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Absence of Stereodirecting Participation by 2-*O*-Alkoxycarbonylmethyl Ethers in 4,6-*O*-Benzylidene-Directed Mannosylation

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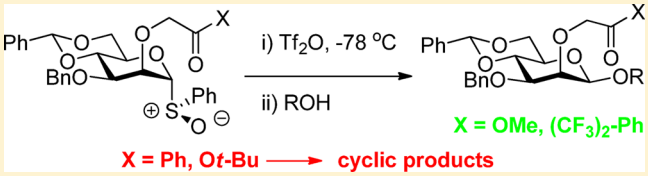
Supporting Information

ABSTRACT: The preparation of a series of mannopyranosyl donors carrying 2-*O*-(2-oxoalkyl) ethers and their use in glycosylation reactions are described. The formation of cyclic products with the simple 2-*O*-phenacyl ether and with the 2-*O*-(*t*-butoxycarbonylmethyl) ether establishes the stereoelectronic feasibility of participation in such systems. The high β-selectivities observed with the bis-trifluoromethyl phenacyl ether indicate that participation can be suppressed through the introduction of electron-withdrawing substituents. The high β-selectivities and absence of cyclic products observed with the 2-*O*-(methoxycarbonylmethyl) ether exclude the effective participation of esters through six-membered cyclic intermediates in this series. The results are discussed in terms of the conformation of cyclic dioxenium ions (*E*,*E*-, *E*,*Z*-, or *Z*,*Z*-) and in the context of "neighboring group" participation by nonvicinal esters in glycosylation. Methods for the deprotection of the 2-*O*-phenacyl and 2-*O*-(methoxycarbonylmethyl) ethers are described.



INTRODUCTION

Stereodirecting neighboring group participation by vicinal esters in the nucleophilic substitution reactions is one of the core concepts of modern organic chemistry,[1] and has been one of the most enduring themes of carbohydrate chemistry and glycosylation reactions.[2−4] Such participation proceeds through the formation of an intermediate dioxalenium ion,[5−7] which is captured by the acceptor alcohol to afford the orthoester as the kinetic product. Subsequent acid or Lewis acid-mediated rearrangement then provides the 1,2-*trans*-glycoside.[8−11] The β-gluco- and α-mannopyranosides owe their relatively facile synthetic availability to stereodirecting neighboring group participation. When participation is associated with kinetic acceleration of the substitution process, the phenomenon is known as anchimeric assistance.[12]

There have been many attempts to extend the phenomenon of stereodirecting neighboring group participation in glycosylation to the use of six or larger-membered cyclic intermediates by more remote esters or by other functional groups.[13] With certain notable exceptions for which cyclic intermediates have been demonstrated spectroscopically or crystallographically,[14−21] the evidence for such effects typically is limited to often modest changes in anomeric selectivity and comparisons with selectivities observed in the presence of nonparticipating groups.[13,22−31] Alternative explanations are always available for such examples, most notably protecting group-induced changes in (i) conformation;[32−34] (ii) through space stabilization of oxocarbenium ions;[35−41] (iii) in the degree of association of the leaving group with the anomeric carbon;[42,43] and (iv) the extent of preassociation of the donor and acceptor through hydrogen bonding.[44,45] By means of isotopic labeling experiments, Wilen demonstrated in simple model systems that participation by esters through six- and even seven-membered ring intermediates is possible albeit significantly retarded with respect to neighboring group participation through five-membered dioxalenium ions.[46] Yu and co-workers, using an isotopic labeling experiment, demonstrated initial participation via a seven-membered ring by the 4-*O*-ester in the formation of a bridged 1,2,4-*O*-orthoacetyl α-glucopyranose derivative on activation of per-*O*-acetyl glucopyranosyl donor.[18] Computational studies have also been advanced in support of participation by ester groups through the formation of six-membered and larger ring intermediates.[27] Notwithstanding these contributions, the question of the relevance of such intermediates under typical glycosylation conditions mostly remains unanswered.

In our laboratory, we introduced the *O*-*t*-butyloxycarbonyl and *O*-(*o*-carboxybenzoate) groups as probes for participation under typical glycosylation conditions and found no evidence in support of intermediates bridging the anomeric position and either the mannopyranose 3- and 4-positions, the galactopyranose 4-position, or the glucopyranose 6-position in pyranosyl donors carrying benzyl ethers at all other positions.[47] An isotopic labeling experiment also failed to provide evidence for participation by a 4-*O*-benzoate in the galactopyranose series under the conditions employed.[47] In contrast, the bridged intermediate resulting from participation by a Boc group at the 3-position in an allopyranosyl donor was readily trapped and isolated.[47]

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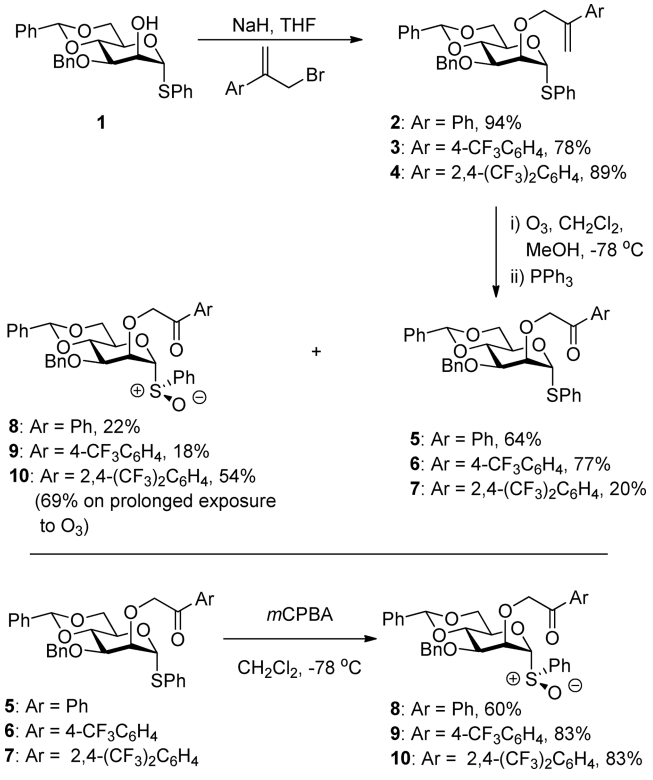
In this Article, we turn our attention to substituted 2-*O*-(2-oxoethyl) ethers in the mannopyranose series as probes of participation by carbonyl groups (in ketones and esters) through six-membered cyclic intermediates. We report that the 2-*O*-phenacyl and 2-*O*-(*t*-butoxycarbonylmethyl) ethers trap the activated glycosyl donor through formation of six-membered cyclic products and that this participation can be readily suppressed by the introduction of electron-withdrawing groups to the phenacyl system. In contrast, the 2-*O*-(methoxycarbonylmethyl) ether does not participate and on the contrary permits the formation of *β*-mannopyranosides in high yield.

RESULTS

Synthesis. Consistent with earlier results,[48] phenacyl ethers were best introduced by alkoxide etherification with 2-phenylallyl bromides followed by oxidative cleavage of the alkene, rather than by direct reaction of the alkoxide with phenacyl bromides. Thus, treatment of thioglycoside **1** with sodium hydride and a series of 2-arylallyl bromides gave the 2-*O*-(2-arylallyl) ethers **2**–**4** in good yield (Scheme 1).

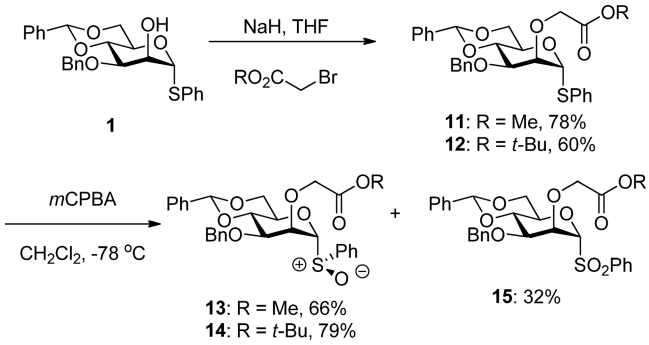
Scheme 1. Synthesis of Thioglycosides 5–7 and Sulfoxides 8–10



Subsequent ozonolytic cleavage of the alkene in dichloromethane/methanol mixtures at −78 °C gave the requisite ketones **5**–**7** together with the sulfoxides **8**–**10** (Scheme 1). With the phenyl and trifluorophenylalkenes **5** and **6**, ozonolytic cleavage of the alkene was the dominant reaction pathway, and the sulfoxides were only minor products; however, with the more electron-deficient bis(trifluoromethyl)phenyl alkene **7**, the sulfoxide **10** was the major product. When **7** was exposed to an excess of ozone and the reaction mixture stirred at −78 °C for a longer time (0.5 h), **10** was obtained in 69% yield. All three sulfoxides obtained from the ozonolytic cleavage were obtained as essentially single diastereomers to which we assign the S_R configuration, consistent with peroxide-mediated oxidations of related *α*-mannopyranosyl thioglycosides.[49−51] This assignment was corroborated by the oxidation of **5**, **6**, and **7** with *m*CPBA in dichloromethane at −78 °C, when the identical sulfoxides **8**, **9**, and **10** were obtained in high yield and selectivity (Scheme 1).

