2 and C-3 centers of compounds **9e-e**−**13e-e**. The identity of **10e-e** was unambiguously established with the help of the X-ray crystallography. Since the diol **13e-e** was converted to **10e-e**, the identity of the former was also unambiguously established. It is reported[4,6] that, for bisprotected gluco analogues and 6-protected gluco analogues, the chemical shift value of the H-1 proton varied within δ 4.73−4.89 with the $J_{1,2}$ values ranging between 3.2 and 3.8 Hz.[10] The chemical shifts and coupling constant values of the H-1 proton of compounds **9e-e** (δ 4.76; 3.6 Hz) and **10e-e** (δ 4.79; 3.0 Hz) prompted us to conclude that these compounds were having gluco configuration.[9]

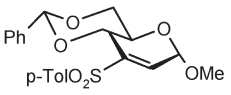
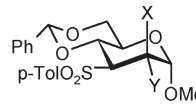
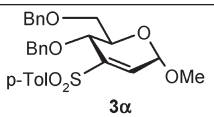
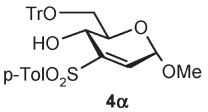
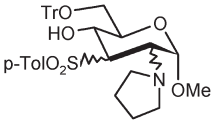
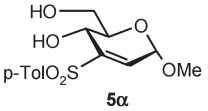
Although reactions of **3α**−**5α** with isopropylamine required 10−14 h for completion (Table 1), **2α** produced **14e-e** within 8 h (Table 1, No. 1.6) with the same amine. On the other hand, **2α** reacted with benzylamine (5 equiv) and cyclohexylamine (5 equiv) in THF at room temperature to produce single compounds **15e-e** (Table 1, No. 1.7) and **16e-e** (Table 1, No. 1.8) in 26 and 28 h, respectively.[9] Notably, reactions of trityl-protected **4α** with both these amines under similar reaction conditions remained incomplete even after 5 days (Table 1), indicating the influence of changed protecting groups.

Compounds **2α** on reaction with pyrrolidine (5 equiv) in THF produced a mixture (isomeric at C-2) of gluco (major) and manno (minor) isomers **17e-e** and **17a-e**, respectively (Table 2, No. 2.1) within 12 h, which was in line with the reported product distribution of the amination of **1α**.[3a] Interestingly, the reactions of the benzylated **3α**, the tritylated **4α**, and the unprotected **5α** with secondary amines produced unexpected and surprising results. Thus, **3α** on treatment with pyrrolidine (5 equiv in THF) at ambient temperature led to the isolation of the starting material after 24 h along with some minor impurities (Table 2, No. 2.2). After prolonged standing in that strongly basic as well as nucleophilic pyrrolidine solution, complete breakdown of the starting material was observed. Compounds **4α** and **5α** were extremely slow to react with pyrrolidine under identical conditions, and even after 5 days at room temperature, the reactions of **4α** and **5α** did not go to completion (Table 2, Nos. 2.3 and 2.4). The products were highly unstable, and in both cases, we were unable to generate clear spectral data.

(9) The products of amination reactions of vinyl sulfones **2α**−**5α** and ***2β***−***5β*** are numbered as follows. **9e-e** represents equatorial bonds at C2 (amino) and C3 (sulfone), whereas **17a-e** is a compound with C2 axial (amino) and C3 equatorial (sulfone) bonds.

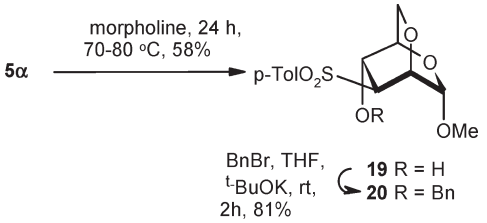
(10) (a) Guangbin, Y.; Fanzuo, K. *Carbohydr. Res.* **1998**, *312*, 77–83. (b) Ogawa, T.; Takahashi, Y.; Matsui, M. *Carbohydr. Res.* **1982**, *102*, 207–215.

TABLE 2. Comparison of Reaction Patterns of α-Anomeric Vinyl Sulfones 2α−5α with Pyrrolidine (5 equiv) in THF at Room temperature

No.	Substrate	Time Yield	Product
2.1	 **2α**	12 h 92%[a]	 **17e-e** X = H; Y = piperidinyl **17a-e** X = piperidinyl; Y = H
2.2	 **3α**	5 d	----[b,c]
2.3	 **4α**	5 d[b,c,d] <15%	 **18**
2.4	 **5α**	5 d	----[b,c]

[a]Mixture of diastereomers as reported (ref 3a) for **1α**. [b]Unidentified products. [c]No reaction/starting material decomposes. [d]Structure proposed on the basis of HRMS only.

SCHEME 3. Anomalous Reaction of 5α with Morpholine

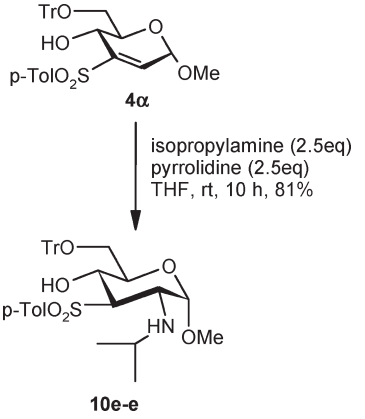


However, only in the case of **4α**, the HRMS data [ES, $(M + H)^+$) calcd for $C_{37}H_{42}NO_6S$ 628.2733, obsd 628.2702] identified one of the products as the probable amino derivatives **18** in less than 15% yield (Table 2, No. 2.3). Both **4α** and **5α** did not react with piperidine in THF at room temperature but produced inseparable mixture of compounds (devoid of amine residue) at an elevated temperature when reacted with piperidine.

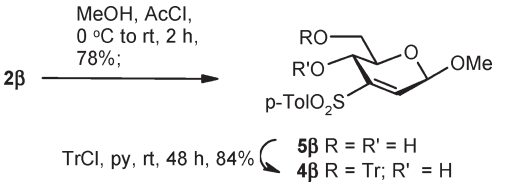
Another secondary amine, morpholine, did not react with **4α** and **5α** at room temperature but reacted at elevated temperature to produce compounds devoid of the morpholino group. The absence of $-CH_2-$ peaks around δ 49.8−51.7 (CH_2−N−CH_2) and δ 66.9−67.4 (CH_2−O−CH_2)[3b] in the ^{13}C NMR spectrum of the reaction products confirmed the absence of morpholino residue. Although **4α** produced an inseparable mixture, it was possible to isolate the major compound from the mixture of products of the reactions of **5α** with morpholine (Scheme 3).

Interestingly, the primary hydroxyl group of **5α** intramolecularly attacked the C-2 position to produce a bicyclic compound **19**; compound **19** was benzylated, and the structure of the product was unambiguously (X-ray) eastablished as **20**. These observations are once again in stark contrast with the reaction patterns of phenylmethylene-protected vinyl sulfone **2α**.

SCHEME 4. Preferential Addition of Primary Amine



SCHEME 5. Synthesis of 4β and 5β from 2β

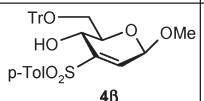
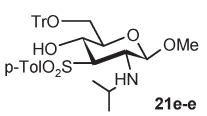
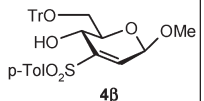
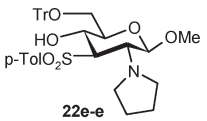
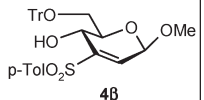
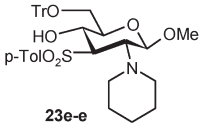
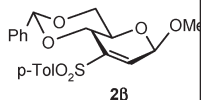
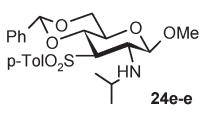
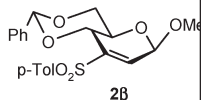
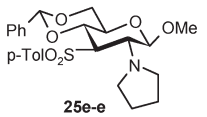
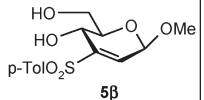
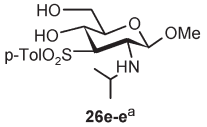
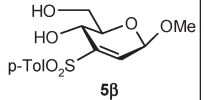
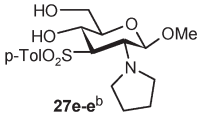


It was therefore clear from the above experiments that the reaction patterns of **3α**−**5α** were highly selective in reacting with primary and secondary amines and are in stark contrast with the same of phenylmethylene-protected vinyl sulfone **2α**. To establish this point further, we reacted **4α** (1 equiv) with a *mixture* of isopropylamine (2.5 equiv) and pyrrolidine (2.5 equiv) at room temperature. After the disappearance of the starting material (ca. 10 h), the reaction mixture was worked up in the usual way and the major product (81%) was identified as the isopropylamino derivative **10e-e** (Scheme 4). The phenylmethylene-protected analogue **2α** produced a mixture of at least three compounds under the similar reaction conditions.

Reaction of Vinyl Sulfones 2β, 4β, and 5β with Primary and Secondary Amines: To extract additional information of the reaction patterns, we also extended the study to the β-series. The trityl-protected **4β** and free diol **5β** were prepared from **2β**. Compound **4β** was synthesized following the literature report.[6] However, compound **5β** was isolated and identified for the present study (Scheme 5).

