JOC The Journal of Organic Chemistry

Article

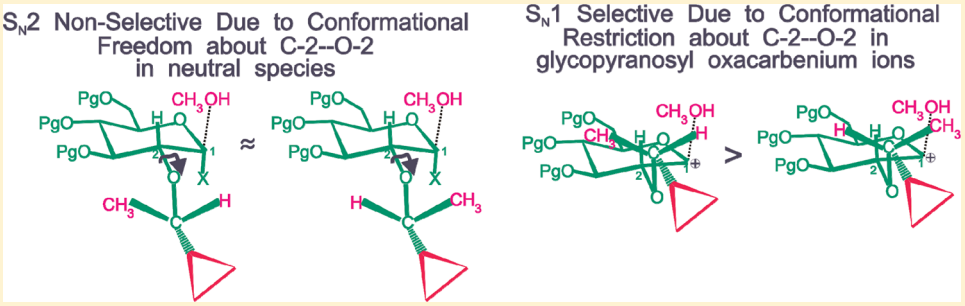
pubs.acs.org/joc

Could Diastereoselectivity in the Presence of O-2 Chiral Nonparticipating Groups Be an Indicator of Glycopyranosyl Oxacarbenium Ions in Glycosylation Reactions?

Rishi Kumar and Dennis M. Whitfield*

National Research Council, Institute for Biological Sciences, 100 Sussex Drive, Ottawa, Ontario, Canada K1A 0R6

Supporting Information



ABSTRACT: Although long postulated, the existence of glycopyranosyl oxacarbenium ions as intermediates or transition states (TS) in chemical glycosylation reactions has not been convincingly demonstrated experimentally. It is anticipated that elucidation of such reactive species will greatly assist synthetic chemists to control the α/β stereoselectivity by rational means. Previous density functional theory (DFT) calculations from our group found that the torsion potential about C-2−O-2 in protected glycopyranosyl donors changed from a conventional 3-fold rotor to a 2-fold rotor with a strong *syn* (CH-2−C-2−O-2−CPg) preference once the donor was ionized to its oxacarbenium ion. This suggested to us that if CPg of the protecting group was a chiral carbon, then diastereoselectivity might be observed in glycosylation reactions that proceed through oxacarbenium ions. The hypothesis to test is as follows: if a nonparticipating O-2 racemic chiral protecting group exhibits diastereoselectivity in glycosylation reactions, then the reaction probably proceeds through an oxacarbenium ion intermediate or TS. We present data for O-2 ether-protected D-glucopyranosyl donors where the racemic protecting group 1-methyl 1′-methylcyclopropylmethyl (MCPM) provides the chirality. MCPM proves to be more activating than the O-2-benzyl ether, and in cases where the donor is otherwise deactivated, several examples of moderate diastereoselectivity are found. These results can be interpreted to indicate that a continuum of reactivity exists where some glycosyl donors form oxacarbenium ions in glycosylation reactions but more reactive donors do not. The strongly activating properties of the cyclopropylmethyl ether functionality and the ability to induce diastereoselectivity with chiral derivatives strongly suggest widespread applications.

1. INTRODUCTION

The assembly of carbohydrate building blocks into oligosaccharides by glycosylation has become a mainstream endeavor in organic synthesis.[1−4] This is mainly due to the numerous applications of synthetic oligosaccharides in glycobiology and increasingly as therapeutic agents such as antithrombotic drugs and preventative vaccines.[5] In recent years, the chemical yields of glycosylation reaction have improved but the control of stereospecificity still lags that of traditional organic chemistry.[6,7] This major shortcoming is at least in part due to the lack of definitive knowledge of the transitions states or reactive intermediates of glycosylation reactions.[8−14] Three significant types of studies have led to some hypotheses for such species namely kinetic isotope effects,[15−19] NMR studies of donor activation conditions[20−24] and computational studies of hypothetical TSs and intermediates.[25−28]

Classical kinetic studies of glycosylation reactions with relatively poor leaving groups, often under solvolysis conditions, suggested that most reactions follow a S_N1 mechanism with only a few cases with very strong nucleophiles that any evidence for the presence of competing S_N2 pathways was found.[29−32] Most authors draw the S_N1 mechanism as involving an isolated in the sense of not ion-paired or otherwise strongly associated oxacarbenium ion. Such delocalized oxacarbenium ions have a well-established position in organic chemistry.[33−36] A further hypothesis is that stereoselectivity of glycosylation would be governed by facially selective attack on oxacarbenium ions. This hypothesis was first made on the basis of density functional theory (DFT) calculations as the two conformer hypothesis.[37] Subsequently, it has been studied experimentally notably by Woerpel's group and in some cases is a satisfactory explanation but for nucleophile: oxacarbenium ion pairs that react at or near diffusion control such selectivity breaks down.[38−45] A second

Received: December 24, 2011
Published: March 19, 2012

   dx.doi.org/10.1021/jo202563f | J. Org. Chem. 2012, 77, 3724−3739

hypothesis that is being increasingly considered is based on the classic model of Winstein and involves reaction through contact ion pairs (CIP) or solvent separated ions pairs (SSIP).[46−50] The original version of this hypothesis considered nucleophilic attack on a CIP to resemble S_N2 and lead to inversion of the stereochemistry of the CIP whereas SSIP would react to favor the anomeric effect and any other steric or electronic factors present in the system. Some recent variations of this mechanism, which include solvent participation[51] and the obligatory proton transfer[26,27] from the nucleophilic hydroxyl, suggest possible additional interactions of the nucleophile with the leaving group.

One early experimental example from Lemieux's group which succinctly summarizes these classical studies is the observation that 3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl chloride under solvolysis conditions in aqueous acetic acid leads to 3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl acetate and the isomeric β-chloride gives the α-acetate. Both reactions were shown to be strictly first order and hence S_N1 like.[52] The facially selective oxacarbenium ion hypothesis above would require that α-anomers ionize to oxacarbenium ions that show opposite facial selectivity from those from β-anomers. Since D-glucopyranosyl oxacarbenium ions can potentially exist in at least two different conformers namely $^4H_3$ and $^5S_1$ then this hypothesis of different conformations hence different products is plausible.[53] Computational ionization studies show that β-positioned leaving groups ionize by a different conformational pathway then isomeric α-positioned leaving groups. This difference is because β-anomers must proceed through antiperiplanar conformations.[54] However, the ultimate conformations from both anomers for D-glucopyranosyl oxacarbenium ions are both $^4H_3$.[55] In this case, a mechanism involving CIPs is more appealing to reconcile Lemieux's observations.

However, like most of these early mechanistic studies the reaction conditions do not reflect the current glycosylation methodologies where highly reactive glycosyl donors are usually activated, often preactivated,[56−62] with strong promoters at low temperatures in relatively nonpolar solvents where the most polar solvent commonly used is acetonitrile and the least polar solvent is toluene. Dichloromethane and a few related chlorohydrocarbon solvents as well as simple dialkyl ethers are also commonly used. The reagents and reactants thus favor ionization but the solvents do not. In the cases where neighboring group participation from O-2 is possible, typically with O-2 esters, then further stabilized dioxolenium ions can be formed. In these cases Density Functional Theory (DFT) computation shows such ions to be about 60 kJ mol^{-1} more stable then their oxacarbenium ion isomers. In accord with this greater stability is that their existence has been confirmed experimentally in the solid state and in solution.[50,63,64] As well, anomeric (thio)-sulphonium ions and some closely related doubly stabilized species can be studied experimentally.[65−69] However, to the best of our knowledge, in the absence of such participation, the existence of oxacarbenium ions in current glycosylation methodologies is still unresolved.

From a synthetic organic chemists viewpoint what is desirable is a condition or set of conditions that allow high stereoselective control proceeding through intermediates and TSs whose structures are known. Such knowledge would allow synthetic chemists to vary protecting groups, leaving groups, promoters, solvents, additives, etc. in a systematic way. Many reactions in traditional organic chemistry have been studied at this level often leading to highly stereoselective processes.[70] The achievement of such knowledge for glycosylation reactions is a primary goal of our research group. In this work we present a novel method that works toward this goal. This method derives from an unexpected DFT computational result on the conformations of glycopyranosyl oxacarbenium ions. We found that the dihedral angle CH-2−C-2−O-2−C(pg) where C(pg) is the first C-atom of the O-2 protecting group of the donor exhibit a unimodal *syn* conformation with the absolute value typically <20°.[71] This effect was further shown to probably arise from a unimodal hyperconjugative interaction of an O-2 lone pair with the O-5−C-1 pseudo double bond of the cation.[72] Further studies supported that this conformation followed ionization.[54] Consideration of the conformational rigidification after ionization suggested to us that it might be possible to test for ionization by making C*(pg) a chiral carbon. The premise is that the inherent 3-fold flexibility about C-2−O-2 in neutral species and CIPs would lead to little or no diastereoselectivity in a glycosylation reaction since low barrier C-2−O-2 rotation could occur but in the ionized state the relatively rigid C-2−O-2 conformation would allow the C*(pg) chirality to affect the facial selectivity, see Figure 1. In the remainder of this manuscript diastereoselectivity refers to the C*(pg) chiral protecting group. We also report α:β ratios but these are not the focus of this work.

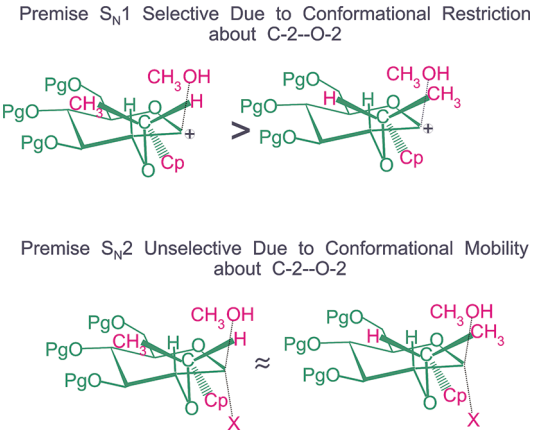


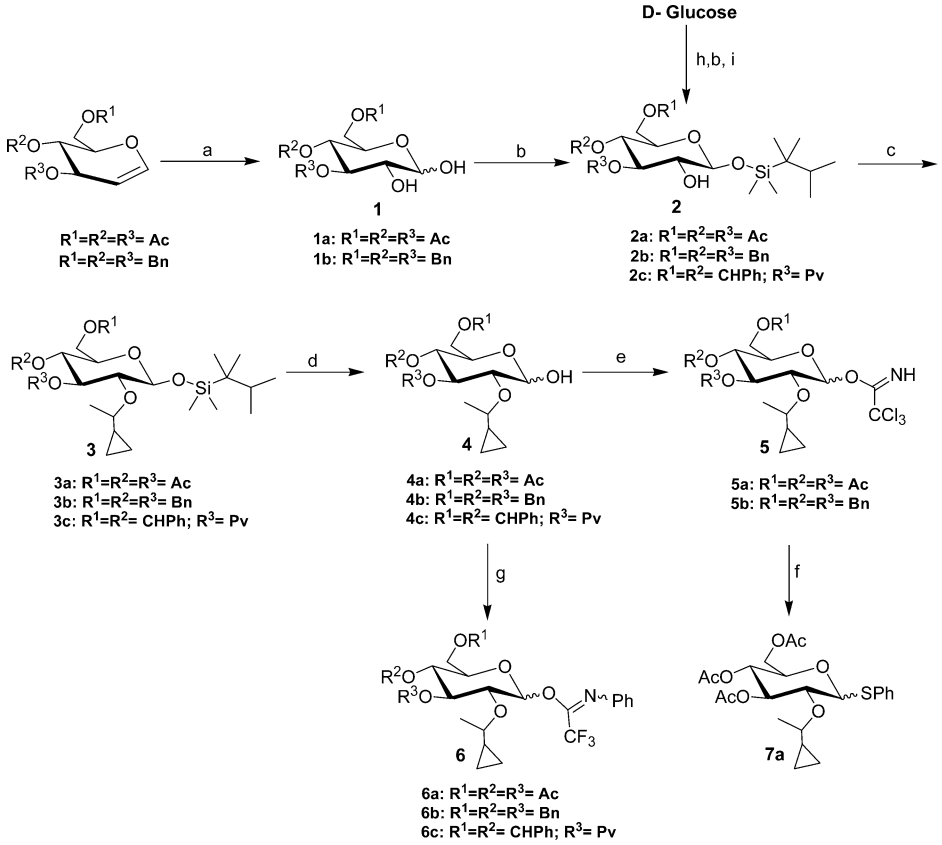
Figure 1. Computationally, ionization has been shown to rigidify the C-2−O-2 dihedral angle such that the chirality at C(pg) may affect facial selective attack in a S_N1 like process. Conformational mobility in neutral S_N2 like species is expected to remove such diastereoselectivity. Methanol is portrayed as the nucleophilic acceptor for simplicity. More complex acceptors can be anticipated to show more pronounced interactions with the chiral protecting group. The conformations drawn are based on our initial premise that the O-2--Cpg torsion should be *trans*, in which case the reactivity could be as shown on steric grounds. This torsional preference is addressed by DFT calculations in this work.

A number of people have studied the effect of O-2 nonparticipating groups on glycosylation reactions. Most studies have focused on the effects on reactivity where electron-donating groups are considered activating and electron withdrawing groups deactivating.[73−76] More recent studies have found further subtleties relating to substituents at other positions[77] including effects on the regioselectivity and stereoselectivity of glycosylations.[78,79]

In this work we synthesized a selection of D-glucopyranosyl donors of differing reactivity with O-2 protected by the 1-methyl 1′-cyclopropylmethyl (MCPM) protecting group.[80] We introduced this group a number of years ago as a cleavable protecting group for polymer-supported oligosaccharide synthesis

dx.doi.org/10.1021/jo202563f | J. Org. Chem. 2012, 77, 3724−3739

Scheme 1. Synthesis of 2-*O*-MCPM Glycosyl Donors[a]



[a](**a**)$RuCl_3$, $CeCl_3$, $NaIO_4$, EtOAc, CH_3CN, H_2O, 1 h, rt; (**b**) Thexylsilyl Chloride, Imidazole, DMF, 16 h, 0 °C; (**c**) MCPMTCI, AgOTf, DCM, 22 h, −40 °C; (**d**) TBAF, AcOH, THF, 2 h, rt; (**e**) CCl_3CN, NaH, DCM, 1−2 h, 0 °C; (**f**) PhSH, $BF_3.Et_2O$, MS4, DCM; (**g**) *N*-phenyl-2, 2,2-triflouroacetimidoyl chloride, K_2CO_3−H_2O, Acetone, 20−24 h, rt; (**h**) α,α-DMT, pTSA, DMF, 3 h, 60 °C; (**i**) PvCl, Pyridine, DMAP, DCM, 26 h, −25 °C.

with examples of its successful use at O-3, O-4 and O-6. These results are complemented by a recent study showing the utility of MCPM as an anomeric protecting group.[81] It is readily installed and cleaved, as well it is electron donating of moderate size and hence an activating group. This work shows that the MCPM group at O-2 is more activating then *O*-benzyl or as it is commonly called arming.[82,83] The anomeric selectivity is also different from typical O-2 benzyl donors.[84−87] Further, we show that in cases where the donor is otherwise disarmed[77,88−91] that the chirality at C*(pg) leads to diastereoselectivity. This principle is not to be confused with chiral auxiliary mediated which relies in most cases on the formation of 6-membered participating rings.[92,93] Some fundamental aspects of the conformational preferences of O-2 MCPM substituted D-glucopyranosyl donors are also studied by DFT calculations.[94−98]

2. RESULTS AND DISCUSSION

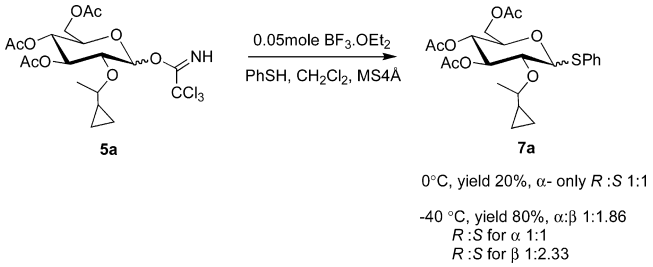
2.1. Synthesis of Donors. Since we wished to investigate the effect of the MCPM group at O-2 we started our syntheses (see Scheme 1) from the readily available tri-*O*-acetyl-D-glucal (for **1a**) or tri-*O*-benzyl-D-glucal (for **1b**) using an oxidative 1,2-diol formation reaction introduced by Misra.[99] The anomeric position could then be selectively protected as its β-D-thexylsilyl derivatives **2a** and **2b**.[100] The free 2-OH could then be MCPM etherified under Lewis acid catalysis[80] in the presence of excess MCPM-trichloroacetimidate to give **3a** and **3b**. Since MCPM is synthesized from racemic 1-methyl 1′-cyclopropylmethanol the resulting ethers are diastereomeric. Within experimental error the two diastereomeric MCPM ethers were a 50:50 mixture. The anomeric silyl group was readily removed to give the hemiacetals **4a** and **4b**.

These were subsequently converted to their trichloroacetimidates **5a** and **5b** or their *N*-phenyl trifluoroacetimidates[101,102] **6a** or **6b**.

Trichloroacetimidates, especially the tri-*O*-benzyl **5b**, were particularly unstable to standard silica gel chromatography even in the presence of triethylamine or diisopropylethylamine (DIEPA) in the chromatography solvents. Thus, a slightly modified version of the original Schmidt NaH procedure was used and the donors **5b** were used without chromatographic purification.[103,104] The *N*-phenyl trifluoroacetimidates were more stable and could be chromatographed before use. Using these protocols the diastereomeric ratios at the MCPM chiral center were very close to 50:50 in all of the donors. After preliminary experiments with **5a**, **5b**, **6a** and **6b** a more deactivated donor was sought. Starting from D-glucose the 4,6-*O*-benzylidene-3-*O*-pivaloyl donor **6c** was synthesized by standard protecting group manipulations.[105,106] Similarly donor **5a** was converted to its phenylthio-glycoside **7a** by treatment with 0.05 mol equiv of $BF_3{\cdot}OEt_2$ in the presence of thiophenol (Scheme 2). When the reaction was done at ice bath temperature an approximately 20% yield of the α-thioglycoside was found. In this product the diastereomeric ratio at the MCPM C was close to 1:1. When the reaction was repeated at −40 °C the yield

dx.doi.org/10.1021/jo202563f | J. Org. Chem. 2012, 77, 3724−3739

Scheme 2. Synthesis of Anomeric Phenylthioglycosides 7



improved to close to 80% and the α:β ratio was 1:1.86. Interestingly the diastereomeric ratio of the MCPM C in the α-thioglycoside was still 1:1 but for the β-thioglycoside 1:2.33, *R*:*S*.