Comparable 2-*O*-(methoxycarbonylmethyl) and 2-*O*-(*t*-butoxycarbonylmethyl) thioglycosides **11** and **12** were obtained by alkylation of the sodium salt of **1** with methyl bromoacetate and *t*-butyl bromoacetate, respectively (Scheme 2). Oxidation of **11** and **12** with *m*CPBA then gave the sulfoxides **13** and **14** again as single diastereomers, together with the sulfone **15** in the case of the methyl ester (Scheme 2).

Scheme 2. Synthesis of the 2-*O*-(Methoxycarbonylmethyl) Derivatives 11–15



Attempted coupling of the phenacyl derivative **5** with adamantanol **16** on activation with diphenyl sulfoxide (DPSO) and triflic anhydride in the presence of the hindered non-nucleophilic base 2,4,6-tri-*tert*-butylpyrimidine (TTBP) in dichloromethane at −78 °C gave a complex reaction mixture in which we were unable to identify the anticipated glycosylation product **19** by ESI-mass spectrometry of the reaction mixture. The major isolated product from this reaction mixture was the tricyclic product **22**, which was isolated in 33% yield (Table 1).

Table 1. Glycosylation Reactions

entry	donor	acceptor	activation	products (% yield)
1	**5**	**16**	DPSO, Tf_2O, TTBP	**22** (33)
2	**7**	**16**	BSP, Tf_2O, TTBP	**20** (62), 3.8:1 *β*:*α*
3	**10**	**16**	Tf_2O, TTBP	**20** (62), 7.9:1 *β*:*α*
4	**10**	**17**	Tf_2O, TTBP	**23** (57), *β*-only
5	**11**	**16**	BSP, Tf_2O, TTBP	**21** (79), 5:1 *β*:*α*
6	**11**	**17**	BSP, Tf_2O, TTBP	**24** (83), *β*-only
7	**11**	**18**	BSP, Tf_2O, TTBP	**26** (87), 2.6:1 *β*:*α*
8	**13**	**17**	Tf_2O, TTBP	**24** (85), *β*-only
9	**13**	**18**	Tf_2O, TTBP	**26** (59), *β*-only
10	**14**	**17**	Tf_2O, TTBP	**25** (3), *β*-only + **27** (70)

With the 4-trifluoromethylphenacyl derivative **6**, under the same conditions conversion was low, and similarly complex reaction mixtures were observed in which the glycoside was not identified. Preactivation of the corresponding sulfoxide **9** with triflic anhydride at −78 °C in dichloromethane in the presence of TTBP followed by addition of the rhamnose 4-ol **17** also gave complex reaction mixtures as demonstrated by TLC and mass spectrometric analysis. Accordingly, the monotrifluoromethyl-substituted donors **6** and **9** were not pursued further.

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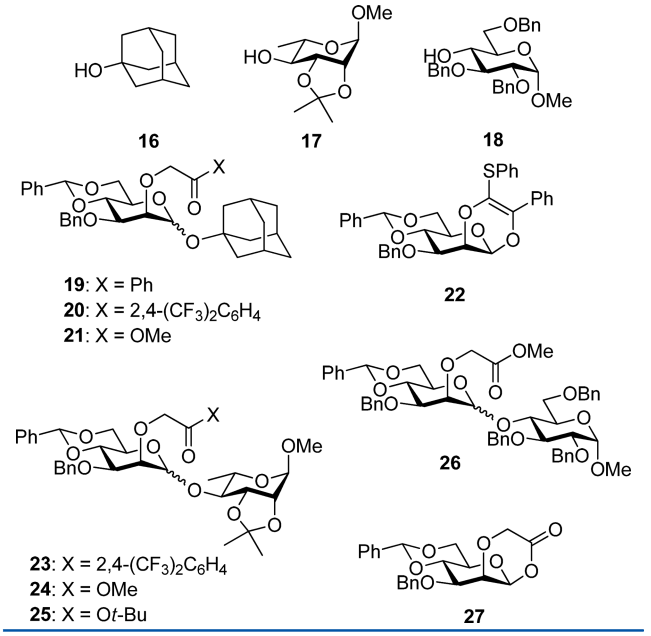
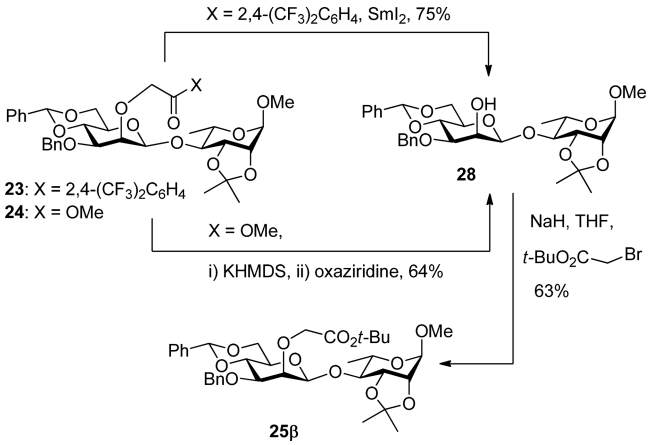
Activation of the 2,4-bis(trifluoro)phenylacyl thioglycoside **7** with 1-benzenesulfinyl piperidine (BSP) and triflic anhydride in the presence of TTBP in dichloromethane at −78 °C, followed by addition of 1-adamantanol, gave the glycoside **20** in 62% yield as a 3.8:1 β:α mixture (Table 1, entry 2). Activation of the corresponding sulfoxide **10** with triflic anhydride at −78 °C followed by addition of 1-adamantanol also gave glycoside **20** in 62% yield, but with selectivity of 7.9:1 in favor of the β-anomer (Table 1, entry 3). With the rhamnosyl acceptor **17**, the sulfoxide donor **10** gave 57% of the glycoside **23** as a single β-anomer (Table 1, entry 4). Coupling of the methoxycarbonylmethyl substituted thioglycoside **11** with acceptors **16**−**18** with activation by BSP under preactivation conditions gave the glycosides **21**, **24**, and **26** in good yield, with selectivities ranging from 2.6:1 for the less reactive acceptor **18** to complete with the rhamnoside **17** (Table 1, entries 5−7). Preactivation of the sulfoxide **13**, derived from thioglycoside **11**, followed by addition of acceptors **17** and **18** gave the glycosides **24** and **26** in good yield both as single diastereomers (Table 1, entries 8 and 9). Preactivation of the corresponding *t*-butoxycarbonylmethyl sulfoxide **14** with triflic anhydride followed by addition of the rhamnosyl acceptor **17** resulted in a 70% isolated yield of the lactone **27**, together with 3% of the glycoside **25** in the form of the β-anomer (Table 1, entry 10). Careful examination of this latter reaction mixture gave no indication of the formation of the α-anomer of **25**. Likewise, no evidence was found for the formation of the *trans*-fused lactone corresponding to **27**, whose central pyranose ring would be expected to adopt a twist boat conformation by analogy with related compounds described previously,[52,53] or of hydroxy acids arising from the hydrolytic ring opening of **27** and its putative *trans*-fused isomer. Although not isolated and fully characterized, a number of byproducts arising from the modification of acceptor **17**, glycoside **25**, and lactone **27** by one or more of the benzenesulfenyl, benzenesulfinyl, and *t*-butyl-based electrophiles generated in the course of the main reaction pathway were revealed in this reaction mixture by mass spectrometry. Comparable results were obtained on activation of the thioglycoside **12** with the BSP/Tf_2O and DPSO/Tf_2O combinations, with the lactone **27** as the major product and no indication of the formation of its *trans*-fused isomer.

Selective removal of the phenacyl-type protecting group following glycosylation was demonstrated by treatment of **23** with samarium iodide in THF when the known glycoside **28** was isolated in 75% yield (Scheme 3). Removal of the methoxycarbonylmethyl group was exemplified by treatment of **24** with potassium hexamethyldisilazide in THF at −78 °C followed by addition of the Davis camphorylsulfonyl oxaziridine,[54] when glycoside **28** was isolated in 64% yield (Scheme 3). In view of the minor amount of the glycoside **25β** obtained from the coupling of **14** and **17** (Table 1, entry 10), an authentic sample was obtained by alkylation of **28** with *t*-butoxy bromoacetate and proved identical in all respects (Scheme 3).