Compound **4β** reacted smoothly with isopropylamine, pyrrolidine, and piperidine to afford **21e-e**, **22e-e**, and **23e-e**, respectively, in excellent yields (Table 3, Nos. 3.1−3.3). Compound **2β** on reaction with isopropylamine and pyrrolidine produced single isomers **24e-e** and **25e-e**, respectively (Table 3, Nos. 3.4 and 3.5).[3a,9] Compound **5β** was reacted with isopropylamine in THF to produce the expected amino derivative **26e-e** (Table 3, No. 3.6), which was identified as its tritylated analogue **21e-e** (Table 3, No. 3.1) obtained from **4β** (mixed ^1H NMR). Compound **5β** also reacted with pyrrolidine to afford **27e-e** (Table 3, No. 3.7). In this case also, **27e-e** was tritylated to **22e-e** and the structure of **22e-e** (Table 3, No. 3.2), and the structure was established unambiguously with the help of X-ray crystallography. In all of these cases, a

TABLE 3. Comparison of Reaction Patterns of β-Anomeric Vinyl Sulfones with Primary and Secondary Amines (5 equiv) in THF at Room Temperature

No.	Substrate	Amine Time Yield	Product
3.1	 **4β**	Isopropyl amine 12 h 93%	 **21e-e**
3.2	 **4β**	Pyrrolidine 36 h 92%	 **22e-e**
3.3	 **4β**	Piperidine 38 h 87%	 **23e-e**
3.4	 **2β**	Isopropyl amine 12 h 89%	 **24e-e**
3.5	 **2β**	Pyrrolidine 15 h 88%	 **25e-e**
3.6	 **5β**	Isopropyl amine 15 h 71%	 **26e-e**[a]
3.7	 **5β**	Pyrrolidine 38 h 70%	 **27e-e**[b]

[a]Identified as the corresponding 6-*O*-trityl derivative **21e-e**. [b]Identified as the corresponding 6-*O*-trityl derivative **22e-e**.

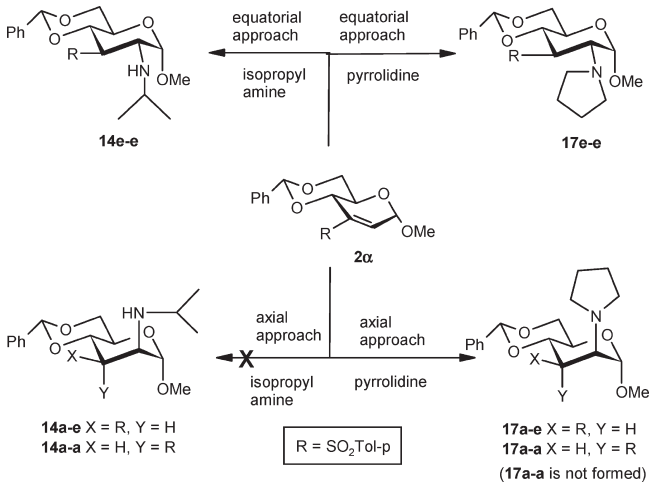
single isomer was obtained because of the predominant equatorial approach of the incoming nucleophile to the VSM hex-2-enopyranosides.[3a]

Although the incoming nucleophile added to all the β-anomeric vinyl sulfones, **2*β***, **4*β***, and **5*β***, with similar diastereoselectivity, the effect of change of protection at the C-6 hydroxyl group was still evident in this case. While pyrrolidine in THF reacted with **2*β*** in 15 h, the more flexible Michael acceptors **4*β*** and **5*β*** took 36−38 h for the complete conversion to **22e-e** and **27e-e** (Table 3). The generality of the reaction pattern was established further because piperidine also required around 38 h for consuming **4*β*** to afford **23e-e** (Table 3, No. 3.3).[9]

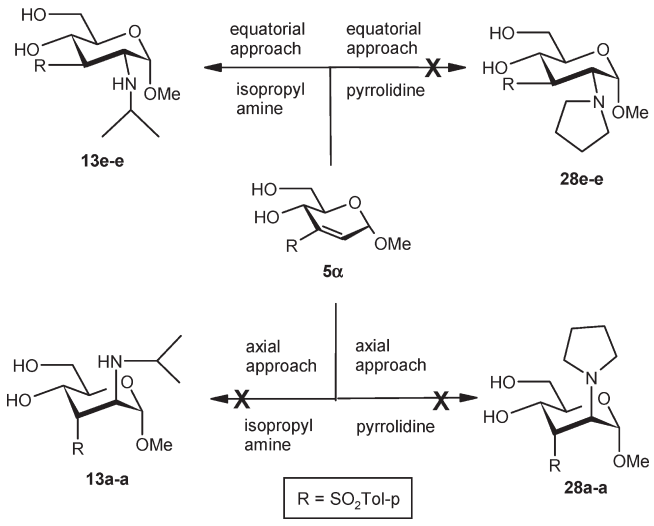
Computational Results. In order to explain the variation in product distributions mentioned above and to examine the

(11) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789. (c) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1988.

SCHEME 6. Product Distribution of 2α under Amination Reaction Conditions



SCHEME 7. Product Distribution of 5α under Amination Reaction Conditions

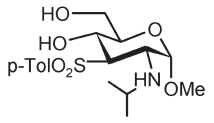
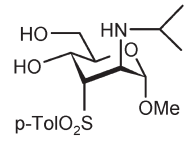
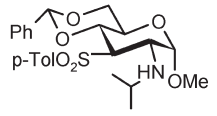
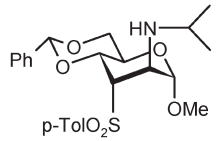
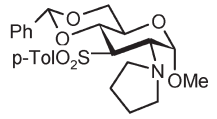
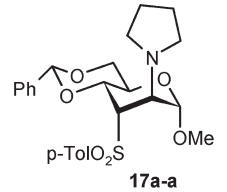
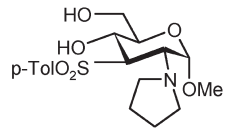
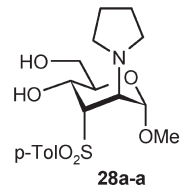


difference in selectivity observed during the nucleophilic addition reaction of amines at VSM carbohydrate for **2α** and **5α**, we undertook a computational study employing quantum chemical ab initio and DFT calculations.[11] It is reported that, in a Michael addition reaction, the addition of amine is possible via a concerted mechanism.[12] We have computed the activation barriers and reaction energies for **2α** and **5α** with isopropylamine and pyrrolidine for both equatorial and axial approaches (Schemes 6 and 7). The reaction energies calculated for **2α** and **5α** with isopropylamine and pyrrolidine are listed in Table 4. The reaction energies calculated for the equatorial approach of both the amines toward the VSM carbohydrates **2α** and **5α** seem to be preferred over the axial approach in both gas and solvent phase (THF), which is in agreement with experimental observations.

Initially, a single amine molecule was considered to calculate the activation barriers for the addition of amines with the

(12) Okumoto, S.; Yamabe, S. *J. Org. Chem.* **2000**, *65*, 1544–1548.

TABLE 4. Reaction Energies (kcal mol^{-1}) Calculated for VSM Carbohydrates 2α and 5α with Isopropylamine and Pyrrolidine for Equatorial/Axial Approaches at RHF/6-31G* and B3LYP/6-31+G*//RHF/6-31G* Levels of Theory (B3LYP/6-31+G* Calculated Single Point Energy in Solvent (THF) Are Given in Square Brackets)

Products	RHF/ 6-31G*	B3LYP/ 6-31+G*
 **13e-e**	-16.9	-15.2 [-14.1]
 **13a-a**	-7.8	-7.3 [-6.2]
 **14e-e**	-13.2	-11.8 [-10.9]
 **14a-a**	-8.2	-7.5 [-6.7]
 **17e-e**	-12.3	-10.3 [-7.6]
 **17a-a**	- 6.5	- 6.1 [-4.7]
 **28e-e**	-15.3	-13.5 [-12.1]
 **28a-a**	- 7.6	-6.5 [-4.7]

RHF/6-31G* basis set. The calculated results suggested that the N···C bond formation and proton transfer take place simultaneously (Figure 2). Therefore, the transition states formed with VSM carbohydrates **2α** and **5α** and isopropylamine are concerted in nature. The four-membered transition states formed are strained, and hence, the computed activation barriers are much higher in energy (Figure 2). The activation barriers were found to be relatively lower with the 6/6-31+G*//RHF/6-31G* level of theory. The methods employed here are discussed in the computational methodology section.