2.2. Glycosylation. As test acceptors a primary alcohol of a 6-OH D-mannose derivative (**8**)[107,108] and a secondary alcohol 4-OH L-rhamnose derivative (**9**)[109] were used. The results of glycosylations are shown in Scheme 3. Reactions with unstable **5b** were performed at −60 °C in a dichloromethane/cyclohexane mixture whereas the slightly more stable donors **5a** were reacted in the same solvent mixture, but at −40 °C. Reactions with purified **6b** were done at −75 °C in dichloromethane and with **6a** at −60 °C. For partially deactivated donor **6c** reaction with primary alcohol **8** proceeded at −75 °C but the secondary alcohol **9** required slight warming to −50 °C to complete the reaction. In all cases, small amounts of trimethylsilyltrifluoromethanesulfonate (TMSOTf) promoted the reaction. The relatively low temperatures for reaction suggested that the 2-*O*-MCPM was an activating protecting group. Note that 3,4,6-tri-*O*-acyl-2-*O*-benzyl-D-glucopyranosyl donors are considered to be superdisarmed.[110] In all cases the disaccharides were the major products with little or no donor left and little or no unreacted acceptors were left too. The only discernible byproducts were small amounts of the hemiacetals **4a**, **4b** or **4c**.

The NMR spectra of the diastereomeric α/β-glycosides were often quite complicated. Assignments were made by standard 2D NMR methods such as ^{1}H−^{1}H-COSY, ^{1}H−^{1}H-TOCSY and ^{13}C−^{1}H-HSQC. In several cases 1D ^{1}H-nuclear Overhauser effect (NOE) spectra were run in order to establish proton−proton proximity that aided in the assignment of diastereomers and anomers. Representative examples are given in the Supporting Information. Diastereomeric ratios as well as α/β ratios were estimated by integration of relevant single peaks in the assigned ^{1}H spectra. Note the absolute configuration at the MCPM C is not known with certainty in any cases and the *R*:*S* ratios (labels) could be reversed in all cases.

The 3,4,6-tri-*O*-benzyl 2-*O*-MCPM donors **5b** and **6b** gave a marked preference for β-glycosides. This is quite different from the usual α-preference for 2-*O*-benzyl donors.[84−86,111] The more deactivated 3,4,6-tri-*O*-acetyl 2-*O*-MCPM donors **5a** and **6a** showed a marked α-preference. DFT calculations of the 2,3,4,6-tetra-*O*-methyl-D-glucopyranosyl oxacarbenium ion suggested that both the $^4H_3$ and $^5S_1$ conformers should be β-selective if hydrogen bonding between the nucleophile and the oxacarbenium ion could occur.[112] Otherwise the $^4H_3$ conformer is α-selective and the $^5S_1$ conformer β-selective on stereoelectronic grounds.[53] These results strongly suggest that the 2-*O*-MCPM group activates the anomeric position differently than 2-*O*-benzyl (Table 1).

To directly compare the reactivity of the 2-*O*-MCPM group, the reactivity was compared by competition with the well-known 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl donor **16**. The results shown in Scheme 4 demonstrate that the 2-*O*-MCPM group is more activating then the 2-*O*-benzyl group, at least in this example.

Reactive donors **5b** and **6b** showed no *R*-, *S*-MCPM diastereoselectivity under any glycosylation conditions. This result suggests that reactive donors do not require oxacarbenium ion formation to permit reactivity. With the less reactive donors **5a**, **5b** and **6c** a small diastereoselectivity was observed especially with the secondary acceptor **9**. For α-glycosides, this ranged from no selectivity to a high of 1.6:1 (*R*:*S*). For β-glycosides, when formed, selectivity was as high as 1:4.66 (*R*:*S*). These observations are consistent with oxacarbenium ion formation according to our hypothesis.

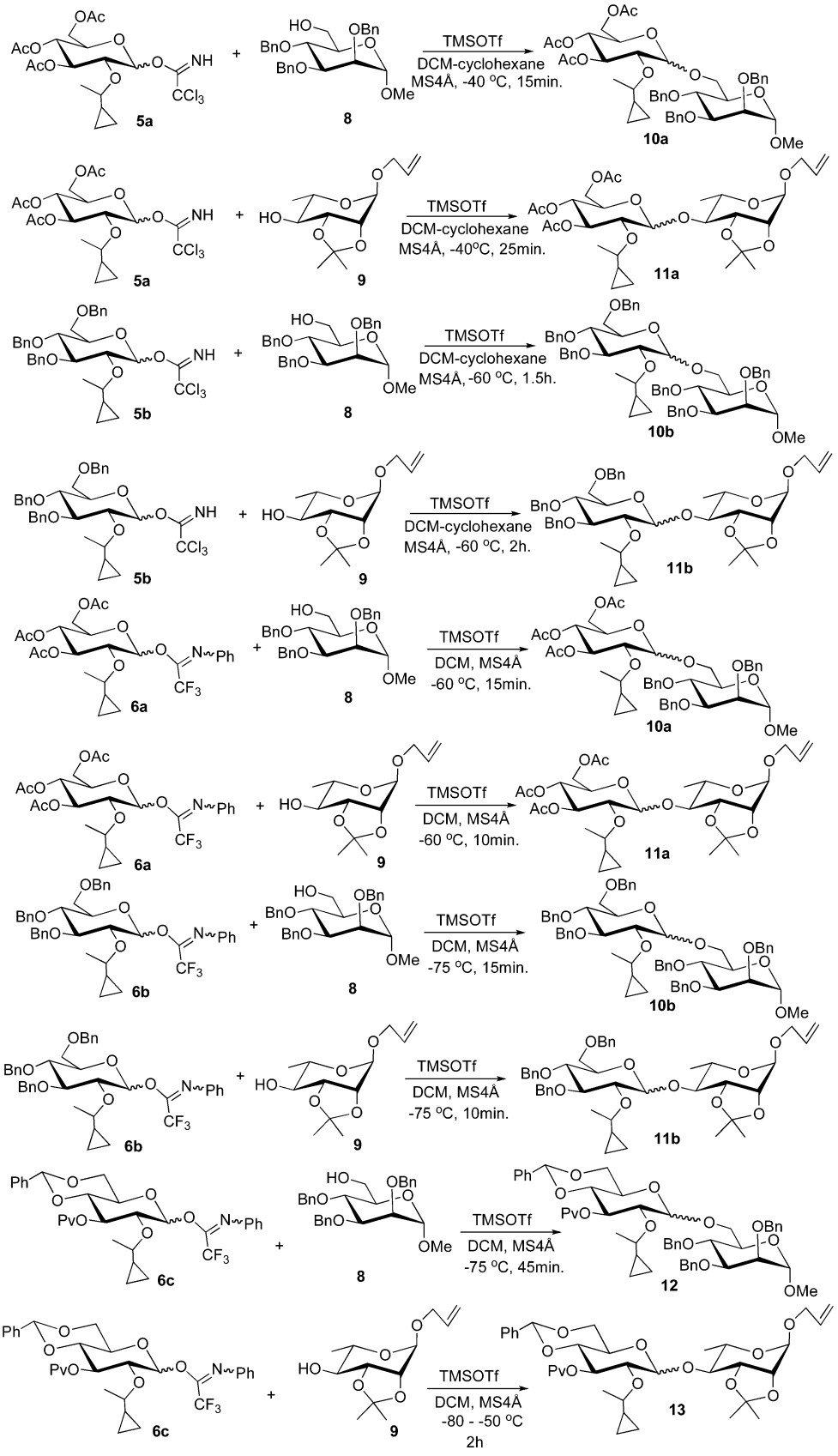
To compare with previously reported conditions the α-thiophenyl donor **7** was preactivated under conditions that should lead to the α-triflate and then reacted with acceptor **8** at −70 °C. The disaccharide **10a** was obtained as an α:β mixture 1:1.7 and the diastereomeric ratio were α 1.17:1 and β 1.56:1 (Scheme 5). The greater diastereoselectivity for β-glycosides fits the observed result with the β-thiophenyl glycoside β-**7** and above for deactivated donor and acceptor combinations above. This is consistent with the model of Figure 1 where the MCPM protecting group should be located on the β-face in the glycopyranosyl oxacarbenium ion.

2.3. Deprotection. The 2-*O*-MCPM group was cleaved from disaccharides **10b** and **11b** by treatment with 10% trifluoroacetic acid (TFA) in dichloromethane for 1.5 h in an ice bath. The acid labile isopropylidene group was also cleaved under these conditions such that for disaccharides **11b** the triols **15** were isolated and for disaccharides **10b** the alcohols **14** were isolated in good yields. Elimination of the MCPM group simplified the NMR spectra and so the α:β ratios could be more reliably determined. In all cases the MCPM protecting group was completely cleaved and the products isolated in good yields without complications (Scheme 6).

2.4.1. Conformational Analysis by DFT Computation. *CH-2−C-2−O-2−C(MCPM) Torsion.* Previous studies from our group have established that the CH-2−C-2−O-2−C(Pg) torsion angle in glycopyranosyl oxacarbenium ions, like the ones expected to form from the donors used in this study, have a bimodal distribution with *anti* and *syn* conformations. In all cases studied to date the *syn* conformation is more stable than *anti*, typically by about 10 kJ mol^{-1}. This preference strongly suggests that in equilibrated glycopyranosyl oxacarbenium ions this will be the only conformation significantly populated. This preference was attributed to a unimodal hyperconjugative interaction between a lone pair on O-2 and the O-5−C-5 pseudo double bond. A π-type orbital associated with this bond is often the LUMO of glycopyranosyl oxacarbenium ions making this association probable. That the MCPM group at O-2 in the $^4H_3$ or the closely related in conformational space E_3 conformations as well as the $^5S_1$ conformation of the glucopyranosyl oxacarbenium ion also showed this preference was readily established by DFT calculations. For calculation details see the Experimental section and ref 71. For the *R*-MCPM isomer, the *syn* to *anti* energy differences were found to be −8.0 and −13.6 kJ mol^{-1} and for the *S*-MCPM −37.3 and −14.6 kJ mol^{-1}. Note that all degrees of freedom were not optimized in each conformer as

dx.doi.org/10.1021/jo202563f | J. Org. Chem. 2012, 77, 3724−3739

Scheme 3. Glycosylation



only the C-2−O-2 torsion was varied. These differences clearly show the "normal" *syn* to *anti, syn* preference, see Table 2. This question was not studied further and all other conformers studied were optimized starting from *syn* C-2−O-2 conformations.

dx.doi.org/10.1021/jo202563f | J. Org. Chem. 2012, 77, 3724−3739

Table 1. Total Yields, α:β Ratios, and MCPM Diastereoselectivity for Glycosylation Reactions

donor	acceptor	R^1	R^2	R^3	$\alpha(R{:}S)^a$	$\beta(R{:}S)^a$	yield[b]
5a	**8**	Ac	Ac	Ac	1:1		50%
5b	**8**	Bn	Bn	Bn	1:1	1:1	69%; 1:2(α:β)
5a	**9**	Ac	Ac	Ac	1.6:1	2.7:1	44%; 3:2(α:β)
5b	**9**	Bn	Bn	Bn	1:1	1:1	65%; 1:3(α:β)
6a	**8**	Ac	Ac	Ac	1:1		55%
6b	**8**	Bn	Bn	Bn	1:1	1:1	77%; 1:2(α:β)
6c	**8**	CHPh	CHPh	Pv	1.27:1		55%
6a	**9**	Ac	Ac	Ac	1.25:1	4.66:1	55%; 4:1(α:β)
6b	**9**	Bn	Bn	Bn	1:1	1:1	70%; 1:3(α:β)
6c	**9**	CHPh	CHPh	Pv	1.13:1		67%

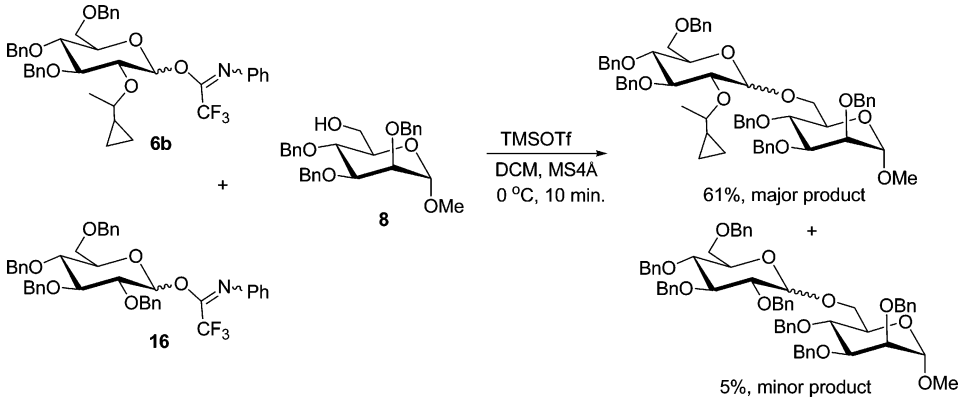
[a]Diastereoselective ratios (*R*:*S*) were obtained from ^{1}H NMR integration and are reproducible to ±5%. [b]Stereoselective ratios were obtained from ^{1}H NMR integration and are reproducible to ±5%.

2.4.2. Glucose Ring Conformations. Our previous DFT studies have shown that besides the $^4H_3$ conformation a ring inverted $^5S_1$ is a distinct minimum on the conformational potential energy surface of a variety of substituted D-glucopyranosyl oxacarbenium ions.[52] Similar ions have been found for the per-*O*-methyl *xylo* and *galacto* configured pyranosyl ions.[27] In all these conformations, O-2−C-2 lie nearly in the C-5−O-5−C-1−C-2 plane. The corresponding C-5−O-5−C-1−C-2 torsion angle (τ_5 in our nomenclature) is expected to be planar in a fully ionized oxacarbenium ion. For the 2,3,4,6-tetra-*O*-methyl-D-glucopyranosyl ion a pathway connecting the $^4H_3$ to $^5S_1$ conformations involving ring flattening through a $^1S_3$ transition state and then pseudorotation, has been found by *ab initio* molecular dynamics (AIMD) calculations.[113] Several local minima are found on this pathway but all are connected by low energy barriers, that is, pseudorotation, and are therefore not predicted to be distinctly populated for glucose derivatives with noninteracting protecting groups. In the donors studied here this is likely the case with a small possibility of some conformations having benzyl-to-benzyl interactions that could be favorable or unfavorable. For modeling studies we have not considered this computationally difficult problem and have used only methyl or acetyl groups on O-3, O-4 and O-6.

For both *R*, *S*-pairs of isomers of 3,4,6-tri-*O*-acetyl (**17**) or tri-*O*-methyl-2-*O*-MCPM-D-glucopyranosyl ions (**16**) both the $^4H_3$ and $^5S_1$ conformations were found as minima, that is, no negative frequencies in second derivative calculations. In all cases the C-5−C-6 exocyclic conformation was optimized. Only the lowest energy conformations are shown. The rotameric profiles show the standard *gt* ≈ *gg* > *tg* preferences. Table 3 shows the energy differences and some selected geometric features of **17**. For example, the ring torsion τ_5 is nearly 0 (i.e., planar) in all cases. As well, the O-5−C-1 bond lengths are all about 1.26 ± 0.02 Å and the O-5−C-1−C-2 bond angles are about 125 ± 2° which is consistent with an oxacarbenium ion structure. The ring conformations are described as descriptors where a value of 1.0 would be a perfect match and 0.0 a perfect mismatch, see Table 2 and Figure 3. This system of classification divides the 6-membered ring conformational space into 38 regions, which occupy the same volume of a 3-dimensional sphere without user bias.[114] All $^4H_3$ conformations of **17** have coefficients close to 1.0 and hence are nearly perfect half chairs with all substituents pseudoequatorial. For **16** the closely related in conformational space E_3 is also populated. The $^5S_1$ conformations show more variability and are displaced from the pseudorotational equator of the conformational sphere toward the $^1C_4$ pole.

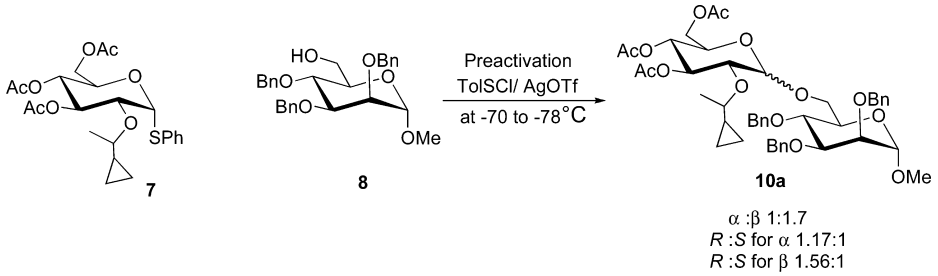
2.4.3. Effect of MCPM Chirality. The simplistic model (see Figure 1), which prompted this study, was partly based on the idea that the remaining degrees of freedom of the MCPM group would be identical and hence the chirality would exhibit itself by reversing the relative positions of the two smallest groups, namely the methyl and the hydrogen. A previous study of chiral at the aglycone carbon of mannosides found this to be true with both isomers having the largest group *anti*.[115] However, our recent study of the neutral mannosides with MCPM at the anomeric center found that the Ψ(C-1−O-1−C(MCPM)−C(Cp) torsion angle had different minima.[80] The *S*-isomer was found in the 180° conformation postulated above but the *R*-isomer in the unexpected 60° conformer. In the present study the postulated oxacarbenium ions are not observable by NMR. Thus, only DFT calculations can be performed. The remaining degree of freedom is the χ_2 = O-2−CH(CH_3)−CHcp−CcpH_2 torsion angle that can be estimated from the ground state NMR from the $J_{CH-CHcp}$ coupling constant. In all cases to date this has a value >8 Hz suggesting a predominant but not exclusive preference for the 180° conformation. No attempt was made to determine the conformational preference of this torsion but in all calculations this torsion was not restrained. Thus it was necessary to attempt to optimize the χ1 = C-2−O-2−CH(CH_3)−CHcp torsion angle. This proved challenging as simple incremental rotations about O-2−C(Cp) led to discontinuities unless the increment size was small. These discontinuities included ring conformational