Scheme 3. Deprotection Methods for Bis(trifluoromethyl)phenacyl and Methoxycarbonylmethyl Ethers and Synthesis of an Authentic Sample of Glycoside 25β



DISCUSSION

Effective glycosylation with the 2-*O*-phenacyl donors **5**−**10** necessitated the inclusion of two trifluoromethyl moieties on the phenacyl group: relatively high glycosylation yields, generally clean reaction mixtures, and β-selectivity were obtained with the bis(trifluoromethyl)phenacyl system (Table 1, entries 2−4). In contrast, the unsubstituted (Table 1, entry 1) and mono(trifluoromethyl)phenacyl systems gave complex reaction mixtures. This pattern of results indicates competing nucleophilic reactivity of the phenacyl system with electrophilic species in the glycosylation reaction mixtures that can be minimized on introduction of two strong electron-withdrawing groups, recalling the classical work of Lemieux on participation by mono-, di-, and trichloroacetates.[55] The tricyclic compound **22** formed on activation of the phenacyl thioglycoside **5** (Table 1, entry 1) is one example of the numerous side reactions that can be envisaged between this class of protecting group and the type of electrophiles present during glycosylation. Mechanistically tricycle **22** can be viewed as the product of initial sulfenylation of the enolized ketone followed by nucleophilic attack of the ketone (or enol) at the anomeric position. Alternatively, **22** can be envisaged as being the result of participation by the phenacyl group, followed by enolization, reaction of the enol with an electrophilic byproduct of the activation process, and deprotonation. Whether sulfenylation occurs before or after ring closure, the formation of the tricyclic compound **22** from the 2-*O*-phenacyl system **5** firmly establishes the possibility of participation through a six-membered cyclic intermediate in the system under study.

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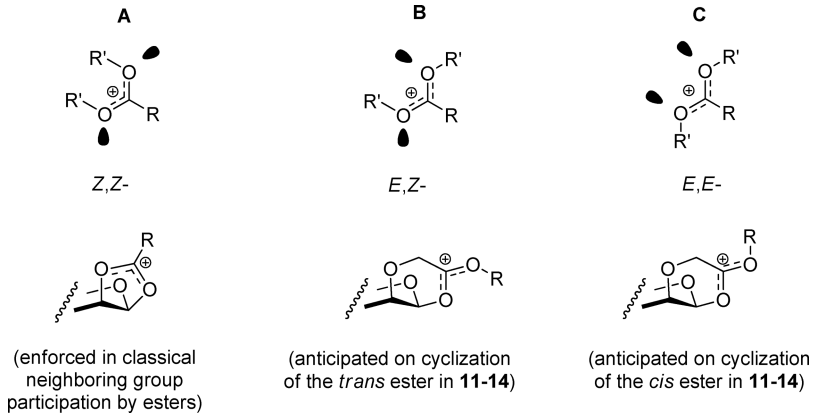

Figure 1. Dialkoxycarbenium ion configurations.

Further precedent for cyclization onto the anomeric center with formation of a six-membered ring is found in the intramolecular Sakurai reaction of mannosyl 2-*O*-(2-trimethylsilylmethallyl) ethers employed as cation clocks[52,53] and in the intramolecular Freidel–Crafts reaction of a mannosyl oxocarbenium ion onto a 2-*O*-benzyl ether.[56] Albeit accessed by an entirely different method, closely related tricyclic systems have also been described previously by Franck and co-workers.[57,58]

The incorporation of two electron-withdrawing trifluoromethyl groups as in the thioglycoside **7** and the related sulfoxide **10** gave clean glycosylation reactions that demonstrated high β-selectivity (Table 1, entries 2–4). The β-selective processes observed with donors **7** and **10** (Table 1, entries 2–4) exclude the possibility of participation by the bis-(trifluoromethyl)ketone as a major reaction pathway in their glycosylation reactions.

Glycosylations conducted with the 2-*O*-(methoxycarbonylmethyl) protected donors **11** and **13** (Table 1, entries 5–9) were all β-selective and high yielding, consistent with the absence of effective participation by the ester, and with the general compatibility of esters with a wide variety of glycosylation reaction conditions. An example demonstrating only modest β-selective glycosylation involved coupling to the less reactive glucose 4-OH acceptor **18** under the BSP conditions (Table 1, entry 7), suggesting a lower degree of association in the transition state.[43,59] Attempted glycosylation with the 2-*O*-(*t*-butoxycarbonylmethyl) protected donors **12** and **14** resulted in the formation of the lactone **27** as the major product along with minor amounts of the β-anomer of the anticipated glycoside (Table 1, entry 10). This observation reinforces the conclusion drawn from the use of the 2-*O*-phenacyl donors **5–10**, that participation through a six-membered ring in the manner anticipated is stereoelectronically feasible. The contrast between the results observed with the 2-*O*-(methoxycarbonylmethyl) and the 2-*O*-(*t*-butoxycarbonylmethyl)-protected systems and the predominant formation of β-glycosides in both cases indicates that for the alkoxycarbonyl methyl systems the association between the ester and the anomeric center is (i) weak, transient, and insufficient to influence the stereochemical outcome of the glycosylation reaction, and (ii) only revealed when cleavage of a *t*-C–O bond is possible, reflecting the difference in stability of the *t*-butyl and methyl cations.[60]

The absence of effective participation by the ester moiety in donors **11–14**, despite the ideal *trans*-diaxial relationship of the ester and the anomeric leaving group, invites careful comparison of the putative intermediates arising from participation by alkoxycarbonylmethyl ethers and from classical participation by esters. Classical neighboring group participation by esters affords planar[5] five-membered cyclic dioxalenium ions in which the *Z,Z*-configuration is enforced on the dialkoxy carbenium ion (Figure 1A), whereas participation by the alkoxycarbonylmethyl groups in **11–14** would afford six-membered cyclic dioxenium ions, in an envelope conformation, with the dialkoxy carbenium configured *E,Z* or *E,E* (Figure 1B and C) according to the conformation (*trans* or *cis*, respectively) of the ester taking part in the cyclization.

In the absence of constraints, the *E,Z*-configuration of dialkoxycarbenium ions is considered to be the most stable of the three possibilities from both steric and stereoelectronic perspectives.[61] This consideration is supported by NMR studies[62–64] and by DFT calculations,[65] which suggest that the *E,Z*-configuration of simple dialkoxycarbenium ions is >2.5 kcal mol^{-1} more stable than the *E,E*-configuration. Furthermore, alkylation of the carbonyl oxygen in δ-lactones gave the corresponding cyclic dialkoxycarbenium ions in the *E,Z*-configuration in two examples for which the structure was established crystallographically.[39] The barrier to rotation about the C–O bond in simple acyclic dialkoxycarbeniun ions has been estimated to be 11 ± 4 kcal mol^{-1} by VT-NMR spectroscopy.[62]

The fundamental reaction step in the cyclization of an alkoxycarbonylmethyl ether onto an oxocarbenium ion, as required for participation in donors such as **11** and **13**, is illustrated for a simple model *trans*-ester leading to the formation of an *E,Z*-dialkoxycarbenium ion in Figure 2A. The basic reaction step for participation by a nonvicinal ester via a six-membered ring (such as from the 3-position of a glycosyl oxocarbenium ion) resulting in the formation of *Z,Z*-configured dialkoxycarbenium ion is illustrated by the simple model methoxyacetate ester presented in Figure 2B. DFT calculations conducted by the B3LYP method in the gas phase with the 6-31+G(d,p) basis set using the Gaussian 09W suite of programs[66–70] indicate a small $\Delta\Delta G$ of 1.74 kcal mol^{-1} between the two homodesmotic possibilities of Figure 2 with the cyclization of the 2-*O*-(alkoxycarbonylmethyl) ether resulting in the *E,Z*-dialkoxycarbenium ion being the more favored of the two. Therefore, other factors being equal, there is no reason to expect that nonvicinal participation by a 3-*O*-ester via a six-membered ring intermediate will be intrinsically more favorable than that of the 2-*O*-alkoxycarbonylmethyl ethers investigated here. Overall, the results argue that, consistent with

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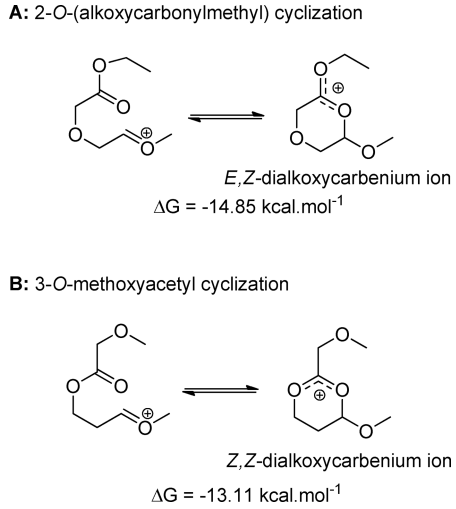
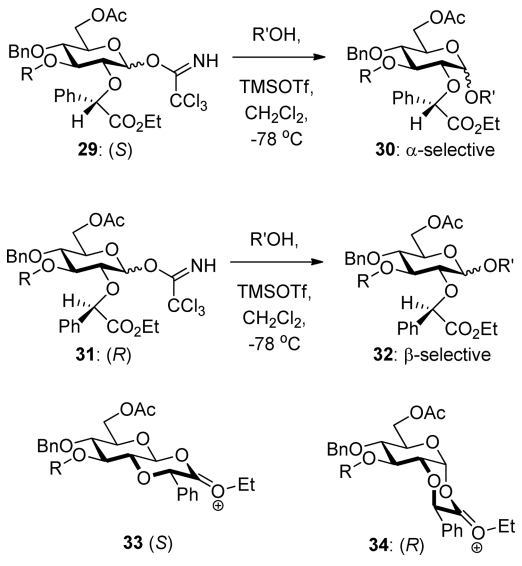


Figure 2. Two scenarios for participation by esters resulting in six-membered ring formation.

earlier work from our laboratory and in the absence of conformational predisposition as with axial esters at the 3-position,[47] effective stereodirecting participation by nonvicinal esters through the formation of six-membered intermediates is unlikely to be a serious contributing factor in glycosylation.