Importantly, the activation barrier for the equatorial approach of isopropylamine toward VSM carbohydrates **5α** and **2α** is 4.9 and 5.6 kcal mol^{-1} lower in energy for **13e-e-TS1** and **14e-e-TS1** compared to that of axial approach **13a-a-TS1** and **14a-a-TS1**, respectively (Figure 2).[9] Activation barriers in tetrahydrofuran (THF) were similar to that of the calculated gas phase barriers at the same level of theory (Figure 2). The computed free energies of activation toward the additions of amines with VSM carbohydrates at the RHF/6-31G* level showed a trend similar to that observed with electronic energies; however, the barriers are relatively higher in the former case (Table S1, Supporting Information). It is known that the computed activation barriers are overestimated at RHF levels of theory.[13]

The product **14a-e** (Scheme 6) was not considered for computational evaluation due to following reasons. The product was not observed experimentally, and the formation of this product would be a stepwise process. Moreover, we have shown in the other case that a stepwise process would be unfavored compared to the concerted process. The high activation barriers obtained for VSM carbohydrates **2α** and **5α** with one molecule of isopropylamine are in agreement with reports by Yamabe et al.[12] Since it is reported that two or three amine molecules can reduce the activation barrier via a proton relay mechanism for such nucleophilic addition,[12] we have also examined the relay mechanism in this case with two amines. Incorporation of a third amine to obtain the transition states was not possible due to steric reasons in these cases. The transition state geometries for the nucleophilic addition with two molecules of isopropylamine are shown in Figure 3. In this case, one of the isopropylamine molecules attacks the most electron-deficient olefinic carbon of VSM carbohydrates, whereas the second amine molecule transfers the N−H proton to the other carbon atom. The first amine transfers its N−H hydrogen to the second nitrogen atom via hydrogen bonding (Figure 3).

The computed activation barriers were found to be 10−19 kcal mol^{-1} lower for transition states with two isopropylamines compared to their corresponding single amine transition states at both ab initio and DFT levels of theory (Figures 2 and 3). Activation barriers were computed with the separated reactants; however, in the relay process, amines were considered as a complexed state, where they are hydrogen bonded (Figure S1, Supporting Information). Comparing the calculated activation barriers for transition states **14e-e-TS2** and **14a-a-TS2**, it appears that the former is kinetically preferred over the latter (Figure 3). This result supports the experimental observation for the formation of **14e-e** from **2α** with isopropylamine. Further, the reaction energies calculated for **14e-e** and **14a-a** also indicate preferential formation of the former product (Table 4). Hence, the equatorial attack of isopropylamine toward **2α** is kinetically

(13) Jones, G. O.; Guner, V. A.; Houk, K. N. *J. Phys. Chem. A* **2006**, *110*, 1216–1224.

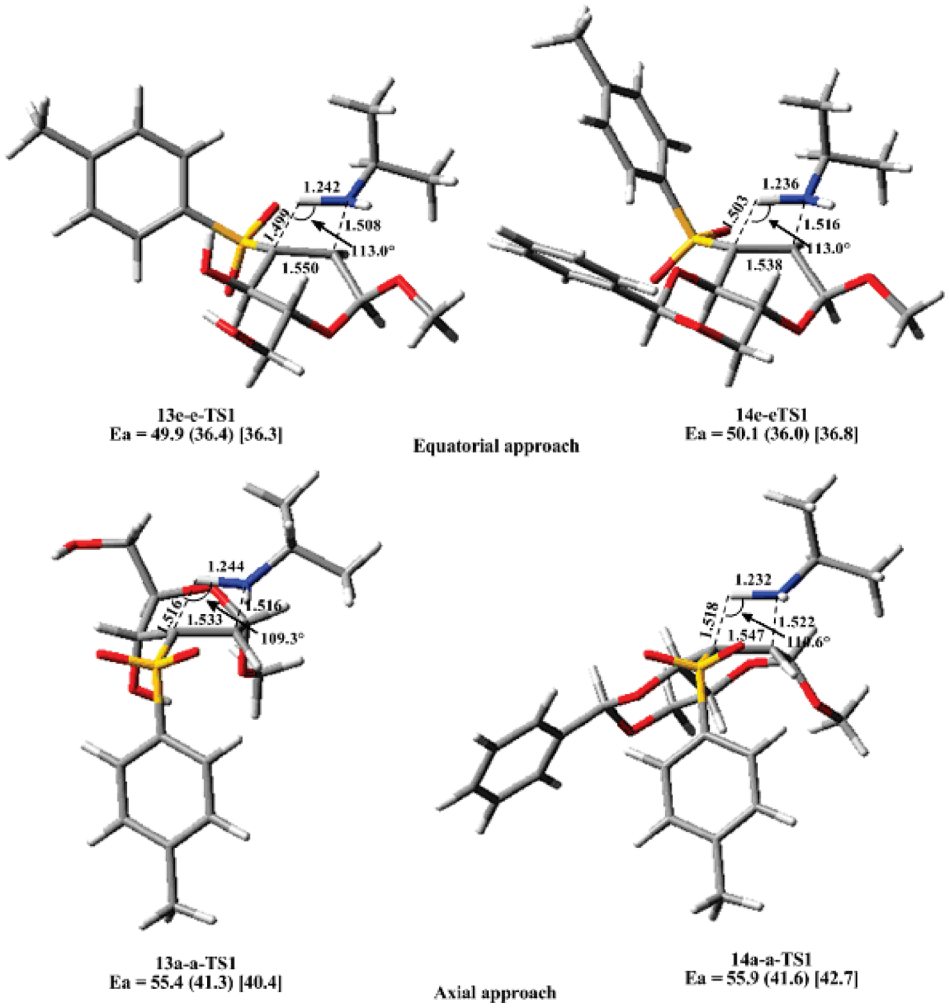


FIGURE 2. RHF/6-31G* optimized transition state geometries (distances in Å) and activation barriers (kcal mol^{-1}) for **5α** and **2α** with single isopropylamine. B3LYP/6-31+G*//RHF/6-31G* calculated activation barriers in the gas phase and in THF are given in parentheses and square brackets, respectively (gray = carbon; blue = nitrogen; red = oxygen; yellow = sulfur; white = hydrogen).

and thermodynamically preferred. In the case of unprotected VSM carbohydrate **5α**, the activation barriers for transition states **13e-e-TS2** and **13a-a-TS2** suggested that the latter transition state was preferred (Figure 3). The activation energy is 1.8 kcal mol^{-1} lower for **13a-a-TS2** than for **13e-e-TS2** at the B3LYP/6-31+G*//RHF/6-31G* level (Figure 3). However, the reaction energies calculated for **13e-e** are ~8 kcal mol^{-1} lower than that of **13a-a**, which supports the formation of **13e-e** as an experimentally observed product (Table 4).

It should be noted that the reaction of **5α** with isopropylamine produced a mixture of at least three compounds. Therefore, it appears that the kinetic and thermodynamic pathways compete with each other for **5α** with isopropylamine. Initially, the lower activation barrier can lead to the formation of product **13a-a**; however, it will equilibrate to the more stable thermodynamic product **13e-e** with time.[9,14] The above-mentioned interpretation can be corroborated with the observed reaction time. The reaction of **2α** with isopropylamine completes within 8 h with a single product, whereas **5α** takes a much longer time (10 h) to complete the reaction process (Table 1). Further, the calculated activation energies also qualitatively support this observation as the barriers are relatively lower for **2α** with isopropylamine than that of **5α** (Figure 3). Activation barrier values in solvent (THF) are similar to the gas phase calculated results at the same level of theory (Figure 3). The free energies of activation computed at RHF/6-31G* showed the similar trend though with larger values (Table S2, Supporting Information).

The secondary amine, pyrrolidine, reacts with **2α** to yield a diastereomeric mixture of **17e-e** and **17a-e** as major and minor isomers, respectively (Scheme 6). The diastereomeric product **17a-e** does not seem to form via concerted amine relay mechanism as observed in other cases. The expected formation of **17a-a** via axial approach of pyrrolidine in a concerted fashion is absent in this case. Since the reaction of **5α** with pyrrolidine does not go to completion even after 5 days (Table 2), the difference in the reactivity of **2α** and **5α** with pyrrolidine was examined computationally. The concerted transition state geometries were obtained for **2α** and **5α** with two pyrrolidines for the equatorial approach (Figure 4); however, such transition states for the axial

(14) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Mill Valley, CA, 2006; p 380.