Scheme 4. Direct Competitive Comparison of 2-*O*-Benzyl and 2-*O*-MCPM Donors



dx.doi.org/10.1021/jo202563f | J. Org. Chem. 2012, 77, 3724−3739

Scheme 5. Preactivation of Thiophenyl Donor *α*-7



Scheme 6. Deprotection of MCPM Ethers

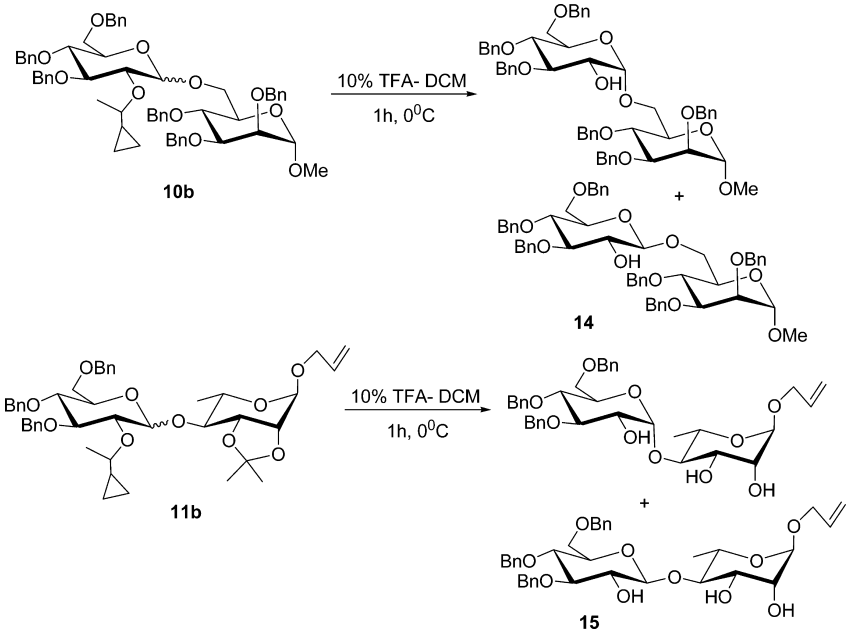


Table 2. Comparison Showing C-2−O-2 *syn*−*anti* Energy Difference and Some Geometric Parameters for *R*-MCPM or *S*-MCPM 3,4,6-tri-*O*-Methyl-2-*O*-MCPM-D-glucopyranosyl Ions, 16

compound	chair[a] descriptor	skew descriptor	boat descriptor	CH-2−C-2−O-2−C (MCPM)°	C-2−O-2 −C(MCPM)−C(Cp)°	CH-5−C-5−C-6−O-6°	ΔE kJ mol^{-1}
R-syn	$\boldsymbol{E_3}$ **0.886**	$^{1}S_5$ 0.039	$B_{O,3}$ 0.055	−38.4	80.9	−45.3	−8.0
R-anti	$\boldsymbol{^4H_3}$ **0.883**	$^{4}C_1$ 0.053	^{2}E 0.114	−162.2	125.2	−41.8	0.0[b]
S-syn	$\boldsymbol{E_3}$ **0.886**	$^{1}S_5$ 0.092	$B_{O,3}$ 0.041	−24.6	−165.6	−44.8	−37.3
S-anti	$\boldsymbol{^4H_3}$ **0.755**	$^{4}C_1$ 0.220	$^{2,5}B$ 0.013	164.8	75.6	−41.5	0.0[b]
R-syn	$^{1}C_4$ 0.308	$\boldsymbol{^5S_1}$ **0.747**	$^{O,3}B$ 0.086	33.1	−55.7	−156.3	−13.6
R-anti	$^{1}C_4$ 0.234	$\boldsymbol{^5S_1}$ **0.829**	$^{O,3}B$ 0.006	175.1	−90.1	−159.2	0.0[b]
S-syn	$^{1}C_4$ 0.196	$\boldsymbol{^5S_1}$ **0.952**	$^{O,3}B$ 0.077	−30.8	−64.9	−157	−14.6
S-anti	$^{1}C_4$ 0.431	$\boldsymbol{^5S_1}$ **0.522**	$^{O,3}B$ 0.085	−164.9	−110.7	−155.8	0.0[b]

[a]Where the conformation is an intermediate conformation (half chair or envelope) the descriptors are permutated to give the conformation in terms of the intermediate conformation and the next two best descriptors. [b]Energy of the *anti* conformer set to 0.0 kJmol^{-1}.

Table 3. Comparison Showing Some Geometric Parameters for *R*-MCPM or *S*-MCPM 3,4,6-tri-*O*-Acetyl-2-*O*-MCPM-D-glucopyranosyl Ions, 17[a]

compound	C-1−O-5 Å	O-5−C-1−C-2°	C-5−O-5−C-1−C-2, τ_5°	CH-2−C-2−O2−C(MCPM)°	C-2−O-2−C(MCPM)−C(Cp)°	CH-5−C-5−C-6−O-6°	ΔE kJ mol^{-1}
R-syn $^{4}H_3$	1.258	125.7	11.1	−10.9	−55.1	37.7	31.2
S-syn $^{4}H_3$	1.259	125.8	12.8	−17.6	−160.8	40	35.4
R-syn $^{5}S_1$	1.263	124.5	3.7	−9.5	54.7	−62.2	0.0[b]
S-syn $^{5}S_1$	1.268	124.6	−5.7	31.3	−55.4	74.1	11.5

[a]For ring descriptors see Figure 3. [b]Lowest energy conformer set to 0.0 kJ mol^{-1}.

dx.doi.org/10.1021/jo202563f | J. Org. Chem. 2012, 77, 3724−3739

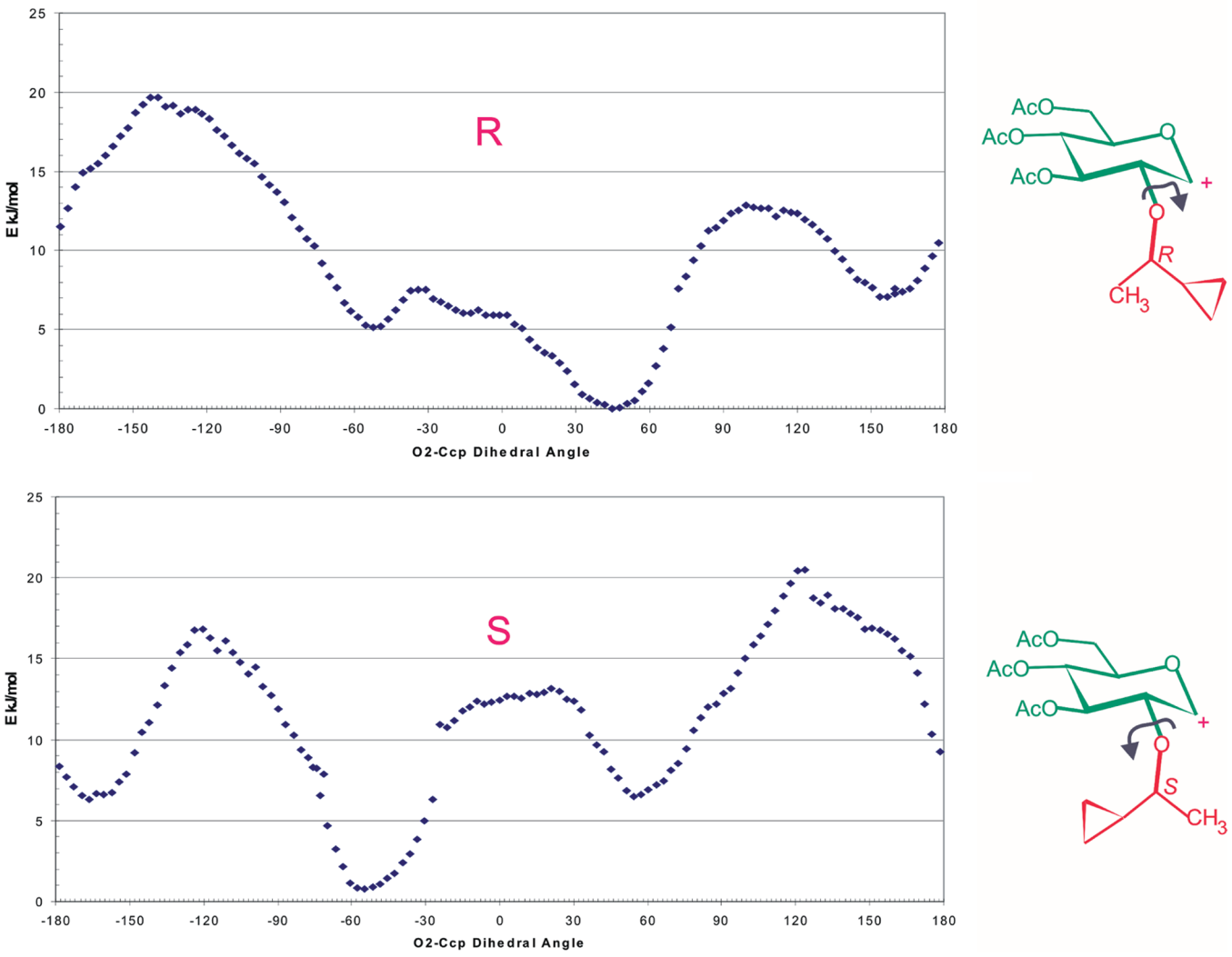


Figure 2. Rotational energy profiles for rotation about O-2−C(Cp), χ_1, for the $^5S_1$ conformations of **17**.

switches between $^4H_3$ or $^5S_1$ and jumps in nonrotated bonds like C-2−O-2 and C-3−O-3 to avoid steric clashes. A representative pair of profiles is shown in Figure 2. Each point in Figure 2 is a full DFT optimization except that the O-2−C(Cp) torsion angle is fixed. The results show that like our results with Ψ variation for anomeric MCPM χ_1 has different minimum for each of *R* and *S*. The large C-2−O-2 *syn*−*anti* difference for *S*-*syn* **16** is likely the result of *S*-*anti* **16** having a different O-2−C(Cp) minimum, which was not optimized.

These results compromise our simplistic interpretation but still suggest that the steric and electronic environment about C-1 differ due to the chirality at the MCPM carbon which is in turn partly due to the rigidification of the C-2−O-2 torsion. Thus, if an equilibrated oxacarbenium ion is formed it is probable that the two faces will have differential reactivity. The experimental results above suggest that the differences are more pronounced for the β-face than the α-face. Figure 3 shows the lowest energy conformations of the oxacarbenium ions (**17**) corresponding to the deactivated donors **5a**, **6a** and **7**. The two $^4H_3$ ions are quite flat whereas the $^5S_1$ isomers are very bent. For the $^4H_3$ conformers the *R*-isomer has the α-face the most shielded whereas for the $^5S_1$ isomers it is the *S*-isomer which most shields the β-face. Thus, in fully equilibrated systems the *R*-isomer of the $^5S_1$ should be the most reactive on the β-face.

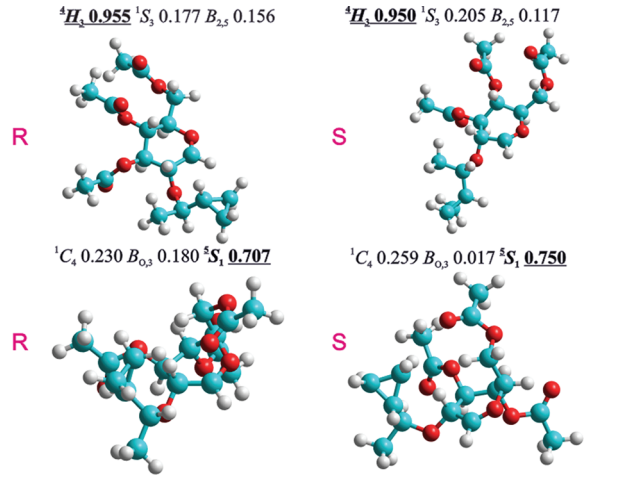


Figure 3. Ball and stick representations of the lowest energy conformations of **17**. Ring descriptors are displayed above the corresponding structures.

2.4.4. Possible R,S-Assignments of the β-SPh Glycosides 7. The disaccharides synthesized in this work are currently too large for DFT calculations but the thiophenyl compound **7** is amenable to DFT. Thus we optimized the *R*- and *S*-isomers of

dx.doi.org/10.1021/jo202563f | J. Org. Chem. 2012, 77, 3724−3739

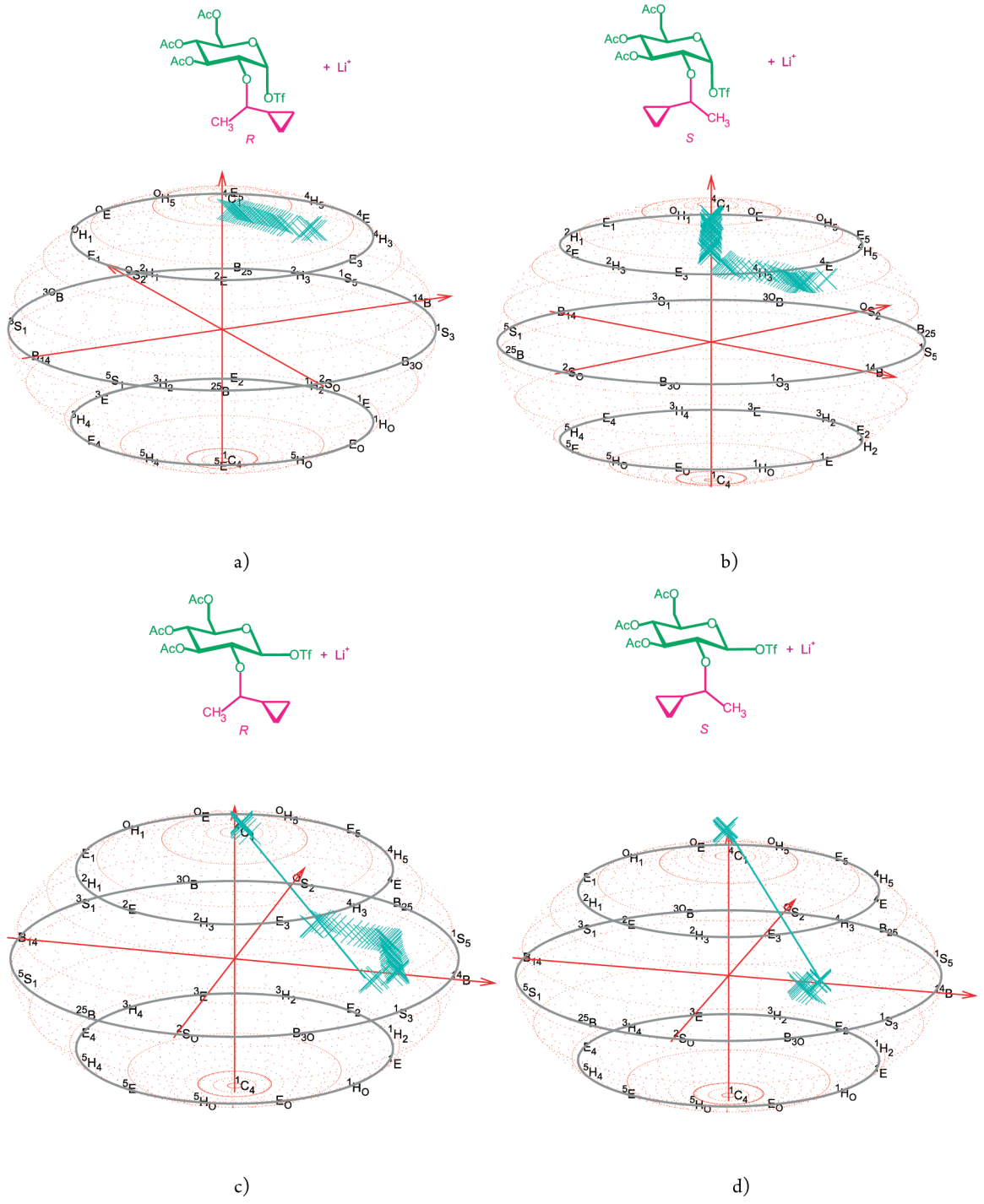


Figure 4. Trajectories of computational ionization leading to **17** in 3D conformational space. (a) α-Triflate(R) and (b) α-triflate(S). (c) β-Triflate(R) and (b) β-triflate(S). Each point is a full DFT optimization including solvation except that the C-1--O_{Tf} is fixed and incremented at each subsequent data point. The lines in (c) and (d) are drawn to connect before and after the conformational jump.

the β-anomer of **7**. We also did some NMR studies of **7b** which clearly showed a marked difference between the NOE's resulting for irradiating CH-2 of the two isomers, see Supporting Information. On the basis of this analysis, the predominant isomer is tentatively assigned as *S*.

2.4.5. Kinetic Questions. A further question that can be addressed by computation is the kinetic pathway to the oxacarbenium ion. We have previously developed a protocol to assess this by slowly lengthening the C-1−X bond where X is a suitable leaving group.[55,116] To avoid discontinuities caused by the accumulating negative charge on the leaving group, a Li^+ ion is placed in a fixed position relative to the leaving group. The trifluoromethanesulfonate(triflate) leaving group was chosen, as there is considerable evidence that in some cases comparable to our experimental an anomeric triflate is formed before *O*-glycosylation. Typically the α-triflate accumulates but this does not guarantee that the less stable and hence more reactive β-triflates are not the active species.[55] We studied 4 cases for this work namely *R*- or *S*-MCPM and α- or β-triflate for the 3,4,6-tri-*O*-acetyl D-glucopyranosyl donors. The results

dx.doi.org/10.1021/jo202563f | J. Org. Chem. 2012, 77, 3724−3739

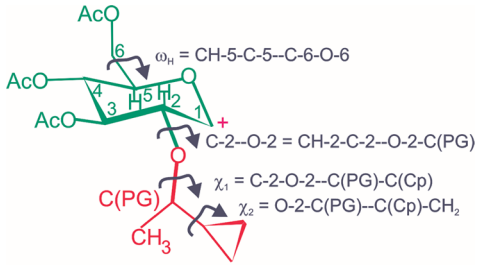
are shown in Figure 4a−d where each point represents a point in the 3D-conformational space of 6-membered ring and is a separate fully optimized DFT calculation. At each point the C-1−O-triflate bond length is constant and at each step this bond length is increased. In all cases the final conformation is close to $^4H_3$ and not $^5S_1$. This kinetic formation of the $^4H_3$ conformers is likely a result of the stabilization by the counterion. The pathway to $^4H_3$ is different for each diastereomer. In the α-cases (a and b) both paths are incremental but follow slightly different arcs in conformational space. For the β-cases (c and d) after a short lengthening the ring undergoes an abrupt conformational change to a conformer that is consistent with the antiperiplanar hypothesis. Such conformers are near the pseudorotational equator on the 3D representation. This is entirely consistent with previous results for a variety of protecting groups, leaving groups and pyranosyl configurations. Subsequently the conformers slowly convert to near $^4H_3$ again with slightly different arcs for *R*- and *S*-MCPM. To arrive at the more stable $^5S_1$ conformation the ions must equilibrate. The AIMD results suggest the barrier is low but what triggers such a change and the role of counterions is still obscure. The current results suggest reaction through $^4H_3$ conformations for the deactivated donors whereas the more reactive donors likely react before becoming ionized. In this case, the counterion likely plays an important role in reactivity and the influence of the conformation about C-2−O-2, which is turn influenced by the configuration at the Cpg−O-2 carbon, plays only a minor role.