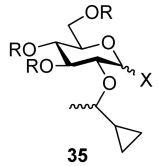
Boons and co-workers have described the influence of the 2-*O*-(ethoxycarbonylbenzyl) protecting group on the stereoselectivity of glucopyranosylation reactions with particular emphasis on participation and the role of the stereogenic center at the benzylic position.[65,71] Thus, the *S*-configured donors **29** were found to afford α-glucosides **30** selectively, while the *R*-configured diastereomers **31** gave the β-glucosides **32** selectively (Scheme 4). These results were rationalized in terms of participation by the ethoxycarbonylbenzyl group with preferential formation of *trans*- and *cis*-decalin-like intermediates **33** and **34** for the *S*- and *R*-series, respectively, so as to accommodate the phenyl group in an equatorial position

Scheme 4. Stereoselective Glucosylation with 2-*O*-(Ethoxycarbonylbenzyl) Protected Donors and the Structures of Possible Intermediates Arising from Participation[70,71]



(Scheme 4). Computations were advanced in support of this hypothesis.[65] In the *S*-series, the use of an ester protecting group for O3 (**29**, R = Ac, Bz, or Alloc) was essential for α-selectivity as ether protection at that position (**29**, R = allyl) gave less selective and even β-selective glucosylation depending on the acceptor employed. In the *R*-series, the dependence of selectivity on the 3-*O*-protecting group was less marked (**31**, R = Allyl, Ac, Bz, or Alloc).[65,71]

The apparent conflict between the clear absence of participation in the glycosylation reactions of donors **11**–**13** and the bridging intermediates **33** and **34** advanced[65,71] in explanation of the selectivities observed with donors **29** and **31**, respectively, may be reconciled in either of two ways. Thus, it is possible that the additional phenyl substituent in **29** and **31** promotes cyclization through conformational restriction in the manner of a Thorpe–Ingold or *gem*-dimethyl effect.[72] Alternatively, it is possible that **33** and **34** are not intermediates in the stereodetermining step in the glycosylation reactions of **29** and **31**, which is simply the result of differential shielding of the two faces of transient oxocarbenium ions formed on activation according to the chirality of the protecting group at the 2-position. In support of this latter hypothesis, Kumar and Whitfield have presented evidence for the influence of protecting group chirality in the anomeric selectivity of glycosylation reactions conducted with the nonparticipating 2-*O*-(1-cyclopropylethyl)-protected series of donors **35**.[73] We are unable to distinguish between the two possibilities on the basis of the data available.



35

R = Ac, Bn, X = $OC(=NH)CCl_3$, $OC(=NPh)CF_3$, SPh

CONCLUSION

The formation and isolation of cyclic products on employment of the 2-*O*-phenacyl and and 2-*O*-(*t*-butoxycarbonylmethyl) ethers in mannopyranosylation establishes that participation by the 2-*O*-(2-oxoalkyl) ether system through a six-membered cyclic intermediate is stereoelectronically feasible. Such participation is diminished when the phenacyl group carries strongly electron-withdrawing substituents. The absence of cyclic products and the high β-selectivities observed exclude participation by the ester function of 2-*O*-(methoxycarbonylmethyl) ethers in mannopyranosylation and argue against participation by simple esters at the 3-position of glycosyl donors. The selective deprotection of the 2-*O*-(bistrifluoromethyl)phenacyl and 2-*O*-(methoxycarbonylmethyl) ethers extends the possible use of these systems beyond that of simple mechanistic probes to potentially useful protecting groups in glycosylation reactions.

EXPERIMENTAL SECTION

General Experimental. All reactions were performed using oven-dried glassware under an atmosphere of argon. All reagents and solvents were purchased from commercial suppliers and were used without further purification unless otherwise specified. Chromatographic purifications were performed on silica gel (230–400 mesh) columns. Reactions were monitored by analytical thin-layer

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chromatography on precoated glass backed plates (w/UV 254) and visualized by UV irradiation (254 nm) or by staining with 25% H_2SO_4 in EtOH or ceric ammonium molybdate solution. Specific rotations were measured on an automatic polarimeter with a path length of 100 mm in the solvent specified. Concentrations are given in g/100 mL. High-resolution mass spectra (HRMS) were recorded with an electrospray ionization (ESI) source coupled to a time-of-flight (TOF) mass analyzer or with an electron impact (EI) source coupled to a TOF mass analyzer. ^{1}H, ^{13}C, and ^{19}F spectra were recorded on a 400, 500, or 600 MHz spectrometer. NMR solvents were used without purification. Chemical shifts are given in ppm (δ), and coupling constants (J) are given in Hz. Multiplicities are given as singlet (s), broad singlet (br s), doublet (d), triplet (t), doublet of doublets (dd), triplet of doublets (td), or multiplet (m).

2-[2′,4′-Bis(trifluoromethyl)phenyl]propene. A solution of 1-[2,4-bis(trifluoromethyl)phenyl]ethanone (50 mg, 0.20 mmol) in diethyl ether (0.5 mL) was added dropwise into a stirred solution of methylmagnesium iodide in diethyl ether (1 M, 1 mL, 1 mmol) under argon at rt. After being stirred at rt for 40 min, the reaction was quenched by adding 3 N HCl (1 mL) slowly. The resulting mixture was extracted with diethyl ether, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification (10% ethyl acetate/hexanes) afforded 2-[2′,4′-bis(trifluoromethyl)phenyl]propan-2-ol as a colorless oil (42 mg, 79%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03−8.00 (m, 1H), 7.83−7.71 (m, 2H), 1.71 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 129.4 (q, J = 33.5 Hz), 129.0, 128.3, 127.9 (q, J = 31.9 Hz), 125.3−124.9 (m), 124.0 (q, J = 273.5 Hz), 123.4 (q, J = 272.0 Hz), 73.6, 32.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ −54.66, −63.01. To a solution of 2-[2′,4′-bis(trifluoromethyl)phenyl]propan-2-ol (42 mg, 0.15 mmol) in benzene (1.5 mL) was added *p*-toluenesulfonic acid monohydrate (2.9 mg, 0.015 mmol) at rt. The mixture was then refluxed for 12 h before cooling to rt and concentration under reduced pressure. Chromatographic purification (hexanes) afforded the title compound as a colorless oil (30 mg, 76%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 5.32−5.28 (m, 1H), 4.93 (s, 1H), 2.09 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1, 142.1, 130.8, 129.5 (q, J = 33.2 Hz), 128.6 (q, J = 31.0 Hz), 128.2 (d, J = 3.9 Hz), 123.4 (q, J = 274.6 Hz, 2*CF_3), 123.5−123.1 (m), 117.0, 24.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.77, −62.86. HRMS (EI-TOF) m/z: calcd for $C_{11}H_8F_6$ ($[M]^{+\cdot}$), 254.0530; found, 254.0543.

1-(3-Bromoprop-1-en-2-yl)-2,4-bis(trifluoromethyl)benzene. A solution of 2-[2′,4′-bis(trifluoromethyl)phenyl]propene (84 mg, 0.33 mmol), *N*-bromosuccinimide (64 mg, 0.36 mmol), and azobis(isobutyronitrile) (5.4 mg, 0.03 mmol) in benzene (1.5 mL) was refluxed at 85 °C under argon for 2 h. After being cooled to rt, the reaction mixture was concentrated under reduced pressure. Chromatographic purification (hexanes) afforded the title compound as a colorless oil (93 mg, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 5.73 (s, 1H), 5.24 (s, 1H), 4.24 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0, 132.9, 132.8, 130.6 (q, J = 33.6 Hz), 129.1 (q, J = 30.9 Hz), 128.2 (d, J = 4.0 Hz), 123.6−123.2 (m), 123.30 (q, J = 274.0 Hz), 123.25 (q, J = 272.2 Hz), 122.1, 35.5 (d, J = 2.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.62, −62.97. HRMS (EI-TOF) m/z: calcd for $C_{11}H_7F_6Br$ ($[M]^{+\cdot}$), 331.9635; found, 331.9630 (1%); calcd for $C_{11}H_7F_6$ ($[M - Br^{\cdot}]^+$), 253.0452; found, 253.0447 (100%).