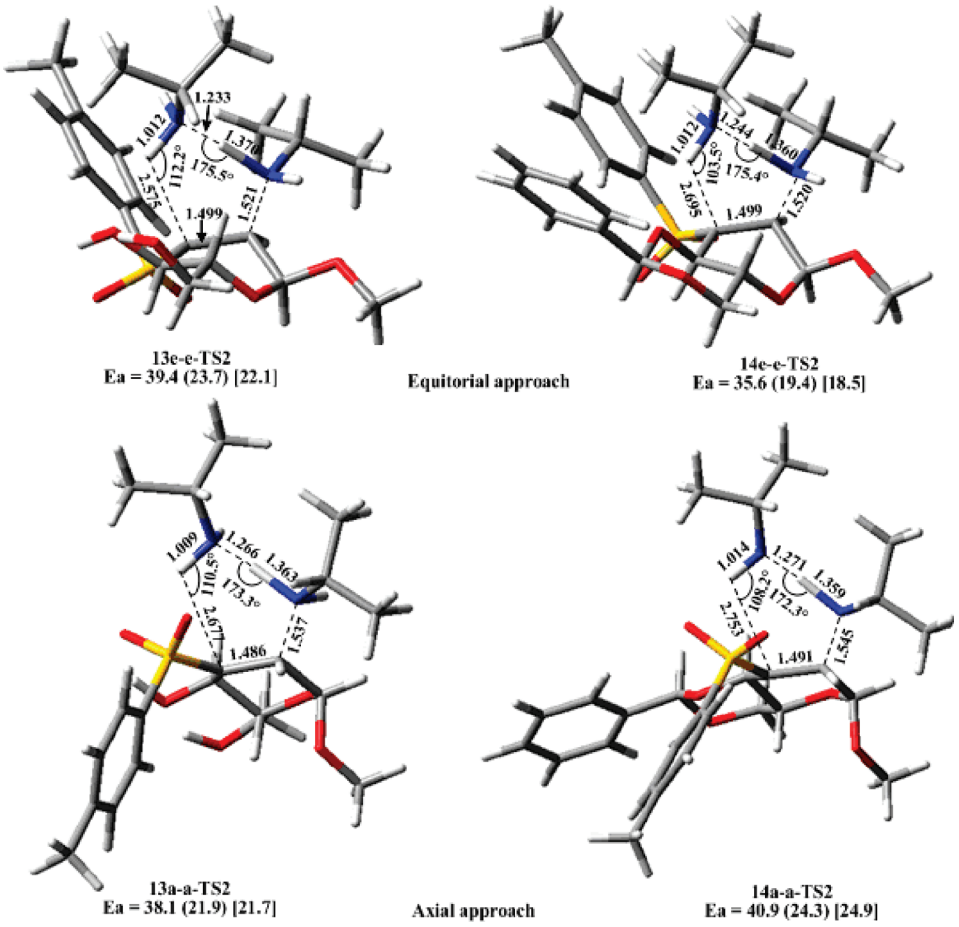


FIGURE 3. RHF/6-31G* optimized transition state geometries (distances in Å) and activation barriers (kcal mol^{-1}) for **5α** and **2α** with two isopropylamines. B3LYP/6-31+G*//RHF/6-31G* calculated activation barriers in the gas phase and in THF are given in parentheses and square brackets, respectively (gray = carbon; blue = nitrogen; red = oxygen; yellow = sulfur; white = hydrogen).

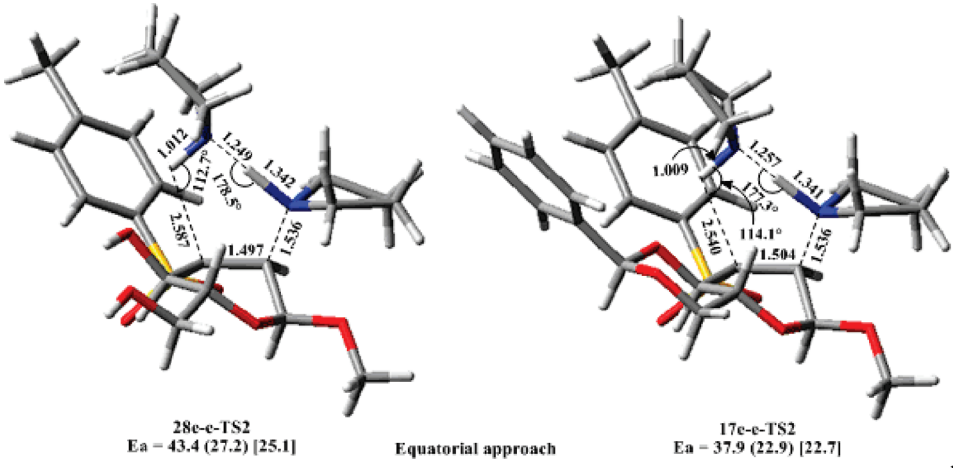


FIGURE 4. RHF/6-31G* optimized transition state geometries (distances in Å) and activation barriers (kcal mol^{-1}) for **5α** and **2α** with two pyrrolidine. B3LYP/6-31+G*//RHF/6-31G* calculated activation barriers in the gas phase and in THF are given in parentheses and square brackets, respectively (gray = carbon; blue = nitrogen; red = oxygen; yellow = sulfur; white = hydrogen).

approach of the amines were not found. The N−H proton transfer to olefinic carbon via proton relay mechanism in the axial approach is not concerted with the formation of the N−C bond. Experimental results suggested that the equatorial approach of pyrrolidine leads to the formation of **17e-e** as a major product for **2α**, but **5α** did not afford desired products with this amine (Table 2). The computed activation barriers suggest that the transition state (**17e-e-TS2**) obtained for **2α** with two pyrrolidine is much lower in energy (∼4−6 kcal mol^{-1}) than the corresponding **5α** transition state (**28e-e-TS2**) (Figure 4). Therefore, these results indicate that the formation of aminosugars with secondary amine for

TABLE 5. B3LYP/6-31 + G* Calculated Strain Energy Derived from Transition State Geometries by Removing the Amines and Their Corresponding Parent Systems

entry	strain energy
13e-e-TS2	50.1
14e-e-TS2	46.6
28e-e-TS2	56.4
17e-e-TS2	53.9

unprotected VSM carbohydrate **5α** is more difficult than the protected VSM carbohydrate **2α**. The experimental findings corroborate the calculated results.

The observed differences in the activation barriers for **5α** and **2α** with isopropylamine (Figure 3) and pyrrolidine (Figure 4) can be rationalized with the strain induced in VSM carbohydrates upon reaction with such amines. We have calculated the strain energies in VSM carbohydrate systems by removing the amines from the transition state geometries and computing the energies for those carbohydrates without perturbing their structures at the B3LYP/6-31+G* level. The energy difference between the parent VSM carbohydrates and their corresponding geometries derived from the transition state structures without amines yields the strain developed with different amines (Table 5). These results clearly show that the strain energies are higher for VSM carbohydrate with pyrrolidine than that of isopropylamine in both cases of **5α** and **2α**, which presumably leads toward the relatively higher activation barrier with the former amine. Further, strain energy data also rationalize the higher activation barriers for **5α** compared to **2α** with respective amines (Table 5).

It should be noted that pyrrolidine on reaction with **2α** afforded **17a-e** as a minor product, but the addition of pyrrolidine and proton transfer is not concerted in nature. The amine residue and proton come from the opposite side of the olefinic carbons (Scheme 6). Therefore, the formation of **17a-e** seems to be a stepwise process, as shown in Figure 5. The transition state **17a-e-Ts1** forms via the abstraction of pyrrolidine proton by the second pyrrolidine ring and goes to **17a-e-complex** for the antiface proton transfer to the olefinic double bond. The protonated pyrrolidine in **17a-e-complex** interacts with sulfone oxygen near the newly formed carbanion, which eventually leads toward the formation of second transition state **17a-e-TS2** with the transfer of proton from the amine to VSM carbohydrate. **17a-e-TS2** is slightly lower in energy compared to the complex, which suggests that the proton transfer process from the protonated pyrrolidine could take place instantaneously without involving these steps. It is known that the proton transfer processes from cationic systems could be spontaneous or barrierless.[15] The influence of solvent seems to be larger in the stepwise process as the gas phase activation barrier for the formation of the **17a-e-Ts1** transition state is stabilized by ~6.0 kcal mol^{-1} in THF. The calculated energy indicates that the reaction is exothermic by 8.8 kcal mol^{-1} in THF. Higher activation barrier (29.5 kcal mol^{-1}) for **17a-e-Ts1** (Figure 5) compared to **17e-e-TS2** (22.7 kcal mol^{-1}; Figure 4) suggests that the latter should be the major product. The observed experimental product ratios are qualitatively in agreement with the calculated results.

(15) Zeng, K.; Cao, Z.-X. *Chin. J. Chem.* **2006**, *24*, 293–298.

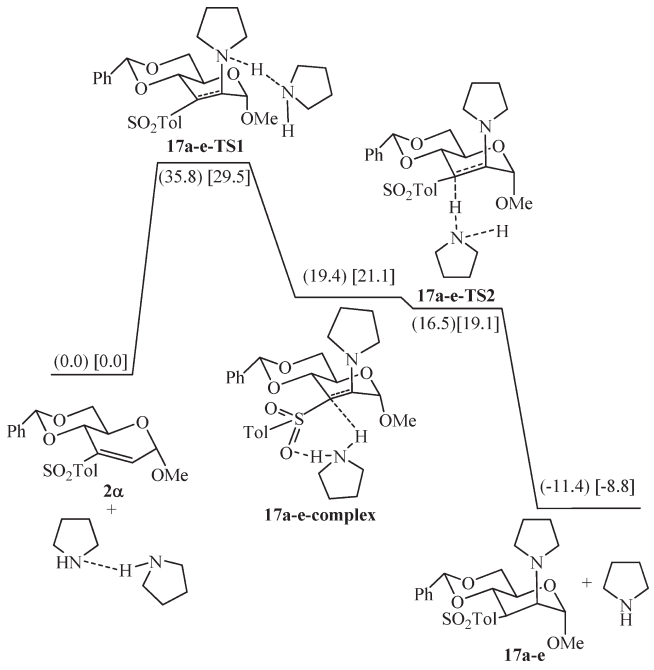


FIGURE 5. Stepwise B3LYP/6-31+G*//RHF/6-31G* calculated potential energy surface for the formation of **17a-e**. Calculated results in solvent (THF) are given in square brackets.