3. CONCLUSION

The electron donating ability of cyclopropylmethyl ethers, the parents of the MCPM protecting group, has been known for some time.[117] However, to the best of our knowledge this property has never been directly compared to O-2 nonparticipating benzyl ethers. The experimental observation that O-2-MCPM is more activating then O-2 benzyl provides another tool in the carbohydrate chemist's toolbox. We chose the method of using 50:50 *R*:*S* at the chiral protecting group and looking for products with enriched *R* or *S* as this was experimentally accessible although the NMR analyses are tedious. The preferred method of separately using optically pure chiral protecting groups requires a highly accurate absolute kinetic method. The development of such a kinetic method is a desirable objective. Further, the observation of modest but real diastereoselectivty in certain glycosylation reactions provide a possible sensor for glycosylation conditions that proceed through oxacarbenium ion species. Our results also suggest that the converse is true and that highly reactive glycosyl donors do not react through oxacarbenium ions but through something closer to CIPs. The TSs of such glycosylation reactions is an active area of research for us. Overall these results should help guide the experimentalist to find a combination of protecting groups, solvent, promoters etc. to enable stereoselective high yielding glycosylation reactions.

4. EXPERIMENTAL SECTION

4.1. Computational Details. Preliminary conformational analysis was done using the AM1 Hamiltonian as implemented in the Hyperchem-version 10 PC based molecular modeling program. The models were built by appropriate modifications of the idealized $^4H_3$ and $^5S_1$ conformations of *R*- or *S*-3,4,6-tri-*O*-methyl-2-*O*-(1-methyl-1′-methylcyclopropylmethyl)-D-glucopyranosyl cation, **16**. The resulting structures were reoptimized with DFT with a total charge of +1. The conformations of the various side chains were optimized as follows. The C-2−O-2 dihedral was set to *syn* or *anti* conformations. The *syn* conformation then had its ω_H conformation searched by rotational variation. Then the χ_1 side chain was optimized by rotational variation. Experimentation revealed that 120 × 3° increments were used to minimize discontinuities. The procedure was then repeated for the 3,4,6-tri-*O*-acetyl analogue **17**. Similarly, the conformations of the neutral *R*- or *S*- at MCPM C, phenyl 3,4,6-tri-*O*-acetyl-2-*O*-(1-methyl-1′-methylcyclopropylmethyl)-1-thio-β-D-glucopyranoside **7** were optimized. In this case, the phi (CH-1−C-1−S−Cip) torsion was optimized too.



The DFT calculations were carried out with the Amsterdam Density Functional (ADF) program system, ADF2005. The atomic orbitals were described as an uncontracted triple-ζ function basis set with a single-π polarization function on all atoms, which were taken from the ADF library (TPZ).[118−122] A set of *s*, *p*, *d*, *f*, and *g* Slater functions centered on all nuclei were used to fit the electron density, and to evaluate the Coulomb and exchange potentials accurately in each SCF cycle. The local part of the V_{xc} potential (LDA) was described using the VWN parametrization,[123] in combination with the gradient corrected (CGA) Becke's functional for the exchange and Perdew's function for correlation (BP86). The CGA approach was applied self-consistently in geometry optimizations. Second derivatives were evaluated numerically by a two point formula. The solvation parameters (CH_2Cl_2) within the COSMO procedure were dielectric constant ε = 9.03, ball radius = 2.4 Å, ball radius = 1.3 Å; with atomic radii of C = 1.989 Å, O = 1.7784 Å and H = 1.3 Å. Initial geometries all started with protected D-glucopyranosyl MCPM glycosides in $^4C_1$ conformations with all side chains (methyl or acetyl protecting groups) in minimum energy conformations. All calculations used internal coordinates. For torsion angle variation starting from a minimized conformation the torsion angle was set as a variable and varied in 3° increments, that is, 120 increments for a full circle. For some torsion variations 6° increments were used. All other internal coordinates were allowed to relax during optimization. All minima were characterized as true minima by frequency calculations.

4.2. General Experimental Details. NMR spectra were recorded on a 400 MHz (^{1}H) and 100 MHz (^{13}C) spectrometer with tetramethylsilane or the residual signal of the solvent as the internal standard. Chemical shifts are quoted in ppm and *J* values in Hz. Mass spectra were recorded on a Quadrupole time-of-flight mass spectrometer using electrospray ionization (ESI) or time-of- flight mass spectrometer using matrix-assisted laser desorption/ionization (MALDI). Analytical thin-layer chromatography was performed on precoated plates of silica gel and visualized with H_2SO_4−H_2O (1:20 v/v) followed by heating. Flash column chromatography was performed using silica gel (230−400 mesh). All solvents and reagents were purified and dried according to standard procedures.

4.3. General Procedure for the Synthesis of 3. A solution of compound **2b** (10 g, 16.867 mmol) and silver triflate (4.76 g, 18.6 mmol) in dichloromethane (50 mL) was flushed with argon gas and cooled to −40 °C. To this well stirred cooled reaction solution was added 1-methyl 1′-cyclopropylmethyl trichloroacetimidate (MCPMTCI) (5.9 mL, 33.7 mmol) slowly over 30 min. The reaction was then allowed to stir for 22 h and was monitored by TLC (10:1 v/v hexane/EtOAc, run ×2). The reaction was quenched by adding excess of ammonium bicarbonate and allowing the solution to stir for a while. The solution was filtered through Celite to remove the solid; the filtrate obtained was concentrated to give the crude product. The crude product was purified by silica gel chromatography using 15:1 v/v

dx.doi.org/10.1021/jo202563f | J. Org. Chem. 2012, 77, 3724−3739

hexane/EtOAc solvent mixture as eluant to afford pure compound **3b** as syrup (8.4 g, 75%).

*Thexylsilyl 3,4,6-tri-O-Acetyl-2-O-(R,S-1-methyl 1′-Cyclopropylmethyl)-β-D-glucopyranoside (**3a**).* Colorless syrup, yield 76%, ^{1}H NMR 400 MHz, $CDCl_3$, δ 5.08 (at, J = 9.4 Hz and 9.6 Hz, H-3 *S*); 5.07 (at, J = 9.4 Hz, 1H, H-3 *R*); 4.95 (at, J = 9.8 Hz and 9.6 Hz, 1H, H-4 *S*); 4.90 (at, J = 9.8 Hz, 1H, H-4 *R*), 4.65 (d, J = 7.4 Hz, 1H, H-1 *R*); 4.60 (d, J = 7.4 Hz, 1H, H-1 *S*); 4.18−4.07 (m, 4H, H-6_{ab} *R*, H-6_{ab} *S*); 3.66−3.61 (m, 2H, H-5 *R*, H-5 *S*); 3.52 (dd, J = 9.4 Hz and 7.6 Hz, 1H, H-2 *S*); 3.40 (dd, J = 9.3 Hz and 7.3 Hz, 1H, H-2 *R*); 3.37−3.30 (m, 1H, CH-mcpm-*R*); 3.26−3.20 (m, 1H, CH-mcpm-*S*); 2.06; 2.02 (2s, 24H, $C\underline{H}_3CO$ × 6); 1.67−1.60 (m, 2H, $C\underline{H}CMe_2$); 1.17 (d, J = 6.2 Hz, 3H, $C\underline{H}_3$-mcpm-*R*); 1.10 (d, J = 6.1 Hz, 3H, CH_3-mcpm *R*); 0.87; 0.85 (2bs, 24H, CH_3 × 8); 0.70−0.55 (m, 2H, C$\underline{H}$); 0.51−0.32 (m, 4H, CH_2); 0.17−0.10 (m, 14H, $Si\underline{Me}_2$ × 4, CH_2 × 2); 0.01−0.04 (m, 1H, CH_2-cp-ring). ^{13}C NMR 100 MHz, $CDCl_3$, δ 170.64, 170.15, 169.99, 169.88 (CO × 6); 98.24 (C-1 *S*); 98.08 (C-1 *R*); 80.15 (C$\underline{H}$-ring-*R*); 78.88 (C$\underline{H}$-ring-*S*); 77.56 (C-2 *S*); 77.54 (C-2 *R*); 74.33 (2C, C-3 *R*, *S*); 71.49 (C-5); 71.39 (C-5); 69.36 (C-4); 69.29 (C-4); 62.73 (C-6); 62.68 (C-6); 33.79 (C$\underline{H}$-thexyl); 33.76 (C$\underline{H}$-thexyl); 24.81; 24.78 (C-thexyl); 21.07 ($C\underline{H}_3$-mcpm-*S*); 20.83, 20.80, 20.70 ($C\underline{H}_3CO$ × 6); 20.07, 20.00, 19.83, 19.73 (CH_3 × 4); 19.32 ($C\underline{H}_3$-mcpm-*R*); 18.53, 18.52, 18.35 (CH_3 × 4); 16.86; 16.34 (CH-mcpm); 5.16, 3.43, 1.34, 0.22 (CH_2-mcpm × 4); −2.18; −2.26; −2.76; −3.11 (Si$\underline{Me}$ × 4). ESI-HRMS: Calcd. for $C_{25}H_{48}NO_9Si$ $[M + NH_4]^+$ m/z 534.3098. Obsd. m/z 534.3079.

*Thexylsilyl 3,4,6-tri-O-Benzyl-2-O-(R,S-1-methyl 1′-Cyclopropylmethyl)-β-D-glucopyranoside (**3b**).* Colorless syrup, yield 75%, ^{1}H NMR 400 MHz, $CDCl_3$, δ 7.36−7.16 (m, 30H, Ar−H); 5.06 (d, J = 11.1 Hz, 1H, C$\underline{H}_2$Ph); 4.96 (d, J = 11.1 Hz, 1H, C$\underline{H}_2$Ph); 4.83−4.76 (m, 4H, C$\underline{H}_2$Ph); 4.61−4.50 (m, 8H, H-1 *R*, H-1 *S*, C$\underline{H}_2$Ph × 6); 3.72 (t, J = 8.5 Hz and 7.9 Hz, 1H, H-2); 3.70 (m, 4H, H-6_{ab} *R*, H-6_{ab} *S*); 3.62−3.52 (m, 5H, H-5 *R*, H-3 *R*, H-4 *R*, H-2 *S*, C$\underline{H}$-mcpm *R*); 3.47−3.41 (m, 4H, H-3 *S*, H-4 *S*, H-5 *S*, C$\underline{H}$-mcpm *S*); 1.69−1.65 (m, 2H, CH-thexyl); 1.23 (d, J = 8.2 Hz, 3H, $C\underline{H}_3$-ring); 1.19 (d, J = 8.2 Hz, 3H, CH_3-ring); 0.94−0.81 (m, 2SH, 8 × Me, C$\underline{H}$-ring); 0.63−0.33 (m, 8H, CH_2-ring × 8); 0.19; 0.16 (2bs, 12H, $SiMe_2$ × 2); 0.00−0.04 (m, 1H, CH-ring). ^{13}C NMR 100 MHz, $CDCl_3$, δ 139.1, 138.9, 138.3 (*ipso*-C × 3); 128.3−127.3 (Ar−C); 98.6 (C-1); 98.4 (C-1); 85.0 (2C, C-4 × 2); 79.6 (C-2); 79.5 (C-2); 79.4 (CH-mcpm); 78.5 (CH-mcpm); 78.1 (2C, C-3 × 2); 75.8; 75.6; 74.9; 74.7 (C-5); 74.6 (C-5); 69.2 (2C, C-6 × 2); 33.7 (2C, $CHMe_2$ × 2); 24.7 (2C, CMe_2 × 2); 20.2; 20.1; 19.8; 19.8; 19.1; 18.6; 18.4; 17.2; 16.3; 5.6; 3.7; 1.3; 0.3; −1.9; −2.0; −2.8; −3.0 ($SiMe_2$ × 4). ESI-HRMS: Calcd. for $C_{40}H_{60}NO_6Si$ $[M + NH_4]^+$ m/z 678.4190. Obsd. m/z 678.4196.

*Thexylsilyl 4,6-O-Benzylidene-2-O-(R,S-1-methyl 1′-Cyclopropylmethyl)-3-O-pivaloyl-β-D-glucopyranoside (**3c**).* Colorless syrup, yield 72%, ^{1}H NMR 400 MHz, C_6D_6, δ 7.61−7.59 (m, Ar−H); 7.19−7.16 (m, Ar−H); 7.10−7.07 (m, Ar−H); 5.54 (t, J = 9.4 Hz, 1H, H-3 *S*); 5.50 (at, J = 9.2 and 9.5 Hz, 1H, H-3 *R*); 5.21 (s, 1H, PhCH); 5.20 (s, 1H, PhCH); 4.51 (d, J = 7.0 Hz, 1H, H-1 *R*); 4.47 (d, J = 7.2 Hz, 1H, H-1 *S*); 4.06−4.03 (m, 2H, H-6_a *R*, H-6_a *S*); 3.81−3.77 (dd, J = 7.2 Hz and 9.0 Hz, 1H, H-2 *S*); 3.64−3.59 (m, 2H, H-2 R, CH-mcpm *R*); 3.53−3.46 (m, 1H, CH-mcpm *S*); 3.44−3.39 (m, 2H, H-6_b *R*, H-6_b *S*); 3.36−3.31 (m, 2H, H-4 *R*, H-4 *S*); 3.08−3.02 (m, 2H, H-5 *R*, H-5 *S*); 1.75−1.65 (m, 2H, C$\underline{H}Me_2$); 1.36 (d, J = 6.2 Hz, 3H, Me-mcpm *S*); 1.26−1.24 (m, 21H, Pv × 2, Me-mcpm *R*); 0.98−0.91 (m, 24H, 8 × Me); 0.89−0.79 (m, 2H, cp-ring); 0.64−0.51 (m, 4H, cp-ring); 0.41−0.22 (m, 4H, cp-ring); 0.19−0.08 (m, 14H, $SiMe_2$ × 2, 2 × cp-ring). ^{13}C NMR 100 MHz, C_6D_6, δ 176.7 (2C, 2 × CO); 128.9−126.4 (Ar−C); 101.2 (2 × Ph$\underline{C}$H); 99.0 (C-1 *R*); 98.9 (C-1 *S*); 79.7 (C-4 *R*); 79.6 (C-4 *S*); 78.9 (O$\underline{C}$H-mcpm *R*); 78.2 (O$\underline{C}$H-mcpm *S*); 78.0 (C-2 *S*); 77.8 (C-2 *R*); 73.7 (C-3 *R*); 73.6 (C-3 *S*); 68.8 (2C, C-6 *R*, C-6 *S*); 65.9 (C-5 *R*); 65.8 (C-5 *S*); 34.2 (C$\underline{H}Me_2$); 27.4 (2C, $\underline{C}Me_3$ of Pv × 2); 25.0 ($\underline{C}Me_2$); 21.2 ($C\underline{H}_3$-mcpm); 20.3 ($C\underline{H}_3$-mcpm); 20.3 (3C), 20.0 (3C) ($C\underline{Me}_3$ × 6); 18.8 (2C), 18.6 (2C), 17.3 (2C), 17.0 (2C) (Me × 8); 5.0 ($C\underline{H}_2$-mcpm); 3.8 ($C\underline{H}_2$-mcpm); 1.3, 0.8 ($C\underline{H}_2$-mcpm); −2.0, −2.2, −2.6, −2.8 (Si$\underline{Me}_2$ × 4). ESI-MS: Calcd. for $C_{31}H_{50}NaO_7Si$ $[M + Na]^+$ m/z = 585.79 obsd. m/z 585.65. ESI-HRMS: Calcd. for $C_{31}H_{54}NO_7Si$ $[M + NH_4]^+$ m/z 580.3670. Obsd. m/z 580.3666.

4.4. General Procedure for the Synthesis of 4. Dried compound **3b** (8.1 g, 12.254 mmol) was taken in a R.B. flask and was dissolved in THF (40 mL) under argon atmosphere. To the well-stirred solution was added 1 M tetrabutylammonium fluoride in THF (24.5 mL, 24.5 mmol), followed by glacial acetic acid (0.7 mL, 12.3 mmol). The reaction was stirred at room temperature for 2 h. The reaction after completion was evaporated under vacuum followed by coevaporation with toluene. The crude was purified over silica gel using 5:1 v/v hexane/ethyl acetate solvent mixture as eluant to afford compound **4b** as a syrup (5.1 g, 81%).

4.5. General Procedure for the Synthesis of Trichloroacetimidate Donor 5. The solution of compound **4** in dichloromethane was stirred under argon atmosphere and cooled to 0 °C. To the cooled solution was added trichloroacetonitrile (3 equiv) by syringe and the solution was allowed to stir. After 15 min was added NaH (95% in oil, 1 equiv) slowly and the reaction was allowed to stir for 2 h on an ice-bath. The reaction was worked up by initially adding few drops of water and then adding more water. The solution was transferred to a separating funnel and the organic layer extracted with DCM, dried with anhyd. sodium sulfate and concentrated to afford crude **5b**. In the case of acetyl protected donor **5a**, the crude was purified by silica gel chromatography using 6:1 v/v hexane/EtOAc solvent mixture as eluant.

4.6. General Procedure for the Synthesis of *N*-Phenyl Trifluoroacetimidate Donor 6. To the solution of compound **4** and *N*-phenyl trifluoroacetimidoyl chloride (2 equiv) in acetone was added few drops of water and K_2CO_3 (2 equiv) and the reaction was allowed to stir for 4 h at rt. After the completion of reaction more acetone was added and the solution was passed through a Celite bed. The filtrate obtained was concentrated and purified by silica gel chromatography using 6:1 v/v hexane/EtOAc solvent mixture as eluant to afford pure donor **5** as colorless oil.

4.7. General Procedure for Glycosylation. The acceptor solution in DCM (1 equiv) along with MS4 Å was stirred under argon atmosphere and cooled to the required temperature. The donor solution (1.2 equiv) in either in cyclohexane (**5**) or DCM (**6**) was injected by syringe/canulation and the reaction solution was stirred for 20 min. To this well stirred and cooled solution was added TMSOTf (equivalent according to Scheme 3). The reaction was allowed to stir at the temperature and time period mentioned in Scheme 3. The reaction was quenched by adding triethylamine. The reaction medium was washed with sat. sodium bicarbonate solution and extracted with DCM. The organic layer was dried, concentrated and then purified by silica gel chromatography to give the pure glycosylated product.