Phenyl 3-O-Benzyl-4,6-O-benzylidene-2-O-(2-phenylprop-2-en-1-yl)-1-thio-α-D-mannopyranoside (2). To a stirred solution of phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (500 mg, 1.1 mmol) in THF (1.5 mL) at 0 °C was added sodium hydride (58 mg, 60% suspension in mineral oil, 1.4 mmol). After the mixture was stirred at 0 °C for 30 min, a solution of 3-bromoprop-1-en-2-yl-benzene (284 mg, 1.4 mmol) in THF (0.4 mL) was added dropwise. The resulting mixture was stirred at rt for 48 h. After completion, ethyl acetate was added, and the reaction mixture was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification (6% ethyl acetate/hexanes) afforded the title compound as a colorless oil (588 mg, 94%): $[\alpha]^{21}_D$ +124.2 (*c* 3.12, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59−7.21 (m, 20H), 5.62 (s, 1H), 5.54 (s, 1H), 5.36 (d, J = 1.2 Hz, 2H), 5.32 (d, J = 1.2 Hz, 2H), 4.84 (d, J = 12.1 Hz, 1H), 4.72−4.63 (m, 2H), 4.57 (d, J = 13.0 Hz, 2H), 4.30−4.22 (m, 2H), 4.19 (dd, J = 10.2, 3.9 Hz, 1H), 4.09 (dd, J = 3.2, 1.4 Hz, 1H), 3.96 (dd, J = 9.5, 3.2 Hz, 1H), 3.85 (t, J = 9.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 144.1, 138.41, 138.39, 137.6, 133.7, 131.9, 131.7, 129.1, 128.9, 128.6, 128.40, 128.37, 128.3, 128.2, 127.9, 127.73, 127.66, 127.6, 126.8, 126.3, 126.1, 115.6, 101.5, 101.4, 87.3, 79.2, 77.6, 76.4, 73.2, 68.5, 65.4. HRMS (ESI-TOF) m/z: calcd for $C_{35}H_{34}O_5SNa$ ($[M + Na]^+$), 589.2025; found, 589.2025.

Phenyl 3-O-Benzyl-4,6-O-benzylidene-2-O-phenacyl-1-thio-α-D-mannopyranoside (5) and Phenyl 3-O-Benzyl-4,6-O-benzylidene-2-O-phenacyl-1-thio-α-D-mannopyranoside S-Oxide (8). O_3 was bubbled into a stirred solution of **2** (268 mg, 0.47 mmol) in DCM (10 mL) at −78 °C for 10 min until the appearance of a deep blue color. Ar was then bubbled through the solution for 15 min, before triphenylphosphine (373 mg, 1.42 mmol) was added and the reaction mixture was allowed to warm to rt. After being stirred at rt for a further 3 h, the mixture was concentrated. Chromatographic purification (14% ethyl acetate/hexanes) afforded the desired ketone product as a colorless oil (161 mg, 60%) $[\alpha]^{21}_D$ +102.2 (*c* 0.7, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86−7.82 (m, 2H), 7.59−7.55 (m, 1H), 7.53−7.25 (m, 17H), 5.99 (d, J = 1.4 Hz, 1H), 5.64 (s, 1H), 5.14−5.04 (m, 2H), 4.92 (d, J = 12.0 Hz, 1H), 4.70 (d, J = 11.9 Hz, 1H), 4.36−4.29 (m, 2H), 4.23 (dd, J = 10.3, 3.8 Hz, 1H), 4.08 (dd, J = 3.0, 1.4 Hz, 1H), 4.00 (dd, J = 9.6, 2.9 Hz, 1H), 3.91−3.87 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 196.5, 138.2, 137.5, 134.7, 133.59, 133.55, 131.5, 129.1, 128.9, 128.7, 128.4, 128.2, 127.81, 127.77, 127.7, 127.5, 126.1, 101.5, 87.9, 80.1, 79.4, 74.9, 73.7, 68.5, 65.3. HRMS (ESI-TOF) m/z: calcd for $C_{34}H_{32}O_6SNa$ ($[M + Na]^+$), 591.1817; found, 591.1790. Further elution (20% ethyl acetate/hexanes) gave the sulfoxide as a colorless oil (51 mg, 18%): $[\alpha]^{21}_D$ −26.4 (*c* 1.48, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75−7.70 (m, 2H), 7.63 (dd, J = 7.6, 1.9 Hz, 2H), 7.57−7.47 (m, 6H), 7.43−7.34 (m, 7H), 7.33−7.26 (m, 3H), 5.63 (s, 1H), 5.10 (d, J = 1.3 Hz, 1H), 5.08 (d, J = 17.4 Hz, 1H), 4.96 (d, J = 11.8 Hz, 1H), 4.88 (d, J = 17.1 Hz, 1H), 4.75 (d, J = 11.8 Hz, 1H), 4.38−4.32 (m, 2H), 4.31 (s, 1H), 4.26 (dd, J = 10.4, 4.9 Hz, 1H), 4.18 (td, J = 9.5, 4.8 Hz, 1H), 3.79 (t, J = 10.2 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 195.6, 141.4, 138.2, 137.2, 134.5, 133.5, 131.6, 129.4, 129.0, 128.6, 128.4, 128.3, 127.9, 127.8, 127.7, 126.1, 124.5, 101.7, 98.2, 78.3, 77.1, 75.8, 75.2, 74.0, 69.9, 68.3. HRMS (ESI-TOF) m/z: calcd for $C_{34}H_{32}O_7SNa$ ($[M + Na]^+$), 607.1766; found, 607.1765.

Compound 8 Was Also Prepared by mCPBA Oxidation of 5. To a stirred solution of **5** (104 mg, 0.18 mmol) in DCM (2 mL) at −78 °C under an argon atmosphere was added a solution of *m*CPBA (77%, 40.9 mg, 0.18 mmol) in DCM (1 mL) dropwise. After the mixture was stirred at this temperature for 3 h, saturated $NaHCO_3$ solution (1 mL) was added, and the mixture was then allowed to warm to rt. DCM (10 mL) was added, and the separated organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification (20% ethyl acetate/hexanes) afforded **8** (64.2 mg, 60%), which was identical to the above sample.

Phenyl 3-O-Benzyl-4,6-O-benzylidene-2-O-[2-(4′-trifluoromethyl)phenylprop-2-en-1-yl])-1-thio-α-D-mannopyranoside (3). To a stirred solution of 3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (100 mg, 0.22 mmol) in THF (0.5 mL) at 0 °C was added sodium hydride (13.3 mg, 60% suspension in mineral oil, 0.33 mmol). After the mixture was stirred at 0 °C for 20 min, a solution of 1-(3-bromoprop-1-en-2-yl)-4-(trifluoromethyl)benzene[1] (88.2 mg, 0.33 mmol) in THF (1.5 mL) was added dropwise. The resulting mixture was stirred at rt for 48 h. After the completion of reaction, ethyl acetate was added, then it was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification (6% ethyl acetate/hexanes) afforded the title compound as a colorless oil (109 mg, 78%): $[\alpha]^{21}_D$ +94.6 (*c* 0.95, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 8.1 Hz, 2H), 7.57−7.48 (m, 4H), 7.44−7.28 (m, 13H), 5.65 (s, 1H), 5.64 (s, 1H), 5.48 (s, 1H), 5.36 (d, J = 1.3 Hz, 1H), 4.91 (d, J = 11.9 Hz, 1H), 4.70

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(d, J = 11.9 Hz, 1H), 4.66 (d, J = 12.5 Hz, 1H), 4.58 (d, J = 12.6 Hz, 1H), 4.34−4.25 (m, 2H), 4.23 (dd, J = 10.3, 4.5 Hz, 1H), 4.11 (dd, J = 3.3, 1.4 Hz, 1H), 4.02 (dd, J = 9.3, 3.2 Hz, 1H), 3.87 (t, J = 9.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.0, 142.0, 138.3, 137.5, 133.6, 131.7, 129.8 (q, J = 32.3 Hz), 129.2, 128.9, 128.4, 128.2, 127.79, 127.76 (2 carbons), 126.7, 126.1, 125.3 (q, J = 3.9 Hz), 124.2 (q, J = 272.0 Hz), 117.8, 101.5, 87.2, 79.3, 78.0, 76.4, 73.5, 73.2, 68.5, 65.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.51. HRMS (ESI-TOF) m/z: calcd for $C_{36}H_{33}F_3O_5SNa$ ($[M + Na]^+$), 657.1898; found, 657.1901.