Conclusion

We have established that the protecting groups of VSM hex-2-enopyranosides present at C-6 and C-4 play an important role in determining the rate and the selectivity of addition of amines to these compounds. The absence of protecting group at 6-OH of **5α** adversely affects its reactivity even with primary amines. Tritylated VSM carbohydrate **4α** is much less reactive toward primary amines and virtually resistant toward Michael addition by secondary amines. We presume that the rigid and more organized structural features of **2α** expose the electrophilic C-2 site toward attacking nucleophiles. The conformational flexibilities of **4α**/**5α** makes the C-2 position of these compounds more hindered toward incoming nucleophilic nitrogen. It is also clear from our present study that primary amines under no circumstances could be delivered from a direction opposite to the disposition of the anomeric methoxy group of **4α** as was the case for the addition of deuterides and carbon nucleophiles to analogous flexible nitroolefin derivatives.[16]

Extensive computational study explains the experimental observations appropriately and, for the first time, speculates into the mechanistic aspects for the Michael addition reactions of free amines to the VSM carbohydrates. In the present investigation, quantum chemical calculations were used to study the addition of the primary and secondary amines to VSM carbohydrates **2α** and **5α**. The difference in the activation barriers for VSM carbohydrates **2α** and **5α** with pyrrolidine arises due to the strain induced on the substrates while interacting with the amine. The calculated activation barrier for the formation of **17a-e-TS1** from **2α** and pyrrolidine via stepwise mechanism was found to be

(16) (a) Seta, A.; Tokuda, K.; Kaiwa, M.; Sakakibara, T. *Carbohydr. Res.* **1996**, *281*, 129–142. (b) Sakakibara, T.; Tokuda, K.; Hayakawa, T.; Seta, A. *Carbohydr. Res.* **2000**, *327*, 489–496.

higher than that of concerted proton relay mechanism **17e-e-TS2**, which is in good agreement with the product ratios obtained in this reaction. The selectivity of addition of nucleophiles to vinyl nitro-modified hex-2-enopyranosides was explained earlier in terms of electrostatic interaction,[17a] stereoelectronic control[17a] steric hindrance,[17a] $A^{(1,3)}$ strain,[17b] and also hydrogen bonding.[17b] The present study emphasizes that, henceforth, any discussion on the selectivity of addition of nucleophiles to electron-deficient hex-2-enopyranosyl systems would require the study of the influence of protecting groups, as well.

Experimental Section

General Method: See Supporting Information

Methyl 3-*C*-*p*-tolylsulfonyl-4,6-di-*O*-(phenylmethylene)-α-D-*altro*-pyranoside 8: To a solution of **6** (3.2 g, 8.99 mmol) in DMF (15 mL) were added *p*-thiocresol (7.51 g, 60.6 mmol) and TMG (4.56 g, 36.36 mmol). The reaction mixture was heated for 4 h at 80−90 °C, cooled to rt, and poured into saturated aq NaCl solution (80 mL). The mixture was extracted with EtOAc (3 × 30 mL). The EtOAc layer was washed with saturated aq $NaHCO_3$ (2 × 25 mL). EtOAc layers were pooled together, dried over anhyd Na_2SO_4, and filtered, and the filtrate was evaporated under reduced pressure. The resulting syrup was purified over silica gel to yield **7** (3.84 g, 89%). To a solution of **7** (4.81 g, 10.0 mmol) in methanol (30 mL) was added MMPP (16.88 g, 34.17 mmol). The reaction mixture was stirred for 6 h at room temperature and filtered, and the filtrate was neutralized with saturated aq $NaHCO_3$ (70 mL). The mixture was extracted with EtOAc (3 × 30 mL). The organic layer was separated, dried over anhyd Na_2SO_4, and filtered, and the filtrate was concentrated to dryness under reduced pressure to yield **8** (5.1 g, 88%): colorless jelly; $[\alpha]^{28}_D$ +18.9 (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 3.42 (s, 3H), 3.54−3.63 (m, 2H), 3.73−3.77 (m, 1H), 4.14−4.16 (m, 1H), 4.18−4.22 (m, 1H), 4.37−4.39 (m, 1H), 4.47−4.55 (m, 4H), 4.62 (d, 1H, *J* = 5.2 Hz), 7.08 (d, 2H, *J* = 8.0 Hz), 7.24−7.39 (m, 10H), 7.75 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR δ 21.5, 56.3, 67.4, 67.5, 70.1 (CH_2), 72.1 (CH_2), 72.6, 73.5 (CH_2), 74.0, 102.8, 127.5, 127.7, 127.8, 127.9, 128.1, 128.5, 129.0, 129.2, 137.4, 144.1. Anal. Calcd for $C_{28}H_{32}O_7SCH_3OH$: C, 63.95; H, 6.66. Found: C, 63.86; H, 7.03.

Methyl 2,3-dideoxy-3-*C*-*p*-tolylsulfonyl-4,6-di-*O*-(phenylmethylene)-α-D-*erythro*-hex-2-enopyranoside 3α: To a solution of **8** (5.12 g, 10.0 mmol) in dry pyridine (25 mL) was added a solution of methanesulfonyl chloride (2.8 mL, 36.45 mmol) in dry pyridine (15 mL) at 0 °C. The mixture was left overnight at 4 °C, poured into saturated aq $NaHCO_3$ (70 mL), and the aqueous phase was extracted with EtOAc (3 × 30 mL). Organic layers were collected together, dried over anhyd Na_2SO_4, and filtered, and the filtrate was evaporated. To the crude residue thus obtained was added dry pyridine (20 mL), and the resulting solution was heated under reflux for 2 h and cooled. Pyridine was evaporated under reduced pressure to get an oily residue. The resulting residue was purified over silica gel (eluent 33% EtOAc/petroleum ether) to yield **3α** (4.95 g, 86%): colorless jelly; $[\alpha]^{28}_D$ −11.4 (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H), 3.47 (s, 3H), 3.64−3.71 (m, 2H), 3.94−3.96 (m, 1H), 4.40 (d, 1H, *J* = 11.2 Hz), 4.48 (d, 1H, *J* = 12.0 Hz), 4.64 (d, 1H, *J* = 12.0 Hz), 4.75 (d, 1H, *J* = 8.8 Hz), 4.84 (d, 1H, *J* = 11.2 Hz), 5.15 (d, 1H, *J* = 2.8 Hz), 6.93−6.95 (m, 3H), 7.04 (d, 2H, *J* = 8.0 Hz), 7.19−7.34 (m, 8H), 7.64 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR δ 21.5, 56.3, 68.1 (CH_2), 70.2, 70.3, 73.5 (CH_2), 73.9 (CH_2), 95.0, 127.3, 127.4, 127.5, 127.8, 127.9, 128.0, 128.4, 129.3, 136.1, 137.5, 137.8, 143.8, 144.8. Anal. Calcd for $C_{28}H_{30}O_6S{\cdot}0.5CH_3OH$: C, 67.04; H, 6.32. Found: C, 67.2; H, 6.75.

Methyl 2,3-dideoxy-3-*C*-*p*-tolylsulfonyl-α-D-*erythro*-hex-2-enopyranoside 5α: Compound **2α** (0.5 g, 1.24 mmol) was dissolved in dry methanol (20 mL) and cooled to 0 °C under nitrogen. To this solution was added acetyl chloride (0.2 mL, 2.82 mmol) dropwise over a period of 0.5 h with continuous stirring. After completion of addition, the reaction mixture was warmed to room temperature and the stirring was continued for another 2 h. The solution was then evaporated to dryness under reduced pressure, and the residual liquid was coevaporated twice with pyridine to get a syrupy compound. The compound thus obtained was dissolved in EtOAc, and the organic layer was washed thoroughly with aq saturated $NaHCO_3$ solution. The organic layer was then separated, dried over anhyd Na_2SO_4, filtered, and evaporated to dryness. The residue was purified over silica gel to yield **5α** (0.38 g, 96%): colorless jelly; $[\alpha]^{28}_D$ −29.9 (*c* 0.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H), 3.40 (s, 3H), 3.65−3.83 (m, 3H), 4.52−4.56 (m, 1H), 5.05 (d, *J* = 3.03 Hz, 1H), 6.81−6.84 (m, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR δ 21.6, 56.4, 61.5, 62.3 (CH_2), 71.5, 94. 9, 128.3, 129.9, 134.8, 136.7. 144.9. Anal. Calcd for $C_{14}H_{18}O_6S$: C, 53.49; H, 5.77. Found: C, 53.66; H, 5.53.

Methyl 2,3-dideoxy-3-*C*-*p*-tolylsulfonyl-β-D-*erythro*-hex-2-enopyranoside 5β: Compound **5β** (0.69 g, 71%, colorless jelly) was prepared from **2β** (1.20 g, 2.98 mmol) following the same procedure as described above for the preparation of **5α**: $[\alpha]^{28}_D$ −10.2 (*c* 0.324, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.16−2.17 (m, 1H), 2.18 (s, 3H), 3.34 (m, 1H), 3.48 (s, 3H), 3.59−3.64 (m, 1H), 3.71−3.74 (m, 1H), 3.89−3.92 (m, 1H), 4.26 (br s, 1H), 5.21 (s, 1H), 6.69 (d, 1H, *J* = 2.0 Hz), 7.36 (d, 2H, *J* = 8.0 Hz), 7.78 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR δ 21.7, 56.5, 61.3, 62.71 (CH_2), 77.8, 95.8, 128.4, 130.1, 135.2, 135.4, 143.3, 145.4; HRMS [ES, $(M + Na)^+$] calcd for $C_{14}H_{18}O_6NaS$ 337.0722, obsd 337.0724.