*Methyl (3,4,6-tri-O-Acetyl-2-O-(R,S-1-methyl 1′-Cyclopropylmethyl)-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-α-D-mannopyranoside (**10a**).* White amorphous solid, yield 50%, ^{1}H NMR, C_6D_6, 400 MHz, δ 7.38−7.32 (m, Ar−H); 7.29−7.27 (m, Ar−H); 7.22−7.06 (m, Ar−H); 5.83 (at, J = 9.6 Hz, 1H, gH-3 *S*); 5.81 (at, J = 9.8 Hz, 1H, gH-3 *R*); 5.38−5.33 (m, 2H, gH-4 *R*, gH-4 *S*); 5.12 (d, J = 3.5 Hz, 1H, gH-1 *R*); 5.10 (d, J = 3.5 Hz, 1H, gH-1 *S*); 5.07−5.02 (m, 2H, O$C\underline{H}_2$Ph × 2); 4.74 (d, J = 1.2 Hz, 1H, mH-1 *R*); 4.72 (d, J = 1.4 Hz, 1H, mH-1 *S*); 4.71−4.46 (m, 6H, O$C\underline{H}_2$Ph × 6); 4.43−4.41 (m, 4H, O$C\underline{H}_2$Ph × 4); 4.38−4.28 (m, 6H, gH-5 *R*, gH-5 *S*, gH-6_a *R*, gH-6_b *R*, gH-6_a *S*, gH-6_b *S*); 4.13−3.87 (m, 10H, mH-3 *R*, mH-3 *S*, mH-4 *R*, mH-4 *S*, mH-5 *R*, mH-5 *S*, mH-6_a *R*, mH-6_b *R*, mH-6_a *S*, mH-6_b *S*); 3.76 (m, 2H, mH-2 *R*, mH-2 *S*); 3.60 (dd, J = 10.0 Hz and 3.3 Hz, 1H, gH-2 *S*); 3.49 (dd, J = 10.0 Hz and 3.5 Hz, 1H, gH-2 *R*); 3.24 (s, 3H, OCH_3 *R*); 3.20 (s, 3H, OCH_3 *S*); 2.84−2.77 (m, 1H, C$\underline{H}$-mcpm *R*); 2.62−2.56 (m, 1H, C$\underline{H}$-mcpm *S*); 1.82 (s, 3H, Ac × 1); 1.81; 1.80; 1.79 (3s, 9H, Ac × 3); 1.74 (bs, 6H, Ac × 2); 1.10−1.08 (m, 6H, $C\underline{H}_3$-mcpm × 2); 0.78−0.60 (m, 2H, C$\underline{H}$-mcpm *R*, C$\underline{H}$-mcpm *S*); 0.34−0.27 (m, 2H, $C\underline{H}_2$-mcpm *R*, $C\underline{H}_2$-mcpm *S*); 0.25−0.14 (m, 4H, $C\underline{H}_2$-mcpm *R*, $C\underline{H}_2$-mcpm *S*); −0.03−0.11 (m, 2H, $C\underline{H}_2$-mcpm *R*, $C\underline{H}_2$-mcpm *S*); ^{13}C NMR, C_6D_6, 100 MHz, δ 170.11 (2C, CO); 169.63 (2C, CO); 169.53 (CO); 169.46 (CO); 139.61 (2C), 139.52, 139.22, 139.16, 139.02 (6 × ipso C); 128.54−127.53 (Ar−C); 99.42 (mC-1 *R*); 99.32 (mC-1 *S*); 97.96 (gC-1 *R*); 97.46 (gC-1 *S*); 81.09

dx.doi.org/10.1021/jo202563f | J. Org. Chem. 2012, 77, 3724−3739

(mC-3 *R*); 81.00 (mC-3 *S*); 80.93 (CH-mcpm *S*); 79.17 (CH-mcpm *R*); 76.92 (gC-2 *R*); 75.91 (mC-2 *R*); 75.88 (mC-2 *S*); 75.79 (2C, mC-4 *R*, mC-4 *S*); 75.65 (OCH_2Ph); 75.13 (OCH_2Ph); 75.07 (OCH_2Ph); 73.25 ($OCH_2Ph \times 2$); 72.53 (gC-3 *R*); 72.48 (gC-3 *S*); 72.27 (OCH_2Ph); 72.14 (2C, mC-5 *R*, mC-5 *S*); 69.52 (gC-4 *R*); 69.46 (gC-4 *S*); 68.04 (gC-5 *R*); 67.99 (gC-5 *S*); 67.89 (mC-6 *R*); 67.11 (mC-6 *S*); 62.38 (gC-6 *R*); 62.34 (gC-6 *S*); 54.60 (OCH_3); 54.56 (OCH_3); 21.11 (CH_3-mcpm *R*); 20.87 (CH_3-mcpm *S*); 20.64, 20.55, 20.43, 20.41, 20.33 (2C, 6 × OAc); 17.36 (CH-mcpm *R*); 16.91 (CH-mcpm *S*); 4.46, 3.90, 1.57, 1.26 (4 × CH_2-mcpm). ESI-HRMS: Calcd. for $C_{45}H_{60}NO_{14}$ $[M + NH_4]^+$ *m*/*z* 838.4008. Obsd. *m*/*z* 838.3996

*Methyl (3,4,6-tri-O-Benzyl-2-O-(R,S-1-methyl 1′-Cyclopropylmethyl)-α-D-glucopyranosyl)−(1→6)-2,3,4-tri-O-benzyl-α-D-mannopyranoside (**10b-α**).* Colorless amorphous solid, ^1H NMR 400Mz, $CDCl_3$, δ 7.32−7.21 (m, Ar−H); 7.07−7.06 (m, Ar−H); 5.04 (d, 1H, gH-1 *R*); 5.00−4.97 (m, 2H, gH-1 *S*, 1 × CH_2Ph); 4.92−4.88 (m, 3H, 3 × CH_2Ph); 4.80−4.54 (m, 16H, mH-1 *R*, mH-1 *S*, 14 × CH_2Ph); 4.43−4.38 (m, 4H, 4 × CH_2Ph); 3.89−3.52 (m, 24H, gH-2 *R*, gH-2 *S*, gH-3 *R*, gH-3*S*, gH-4 *R*, gH-4 *S*, gH-5 *R*, gH-5 *S*, gH-6_{ab} *R*, gH-6_{ab} *S*, mH-2 *R*, mH-2 *S*, mH-3 *R*, mH-3 *S*, mH-4 *R*, mH-4 *S*, mH-5 *R*, mH-5 *S*, mH-6_{ab} *R*, mH-6_{ab} *S*); 3.27 (s, 3H, OCH_3 *R*); 3.26 (s, 3H, OCH_3 *S*); 3.15−3.04 (m, 1H, CH-mcpm *R*); 2.98−2.92 (m, 1H, CH-mcpm *S*); 1.22−1.19 (m, 6H, CH_3-mcpm *R*, CH_3-mcpm *S*); 0.89−0.81 (m, 2H, 2 × CH_2); 0.52−0.42 (m, 2H, CH); 0.37−0.27 (m, 4H, CH); 0.07−0.02 (m, 2H, CH). ^{13}C NMR 100 MHz, $CDCl_3$, δ 138.18, 138.03, 137.73, 137.57, 137.39, 137.15 (*ipso*-C × 12), 127.34−126.31 (Ar−C); 97.95 (2C, mC-1*R*, mC-1*S*); 97.13 (gC-1*R*); 96.37 (gC-1*S*); 80.77, 80.63 (gC-3*R*, gC-3*S*); 79.54, 79.45, 79.39 (mC-3*R*, mC-3*S*, CH-mcpm *R*); 77.79 (2C, gC-2*R*, CH-mcpm *S*); 76.84, 76.77 (gC-2*S*, mC-4*R*, mC-4*S*); 74.46, 74.39, 74.32, 74.19, 74.02, 73.93, 73.87, 73.80, 73.75, 72.42, 71.73, 71.10, 70.58, 70.47 (12 × CH_2Ph, gC-4*R*, gC-4*S*, mC-2*R*, mC-2*S*); 69.08 (mC-5*R*, mC-5*S*); 67.66 (mC-6*R*, mC-6*S*); 66.40, 65.72 (gC-6*R*, gC-6*S*); 53.81, 53.77 (OCH_3); 20.06, 19.83 (CH_3-mcpm); 16.23, 15.68 (CH); 3.88, 3.72 (CH_2); 0.37, 0.00 (CH_2). MALDI-HRMS: Calcd. for $C_{60}H_{68}NaO_{11}$ $[M + Na]^+$ *m*/*z* 987.4654. Obsd. *m*/*z* 987.4689

*Methyl (3,4,6-tri-O-benzyl-2-O-(R,S-1-methyl 1′-cyclopropylmethyl)-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-α-D-mannopyranoside (**10b-β**).* Colorless amorphous solid, ^1H NMR 400 MHz, $CDCl_3$, δ 7.36−7.26 (m, 56H, Ar−H); 7.16−7.14 (m, 4H, Ar−H); 5.08 (d, 1H, *J* = 11.1 Hz, 1 × CH_2Ph); 5.01 (d, 1H, *J* = 11.4 Hz, 1 × CH_2Ph); 4.93−4.91 (m, 2H, 2 × CH_2Ph); 4.82−4.73 (m, 4H, 4 × CH_2Ph); 4.72−4.70 (m, 7H, mH-1 *R*, mH-1 *S*, 5 × CH_2Ph); 4.62−4.49 (m, 11H, 11 × CH_2Ph); 4.37 (d, 1H, *J* = 7.6 Hz, gH-1 *R*); 4.33 (d, 1H, *J* = 7.6 Hz, gH-1 *S*); 4.22−4.19 (m, 2H, mH-6_a *R*, mH-6_a *S*); 3.89−3.75 (m, 9H, gH-2 *S*, gH-4 *R*, gH-4 *S*, mH-3 *R*, mH-3 *S*, mH-2 *R*, mH-2 *S*, mH-5 *R*, mH-5 *S*); 3.71−3.67 (m, 6H, mH-6_b *R*, mH-6_b *S*, gH-6_a *R*, gH-6_a *S*, gH-6_b *R*, gH-6_b *S*); 3.59−3.57 (m, 4H, gH-3 *R*, gH-3 *S*, mH-4 *R*, mH-4 *S*); 3.50−3.41 (m, 5H, gH-2 *R*, gH-5 *R*, gH-5 *S*, CH-mcpm *R*, CH-mcpm *S*); 3.30, 3.29 (2s, 6H, 2 × OCH_3); 1.24 (d, 3H, *J* = 6.4 Hz, CH_3-mcpm *R*); 1.18 (d, 3H, *J* = 6.2 Hz, 3H, CH_3-mcpm *S*); 1.01−0.79 (m, 2H, 2 × CH-mcpm); 0.56−0.27 (m, 6H, 6 × CH_2-mcpm); 0.09−0.02 (m, 1H, 1 × CH_2-mcpm); −0.05- −0.12 (m, 1H, 1 × CH_2-mcpm). ^{13}C NMR 100 MHz, $CDCl_3$, δ 138.94, 138.72, 138.52 (4C), 138.35 (2C), 138.26 (2C), 138.24 (2C) (12 × *ipso*-C); 128.30−127.36 (60 × Ar−C); 104.34, 104.26 (2 × gC-1); 98.92, 98.73 (2 × mC-1); 84.93, 84.81 (2 × gC-3); 80.21, 80.15 (2 × mC-3); 79.79, 79.65 (2 × CH-mcpm); 78.21 (gC-2 *S*); 78.14 (gC-2 *R*); 77.98 (2C, 2 × mC-4); 75.86 (2C), 75.66 (2C), 75.16 (2C, 6 × CH_2Ph); 74.98, 74.93 (2 × gC-4); 74.83 (2 × CH_2Ph); 74.78, 74.71 (2 × gC-5); 74.64 (2 × CH_2Ph); 73.47, 72.73 (2 × mC-2); 72.00 (2 × CH_2Ph); 71.45, 71.33 (2 × mC-5); 69.76 (2C, 2 × mC-6); 69.13, 69.08 (2 × gC-6); 54.75, 54.69 (2 × OCH_3); 21.34, 19.35 (2 × CH_3-mcpm); 17.36, 16.34 (2 × CH-mcpm); 5.53, 3.95, 1.70, 0.42 (4 × CH_2-mcpm). MALDI-HRMS: Calcd. for $C_{60}H_{68}NaO_{11}$ $[M + Na]^+$ *m*/*z* 987.4654. Obsd. *m*/*z* 987.4693

*Allyl (3,4,6-tri-O-Acetyl-2-O-(R,S-1-methyl 1′-Cyclopropylmethyl)-α-D-glucopyranosyl)-(1→4)-2,3-O-isopropylidene-α-L-rhamnopyranoside (**11a-α**).* Colorless oil, ^1H NMR 400 MHz, C_6D_6, δ 5.85−5.76 (m, 4H, gH-3*R*, gH-3*S*, =CH × 2), 5.55−5.48 (m, 2H, gH-4*R*, gH-4*S*), 5.29−5.25 (m, 2H, $=CH_2 \times 2$); 5.10 (d, *J* = 3.5 Hz, 1H, gH-1*R*); 5.02−5.00 (m, 2H, $CH_2= \times 2$); 4.90 (d, *J* = 3.5 Hz, 1H, gH-1*S*); 4.72 (dd, *J* = 4.4 and 12.3 Hz, 1H, gH-6_a *R*), 4.71 (dd, *J* = 4.8 Hz and 12.1 Hz, 1H, gH-6_a *S*); 4.51−4.39 (m, 6H, gH-5*R*, gH-5*S*, gH-6_b*R*, gH-6_b*S*, rH-1*R*, rH-1*S*); 4.27 (dd, *J* = 13.2 Hz and 4.5 Hz, 2H, OCH_2-CH=$CH_2 \times 2$), 3.93−3.88 (m, 4H, rH-2*R*, OCH_2-CH=$CH_2 \times 2$, rH-2*S*); 3.80−3.69 (m, 4H, rH-3*R*, rH-3*S*, rH-4*R*, rH-4*S*), 3.54 (at, *J* = 10.2 Hz, 1H, gH-2*R*); 3.51 (at, *J* = 10.3 Hz, 1H, gH-2*S*); 3.28−3.14 (m, 2H, rH-5*R*, rH-5*S*); 2.83−277 (m, 1H, OCH-Me-cp *R*); 2.62−2.55 (m, 1H, OCH-Me-cp *S*); 1.83 (bs, 12H, $CH_3CO \times 4$); 1.77 (bs, 6H, $CH_3CO \times 2$); 1.56 (bs, 6H, iso-$CH_3 \times 2$); 1.48 (d, *J* = 6.0 Hz, 3H, rCH_3 *R*); 1.41 (d, *J* = 6.2 Hz, 3H, rCH_3 *S*); 1.20 (bs, 6H, iso-$CH_3 \times 2$); 1.10 (d, *J* = 6.1 Hz, 3H, CH_3-mcpm *R*); 0.95 (d, *J* = 6.1 Hz, 3H, CH_3-mcpm *S*); 0.65−0.57 (m, 2H, CH-cp × 2); 0.33−0.14 (m, 5H, CH_2-ring × 5); 0.10- −0.10 (m, 2H, CH_2-ring × 2); −0.16−0.22 (m, 1H, CH_2-ring). ^{13}C NMR 100 MHz, C_6D_6, δ 170.22, 169.66, 169.60 (CO × 6); 134.75 (2C, CH=$CH_2 \times 2$); 116.55, 116.52 (=$CH_2 \times 2$); 110.30 (2C, iso-C × 2); 99.87 (gC-1*R*); 99.54 (gC-1*S*); 97.57 (2C, rC-1*R*, rC-1*S*); 82.38, 82.35 (rC-4*R*, rC-4*S*); 82.28 (OCH-Me-cp *S*); 79.86 (OCH-Me-cp *R*); 78.55, 78.49 (rC-3*R*, rC-3*S*); 77.52, 75.67 (gC-2*R*, gC-2*S*); 74.89 (2C, rC-2 × 2); 72.97, 72.82 (gC-3*R*, gC-3*S*); 70.36, 70.29 (rC-5*R*, rC-5*S*); 69.34, 69.24 ($OCH_2 \times 2$); 68.18, 68.14 (gC-5*R*, gC-5*S*); 61.95, 61.91 (gC-6*R*, gC-6*S*); 27.73 (2C), 26.20 (2C)-(isopropylidine $CH_3 \times 4$); 21.14 (CH_3−CH-cp *R*); 20.63 (CH_3CO); 20.54 (CH_3−CH-cp *S*); 20.41, 20.34 (CH_3CO);19.01 (rCH_3 *R*); 18.80 (rCH_3 *S*): 17.46, 17.01 (CH-ring × 2); 4.54, 3.84, 1.32, 1.25 (CH_2 ring × 4). ESI-HRMS: Calcd. for $C_{29}H_{48}NO_{13}$ $[M + NH_4]^+$ *m*/*z* 618.3120. Obsd. *m*/*z* 618.3147.

*Allyl (3,4,6-tri-O-Acetyl-2-O-(R,S-1-methyl 1′-Cyclopropylmethyl)-β-D-glucopyranosyl)-(1→4)-2,3-O-isopropylidene-α-L-rhamnopyranoside (**11a-β**).* Colorless oil, ^1H NMR 400 MHz, C_6D_6, δ 5.88−5.78 (m, 2H, CH_2=CH-$CH_2O \times 2$); 5.38 (at, *J* = 9.2 Hz and 9.4 Hz, 1H, H-3*S*); 5.31 (at, *J* = 9.2 Hz and 9.4 Hz, 1H, H-3*R*); 5.32−5.20 (m, 4H, CH_2=CH−$CH_2O \times 2$, gH-4*R*, gH-4*S*); 5.05−5.02 (m, 2H, CH_2=CH−$CH_2O \times 2$); 4.97 (d, *J* = 7.8 Hz, 1H, gH-1*R*); 4.92 (d, *J* = 7.8 Hz, 1H, gH-1*S*); 4.59 (d, *J* = 2.7 Hz, 1H, rH-1*R*); 4.56 (d, *J* = 2.7 Hz, 1H, rH-1*S*); 4.32−4.13 (m, 8H, OCH_2-CH=$CH_2 \times 2$, rH-3*R*, rH-3*S*, rH-4*R*, rH-4*S*, gH-6_a*R*, gH-6_a*S*); 4.04−3.90 (m, 6H, OCH_2-CH=$CH_2 \times 2$, rH-2*R*, rH-2*S*, gH-6_b*R*, gH-6_b*S*); 3.67 (at, *J* = 9.4 Hz and 7.8 Hz, 1H, gH-2*S*); 3.43−3.28 (m, 5H, gH-2*R*, rH-5*R*, rH-5*S*, CH-mcpm-*R*, CH-mcpm-*S*); 3.21−3.17 (m, 2H, gH-5*R*, gH-5*S*); 1.81 (s, 3H, CMe_2 *S*); 1.74 (s, 3H, CMe_2 *R*); 1.70 (s, 3H, CMe_2 *S*); 1.68 (s, 3H, CMe_2 *R*); 1.49 (d, *J* = 6.2 Hz, 3H, rCH_3 *S*); 1.48 (d, *J* = 6.2 Hz, 3H, rCH_3 *R*); 1.30 (d, *J* = 6.0 Hz, 3H, CH_3-mcpm *S*); 1.11 (d, *J* = 6.0 Hz, 3H, CH_3-mcpm *R*); 0.92−0.81 (m, 2H, CH-ring × 2); 0.58−0.52 (m, 2H, CH_2-ring × 2); 0.47−0.38 (m, 1H, CH_2-ring × 1); 0.37−0.22 (m, 2H, CH_2-ring × 2); 0.04−0.02 (m, 1H, CH_2-ring × 1). ^{13}C NMR 100 MHz, C_6D_6, δ 169.87 (2C), 169.43 (2C), 169.36 (2C)(6 × CO); 134.79 (2C, CH_2=CH × 2); 116.46 (2C, CH_2=CH × 2); 110.68 (2C, $OCOMe_2 \times 2$); 101.63 (2C, gC-1*R*, gC-1*S*); 97.51, 97.42 (rC-1*R*, rC-2*S*); 80.29 (CH_3-mcpm-*S*); 79.43, 79.25 (rC-3*R*, rC-3*S*); 79.00 (CH_3-mcpm-*R*); 78.61 (2C, rC-4*R*, rC-4*S*); 77.50, 77.23 (gC-2*R*, gC-2*S*); 74.91, 74.62 (rC-2*R*, rC-2*S*); 71.83 (2C, gC-5*R*, gC-5*S*); 70.70 (2C, rC-5*R*, rC-5*S*); 69.24 (2C, gC-6*RS*); 69.10 (2C, gC-4*R*, gC-4*S*); 61.89 (2C, CH_2−CH=$CH_2 \times 2$); 21.48 (CH_3-mcpm *R*); 20.45 (2C), 20.24 (2C)($CMe_2 \times 4$); 19.99 (CH_3-mcpm *S*); 19.53 (2C, rCH_3 *R*, rCH_3 *S*); 17.58, 16.96 (CH-ring × 2); 4.66, 3.41, 1.84, 0.68 (CH_2-ring × 4). ESI-HRMS: Calcd. for $C_{29}H_{48}NO_{13}$ $[M + NH_4]^+$ *m*/*z* 618.3120. Obsd. *m*/*z* 618.3035.