*Phenyl 3-O-Benzyl-4,6-O-benzylidene-2-O-(4′-trifluoromethylphenacyl)-1-thio-α-D-mannopyranoside (**6**) and Phenyl 3-O-Benzyl-4,6-O-benzylidene-2-O-(4′-trifluoromethylphenacyl)-1-thio-α-D-mannopyranoside S-Oxide (**9**).* O_3 was bubbled into a stirred solution of **3** (100 mg, 0.16 mmol) in DCM (4 mL) and methanol (1 mL) at −78 °C for 5 min until the appearance of a deep blue color. Ar was then bubbled through the solution for 15 min, before triphenylphosphine (124 mg, 0.47 mmol) was added and the reaction mixture was allowed to warm to rt. After being stirred at rt for a further 3 h, the mixture was concentrated. Chromatographic purification (14% ethyl acetate/hexanes) afforded the desired ketone product as a colorless oil (78 mg, 77%): $[\alpha]^{21}_D$ +72.7 (c 1.245, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 8.2 Hz, 2H), 7.56−7.46 (m, 4H), 7.44−7.28 (m, 11H), 5.91 (d, J = 1.4 Hz, 1H), 5.64 (s, 1H), 5.10−5.00 (m, 2H), 4.94 (d, J = 11.7 Hz, 1H), 4.70 (d, J = 11.8 Hz, 1H), 4.36 (td, J = 9.6, 4.7 Hz, 1H), 4.30 (t, J = 9.5 Hz, 1H), 4.26 (dd, J = 10.3, 4.7 Hz, 1H), 4.10 (dd, J = 3.0, 1.5 Hz, 1H), 4.04 (dd, J = 9.5, 3.0 Hz, 1H), 3.89 (t, J = 10.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.7, 138.1, 137.5, 137.4, 134.7 (q, J = 32.7 Hz), 133.5, 131.6, 129.2, 129.0, 128.5, 128.4, 128.2, 127.9, 127.8, 127.7, 126.1, 125.7 (q, J = 3.9 Hz), 123.5 (q, J = 272.7 Hz), 101.6, 87.8, 80.4, 79.5, 77.0, 75.2, 74.0, 68.5, 65.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.19. HRMS (ESI-TOF) m/z: calcd for $C_{35}H_{31}F_3O_6SNa$ ($[M + Na]^+$), 659.1691; found, 659.1662. Further elution (20% ethyl acetate/hexanes) gave the sulfoxide as a colorless oil (19 mg, 18%): $[\alpha]^{21}_D$ −10.4 (c 0.94, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85−7.81 (m, 2H), 7.63 (dd, J = 7.6, 1.8 Hz, 4H), 7.57−7.52 (m, 3H), 7.49 (dd, J = 7.7, 1.9 Hz, 2H), 7.41−7.33 (m, 5H), 7.32−7.26 (m, 3H), 5.62 (s, 1H), 5.03 (d, J = 16.9 Hz, 1H), 4.97 (s, 1H), 4.96 (d, J = 11.8 Hz, 1H), 4.84 (d, J = 16.9 Hz, 1H), 4.72 (d, J = 11.6 Hz, 1H), 4.33 (m, 3H), 4.25 (dd, J = 10.4, 4.9 Hz, 1H), 4.15 (td, J = 9.5, 4.9 Hz, 1H), 3.77 (t, J = 10.2 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 194.9, 141.5, 138.1, 137.2, 137.1, 134.7 (q, J = 32.8 Hz), 131.7, 129.4, 129.1, 128.4, 128.27, 128.26, 128.0, 127.9, 126.0, 125.6 (q, J = 3.7 Hz), 124.5, 123.4 (q, J = 272.7 Hz), 101.7, 98.1, 78.4, 77.1, 75.9, 75.5, 74.3, 69.9, 68.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.21. HRMS (ESI-TOF) m/z: calcd for $C_{35}H_{31}F_3O_7SNa$ ($[M + Na]^+$), 675.1640; found, 675.1640.

*Compound **9** Was Also Prepared by mCPBA Oxidation of **6**.* To a stirred solution of **6** (37 mg, 0.06 mmol) in DCM (0.8 mL) at −78 °C under argon atmosphere was added a solution of *m*CPBA (77%, 13.1 mg, 0.06 mmol) in DCM (0.4 mL) dropwise. After the mixture was stirred at this temperature for 4 h, saturated $NaHCO_3$ solution (1 mL) was added, and the mixture was then allowed to warm to rt. DCM (10 mL) was added, and the separated organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification (20% ethyl acetate/hexanes) afforded **9** (31.6 mg, 83%), which was identical to the above sample.

*Phenyl 3-O-Benzyl-4,6-O-benzylidene-2-O-[2-(2′,4′-bis-trifluoromethyl)phenylprop-2-en-1-yl])-1-thio-α-D-mannopyranoside (**4**).* To a solution of 3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (100 mg, 0.22 mmol) and tetrabutylammonium iodide (4.1 mg, 0.01 mmol) in DMF (0.8 mL) was added sodium hydride (13.4 mg, 60% suspension in mineral oil, 0.33 mmol) at 0 °C. After the mixture was stirred at this temperature for 30 min, a solution of 1-(3-bromoprop-1-en-2-yl)-2,4-bis(trifluoromethyl)benzene (97 mg, 0.29 mmol) in DMF (0.7 mL) was added dropwise. After that, the reaction mixture was stirred at rt for 6 h before it was diluted with ethyl acetate, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification (6% ethyl acetate/hexanes) afforded the title compound as a colorless oil (140 mg, 89%): $[\alpha]^{21}_D$ +80.5 (c 1.225, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 1.7 Hz, 1H), 7.61−7.53 (m, 3H), 7.53−7.29 (m, 14H), 5.72 (d, J = 1.5 Hz, 1H), 5.68 (s, 1H), 5.51 (d, J = 1.3 Hz, 1H), 5.22 (s, 1H), 4.94 (d, J = 11.8 Hz, 1H), 4.73 (d, J = 11.9 Hz, 1H), 4.40 (m, 2H), 4.35 (td, J = 9.7, 5.1 Hz, 1H), 4.29 (t, J = 10.0 Hz, 1H), 4.28 (dd, J = 10.2, 5.0 Hz, 1H), 4.10 (dd, J = 3.1, 1.4 Hz, 1H), 4.05 (dd, J = 9.7, 3.1 Hz, 1H), 3.90 (t, J = 10.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.0, 142.0, 138.2, 137.5, 133.6, 132.3, 131.8, 130.0 (q, J = 33.4 Hz), 129.3 (q, J = 30.7 Hz), 129.2, 129.0, 128.4, 128.3, 128.0 (d, J = 3.6 Hz), 127.89, 127.85, 127.8, 126.1, 123.43 (q, J = 274.1 Hz), 123.37 (q, J = 272.4 Hz), 123.4−123.0 (m), 118.8, 101.6, 87.0, 79.4, 79.3, 76.3, 74.0, 73.6, 68.6, 65.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.22, −62.81. HRMS (ESI-TOF) m/z: calcd for $C_{37}H_{32}F_6O_5SNa$ ($[M + Na]^+$), 725.1772; found, 725.1763.