General Procedure for the Addition of Primary and Secondary Amines to 2α, 2β, 3α, 4α, 4β, 5α, and 5β: To a solution of the appropriate vinyl sulfone-modified carbohydrate in dry THF (1 mL/mmol) was added an amine (5 equiv) and was either stirred at room temperature or heated at 90−100 °C. After completion of the reaction (TLC), THF was evaporated under reduced pressure. The residue obtained was triturated with EtOAc, and the organic layer was washed with saturated aq solution of $NaHCO_3$. The organic layer was separated, dried over anhyd Na_2SO_4, and filtered, and the filtrate was evaporated under reduced pressure. The residue was purified over silica gel to afford the product.

Methyl 2,3-dideoxy-2-*C*-isopropylamino3-*C*-*p*-tolylsulfonyl-4,6-di-*O*-(phenylmethylene)-α-D-glucopyranoside 9e-e: Following the general procedure, isopropylamine was reacted with **3α** (0.5 g, 1.01 mmol) at rt for 14 h to yield **9e-e** (0.53 g, 93%): hygroscopic solid; $[\alpha]^{28}_D$ +26.8 (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.9 (d, 3H, *J* = 6.3 Hz), 0.99 (d, 3H, *J* = 6.3 Hz), 2.36 (s, 3H), 2.84−2.91 (m, 1H), 3.33 (s, 3H), 3.35−3.38 (m, 5H), 4.20−4.31 (m, 2H), 4.52 (d, 1H, *J* = 12.0 Hz), 4.71−4.76 (m, 2H), 4.99 (d, 1H, *J* = 10.4 Hz), 7.11−7.36 (m, 12H), 7.83 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR δ 21.5, 21.9, 24.4, 46.0, 54.4, 55.0, 68.5 (CH_2), 69.1, 69.8, 71.2, 73.2 (CH_2), 73.6 (CH_2), 97.4, 127.4, 127.8, 127.9, 128.1, 128.4, 128.9, 137.5, 138.2, 140.5, 143.3. Anal. Calcd for $C_{31}H_{39}O_6S{\cdot}1CH_3OH$: C, 65.62; H, 7.40; N, 2.39. Found: C, 65.69; H, 7.57; N, 2.79.

Methyl 2,3-dideoxy-2-*C*-isopropylamino-3-*C*-*p*-tolylsulfonyl-6-*O*-trityl-α-D-glucopyranoside 10e-e: Following the general procedure, isopropylamine was reacted with **4α** (0.15 g, 0.27 mmol) at rt for 12 h to yield **10e-e** (0.158 g, 91%): white crystal; mp 126−127 °C; $[\alpha]^{28}_D$ +42.9 (*c* 0.366, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.85−0.97 (m, 6H), 2.42 (s, 3H), 2.87 (m, 1H), 3.23−3.43 (m, 4H), 3.42 (s, 3H), 3.73−3.80 (m, 1H), 4.08−4.17 (m, 1H), 4.43 (br s, 1H), 4.79 (d, 1H, *J* = 3.0 Hz),

(17) (a) Sakakibara, T.; Sudoh, R. *J. Org. Chem.* **1977**, *42*, 1746–1750. (b) Sakaibara, T.; Tachimori, Y.; Sudoh, R. *Tetrahedron* **1984**, *40*, 1533–1539.

7.19−7.50 (m, 17H), 7.81 (d, 2H, J = 8.2 Hz); ^{13}C NMR δ 21.6, 24.4, 30.9, 45.4, 53.9, 54.9, 63.3 (CH_2), 64.7, 69.5, 70.2, 76.4, 86.5, 96.6, 126.9, 127.7, 128.7, 128.7, 128.9, 139.0, 144.0. Anal. Calcd for $C_{36}H_{41}NO_6S\cdot0.5CHCl_3$: C, 64.90; H, 6.19; N, 2.07. Found: C, 64.90; H, 5.99; N, 1.95.

Methyl 2,3-dideoxy-2-*C*-benzylamino-3-C-*p*-tolylsulfonyl-6-*O*-trityl-α-D-glucopyranoside 11e-e: Following the general procedure, benzylamine was reacted with **4α** (0.15 g, 0.27 mmol) at 90−100 °C for 12 h to yield **11e-e** (0.163 g, 91%): hygroscopic solid; $[\alpha]^{28}_D$ +41.2 (c 0.315, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H), 3.05−3.33 (m, 2H), 3.41 (s, 3H), 3.45−3.63 (m, 2H), 3.70−3.79 (m, 2H), 4.05−4.15 (m, 1H), 4.34 (br s, 1H), 4.56 (d, 1H, J = 3.1 Hz), 7.07−7.34 (m, 17H), 7.44−7.49 (m, 5H), 7.78 (d, 2H, J = 8.1 Hz); ^{13}C NMR 22.0, 52.0 (CH_2), 55.3, 57.3, 63.7 (CH_2), 65.2, 70.2, 70.6, 87.0, 96.9, 127.4, 127.5, 128.2, 128.8, 128.9, 129.2, 129.7, 138.7, 140.6, 144.5, 144.7; HRMS (ES, (M + H)$^+$) calcd for $C_{40}H_{42}NO_6S$ 664.2733, obsd 664.2715.

Methyl 2,3-dideoxy-2-*C*-cyclohexylamino-3-*C*-*p*-tolylsulfonyl-6-*O*-trityl-α-D-glucopyranoside 12e-e: Following the general procedure, cyclohexylamine was reacted with **4α** (0.15 g, 0.27 mmol) at 90−100 °C for 12 h to yield **12e-e** (0.168 g, 93%): glassy solid; $[\alpha]^{28}_D$ +24.8 (c 0.716, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.84−1.81 (m, 10H), 2.43 (s, 3H), 3.21−3.41 (m, 4H), 3.44 (s, 3H), 3.50−3.78 (m, 1H), 4.09−4.15 (m, 1H), 4.43 (br s, 1H), 4.77 (d, 1H, J = 3.1 Hz), 7.17−7.34 (m, 12H), 7.40−7.59 (m, 5H), 7.79 (d, 2H, J = 8.2 Hz); ^{13}C NMR δ 22.0, 25.3 (CH_2), 25.4 (CH_2), 26.5 (CH_2), 54.0, 54.5, 55.3, 63.7 (CH_2), 65.2, 70.1, 70.6, 86.9, 97.5, 127.3, 128.2, 129.0, 129.2, 129.4, 139.6, 144.5; HRMS (ES, (M + H)$^+$) calcd for $C_{39}H_{46}NO_6S$ 656.3046, obsd 656.3071.

Synthesis of 10e-e from 13e-e: Following the general procedure, isopropylamine was reacted with **5α** (0.15 g, 0.27 mmol) at rt for 10 h to yield a mixture from which **13e-e** was separated (0.09 g, 53%). Compound **13e-e** was tritylated using tritylchloride in pyridine under standard conditions afforded the trityl analogue **10e-e** in 45% overall yield.

Methyl 2,3-dideoxy-2-*C*-isopropylamino-4,6-*O*-(phenylmethylene)-3-*C*-*p*-tolylsulfonyl-α-D-glucopyranoside 14e-e: Following the general procedure, isopropylamine was reacted with **2α** (0.74 g, 1.84 mmol) at rt for 8 h to yield **14e-e** (0.73 g, 90%): white crystal; mp 99−101 °C; $[\alpha]^{28}_D$ +34.6 (c 0.625, $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.06−1.16 (m, 6H), 2.17 (s, 3H), 2.95−3.01 (m, 1H), 3.43 (s, 3H), 3.48−3.58 (m, 1H), 3.69−3.89 (m, 4H), 4.15−4.21 (m, 1H), 4.73 (d, 1H, J = 3.3 Hz), 5.24 (s, 1H), 6.97−7.01 (m, 4H), 7.19−7.30 (m, 3H), 7.63 (d, 2H, J = 8.2 Hz); ^{13}C NMR δ 21.1, 22.0, 23.9, 46.7, 54.7, 55.0, 61.8, 64.4, 68.9 (CH_2), 76.0, 98.4, 101.3, 125.7, 127.4, 127.67, 128.6, 128.7, 136.0, 138.6, 143.7. Anal. Calcd for $C_{24}H_{31}NO_6S$: C, 62.45; H, 6.77, N, 3.03. Found: C, 62.63; H, 6.60; N, 2.96.