*Allyl (3,4,6-tri-O-Benzyl-2-O-(R,S-1-methyl 1′-Cyclopropylmethyl)-β-D-glucopyranosyl)-(1→4)-2,3-O-isopropylidene-α-L-rhamnopyranoside (**11b-β**).* Colorless amorphous solid, ^1H NMR 400 MHz, C_6D_6, δ 7.42−7.37 (m, ArH); 7.31−7.29 (m, ArH); 7.20−7.05 (m, ArH); 5.86−5.77 (m, 2H, $OCH_2CH=CH_2 \times 2$); 5.30−5.26 (m, 2H, $OCH_2CH=CH_2 \times 2$); 5.19 (d, *J* = 11.5 Hz, 1H, CH_2Ph); 5.05−5.00 (m, 5H, gH-1 *R*, gH-1 *S*, CH_2Ph, $OCH_2CH=CH_2 \times 2$); 4.88 (d, *J* = 11.5 Hz, 1H, CH_2Ph); 4.87 (d, *J* = 11.5 Hz, 1H, CH_2Ph); 4.84 (d, *J* = 11.5 Hz, 1H, CH_2Ph); 4.80 (d, *J* = 11.5 Hz, 1H, CH_2Ph); 4.60−4.57 (m, 4H, rH-1 *R*, rH-1 *S*, $CH_2Ph \times 2$); 4.47−4.37 (m, 4H, $CH_2Ph \times 4$); 4.36−4.26 (m, 5H, rH-3 *R*, rH-4 *R*, rH-4 *S*, $OCH_2CH=CH_2 \times 2$);

dx.doi.org/10.1021/jo202563f | J. Org. Chem. 2012, 77, 3724−3739

4.21 (at, J = 6.6 Hz and 6.4 Hz, 1H, rH-3 *S*); 4.06−4.01 (m, 2H, rH-2 *R*, rH-2 *S*); 3.97−3.90 (m, 3H, gH-6$_a$ *R*, OC$\underline{H}_2$CH=CH$_2$ × 2); 3.82−3.73 (m, 2H, gH-3 *R*, gH-2 *S*); 3.67−3.55 (m, 9H, gH-4 *S*, gH-5 *R*, gH-2 *R*, gH-3 *S*, gH-6$_b$ *R*, gH-6$_a$ *S*, gH-6$_b$ *S*, CH-mcpm *R*, CH-mcpm *S*); 3.45−3.37 (m, 4H, gH-4 *R*, gH-5 *S*, rH-5 *R*, rH-5 *S*); 1.58−1.55 (m, 12H, rC$\underline{H}_3$ *R*, rC$\underline{H}_3$ *S*, OCO$\underline{Me}_2$ × 2); 1.42 (d, J = 6.0 Hz, 3H, C$\underline{H}_3$-mcpm *R*); 1.31−1.28 (m, 9H, OCO$\underline{Me}_2$ × 2, C$\underline{H}_3$-mcpm *S*); 1.01−0.87 (m, 2H, CH-ring × 2); 0.63−0.60 (m, 1H, C$\underline{H}_2$-ring); 0.52−0.50 (m, 3H, C$\underline{H}_2$-ring × 3); 0.41−0.35 (m, 2H, C$\underline{H}_2$-ring × 2); 0.28−0.22 (m, 1H, C$\underline{H}_2$-ring); 0.07−0.01 (m, 1H, C$\underline{H}_2$-ring). ^{13}C NMR 100 MHz, C_6D_6, δ 139.92, 139.66, 139.35 (2C), 139.05 (2C)(*ipso*-C × 6); 134.84, 134.83 (OCH$_2$C$\underline{H}$=CH$_2$ × 2); 128.53−127.41 (Ar−C); 116.48, 116.41 (OCH$_2$CH=C$\underline{H}_2$ × 2); 110.62, 110.61 (C$\underline{Me}_2$ × 2); 102.63 (gC-1 *S*); 102.14 (gC-1 *R*); 97.54 (rC-1 *R*); 97.47 (rC-1 *S*); 85.43, 85.18 (C$\underline{H}$-mcpm × 2); 79.89 (gC-5 x1); 79.80, 79.72 (rC-3 × 2); 79.54 (gC-3 × 1); 79.23 (gC-5 × 1); 78.78, 78.40 (rC-4 × 2); 78.38 (2C, gC-2 × 2); 78.34 (2C, gC-3 × 1, gC-4 × 1); 75.85 (C$\underline{H}_2$Ph × 1); 75.71 (C$\underline{H}_2$Ph × 1); 75.39 (gC-4 × 1); 74.98 (2C, rC-2 × 2); 74.77 (C$\underline{H}_2$Ph × 1); 74.70 (C$\underline{H}_2$Ph × 1); 73.50 (2C, C$\underline{H}_2$Ph × 2); 70.37 (2C, rC-5 × 2); 69.18 (2C), 69.14 (2C)(OCH$_2$ × 2, gC-6 × 2); 27.54 (2C), 26.21, 26.17 (C$\underline{Me}_2$ × 4); 21.72 (CH$_3$-mcpm); 19.91 (CH$_3$-mcpm); 19.68 (2C, rC$\underline{H}_3$ × 2); 17.87, 16.99 (CH-ring × 2); 5.45, 3.54, 1.82, 0.74 (CH$_2$-ring × 4). ESI-HRMS: Calcd. for $C_{44}H_{60}NO_{10}$ $[M + NH_4]^+$ m/z 762.4211. Obsd. m/z 762.4209.

*Allyl (3,4,6-tri-O-Benzyl-2-O-(R,S-1-methyl 1′-Cyclopropylmethyl)-α-D-glucopyranosyl)-(1→4)-2,3-O-isopropylidene-α-L-rhamnopyranoside (**11b-α**).* Colorless amorphous solid, ^{1}H NMR 400 MHz, $CDCl_3$, δ 7.37−7.25 (m, 26H, Ar−H); 7.17−7.13 (m, 4H, Ar−H); 6.01−5.91 (m, 2H, OCH$_2$−C$\underline{H}$=CH$_2$ × 2); 5.32 (d, J = 17.2 Hz, 1H, OCH$_2$−CH=C$\underline{H}_2$ × 1); 5.31 (d, J = 17.4 Hz, 1H, OCH$_2$−CH=C$\underline{H}_2$ × 1); 5.25 (d, J = 10.2 Hz, 1H, OCH$_2$−CH=C$\underline{H}_2$ × 1); 5.24 (d, J = 10.3 Hz, 1H, OCH$_2$−CH=C$\underline{H}_2$ × 1); 5.13 (d, J = 3.9 Hz, 1H, gH-1 *R*); 5.05 (d, J = 11.1 Hz, 2H, OC$\underline{H}_2$Ph × 2); 5.00 (d, J = 3.7 Hz, 1H, gH-1 *S*); 4.95 (d, J = 10.7 Hz, 1H, OC$\underline{H}_2$Ph × 1); 4.87−4.80 (m, H, OC$\underline{H}_2$Ph × 6); 4.75−4.70 (m, 2H, rH-1 *R*, rH-1 *S*); 4.67−4.63 (m, 2H, OC$\underline{H}_2$Ph × 2); 4.53−4.50 (m, H, OC$\underline{H}_2$Ph × 1); 4.46−4.41 (m, 2H, OC$\underline{H}_2$-CH=CH$_2$ × 2); 4.21−4.13 (m, 6H, OC$\underline{H}_2$-CH=CH$_2$ × 2, rH-2 *R*, rH-2 *S*, rH-3 *R*, rH-3 *S*); 4.06−4.02 (m, 2H, gH-5 *R*, gH-5 *S*); 3.90−3.66 (m, 10H, gH-2 *R*, gH-2 *S*, g H-3 *R*, gH-3 *S*, gH-4 *R*, gH-4 *S*, gH-6$_a$ *R*, gH-6$_a$ *S*, gH-6$_b$ *R*, gH-6$_b$ *S*); 3.57−3.45 (m, 4H, rH-4 *R*, rH-4 *S*, rH-5 *R*, rH-5 *S*); 3.21−3.14 (m, 1H, CH-mcpm *R*); 3.12−3.06 (m, 1H, CH-mcpm *S*); 1.53, 1.52 (2bs, 6H, iso-CH$_3$ × 2); 1.45 (d, J = 6.1 Hz, 3H, rC$\underline{H}_3$ *R*); 1.41 (d, J = 5.7 Hz, 3H, rC$\underline{H}_3$ *S*); 1.32, 1.31 (2bs, 6H, iso-CH$_3$ × 2); 1.29−1.27 (m, 3H, C$\underline{H}_3$-mcpm *S*); 1.23 (d, 3H, C$\underline{H}_3$-mcpm *R*); 0.95−0.81 (m, 2H, CH-ring × 2); 0.62−0.52 (m, 2H, C$\underline{H}_2$-ring × 2); 0.49−0.39 (m, 3H, C$\underline{H}_2$-ring); 0.34−0.29 (m, 1H, C$\underline{H}_2$-ring × 1); 0.13−0.06 (m, 2H, C$\underline{H}_2$-ring × 2). ^{13}C NMR 100 MHz, $CDCl_3$, **δ** 139.06, 138.88 (2C), 138.36 (2C), 138.08 (*ipso*-C × 6); 133.79 (2C, OCH$_2$-C$\underline{H}$=CH$_2$ × 2); 128.35−127.32 (Ar−C); 118.24 (2C, OCH$_2$−CH=C$\underline{H}_2$ × 2); 110.31 (2C, C$\underline{(CH_3)_2}$ × 2); 99.58 (gC-1 *R*); 99.02 (gC-1 *S*); 96.90 (2C, rC-1 *R*, rC-1 *S*); 82.04 (C$\underline{H}$-mcpm); 80.85, 80.79 (rC-4 *R*, rC-4 *S*); 80.11 (C$\underline{H}$-mcpm); 78.74 (2C, gC-2 *R*, gC-2 *S*); 78.45 (2C, rC-3 *R*, rC-3 *S*); 78.01 (2C, gC-3 *R*, gC-3 *S*); 77.43 (2C, gC-4 *R*, gC-4 *S*); 75.53, 75.41, 75.08 (OC$\underline{H}_2$Ph); 74.69 (2C, rC-2 *R*, rC-2 *S*); 73.56 (OC$\underline{H}_2$Ph); 71.01, 70.92 (rC-5 *R*, rC-5 *S*); 70.35 (2C, gC-5 *R*, gC-5 *S*); 70.16 (2C, OC$\underline{H}_2$−CH=CH$_2$ × 2); 68.24, 68.14 (gC-6 *R*, gC-6 *S*); 27.95, 26.36 (C($\underline{C}$H$_3$)$_2$ × 4); 21.19, 20.24 (2C, CH$_3$-mcpm *R*, CH$_3$-mcpm *S*); 18.24, 18.13 (rCH$_3$ *R*, rCH$_3$ *S*); 17.17, 16.77 (CH-ring × 2); 5.14, 4.84, 1.02, 0.85 (CH$_2$-ring × 4). **ESI-HRMS:** Calcd. for $C_{44}H_{60}NO_{10}$ $[M + NH_4]^+$ m/z 762.4211. Obsd. m/z 762.4209.

*Methyl (4,6-O-Benzylidene-2-O-(R,S-1-methyl 1′-Cyclopropylmethyl)-3-O-pivaoyl-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-α-D-mannopyranoside (**12**).* colorless syrup, yield, 55%, ^{1}H NMR 400 MHz, C_6D_6, δ 7.63−7.61 (m,2H, Ar−H); 7.41−7.27 (m, 8H, Ar−H); 7.22−7.06 (m, 30H, Ar−H); 6.02−5.94 (m, 2H, gH-3*R*, gH-3*S*); 5.34 (s, 1H, PhC$\underline{H}_2$ *R*); 5.33 (s, 1H, PhC$\underline{H}_2$ *S*); 5.25 (d, J = 3.5 Hz, 1H, gH-1*R*); 5.22 (d, J = 3.5 Hz, 1H, gH-1*S*); 5.08 (d, J = 11.7 Hz, 1H, C$\underline{H}_2$Ph); 5.04 (d, J = 11.9 Hz, 1H, C$\underline{H}_2$Ph); 4.77 (d, J = 11.7 Hz, 1H, C$\underline{H}_2$Ph);4.69 (d, J=1.6 Hz, 1H, mH-1*R*); 4.68 (d, J = 1.7 Hz, 1H, mH-1*S*); 4.65 (d, J = 12.8 Hz, 1H, PhC$\underline{H}_2$); 4.55−4.54 (m, 2H, PhC$\underline{H}_2$ × 2); 4.52 (bs, 2H, PhC$\underline{H}_2$ × 2); 4.44−4.40 (m, 4H, PhC$\underline{H}_2$ × 4); 4.34−4.17 (m, 4H, gH-6$_a$ *R*, gH-6$_a$ *S*, gH-5 *R*, gH-5 *S*); 4.14−4.06 (m, 2H, mH-5 *R*, mH-5 *S*); 4.02−3.85 (m, 8H, mH-3 *R*, mH-3 *S*, mH-4 *R*, mH-4 *S*, mH-6$_{ab}$ *R*, mH-6$_{ab}$ *S*); 3.81 (dd, J = 9.7 Hz and 3.5 Hz, 1H, gH-2 *S*); 3.74 (bs, 2H, mH-2 *R*, mH-2 *S*); 3.66 (dd, J = 9.6 Hz and 3.5 Hz, 1H, gH-2*R*); 3.59−3.45 (m, 4H, gH-6$_b$ *R*, gH-6$_b$ *S*, gH-4 *R*, gH-4 *S*); 3.17 (s, 3H, CH$_3$O *R*); 3.12−3.05 (m, 4H, CH$_3$O *S*, C$\underline{H}$-mcpm *S*); 2.84−2.78 (m, 1H, C$\underline{H}$-mcpm *R*); 1.28−1.26 (m, 18H, C$\underline{Me}_3$C × 6); 1.23−1.20 (m, 6H, C$\underline{H}_3$-mcpm *R*, C$\underline{H}_3$-mcpm *S*); 0.96−0.74 (m, 2H, C$\underline{H}$-ring × 2); 0.47−0.29 (m, 4H, C$\underline{H}_2$-ring × 4); 0.27−0.18 (m, 2H, C$\underline{H}_2$-ring × 2); 0.09−0.03 (m, 1H, C$\underline{H}_2$-ring × 1); 0.01−0.05 (m, C$\underline{H}_2$-ring × 1). ^{13}C NMR 100 MHz, C_6D_6, δ 176.55 (2C, CO × 2); 139.71, 139.63 (*ipso*-C-benzilidene × 2); 139.26 (2C), 139.23 (2C), 139.13, 138.32 (*ipso*-C- CH$_2$Ph × 6); 128.84−126.51 (Ar−C × 40); 101.47 (2C, PhC$\underline{H}$ × 2); 99.50, 99.34 (mC-1 × 2); 99.03 (gC-1 *R*); 98.22 (gC-1 *S*); 81.08, 80.97 (mC-3 × 2); 80.71 (OC$\underline{H}$-mcpm *R*); 80.69 (2C, gC-4 × 2); 78.07 (OC$\underline{H}$-mcpm *S*); 77.39 (gC-2 *R*); 75.99, 75.96 (mC-2 × 2); 75.89 (gC-2 *S*); 75.73, 75.55 (mC-5 × 2); 75.17, 75.10 (OC$\underline{H}_2$Ph × 2); 73.17, 73.12 (OC$\underline{H}_2$Ph × 2); 72.50, 72.31 (mC-4 × 2); 72.20, 72.14 (OC$\underline{H}_2$Ph × 2); 71.13, 71.08 (gC-3 × 2); 69.38, 69.33 (gC-6 × 2); 67.56, 66.52 (mC-6 × 2); 62.92, 62.87 (gC-5 × 2); 54.65, 54.56 (OMe × 2); 38.98, 38.87 (C$\underline{Me}_3$ × 2); 27.46 (3C), 27.40 (3C)(C$\underline{Me}_3$ × 6); 21.06 (2C, C$\underline{H}_3$-mcpm × 2); 17.35, 16.94 (C$\underline{H}$-ring × 2); 4.86, 4.19, 1.37, 1.11 (C$\underline{H}_2$-ring × 4). ESI-HRMS: Calcd. for $C_{51}H_{66}NO_{12}$ $[M + NH_4]^+$ m/z 884.4579. Obsd. m/z 884.4561.