*Phenyl 3-O-Benzyl-4,6-O-benzylidene-2-O-(2′,4′-bis-trifluoromethylphenacyl)-1-thio-α-D-mannopyranoside (**7**) and Phenyl 3-O-Benzyl-4,6-O-benzylidene-2-O-(2′,4′-bis-trifluoromethylphenacyl)-1-thio-α-D-mannopyranoside S-Oxide (**10**).* O_3 was bubbled into a stirred solution of **4** (124 mg, 0.18 mmol) in DCM (4 mL) and methanol (1 mL) at −78 °C for 15 min until the appearance of a deep blue color. Ar was then bubbled through the solution for 15 min, before triphenylphosphine (139 mg, 0.53 mmol) was added and the reaction mixture was allowed to warm to rt. After being stirred at rt for a further 1 h, the mixture was concentrated. Chromatographic purification (14% ethyl acetate/hexanes) afforded the desired ketone product as a colorless oil (25 mg, 20%): $[\alpha]^{21}_D$ +108.1 (c 0.67, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.76−7.71 (m, 1H), 7.54−7.27 (m, 16H), 5.71 (d, J = 1.5 Hz, 1H), 5.60 (s, 1H), 4.92 (d, J = 11.7 Hz, 1H), 4.83 (s, 2H), 4.69 (d, J = 11.7 Hz, 1H), 4.31 (td, J = 9.7, 4.8 Hz, 1H), 4.23 (dd, J = 10.6, 5.1 Hz, 1H), 4.18 (t, J = 9.7 Hz, 1H), 4.09 (dd, J = 3.0, 1.5 Hz, 1H), 4.02 (dd, J = 9.8, 2.9 Hz, 1H), 3.83 (t, J = 10.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.3, 140.4, 138.1, 137.4, 133.2, 132.7 (q, J = 33.8 Hz), 131.8, 129.2, 129.0, 128.62, 128.60 (q, J = 32.9 Hz), 128.5, 128.4, 128.2, 127.92, 127.90, 127.8, 126.0, 124.0−123.8 (m), 122.8 (q, J = 272.5 Hz), 122.7 (q, J = 274.5 Hz), 101.6, 88.0, 80.4, 79.6, 77.0, 76.7, 74.1, 68.5, 65.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.27, −63.17. HRMS (ESI-TOF) m/z: calcd for $C_{36}H_{30}F_6O_6SNa$ ($[M + Na]^+$), 727.1565; found, 727.1570. As well as sulfoxide product, further elution (20% ethyl acetate/hexanes) gave the sulfoxide as a colorless oil (69 mg, 54%): $[\alpha]^{21}_D$ −36.4 (c 0.963, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 1.6 Hz, 1H), 7.73 (dd, J = 8.0, 1.6 Hz, 1H), 7.65−7.47 (m, 7H), 7.45−7.23 (m, 9H), 5.61 (s, 1H), 4.97 (d, J = 11.6 Hz, 1H), 4.84 (d, J = 17.0 Hz, 1H), 4.82 (s, 1H), 4.74 (d, J = 11.5 Hz, 1H), 4.67 (d, J = 18.4 Hz, 1H), 4.38 (dd, J = 9.7, 3.2 Hz, 1H), 4.34 (dd, J = 3.3, 1.4 Hz, 1H), 4.27 (dd, J = 9.8, 4.2 Hz, 1H), 4.24 (t, J = 9.0 Hz, 1H), 4.18 (td, J = 9.5, 4.7 Hz, 1H), 3.75 (t, J = 10.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.8, 141.2, 140.2, 138.1, 137.1, 132.7 (q, J = 33.9 Hz), 131.8, 129.5, 129.1, 128.63 (d, J = 3.8 Hz), 128.57 (q, J = 33.4 Hz), 128.5, 128.33, 128.30, 128.1, 128.0, 126.0, 124.4, 124.0−123.7 (m), 122.7 (q, J = 264.5 Hz), 122.6 (q, J = 274.2 Hz), 101.7, 98.2, 78.5, 77.6, 77.1, 75.6, 74.4, 69.9, 68.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.32, −63.16. HRMS (ESI-TOF) m/z: calcd for $C_{36}H_{30}F_6O_7SNa$ ($[M + Na]^+$), 743.1514; found, 743.1486.

*Compound **10** Was Also Prepared by mCPBA Oxidation of **7**.* To a stirred solution of **7** (46 mg, 0.07 mmol) in DCM (1 mL) at −78 °C under argon atmosphere was added a solution of *m*CPBA (77%, 14.6 mg, 0.07 mmol) in DCM (0.5 mL) dropwise. After the mixture was stirred at this temperature for 4 h, saturated $NaHCO_3$ solution (1 mL) was added, and the mixture was then allowed to warm to rt. DCM (10 mL) was added, and the separated organic layer was washed with saturated $NaHCO_3$ solution once, brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification (20% ethyl acetate/hexanes) afforded **10** (39 mg, 83%), which was identical to the above sample.

*Phenyl 3-O-Benzyl-4,6-O-benzylidene-2-O-(methoxycarbonylmethyl)-1-thio-α-D-mannopyranoside (**11**).* To a stirred solution of 3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (100 mg, 0.22 mmol) in THF (0.8 mL) at 0 °C was added sodium hydride (13.3 mg, 60% suspension in mineral oil, 0.33 mmol). After the mixture was

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stirred at 0 °C for 25 min, a solution of methyl bromoacetate (51 mg, 0.33 mmol) in THF (0.2 mL) was added dropwise. The resulting mixture was stirred at rt for 5 h. After the completion of reaction, ethyl acetate was added, and then it was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification (14% ethyl acetate/hexanes) afforded the title compound as a colorless oil (89 mg, 78%): $[\alpha]^{21}_D$ +167.7 (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.7, 1.9 Hz, 2H), 7.50−7.46 (m, 2H), 7.35 (m, 11H), 5.86 (d, *J* = 1.5 Hz, 1H), 5.67 (s, 1H), 4.94 (d, *J* = 12.0 Hz, 1H), 4.75 (d, *J* = 12.0 Hz, 1H), 4.49−4.38 (m, 2H), 4.36−4.29 (m, 2H), 4.25 (dd, *J* = 10.3, 3.8 Hz, 1H), 4.09 (dd, *J* = 3.0, 1.5 Hz, 1H), 4.01 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.91 (t, *J* = 9.9 Hz, 1H), 3.72 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 138.2, 137.5, 133.6, 131.6, 129.2, 128.9, 128.5, 128.2, 127.8, 127.7, 127.6, 126.1, 101.5, 88.0, 80.4, 79.4, 77.31, 77.25, 77.1, 76.8, 76.7, 73.7, 69.4, 68.5, 65.3, 51.9. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{29}H_{30}O_7SNa$ ([M + Na]$^+$), 545.1610; found, 545.1622.

*Phenyl 3-O-Benzyl-4,6-O-benzylidene-2-O-(t-butoxycarbonylmethyl)-1-thio-α-D-mannopyranoside (**12**).* To a stirred solution of 3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (100 mg, 0.22 mmol) in THF (1.0 mL) at 0 °C was added sodium hydride (13.3 mg, 60% suspension in mineral oil, 0.33 mmol). After the mixture was stirred at 0 °C for 20 min, a solution of *tert*-butyl bromoacetate (65.0 mg, 0.33 mmol) in THF (0.4 mL) was added dropwise. The resulting mixture was stirred at rt for 5 h. After the completion of the reaction, ethyl acetate was added, and the reaction mixture was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification (8% ethyl acetate/hexanes) afforded the title compound as a colorless oil (75 mg, 60%): $[\alpha]^{21}_D$ +140.3 (*c* 1.21, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52−7.49 (m, 2H), 7.47−7.43 (m, 2H), 7.41−7.33 (m, 7H), 7.32−7.23 (m, 4H), 5.86 (d, *J* = 1.4 Hz, 1H), 5.64 (s, 1H), 4.92 (d, *J* = 12.0 Hz, 1H), 4.73 (d, *J* = 12.1 Hz, 1H), 4.33−4.25 (m, 4H), 4.24−4.21 (m, 1H), 4.03 (dd, *J* = 3.0, 1.5 Hz, 1H), 3.99−3.97 (m, 1H), 3.92−3.87 (m, 1H), 1.43 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.7, 138.3, 137.5, 133.7, 131.3, 129.1, 128.9, 128.4, 128.2, 127.72, 127.67, 127.5, 126.0, 101.5, 87.9, 81.8, 80.1, 79.4, 76.7, 73.6, 70.2, 68.5, 65.2, 28.1. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{32}H_{36}O_7SNa$ ([M + Na]$^+$), 587.2079; found, 587.2083.

*Phenyl 3-O-Benzyl-4,6-O-benzylidene-2-O-(methoxycarbonylmethyl)-1-thio-α-D-mannopyranoside S-Oxide (**13**) and Phenyl 3-O-Benzyl-4,6-O-benzylidene-2-O-(methoxycarbonylmethyl)-1-thio-α-D-mannopyranoside Sulfone (**15**).* To a stirred solution of **11** (104 mg, 0.20 mmol) in DCM (2 mL) at −78 °C under argon atmosphere was added a solution of *m*CPBA (77%, 44.4 mg, 0.20 mmol) in DCM (2 mL) dropwise. After the mixture was stirred at this temperature for 6 h, saturated $NaHCO_3$ solution (1 mL) was added, and the mixture was then allowed to warm to rt. DCM (10 mL) was added, and the separated organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification (33% ethyl acetate/hexanes) afforded the sulfoxide product as a colorless oil (70.2 mg, 66%). $[\alpha]^{21}_D$ −4.8 (*c* 0.15, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67−7.60 (m, 2H), 7.57 (dt, *J* = 4.7, 2.9 Hz, 3H), 7.54−7.48 (m, 2H), 7.45−7.30 (m, 8H), 5.65 (s, 1H), 4.97 (s, 1H), 4.96 (d, *J* = 10.7 Hz, 1H), 4.78 (d, *J* = 11.9 Hz, 1H), 4.40 (d, *J* = 16.9 Hz, 1H), 4.38−4.31 (m, 3H), 4.28 (d, *J* = 16.9 Hz, 1H), 4.27 (dd, *J* = 10.3, 4.9 Hz, 2H), 4.15 (td, *J* = 8.6, 7.5, 4.6 Hz, 1H), 3.80 (t, *J* = 10.2 Hz, 1H), 3.62 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 141.7, 138.1, 137.2, 131.7, 129.4, 129.0, 128.5, 128.3, 127.84, 127.81, 126.0, 124.5, 101.7, 98.2, 78.3, 76.7, 75.4, 74.0, 70.1, 69.9, 68.2, 51.8. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{29}H_{30}O_8SNa$ ([M + Na]$^+$), 561.1559; found, 561.1550. The sulfone **15** (20% ethyl acetate/hexanes) was also isolated as a colorless oil (35.4 mg, 32%): $[\alpha]^{21}_D$ +81.5 (*c* 0.15, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97−7.90 (m, 2H), 7.75−7.68 (m, 1H), 7.61 (t, *J* = 7.9 Hz, 2H), 7.54−7.47 (m, 2H), 7.43−7.29 (m, 8H), 5.62 (s, 1H), 5.33 (s, 1H), 4.97 (d, *J* = 11.7 Hz, 1H), 4.77 (d, *J* = 11.7 Hz, 1H), 4.63−4.53 (m, 2H), 4.48 (d, *J* = 17.1 Hz, 1H), 4.44 (dd, *J* = 10.1, 3.4 Hz, 1H), 4.39 (d, *J* = 17.1 Hz, 1H), 4.27 (t, *J* = 9.8 Hz, 1H), 4.15 (dd, *J* = 10.3, 4.9 Hz, 1H), 3.73 (s, 3H), 3.69 (t, *J* = 10.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 138.1, 137.3, 136.5, 134.4, 129.3, 129.0, 128.9, 128.5, 128.3, 127.88, 127.86, 126.1, 101.7, 93.6, 78.1 77.0, 74.8, 74.3, 70.6, 68.5, 68.4, 52.0. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{29}H_{30}O_9SNa$ ([M + Na]$^+$), 577.1508; found, 577.1510.