Methyl 2,3-dideoxy-2-*C*-benzylamino-4,6-*O*-(phenylmethylene)-3-*C*-*p*-tolylsulfonyl-α-D-glucopyranoside 15e-e: Following the general procedure, benzylamine was reacted with **2β** (0.21 g, 0.52 mmol) at room temperature for 12 h to yield **15e-e** (0.21 g, 80%): yellowish solid; mp 126−128 °C; $[\alpha]^{28}_D$ +42.2 (c 0.856, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.19 (s, 3H), 3.35 (s, 3H), 3.50−3.54 (dd, 1H, J = 3.2, 10.0 Hz), 3.64−3.69 (m, 1H), 3.74−3.86 (m, 3H), 3.92 (s, 2H), 4.14−4.17 (dd, 1H, J = 3.6, 10.0 Hz), 4.59 (d, 1H, J = 3.2 Hz), 5.23 (s, 1H), 7.00 (d, 2H, J = 8.0 Hz), 7.04−7.06 (m, 2H), 7.22−7.43 (m, 8H), 7.64 (d, 2H, J = 8.0 Hz); ^{13}C NMR δ 21.4, 51.5 (CH_2), 55.3, 56.1, 62.0, 64.8, 69.2 (CH_2), 76.2, 98.1, 101.6, 126.1, 127.1, 127.8, 128.1, 128.3, 128.5, 128.9, 129.1, 136.4, 138.6, 140.0, 144.2; HRMS (ES, (M + H)$^+$) calcd for $C_{28}H_{32}NO_6S$ 510.1950, obsd 510.1946.

Methyl 2,3-dideoxy-2-*C*-cyclohexylamino-4,6-*O*-(phenylmethylene)-3-*C*-*p*-tolylsulfonyl-α-D-glucopyranoside 16e-e: Following the general procedure, cyclohexylamine was reacted with **2β** (0.25 g, 0.62 mmol) at room temperature for 12 h to yield **16e-e** (0.24 g, 78%): dark brownish jelly; $[\alpha]^{28}_D$ +39.7 (c 0.625, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.86−1.32 (m, 2H), 1.55−1.59 (m, 1H), 1.70−1.82 (m, 3H), 1.96−1.99 (m, 1H), 2.13 (s, 3H), 2.24−2.29 (m, 1H), 2.54−2.60 (m, 1H), 3.40 (s, 3H), 3.57−3.61 (dd, 1H, J = 3.6, 11.6 Hz), 3.64−3.72 (m, 2H), 3.74−3.87 (m, 2H), 4.14−4.17 (dd, 1H, J = 4.4, 10.4 Hz), 4.70 (d, 1H, J = 3.2 Hz), 5.20 (s, 1H), 6.95−7.00 (m, 4H), 7.18−7.29 (m, 3H), 7.61 (d, 2H, J = 8.4 Hz); ^{13}C NMR δ 21.4, 24.8 (CH_2), 24.9 (CH_2), 25.9 (CH_2), 32.7 (CH_2), 34.9 (CH_2), 54.6, 54.8, 55.3, 62.2, 64.9, 69.3 (CH_2), 76.3, 98.9, 101.6, 126.1, 127.7, 128.0, 129.0, 136.4, 139.0, 144.0; HRMS (ES, (M + H)$^+$) calcd for $C_{27}H_{36}NO_6S$ 502.2263, obsd 502.2261.

Methyl 2,3-dideoxy-2-*C*-pyrrolidino-4,6-*O*-(phenylmethylene)-3-*C*-*p*-tolylsulfonyl-α-D-glucopyranoside 17e-e and Methyl 2,3-dideoxy-2-*C*-pyrrolidino-4,6-*O*-(phenylmethylene)-3-*C*-*p*-tolylsulfonyl-α-D-mannopyranoside 17a-e: Following the general procedure, pyrrolidine was reacted with **2α** (0.62 g, 1.54 mmol) at rt for 12 h to yield a diastereomeric mixture from which **17e-e** (0.41 g, 55%) was isolated by column chromatography over silica gel: white crystal; mp 89−92 °C; $[\alpha]^{28}_D$ + 45.6 (c 0.71, $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.25−1.58 (m, 4H), 2.16 (s, 3H), 2.69−2.74 (m, 2H), 2.91−2.94 (m, 2H), 3.43 (s, 3H), 3.66−3.74 (m, 2H), 3.80−3.93 (m, 2H), 3.97−4.03 (m, 1H), 4.18−4.22 (m, 1H), 4.83 (d, 1H, J = 3.2 Hz), 5.25 (s, 1H), 7.04−7.06 (d, 2H, J = 8.0 Hz), 7.16−7.17 (m, 2H), 7.28−7.31 (m, 3H), 7.68 (d, 2H, J = 8.0 Hz); ^{13}C NMR δ 21.3, 24.1 (CH_2), 47.9 (CH_2), 54.6, 57.7, 62.4, 62.4, 69.4 (CH_2), 76.4, 98.9, 101.4, 126.0, 127.8, 128.0, 128.8, 128.9, 136.6, 139.2, 143.7. Anal. Calcd for $C_{25}H_{31}NO_6S\cdot1H_2O$: C, 61.08; H, 6.77; N, 2.85. Found: C, 60.80; H, 6.51; N, 2.87. The slower moving compound in TLC, **17a-e**, was isolated by column chromatography over silica gel (0.27 g, 37%): yellow jelly; $[\alpha]^{28}_D$ +36.6 (c 0.71, $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.80−1.82 (m, 4H), 2.30 (s, 3H), 2.68−2.73 (m, 4H), 3.45 (s, 3H), 3.66−3.69 (m, 1H), 3.79−3.83 (m, 2H), 4.23−4.34 (m, 2H), 4.69−4.80 (m, 1H), 4.83 (s, 1H), 5.40 (s, 1H), 6.94 (d, 2H, J = 8.0 Hz), 7.33−7.39 (m, 5H), 7.67 (d, 2H, J = 8.0 Hz); ^{13}C NMR δ 21.4, 23.4 (CH_2), 51.6 (CH_2), 54.4, 57.9, 61.2, 61.6, 69.4 (CH_2), 75.3, 98.4, 102.2, 126.4, 127.9, 128.8, 128.9, 129.0, 136.8, 139.5, 143.5; HRMS (ES, (M + H)$^+$) calcd for $C_{25}H_{32}NO_6S$ 474.1950, obsd 474.1940.

(1*R*,3*S*,4*R*,7*R*,8*S*)-7-Benzyloxy-3-methoxy-8-[(4-methylphenyl)-sulfonyl)]-2,5 dioxabicyclo[2.2.2]octane 20: A solution of compound **5α** (1.57 g, 5.0 mmol) in neat morpholine (5 mL) was heated at 70−80 °C for 24 h under N_2. Morpholine was evaporated under reduced pressure, and the resulting residue was dissolved in EtOAc (30 mL). The organic layer was washed with water (2 × 25 mL), separated, and dried over anhyd Na_2SO_4. Organic layer was filtered, and the filtrate was evaporated under reduced pressure. The residue obtained was purified over silica gel to afford **19**: colorless jelly (0.91 g, 58%). To a suspension of 90% *t*-BuOK (0.673 g, 6.0 mmol) in dry THF (10 mL/mmol) at 0 °C was added a solution of **19** (0.785 g, 2.5 mmol) in dry THF (15 mL), and the resulting solution was stirred for 15 min under N_2. The reaction mixture was alloewd to come to room temperature, and to this reaction mixture was added benzylbromide (0.72 mL, 6.1 mmol) under stirring; the reaction was continued for 2 h. The organic solvent was evaporated, and the residue was dissolved in EtOAc (25 mL), washed with saturated aq NH_4Cl (70 mL), and separated. Organic layer was dried over anhyd Na_2SO_4 and filtered, and the filtrate was evaporated. The resulting residue was purified over silica gel to yield **20** (0.82 g, 81%): white crystal; mp 131−133 °C; $[\alpha]^{28}_D$ +15.2 (c 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 3.43 (s, 3H), 3.53−3.58 (m, 1H), 3.80−3.83 (m, 1H), 3.87−3.94 (m, 1H), 4.05−4.13 (m, 3H), 4.60 (dd, 2H, J = 12.2, 14.6 Hz), 7.22−7.38 (m, 7H), 7.77 (d, 2H, J = 8.2 Hz); ^{13}C NMR δ 21.6, 55.2, 65.1 (CH and CH_2), 65.4, 67.5, 70.6, 72.2 (CH_2), 98.9, 127.7, 127.8, 128.3, 129.0, 134.7, 137.4. 145.0; HRMS (ES^+), m/z calcd for (M + Na)$^+$ $C_{21}H_{24}O_6SNa$ 427.1191, found 427.1187.

Methyl 2,3-dideoxy-2-*C*-isopropylamino-3-C-*p*-tolylsulfonyl-6-*O*-trityl-β-D-glucopyranoside 21e-e: Following the general procedure, isopropylamine was reacted with **4β** (0.21 g, 0.37 mmol) at room temperature for 12 h to yield **21e-e**

(0.22 g, 93%): colorless jelly; $[\alpha]^{28}_D$ −18.7 (*c* 0.856, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.93−1.26 (m, 6H), 2.47 (s, 3H), 2.92−3.02 (m, 1H), 3.11−3.40 (m, 4H), 3.48 (s, 3H), 4.02−4.11 (m, 2H), 4.19 (d, 1H, *J* = 6.9 Hz), 7.18−7.48 (m, 17H), 7.81 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR δ 21.6, 22.0, 24.5, 46.1, 54.6, 56.1, 63.1 (CH_2), 64.9, 72.3, 75.9, 86.4, 106.4, 126.9, 127.7, 128.7, 129.1, 129.6, 135.3, 143.9, 145.1. Anal. Calcd for $C_{36}H_{41}NO_6S$: C, 70.22; H, 6.71; N, 2.27. Found: C, 70.17; H, 6.47; N, 2.33.