*Allyl (4,6-O-benzylidene-2-O-(R,S-1-methyl 1′-cyclopropylmethyl)-3-O-pivaoyl-α-D-glucopyranosyl)-(1→4)-2,3-O-isopropylidene-α-L-rhamnopyranoside (**13**).* Colorless oil, ^{1}H NMR 400 MHz, C_6D_6, δ 7.67−7.65 (m, 2H, ArH); 7.18−7.14 (m, 4H, ArH); 7.10−7.06 (m, 4H, ArH); 5.98 (at, J = 9.8 Hz and 9.6 Hz, 1H, gH-3 *R*); 5.97 (at, J = 9.6 Hz and 9.8 Hz, 1H, gH-3 *S*); 5.86−5.76 (m, 2H, OCH$_2$C$\underline{H}$=CH$_2$ × 2); 5.40 (s, 1H, PhC$\underline{H}$); 5.38 (s, 1H, PhC$\underline{H}$); 5.29 (d, J = 1.8 Hz, 1H, OCH$_2$CH=C$\underline{H}_2$); 5.24 (d, J = 1.7 Hz, 1H, OCH$_2$CH=C$\underline{H}_2$); 5.19 (d, J = 3.5 Hz, 1H, gH-1 *R*); 5.01 (bs, 1H, OCH$_2$CH=C$\underline{H}_2$); 4.99 (bs, 1H, OCH$_2$CH=C$\underline{H}_2$); 4.93 (d, J = 3.5 Hz, 1H, gH-1 *S*); 4.52 (d, J = 2.5 Hz, 1H, rH-1 *R*); 4.50 (d, J = 2.5 Hz, 1H, rH-1 *S*); 4.48−4.44 (m, 2H, gH-6$_a$ *R*, gH-6$_a$ *S*); 4.35−4.25 (m, 4H, gH-5 *R*, gH-5 *S*, OC$\underline{H}_2$CH=CH$_2$ × 2); 3.92−3.87 (m, 4H, OC$\underline{H}_2$CH=CH$_2$ × 2, rH-2 *R*, rH-2 *S*); 3.78 (dd, J = 10 Hz and 6.8 Hz, 1H, rH-4 *R*); 3.72−3.58 (m, 7H, rH-4 *S*, gH-2 *R*, gH-2 *S*, gH-6$_b$ *R*, gH-6$_b$ *S*, rH-3 *R*, rH-3 *S*); 3.50 (at, J = 9.8 Hz, 1H, gH-4 *R*); 3.46 (at, J = 9.8 Hz, 1H, gH-4 *S*); 3.30−3.23 (m, 1H, rH-5 *S*); 3.22−3.10 (m, 2H, rH-5 *R*, OC$\underline{H}$-mcpm *S*); 2.89−2.82 (m, 1H, OC$\underline{H}$-mcpm *R*); 1.53−1.52 (m, 3H, rCH$_3$ *S*); 1.43 (d, J = 6.2 Hz, 3H, rC$\underline{H}_3$ *R*); 1.27 (bs, 9H, C$\underline{Me}_3$); 1.25 (bs, 9H, C$\underline{Me}_3$); 1.21 (d, J = 6.2 Hz, 3H, C$\underline{H}_3$-mcpm *R*); 1.06 (d, J = 6.1 Hz, 3H, C$\underline{H}_3$-mcpm *S*); 0.75−0.61 (m, 2H, CH-ring × 2); 0.45−0.16 (m, 7H, C$\underline{H}_2$-ring × 7); −0.09−0.15 (m, 1H, C$\underline{H}_2$-ring). ^{13}C NMR 100 MHz, C_6D_6, δ 176.76, 176.73 (2 × CO); 138.26, 138.22 (*ipso*-C_6H_5 × 2); 134.84 (2C, OCH$_2$C$\underline{H}$=CH$_2$ × 2); 128.89−127.48 (Ar−C); 116.45, 116.41 (OCH$_2$CH=C$\underline{H}_2$ × 2); 110.13, 110.08 (C$\underline{Me}_2$ × 2); 101.59 (2C, PhC$\underline{H}$ × 2); 100.70 (gC-1 *R*); 100.10 (gC-1 *S*); 97.56, 97.55 (rC-1 *R*, rC-1 *S*); 82.58 (rC-4 *R*); 82.38 (rC-4 *S*); 82.02 (C$\underline{H}$-mcpm *R*); 80.70 (2C, gC-4 *R*, gC-4 *S*); 78.46 (rC-3 *R*); 78.39 (C$\underline{H}$-mcpm *S*); 77.96 (gC-2 *R*); gC-2 *S*); 76.00 (rC-3 *S*); 74.81 (2C, rC-2 *R*, rC-2 *S*); 71.52, 71.37 (gC-3 *R*, gC-3 *S*); 70.20, 70.13 (rC-5 *R*, rC-5 *S*); 69.53, 69.50 (gC-6 *R*, gC-6 *S*); 69.26, 69.24 (OC$\underline{H}_2$CH=CH$_2$ × 2); 63.30, 63.20 (gC-5 *R*, gC-5 *S*); 38.96, 38.91 (C$\underline{Me}_3$ × 2); 27.69, 27.66 (OCO$\underline{Me}_2$ × 2); 27.43 (3C), 27.38 (3C)(C$\underline{Me}_3$ × 6); 26.19, 26.18 (OCO$\underline{Me}_2$ × 2); 21.33 (C$\underline{H}_3$-mcpm *R*); 20.45 (C$\underline{H}_3$-mcpm *S*); 19.22, 18.93 (rCH$_3$ *R*, rCH$_3$ *S*); 17.37, 17.01 (CH-ring × 2); 4.86, 3.47, 1.25, 0.96 (CH$_2$-ring × 4). ESI-HRMS: Calcd. for $C_{35}H_{54}NO_{11}$ $[M + NH_4]^+$ m/z 664.3691. Obsd. m/z 664.3666.

*Phenyl 3,4,6-tri-O-acetyl-2-O-(R,S-1-methyl 1′-cyclopropylmethyl)-1-thio-β-D-glucopyranoside (**7a-β**).* Colorless amorphous solid, ^{1}H NMR, $CDCl_3$, 400 MHz, δ 7.48 (m, 4H, ArH), 7.23 (m, 6H, ArH), 5.15 (m, 2H, H-3 *R*, H-3 *S*), 4.95 (m, 2H, H-4 *R*, H-4 *S*), 4.61 (d, $J_{1,2}$ = 9.8 Hz, 1H, H-1*S*), 4.55 (d, $J_{1,2}$ =9.8 Hz, 1H, H-1 *R*), 4.27 - 4.02 (m, 4H, H-6$_a$ *R*, H-6$_a$ *S*, H-6$_b$ *R*, H-6$_b$ *S*), 3.79 (m, 1H, H-5 *R*), 3.69

dx.doi.org/10.1021/jo202563f | J. Org. Chem. 2012, 77, 3724−3739

(brt, $J_{2,3}$ = 9.4 Hz, 1H, H-2 *R*), 3.61 (m, 1H, H-5 *S*), 3.48 (brt, $J_{2,3}$ = 9.4 Hz, 1H, H-2 *S*), 3.12 (m, 2H, CH-mcpm *R*, CH-mcpm *S*), 2.03−1.95 (m, 18H, Ac-CH_3), 1.26 (d, *J* = 6.2 Hz, 3H, CH_3-mcpm *R*), 1.15 (d, *J* = 6.2 Hz, 3H, CH_3-mcpm *S*), 0.92 (m, 1H, CH-ring *S*), 0.60 (m, 1H,CH-ring *R*), 0.24 (m, 1H,CH_2-ring *S*), 0.22 (m, 1H, CH_2-ring *R*), 0.16 (m, 5H,CH_2-ring *R*,*S*), −0.01 (m, 1H, CH_2-ring *S*). ^{13}C NMR, $CDCl_3$, 100 MHz, δ170.6, 170.0, 169.81, 169.77 169.6 (C═O, Ac), 133.6 (SPh_{ip}), 131.9, 131.8 (SPh_o), 128.9 (SPh_m), 127.7 (SPh_p), 88.5 (C-1 *R*, C-1 *S*), 81.5 (CH-mcpm *S*), 81.2 (CH-mcpm *R*), 75.7 - 75.3 (6C, C-2, C-4, C-5 (*R*,*S*)), 69.7 (C-3 *S*), 67.9 (C-3 *R*), 62.5 (C-6 *S*), 61.5 (C-6 *R*), 21.0 (MCPM-CH_3 *S*), 20.8, 20.7, 20.6 (Ac-CH_3), 20.1 (MCPM-CH_3 *R*), 17.1 (MCPM-CH *S*), 16.5 (MCPM-CH *R*), 5.3 (MCPM-CH_2 *R*), 4.4 (MCPM-CH_3 *S*), 1.9 (MCPM-CH_3 *S*), 0.5 (MCPM-CH_2 *R*). ESI-HRMS: Calcd. for $C_{23}H_{34}NO_8S$ $[M + NH_4]^+$ *m*/*z* 484.2005. Obsd. *m*/*z* 484.1996.

*Phenyl 3,4,6-tri-O-Acetyl-2-O-(R,S-1-methyl 1′-Cyclopropylmethyl)-1-thio-α-D-glucopyranoside (**7a-α**).* Colorless amorphous solid, ^{1}H NMR, $CDCl_3$, 400 MHz, δ 7.49 (m, 4H, ArH), 7.30 (m, 6H, ArH), 5.81 (d, $J_{1,2}$ = 5.6 Hz, 1H, H-1 *R*), 5.75 (d, $J_{1,2}$ = 5.6 Hz, 1H, H-1 *S*), 5.28 (m, 2H, H-3 *R*, H-3 *S*), 5.01 (m, 2H, H-4 *R*, H-4 *S*), 4.55 (m, 2H, H-5 *R*,H-5 *S*), 4.29 (dd, $J_{5,6}$ = 5.3 Hz, $J_{6,6'}$ = 12.3 Hz, 2H, H-6 *R*, H-6 *S*), 4.08 (dd, $J_{2,3}$ = 10.0 Hz, 1H, H-2 *R*), 4.02 (brd, 2H, H-6′ *R*, H-6′ *S*), 3.90 (dd, $J_{2,3}$ = 10.0 Hz, 1H, H-2 *S*), 3.03 (m, 1H, MCPM-CHO *R*), 2.90 (m, 1H, MCPM-CHO *S*), 2.10−2.01 (18H, Ac-CH_3), 1.27 (d, *J* = 6.2 Hz, 3H, MCPM-CH_3 *R*), 1.23 (d, *J* = 6.2 Hz, 3H, MCPM-CH_3 *S*), 0.85 (m, 1H, MCPM-CH *R*), 0.57 (m, 1H, MCPM-CH *S*), 0.51, 0.47, 0.38, 0.33, 0.13 (m, 8H, MCPM-CH_2 *R*, MCPM-CH_2 *S*). ^{13}C NMR, $CDCl_3$, 100 MHz, δ 170.6, 170.0, 169.9 (C═O, Ac), 133.7 (SPh_{ip}), 131.6 (SPh_o), 129.0 (SPh_m), 127.3 (SPh_p), 87.5 (C-1 *R*), 87.0 (C-1 *S*), 81.9 (MCPM-CHO *S*), 79.8 (MCPM-CHO *R*), 76.0 (C-2 *S*), 74.7 (C-2 *R*), 72.4 (C-3 *S*), 72.3 (C-2 *R*), 68.8 (C-4 *R*, C-4 *S*), 68.0 (C-5 *R*, C-5 *S*), 62.2 (C-6 *R*, C-6 *S*), 21.1 (MCPM-CH_3 *R*), 20.78, 20.74, 20.69 (Ac-CH_3), 20.6 (MCPM-CH_3 *S*), 17.1 (MCPM-CH *S*), 16.2 (MCPM-CH *R*), 4.8 (MCPM-CH_2 *R*), 4.3 (MCPM-CH_3 *S*), 1.8 (MCPM-CH_3 *S*), 1.0 (MCPM-CH_2*R*). ESI-HRMS: Calcd. for $C_{23}H_{34}NO_8S$ $[M + NH_4]^+$ *m*/*z* 484.2005. Obsd. *m*/*z* 484.2021.

4.8. General Procedure for the Removal of MCPM Protection. To the ice cooled solution of the glycosylated compound in DCM was added trifluoroacetic acid (10% by volume) under argon atmosphere and the reaction was allowed to stir for 1.5 h. After reaction completion, more DCM and sat. sodium bicarbonate solution was added and stirred for 30 min. The solution was transferred to a separating funnel and the organic layer was extracted with DCM. The organic layer was dried with anhyd. sodium sulfate and concentrated to give the crude product. The crude was column purified over silica gel to afford the pure MCPM deprotected product.

*Methyl (3,4,6-tri-O-Benzyl-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-α-D-mannopyranoside (**15-α**).* Colorless oil, ^{1}H NMR, $CDCl_3$, 400 MHz, δ 7.37−7.22 (m, Ar−H); 7.15−7.13 (m, Ar−H); 4.99 (bs, 1H, gH-1); 4.96 (d, *J* = 11.1 Hz, 1H, OCH_2Ph × 1); 4.90 (d, *J* = 11.4 Hz, 1H, OCH_2Ph × 1); 4.83 (d, *J* = 10.5 Hz, 1H, OCH_2Ph × 1); 4.71−4.68 (m, 4H, mH-1, OCH_2Ph × 3); 4.62−4.58 (m, 4H, OCH_2Ph × 4); 4.47 (d, *J* = 11.4 Hz, 2H, OCH_2Ph × 2); 4.08−4.01 (m, 2H, mH-4, gH-6_a); 3.89 (dd, *J* = 9.4 and 7 Hz, 1H, mH-3); 3.79−3.77 (m, 2H, mH-2, gH-5); 3.71−3.57 (m, 7H, gH-2, gH-3, gH-4, gH-6b, mH-5, mH-6_a, mH-6_b); 3.28 (s, 3H, OCH_3). ^{13}C NMR, $CDCl_3$, 100 MHz, δ 138.93, 138.51, 138.38 (2C); 138.01 (2C)(*ipso*-C × 6); 128.38−127.43 (Ar−C); 100.61 (gC-1); 98.94 (mC-1); 83.38 (gC-3); 79.92 (mC-3); 77.26 (gC-4); 75.16 (OCH_2Ph); 75.08 (OCH_2Ph); 74.96 (OCH_2Ph); 74.32 (gC-5); 74.18 (mC-4); 73.80 (mC-2); 73.44 (OCH_2Ph); 72.81 (OCH_2Ph); 72.07 (OCH_2Ph); 71.33 (mC-5); 70.69 (gC-2); 68.53 (mC-6); 67.78 (gC-6); 54.90 (OCH_3). ESI-HRMS: Calcd. for $C_{55}H_{64}NO_{11}$ $[M + NH_4]^+$ *m*/*z* 914.4474. Obsd. *m*/*z* 914.4472.

*Methyl (3,4,6-tri-O-Benzyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-α-D-mannopyranoside (**15-β**).* Colorless oil, ^{1}H NMR, $CDCl_3$, 400 MHz, δ 7.40−7.25 (m, 29H, Ar−H); 7.18−7.16 (m, 1H, Ar−H); 4.99 (d, *J* = 11.1 Hz, 1H, OCH_2Ph × 1); 4.94 (d, *J* = 10.9 Hz, 1H, OCH_2Ph × 1); 4.85 (d, *J* = 10.7 Hz, 1H, OCH_2Ph × 1); 4.76 (d, *J* = 12.5 Hz, 1H, OCH_2Ph × 1); 4.71 (d, *J* = 1.8 Hz, 1H, mH-1); 4.70 (d, *J* = 12.5 Hz, 1H, OCH_2Ph × 1); 4.65−4.60 (m, 4H, OCH_2Ph × 4); 4.55−4.52 (m, 2H, OCH_2Ph × 2); 4.35 (d, *J* = 7.2 Hz, gH-1); 4.21−4.19 (m, 1H, gH-6_a); 3.95−3.88 (m, 2H, gH-4, mH-3); 3.82−3.59 (m, 8H, mH-2, mH-4, mH-5, mH-6_a, mH-6_b, gH-2, gH-3, gH-6_b); 3.49−3.46 (m, 1H, gH-5); 3.32 (s, 3H, OCH_3). ^{13}C NMR, $CDCl_3$, 100 MHz, δ 138.83, 138.40, 138.37, 138.20 (2C), 138.07 (ipso-C × 6); 128.36−127.52 (Ar−C); 103.48 (gC-1); 99.06 (mC-1); 84.41 (gC-2); 80.04 (mC-3); 77.32 (mC-4); 75.27 (gC-5); 75.09 (gC-4); 75.02, 74.99 (OCH_2Ph × 7); 74.47 (mC-5); 74.41 (gC-3); 73.42 (2C), 72.85 (2C), 72.13 (OCH_2Ph × 5); 71.34 (mC-2); 68.90 (mC-6); 68.23 (gC-6); 54.89 (OCH_3) ESI-HRMS: Calcd. for $C_{55}H_{64}NO_{11}$ $[M + NH_4]^+$ *m*/*z* 914.4474. Obsd. *m*/*z* 914.4469.

*Allyl (3,4,6-tri-O-Benzyl-α-D-glucopyranosyl)-(1→4)-α-L-rhamnopyranoside (**16-α**).* Colorless oil, ^{1}H NMR, $CDCl_3$, 400 MHz, δ 7.33−7.24 (m, Ar−H); 7.15−7.13 (m, Ar−H); 5.95−5.86 (m, 1H, OCH_2CH═CH_2); 5.27 (d, *J* = 17.4 Hz, 1H, OCH_2CH═CH_2); 5.19 (d, *J* = 10.6 Hz, 1H, OCH_2CH═CH_2); 4.98 (bs, 1H, gH-1); 4.86 (d, *J* = 11.1 Hz, OCH_2Ph × 1); 4.83 (m, 2H, OCH_2Ph × 2); 4.78 (d, *J* = 11.5 Hz, 1H, OCH_2Ph × 1); 4.57 (d, *J* = 12.1 Hz, 1H, OCH_2Ph × 1); 4.50−4.47 (m, 2H, OCH_2Ph × 2); 4.45 (s, 1H, rH-1); 4.37 (dd, *J* = 12.7 and 4.9 Hz, 1H, OCH_2CH═CH_2 × 1); 4.12−4.07 (m, 2H, OCH_2CH═CH_2 × 1, gH-5); 3.98 (bs, 1H, rH-2); 3.92 (bs, 1H, r−OH); 3.74−3.60 (m, 4H, gH-2, gH-3, gH-6_a, gH-6_b); 3.54−3.43 (m, 3H, gH-4, rH-3, rH-4); 3.37−3.30 (m, 1H, rH-5); 2.51 (bs, 1H, r−OH); 2.06 (bs,1H, g−OH); 1.38 (d, *J* = 6.0 Hz, 3H, r-CH_3). ^{13}C NMR, $CDCl_3$, 100 MHz, δ 138.30, 138.10, 138.0 (*ipso*-C); 133.66 (OCH_2-CH═CH_2); 129.10−128.05 (Ar−C); 117.96 (CH_2═CH−OCH_2); 99.93 (gC-1); 98.51 (rC-1); 83.76 (rC-4); 82.68 (gC-3); 77.91 (rC-3); 75.50 (OCH_2Ph); 75.07 (OCH_2Ph); 73.77 (OCH_2Ph); 72.74 (gC-2); 72.49 (gC-4); 71.50 (gC-5); 71.24 (rC-2); 70.96 (rC-5); 70.04 (OCH_2−CH═CH_2); 68.77 (gC-6); 18.02 (rCH_3). ESI-HRMS: Calcd. for $C_{36}H_{48}NO_{10}$ $[M + NH_4]^+$ *m*/*z* 654.3272. Obsd. *m*/*z* 654.3235.