Methyl 2,3-dideoxy-2-*C*-pyrrolidino-3-*C*-*p*-tolylsulfonyl-6-*O*-trityl-β-D-glucopyranoside 22e-e: Following the general procedure, pyrrolidine was reacted with **4β** (0.30 g, 0.54 mmol) at rt for 36 h to yield **22e-e** (0.32 g, 93%): brown solid; mp 119−121 °C; $[\alpha]^{28}_D$ −10.4 (*c* 0.35, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.08−1.39 (m, 4H), 2.35 (s, 3H), 2.42−2.53 (m, 4H), 3.15−3.46 (m, 4H), 3.49 (s, 3H), 4.16−4.25 (m, 1H), 4.34 (d, 1H, *J* = 1.7 Hz), 4.47 (d, 1H, *J* = 8.0 Hz), 7.18−7.40 (m, 11H), 7.46−7.52 (m, 6H), 7.72 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR δ 21.5, 23.2 (CH_2), 47.1 (CH_2), 55.7, 58.4, 63.2 (CH_2), 65.1, 69.4, 76.8, 86.4, 102.3, 126.9, 127.4, 127.7, 128.7, 129.0, 138.6, 144.0. Anal. Calcd for $C_{37}H_{41}NO_6S \cdot 0.5CH_2Cl_2$: C, 67.2; H, 6.32; N, 2.09. Found: C, 67.54; H, 6.29; N, 1.92.

Methyl 2,3-dideoxy-2-*C*-piperidino-3-*C*-*p*-tolylsulfonyl-6-*O*-trityl-β-D-glucopyranoside 23e-e. Following the general procedure, pyrrolidine was reacted with **4β** (0.30 g, 0.54 mmol) at rt for 38 h to yield **23e-e** (0.30 g, 87%): brownish solid; mp 103−104 °C (decomposed); $[\alpha]^{28}_D$ −16.3 (*c* 0.35, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.73 (br m, 2H), 1.17−1.25 (m, 4H), 2.28−2.36 (m, 2H), 2.43 (s, 3H), 2.61−2.79 (m, 3H), 3.29−3.48 (m, 4H), 3.55 (s, 3H), 4.14−4.16 (m, 1H), 4.33 (d, 1H, *J* = 1.8 Hz), 4.40−4.45 (m, 1H), 7.10−7.30 (m, 11H), 7.47−7.51 (m, 6H), 7.77 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR δ 21.5, 24.2 (CH_2), 25.1, 50.1 (CH_2), 55.6, 63.3 (CH_2), 64.0, 65.3, 68.6, 76.7, 86.4, 102.6, 126.9, 127.7, 127.9, 128.8, 129.3, 138.5, 144.1; HRMS (ES, $(M + H)^+$) calcd for $C_{38}H_{44}NO_6S$ 642.2878, obsd 642.2889.

Methyl 2,3-dideoxy-2-*C*-isopropylamino-4,6-*O*-(phenylmethylene)-3-*C*-*p*-tolylsulfonyl-β-D-glucopyranoside 24e-e: Following the general procedure, isopropylamine was reacted with **2β** (0.30 g, 0.75 mmol) at rt for 12 h to yield **24e-e** (0.31 g, 89%): brownish-yellow solid; mp 112−115 °C; $[\alpha]^{28}_D$ +40.5 (*c* 0.71, $CDCl_3$); ^1H NMR ($CDCl_3$) δ 1.06−1.24 (m, 6H), 2.20 (s, 3H), 3.15−3.21 (m, 1H), 3.44−3.51 (m, 2H), 3.53 (s, 3H), 3.55−3.58 (m, 1H), 3.65−3.70 (m, 1H), 3.98−4.03 (m, 1H), 4.22−4.26 (m, 1H), 4.43 (d, 1H, *J* = 5.6 Hz), 5.23 (s, 1H), 6.96−7.05 (m, 4H), 7.20−7.31 (m, 3H), 7.65 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR δ 21.5, 22.1, 24.3, 47.2, 54.3, 56.7, 66.7, 67.5, 69.2 (CH_2), 75.6, 101.4, 106.1, 126.1, 127.9, 128.3, 129.0, 129.6, 136.3, 137.8, 144.5; HRMS (ES, $(M + H)^+$) calcd for $C_{24}H_{32}NO_6S$ 462.1950, obsd 462.1970.

Methyl 2,3-dideoxy-2-*C*-pyrrolidino-4,6-*O*-(phenylmethylene)-3-*C*-*p*-tolylsulfonyl-β-D-glucopyranoside 25e-e: Following the general procedure, pyrrolidine was reacted with **2β** (0.3 g, 0.75 mmol) at rt for 15 h to yield **25e-e** (0.30 g, 89%): brown solid; mp 108−110 °C; $[\alpha]^{28}_D$ −16.8 (*c* 0.327, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.39−1.66 (m, 4H), 2.33 (s, 3H), 2.66−2.72 (m, 4H), 3.43 (s, 3H), 3.57−3.64 (m, 2H), 3.67−3.77 (m, 2H), 4.29−4.31 (m, 1H), 4.41−4.46 (m, 1H), 4.71 (d, 1H, *J* = 3.6 Hz), 5.45 (s, 1H), 7.17 (d, 2H, *J* = 8.0 Hz), 7.24−7.35 (m, 5H), 7.73 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR δ 21.5, 23.3 (CH_2), 49.6 (CH_2), 55.6, 60.0, 65.1, 66.6, 69.7 (CH_2), 75.0, 100.7, 101.0, 125.9, 128.1, 128.2, 128.8, 129.1, 136.7, 138.4, 144.0; HRMS (ES, $(M + H)^+$) calcd for $C_{25}H_{32}NO_6S$ 474.1950, obsd 474.1941.

Computational Methods: All geometries were fully optimized with restricted Hartree−Fock method[18] using the 6-31G* basis set. To calculate the energies with a higher basis set, single point calculations were performed at the B3LYP/6-31+G* level[11] using RHF/6-31G* optimized geometries. To validate the B3LYP/6-31+G*//RHF/6-31G* calculated results, full optimization of transition state geometries of VSM carbohydrates **2α** and **5α** was performed with single isopropylamine. The calculated activation barriers with B3LYP/6-31+G* level are similar to that of B3LYP/6-31+G*//RHF/6-31G* calculated results (Table 6). Therefore, further calculations were carried out with the B3LYP/6-31+G*//RHF/6-31G* level of theory, which would be economical with similar accuracy for the studied systems herein. The optimized transition state structures with B3LYP/6-31+G* and RHF/6-31G* are quite similar in nature, and no significant deviations were observed (Figure S2, Supporting Information). To account for the solvation effect, single point calculations were performed at the B3LYP/6-31+G* level in solvent THF (ε = 7.58) using the polarizable continuum solvation model (PCM)[19] and UFF topological radii.[20] Complete vibrational analyses were performed to characterize the transition states and ground state geometries. All calculations were performed with the Gaussian 03 suite program on Windows-based dual core Intel xeon machines.[21]

TABLE 6. B3LYP/6-31+G*//RHF/6-31G* and B3LYP/6-31+G* Calculated Activation Barriers (kcal mol^{-1}) for 5α and 2α with Single Isopropylamine

	B3LYP/6-31+G* //RHF/6-31G*	B3LYP/6-31+G*
13e-e-TS1	36.4	36.3
13a-a-TS1	41.3	41.2
14e-e-TS1	36.0	35.9
14a-a-TS1	41.6	41.8

Acknowledgment. T.P. thanks the Department of Science and Technology (DST), New Delhi, for financial support. R.B. and C.M. thank CSIR, New Delhi, for a fellowship. D.S.T. is also thanked for the creation of 400 MHz facility under IRPHA program and DST-FIST for single crystal X-ray facility. M.K.K. thanks UGC, New Delhi. for a fellowship.

Supporting Information Available: Experimental procedures, full spectroscopic data of selected compounds. and CIF files of compounds **10e-e**, **20**, and **22e-e**. Supporting Information also includes calculated total energies and Cartesian coordinates of products and parent compounds along with the calculated total energies, imaginary frequencies, and Cartesian coordinates of transition states for **5α** and **2α** with two amines. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) Roothaan, C. C. J. *Rev. Mod. Phys.* **1951**, *23*, 69–89.

(19) (a) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027–2094. (b) Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *255*, 327–335. (c) Barone, V.; Cossi, M.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3210–3221. (d) Barone, V.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404–417. (e) Cossi, M.; Barone, V. *J. Chem. Phys.* **1998**, *109*, 6246–6254.

(20) Rappe, A. K.; Casewit, C. J.; Colwell, K. S.; Goddard, W. A.; Skiff, W. M. *J. Am. Chem. Soc.* **1992**, *114*, 10024–10035.

(21) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R. J.; Montgomery, A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision E.01; Gaussian, Inc.: Wallingford, CT, **2004**.