*Allyl (3,4,6-tri-O-Benzyl-β-D-glucopyranosyl)-(1→4)-α-L-rhamnopyranoside (**16-β**).* Colorless oil, ^{1}H NMR, $CDCl_3$, 400 MHz, δ 7.33−7.23 (m, Ar−H); 7.19−7.17 (m, Ar−H); 5.93−5.84 (m, 1H, CH_2═CH-OCH_2); 5.26 (d, *J* = 17.2 Hz, 1H, CH_2═CH−OCH_2); 5.18 (d, *J* = 10.3 Hz, 1H, CH_2═CH−OCH_2); 4.83 (m, 2H, OCH_2Ph × 2); 4.79 (d, *J* = 10.9 Hz, 1H, OCH_2Ph × 1); 4.57 (d, *J* = 12.1 Hz, 1H, OCH_2Ph × 1); 4.56 (d, *J* = 10.9 Hz, 1H, OCH_2Ph × 1); 4.50 (d, *J* = 12.3 Hz, 1H, OCH_2Ph × 1); 4.46−4.45 (m, 2H, gH-1, rH-1); 4.38−4.34 (m, 1H, OCH_2CH═CH_2 × 1); 4.10−4.06 (dd, *J* = 12.7 and 6.4 Hz, 1H, OCH_2CH═CH_2 × 1); 3.99 (d, *J* = 2.4 Hz, 1H, rH-2); 3.68−3.67 (m, 2H, gH-6_a, gH-6_b); 3.62−3.59 (m, 2H, rH-3, gH-4); 3.55−3.42 (m, 4H, gH-2, rH-4, gH-3, gH-5); 3.33−3.26 (m, 1H, rH-5); 1.41 (d, *J* = 6.0 Hz, 3H, rCH_3). ^{13}C NMR, $CDCl_3$, 100 MHz, δ138.49, 138.10, 138.01 (*ipso*-C); 133.65 (OCH_2-CH═CH_2); 128.56−127.57 (Ar−C); 117.97 (CH_2═CH−OCH_2); 105.45 (gC-1); 98.24 (rC-1); 84.62 (rC-4); 84.51 (gC-3); 77.42 (rC-3); 75.19 (gC-5); 75.16 (gC-2); 75.02 (OCH_2Ph); 74.90 (OCH_2Ph); 73.70 (gC-4); 73.44 (OCH_2Ph); 70.82 (rC-2); 70.78 (rC-5); 69.84 (OCH_2−CH═CH_2); 68.72 (gC-6); 17.53 (rCH_3). ESI-HRMS: Calcd. for $C_{36}H_{48}NO_{10}$ $[M + NH_4]^+$ *m*/*z* 654.3272. Obsd. *m*/*z* 654.3269.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dennis.whitfield@nrc-cnrc.gc.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the help of the NRC computer support group and the Mass Spectral group. This is NRC publication #50014.

REFERENCES

(1) Galonić, D. P.; Gin, D. Y. *Nature* **2007**, *446*, 1000.
(2) Mydock, L. K.; Demchenko, A. V. *Org. Biomol. Chem.* **2010**, *8*, 497.
(3) Boltje, T. J.; Buskas, T.; Boons, G. J. *Nat. Chem.* **2009**, *1*, 611.
(4) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900.
(5) Schofield, L.; Hewitt, M. C.; Evans, K.; Siomos, M. A.; Seeberger, P. H. *Nature* **2002**, *418*, 785.
(6) Bohé, L.; Crich, D. *Comptes Rendus Chim.* **2011**, *14*, 3.
(7) Kaeothip, S.; Demchenko, A. V. *J. Org. Chem.* **2011**, *76*, 7388.
(8) Whitfield, D. M.; Douglas, S. P. *Glycoconjugate J.* **1996**, *13*, 5.
(9) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155.
(10) Kochetkov, N. E. In *Stud. Nat. Product Chemistry*; Rahman, A., Ed.; 1994; Vol. *14*, p 201.
(11) Banait, N. S.; Jencks, W. P. *J. Am. Chem. Soc.* **1991**, *113*, 7951.
(12) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7888.
(13) Walvoort, M. T.; Lodder, G.; Overkleeft, H. S.; Codee, J. D.; van der Marel, G. A. *J. Org. Chem.* **2010**, *75*, 7990.
(14) Bucher, C.; Gilmour, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 8724.
(15) Berti, P. J.; McCann, J. A. *Chem. Rev.* **2006**, *106*, 506.
(16) Schramm, V. L. *Curr. Opin. Struct. Biol.* **2005**, *15*, 604.
(17) Bennet, A. J.; Sinnott, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 7287.
(18) Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5386.
(19) El-Badri, M. H.; Willenbring, D.; Tantillo, D. J.; Gervay-Hague, J. *J. Org. Chem.* **2007**, *72*, 4663.
(20) Nokami, T.; Shibuya, A.; Manabe, S.; Ito, Y.; Yoshida, J.-i. *Chem.—Eur. J.* **2009**, *15*, 2252.
(21) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217.
(22) Zeng, Y.; Wang, Z.; Whitfield, D.; Huang, X. *J. Org. Chem.* **2008**, *73*, 7952.
(23) Nokami, T.; Shibuya, A.; Tsuyama, H.; Suga, S.; Bowers, A. A.; Crich, D.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2007**, *129*, 10922.
(24) Chao, C.-S.; Yen, Y.-F.; Hung, W.-C.; Mong, K.-K. T. *Adv. Synth. Catal.* **2011**, *353*, 879.
(25) Nukada, T.; Berces, A.; Zgierski, M. Z.; Whitfield, D. M. *J. Am. Chem. Soc.* **1998**, *120*, 13291.
(26) Whitfield, D. M.; Nukada, T. *Carbohydr. Res.* **2007**, *342*, 1291.
(27) Whitfield, D. M. In *Advances in Carbohydrate Chemistry and Biochemistry*; Derek, H., Ed.; Academic Press: New York, 2009; Vol. *62*, p 83.
(28) Li, Z. *Carbohydr. Res.* **2010**, *345*, 1952.
(29) Marousek, V.; Lucas, T. J.; Wheat, P. E.; Schuerch, C. *Carbohydr. Res.* **1978**, *60*, 85.
(30) Newth, F. H.; Phillips, G. O. *J. Chem. Soc.* **1953**, 2904.
(31) Rhind-Tutt, A. J.; Vernon, C. A. *J. Chem. Soc.* **1960**, 4637.
(32) Bowden, T.; Garegg, P. J.; Maloisel, J.-L.; Konradsson, P. *Isr. J. Chem.* **2000**, *40*, 271.
(33) Fraschetti, C.; Novara, F. R.; Filippi, A.; Speranza, M.; Trout, N. A.; Adcock, W.; Marcantoni, E.; Renzi, G.; Roselli, G.; Marcolini, M. *J. Org. Chem.* **2009**, *74*, 5135.
(34) Cozzi, P. G.; Benfatti, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 256.
(35) Denegri, B.; Matić, M.; Kronja, O. *Eur. J. Org. Chem.* **2010**, *2010*, 1440.
(36) Adcock, W.; Trout, N. A. *J. Phys. Org. Chem.* **2008**, *21*, 68.
(37) Nukada, T.; Berces, A.; Whitfield, D. M. *Carbohydr. Res.* **2002**, *337*, 765.
(38) Shenoy, S. R.; Woerpel, K. A. *Org. Lett.* **2005**, *7*, 1157.
(39) Smith, D. M.; Woerpel, K. A. *Org. Biomol. Chem.* **2006**, *4*, 1195.
(40) Lucero, C. G.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 2641.
(41) Shenoy, S. R.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 8671.
(42) Beaver, M. G.; Woerpel, K. A. *J. Org. Chem.* **2010**, *75*, 1107.
(43) Krumper, J. R.; Salamant, W. A.; Woerpel, K. A. *J. Org. Chem.* **2009**, *74*, 8039.
(44) Walvoort, M. T.; Moggre, G. J.; Lodder, G.; Overkleeft, H. S.; Codee, J. D.; van der Marel, G. A. *J. Org. Chem.* **2011**, *76*, 7301.
(45) Walvoort, M. T.; Dinkelaar, J.; van den Bos, L. J.; Lodder, G.; Overkleeft, H. S.; Codee, J. D.; van der Marel, G. A. *Carbohydr. Res.* **2010**, *345*, 1252.
(46) Winstein, S.; Buckles, R. E. *J. Am. Chem. Soc.* **1942**, *64*, 2780.
(47) Frush, H. L.; Isbell, H. S. *J. Natl. Bur. Stand* **1941**, *27*, 413.
(48) Garegg, P. J.; Kvarnström, I. *Acta Chem. Scand.* **1977**, *B31*, 509.
(49) Tichý, M.; Pánková, M. *Collect. Czech. Chem. Commun.* **1975**, *40*, 647.
(50) Crich, D.; Dai, Z.; Gastaldi, S. *J. Org. Chem.* **1999**, *64*, 5224.
(51) Satoh, H.; Hansen, H. S.; Manabe, S.; van Gunsteren, W. F.; Hunenberger, P. H. *J. Chem. Theor. Comp.* **2010**, *6*, 1783.
(52) Lemieux, R. U.; Huber, G. *Can. J. Chem.* **1955**, *33*, 128.
(53) Nukada, T.; Berces, A.; Wang, L.; Zgierski, M. Z.; Whitfield, D. M. *Carbohydr. Res.* **2005**, *340*, 841.
(54) Deslongchamps, P.; Li, S.; Dory, Y. L. *Org. Lett.* **2004**, *6*, 505.
(55) Whitfield, D. M. *Carbohydr. Res.* **2007**, *342*, 1726.
(56) Gildersleeve, J.; Pascal, R. A.; Kahne, D. *J. Am. Chem. Soc.* **1998**, *120*, 5961.
(57) Huang, X.; Huang, L.; Wang, H.; Ye, X.-S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5221.
(58) Codee, J. D.; Litjens, R. E.; den Heeten, R.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1519.
(59) Demchenko, A. V.; Malysheva, N. N.; De Meo, C. *Org. Lett.* **2003**, *5*, 455.
(60) Pornsuriyasak, P.; Demchenko, A. V. *Chem.—Eur. J.* **2006**, *12*, 6630.
(61) Kim, K. S.; Jeon, H. B. *Chem. Rec.* **2008**, *8*, 46.
(62) Kalikanda, J.; Li, Z. *J. Org. Chem.* **2011**, *76*, 5207.
(63) Wallace, J. E.; Schroeder, L. R. *J. Chem. Soc., Perkin Trans. 2* **1977**, 795.
(64) Paulsen, H.; Schüttpelz, E. *Chem. Ber.* **1979**, *112*, 3214.
(65) Boltje, T. J.; Kim, J. H.; Park, J.; Boons, G. J. *Org. Lett.* **2011**, *13*, 284.
(66) Park, J.; Kawatkar, S.; Kim, J. H.; Boons, G. J. *Org. Lett.* **2007**, *9*, 1959.
(67) Mydock, L. K.; Kamat, M. N.; Demchenko, A. V. *Org. Lett.* **2011**, *13*, 2928.
(68) Nokami, T.; Nozaki, Y.; Saigusa, Y.; Shibuya, A.; Manabe, S.; Ito, Y.; Yoshida, J. *Org. Lett.* **2011**, *13*, 1544.
(69) Saito, K.; Ueoka, K.; Matsumoto, K.; Suga, S.; Nokami, T.; Yoshida, J.-i. *Angew. Chem., Int. Ed.* **2011**, *50*, 5153.
(70) Crich, D. *Acc. Chem. Res.* **2010**, *43*, 1144.
(71) Ionescu, A.; Wang, L.; Zgierski Marek, Z.; Nukada, T.; Whitfield, D. M. In *NMR Spectroscopy and Computer Modeling of Carbohydrates*; Vliegenthar, J. F. G., Woods, R. J., Eds.; American Chemical Society: Washington, D.C., 2006; Vol. *930*, p 302.
(72) Ionescu, A. R.; Whitfield, D. M.; Zgierski, M. Z. *Carbohydr. Res.* **2007**, *342*, 2793.
(73) Fraser-Reid, B.; Udodong, U. E.; Wu, Z.; Ottosson, H.; Merritt, J. R.; Rao, C. S.; Roberts, C.; Madsen, R. *Synlett* **1992**, *1992*, 927.
(74) Fraser-Reid, B.; Merritt, J. R.; Handlon, A. L.; Andrews, C. W. *Pure Appl. Chem.* **1993**, *65*, 779.
(75) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734.
(76) Douglas, N. L.; Ley, S. V.; Lucking, U.; Warriner, S. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 51.
(77) Premathilake, H. D.; Mydock, L. K.; Demchenko, A. V. *J. Org. Chem.* **2010**, *75*, 1095.
(78) Fraser-Reid, B.; Lopez, J. C.; Radhakrishnan, K. V.; Mach, M.; Schlueter, U.; Gomez, A. M.; Uriel, C. *J. Am. Chem. Soc.* **2002**, *124*, 3198.
(79) Crich, D.; Jayalath, P. *Org. Lett.* **2005**, *7*, 2277.
(80) Eichler, E.; Yan, F.; Sealy, J.; Whitfield, D. M. *Tetrahedron* **2001**, *57*, 6679.
(81) Yu, S. H.; Whitfield, D. M. *Tetrahedron* **2011**, *67*, 5750.
(82) Pedersen, C. M.; Nordstrom, L. U.; Bols, M. *J. Am. Chem. Soc.* **2007**, *129*, 9222.
(83) Jensen, H. H.; Pedersen, C. M.; Bols, M. *Chem.—Eur. J.* **2007**, *13*, 7576.

(84) Mulard, L. A.; Costachel, C.; Sansonetti, P. J. *J. Carbohydr. Chem.* **2000**, *19*, 849.
(85) Zhu, T.; Boons, G.-J. *Tetrahedron Lett.* **1998**, *39*, 2187.
(86) Wang, P.; Haldar, P.; Wang, Y.; Hu, H. *J. Org. Chem.* **2007**, *72*, 5870.
(87) Li, Z. J.; Li, H.; Cai, M. S. *Carbohydr. Res.* **1999**, *320*, 1.
(88) Codée, J. D. C.; Ali, A.; Overkleeft, H. S.; van der Marel, G. A. *Comptes Rendus Chim.* **2011**, *14*, 178.
(89) Mydock, L. K.; Demchenko, A. V. *Org. Lett.* **2008**, *10*, 2103.
(90) Mydock, L. K.; Demchenko, A. V. *Org. Lett.* **2008**, *10*, 2107.
(91) Kamkhachorn, T.; Parameswar, A. R.; Demchenko, A. V. *Org. Lett.* **2010**, *12*, 3078.
(92) Boltje, T. J.; Kim, J. H.; Park, J.; Boons, G. J. *Nat. Chem.* **2010**, *2*, 552.
(93) Kim, J.-H.; Yang, H.; Khot, V.; Whitfield, D.; Boons, G.-J. *Eur. J. Org. Chem.* **2006**, *2006*, 5007.
(94) Kóňa, J.; Tvaroška, I. *Chem. Pap.* **2009**, *63*, 598.
(95) Greig, I. R.; Zahariev, F.; Withers, S. G. *J. Am. Chem. Soc.* **2008**, *130*, 17620.
(96) Abdel-Rahman, A. A. H.; Jonke, S.; El Ashry, E. S. H.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2972.
(97) Ruiz Pernia, J. J.; Tunon, I.; Williams, I. H. *J. Phys. Chem. B* **2010**, *114*, 5769.
(98) Chiappe, C.; Moro, G. L.; Munforte, P. *Tetrahedron* **1997**, *53*, 10471.
(99) Tiwari, P.; Misra, A. K. *J. Org. Chem.* **2006**, *71*, 2911.
(100) Wetter, H. r.; Oertle, K. *Tetrahedron Lett.* **1985**, *26*, 5515.
(101) Yu, B.; Tao, H. *Tetrahedron Lett.* **2001**, *42*, 2405.
(102) Yu, B.; Tao, H. *J. Org. Chem.* **2002**, *67*, 9099.
(103) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212.
(104) Schmidt, R. R.; Stumpp, M. *Liebigs Ann. Chem.* **1983**, *1983*, 1249.
(105) Barili, P. L.; Berti, G.; Catelani, G.; Cini, C.; D'Andrea, F.; Mastrorilli, E. *Carbohydr. Res.* **1995**, *278*, 43.
(106) Westman, J.; Nilsson, M.; Ornitz, D. M.; Svahn, C.-M. *J. Carbohydr. Chem.* **1995**, *14*, 95.
(107) Belakhov, V.; Dovgolevsky, E.; Rabkin, E.; Shulami, S.; Shoham, Y.; Baasov, T. *Carbohydr. Res.* **2004**, *339*, 385.
(108) Borén, H. B.; Eklind, K.; Garegg, P. J.; Lindberg, B.; Pilotti, A. *Acta Chem. Scand.* **1972**, *26*, 4143.
(109) Zhang, J.; Mao, J.; Chen, H.; Cai, M. *Tetrahedron: Asymmetry* **1994**, *5*, 2283.
(110) Kamat, M. N.; Demchenko, A. V. *Org. Lett.* **2005**, *7*, 3215.
(111) Kaeothip, S.; Akins, S. J.; Demchenko, A. V. *Carbohydr. Res.* **2010**, *345*, 2146.
(112) Crich, D.; Sharma, I. *Org. Lett.* **2008**, *10*, 4731.
(113) Ionescu, A. R.; Whitfield, D. M.; Zgierski, M. Z.; Nukada, T. *Carbohydr. Res.* **2006**, *341*, 2912.
(114) Berces, A.; Whitfield, D. M.; Nukada, T. *Tetrahedron* **2001**, *57*, 477.
(115) Yuan, J.; Frauenrath, H. *Eur. J. Org. Chem.* **2009**, *2009*, 43.
(116) Stubbs, J. M.; Marx, D. *Chem.—Eur. J.* **2005**, *11*, 2651.
(117) Schmidt, R. R.; Ali, I. A. I.; Zhu, X.; El Ashry, E. S. H. *ARKIVOC* **2012**, *2012 (vi)*, 35.
(118) Baerends, E. J.; Ellis, D. E.; Ros, P. *Chem. Phys.* **1973**, *2*, 41.
(119) te Velde, G.; Baerends, E. J. *J. Comput. Phys.* **1992**, *99*, 84.
(120) Fonseca Guerra, C.; Snijders, J. G.; te Velde, G.; Baerends, E. J. *Theor. Chim. Acta* **1998**, *99*, 391.
(121) Versluis, L.; Ziegler, T. *J. Chem. Phys.* **1988**, *88*, 322.
(122) Fan, L.; Ziegler, T. *J. Chem. Phys.* **1992**, *96*, 9005.
(123) Hricovini, M. *Carbohydr. Res.* **2006**, *341*, 2575.