*Phenyl 3-O-Benzyl-4,6-O-benzylidene-2-O-(t-butoxycarbonylmethyl)-1-thio-α-D-mannopyranoside S-Oxide (**14**).* To a stirred solution of **12** (47 mg, 0.08 mmol) in DCM (1 mL) at −78 °C under argon atmosphere was added a solution of *m*CPBA (77%, 18.5 mg, 0.08 mmol) in DCM (0.5 mL) dropwise. After being stirred at this temperature for 3 h, saturated $NaHCO_3$ solution (1 mL) was added, and the mixture was then allowed to warm to rt. DCM (10 mL) was added, and the separated organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification (17% ethyl acetate/hexanes) afforded the sulfoxide product as a colorless oil (38.0 mg, 79%). $[\alpha]^{21}_D$ −9.0 (*c* 1.26, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.58 (m, 2H), 7.57−7.46 (m, 5H), 7.44−7.28 (m, 8H), 5.64 (s, 1H), 5.00 (d, *J* = 1.3 Hz, 1H), 4.94 (d, *J* = 12.0 Hz, 1H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.38−4.28 (m, 3H), 4.27 (d, *J* = 16.9 Hz, 1H), 4.25 (dd, *J* = 10.2, 4.9 Hz, 1H), 4.20−4.13 (m, 1H), 4.12 (d, *J* = 16.9 Hz, 1H), 3.79 (t, *J* = 10.1 Hz, 1H), 1.40 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 141.5, 138.2, 137.2, 131.5, 129.3, 129.0, 128.4, 128.2, 127.8, 127.7, 126.0, 124.5, 101.6, 98.1, 81.8, 78.3, 76.7, 75.4, 73.8, 70.8, 69.8, 68.2, 28.1. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{32}H_{36}O_8SNa$ ([M + Na]$^+$), 603.2029; found, 603.2015.

General Procedure I: Glycosylation with Thioglycosides. A mixture of glycosyl donor (1 equiv), diphenylsulfoxide or 1-benzenesulfinyl piperidine (1.1 equiv), tri-*tert*-butylpyrimidine (2 equiv), and activated 3 Å molecular sieves (2 g per mmol of donor) was stirred in dry DCM (13.3 mL per 1 mmol of donor) for 1 h at rt before it was cooled to −78 °C, and then trifluoromethanesulfonic anhydride (1.1 equiv) was added. After the mixture was stirred at the same temperature for 10 min, a solution of acceptor (1.5 equiv) in dry DCM (4.4 mL per 1 mmol of acceptor) was added dropwise. The resulting mixture was then stirred at −78 °C for 3 h before quenching with saturated $NaHCO_3$ solution at the same temperature. After being warmed to rt, the mixture was filtered and the filtrate was extracted with DCM, and the combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification afforded the product.

General Procedure II: Glycosylation with Sulfoxides. A mixture of glycosyl donor (1 equiv), tri-*tert*-butylpyrimidine (2 equiv), and activated 3 Å molecular sieves (2 g per mmol of donor) was stirred in dry DCM (13 mL per 1 mmol of donor) for 1 h at rt before it was cooled to −78 °C, and then trifluoromethanesulfonic anhydride (1.1 equiv) was added. After being stirred at the same temperature for 10 min, a solution of acceptor (1.5 equiv) in dry DCM (4.4 mL per 1 mmol of acceptor) was added dropwise. The resulting mixture was then stirred at −78 °C for 3 h before quenching with saturated aqueous $NaHCO_3$. After being warmed to rt, the mixture was filtered and the filtrate was extracted with DCM, and the combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification afforded the product.

*1-Adamantanyl 4,6-O-Benzylidene-2-O-(2′,4′-bis-trifluoromethylphenacyl)-3-O-benzyl-β-D-mannopyranoside (**20β**).* **20β** was obtained from **10** by following general procedure II, 10% ethyl acetate/hexanes, colorless oil (34.3 mg, 50%): $[\alpha]^{21}_D$ −31.0 (*c* 0.545, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.74 (d, *J* = 1.6 Hz, 2H), 7.51−7.45 (m, 2H), 7.42−7.27 (m, 8H), 5.53 (s, 1H), 5.01−4.84 (m, 2H), 4.83−4.71 (m, 3H), 4.25 (dd, *J* = 10.4, 4.8 Hz, 1H), 3.98 (t, *J* = 9.6 Hz, 1H), 3.87 (d, *J* = 3.1 Hz, 1H), 3.81 (t, *J* = 10.3 Hz, 1H), 3.64 (dd, *J* = 9.9, 3.1 Hz, 1H), 3.30 (td, *J* = 9.7, 4.8 Hz, 1H), 2.22−2.10 (m, 3H), 1.84−1.68 (m, 6H), 1.68−1.53 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.4, 140.8, 138.3, 137.5, 132.3 (q, *J* = 33.8 Hz), 129.4, 128.9, 128.6 (q, *J* = 33.8 Hz), 128.32, 128.26, 128.20, 127.8, 127.6, 126.0, 123.9−123.5 (m), 122.94 (q, *J* = 271.6 Hz), 122.87 (q, *J* = 274.2 Hz), 101.4, 94.8, 80.0, 78.4, 77.6, 77.4, 75.8, 72.6, 68.8, 67.2, 42.3, 36.1, 30.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.19,

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−63.12. HRMS (ESI-TOF) m/z: calcd for $C_{40}H_{40}F_6O_7Na$ ([M + Na]$^+$), 769.2576; found, 769.2543.

*1-Adamantanyl 3-O-Benzyl-4,6-O-benzylidene-2-O-(methoxycarbonylmethyl)-α-D-mannopyranoside (**21α**).* **21α** was obtained from **11** by following general procedure I using DPSO as activation agent, 14% ethyl acetate/hexanes, colorless oil (5.2 mg, 16%): $[\alpha]^{21}_D$ +60.4 (c 0.26, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (dd, J = 7.7, 1.6 Hz, 2H), 7.38−7.26 (m, 8H), 5.62 (s, 1H), 5.50 (d, J = 1.8 Hz, 1H), 4.90 (d, J = 11.9 Hz, 1H), 4.68 (d, J = 11.9 Hz, 1H), 4.41 (s, 2H), 4.21 (dd, J = 10.5, 5.1 Hz, 1H), 4.18 (t, J = 9.6 Hz, 1H), 4.03 (dd, J = 9.8, 3.2 Hz, 1H), 4.01 (td, J = 9.8, 4.8 Hz, 1H), 3.82 (t, J = 10.3 Hz, 1H), 3.71 (s, 3H), 3.68−3.66 (m, 1H), 2.13 (q, J = 3.3 Hz, 3H), 1.86−1.74 (m, 6H), 1.61 (q, J = 12.5 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.4, 138.7, 137.8, 128.7, 128.3, 128.1, 127.48, 127.47, 126.0, 101.3, 93.5, 80.3, 79.9, 77.0, 74.9, 73.8, 69.4, 68.9, 63.6, 51.7, 42.4, 36.2, 36.1, 30.7, 30.6. HRMS (ESI-TOF) m/z: calcd for $C_{33}H_{40}O_8Na$ ([M + Na]$^+$), 587.2621; found, 587.2595.

*1-Adamantanyl 3-O-Benzyl-4,6-O-benzylidene-2-O-(methoxycarbonylmethyl)-β-D-mannopyranoside (**21β**).* **21β** was obtained from **11** by following general procedure I using DPSO as activation agent, 20% ethyl acetate/hexanes, colorless oil (20.6 mg, 63%): $[\alpha]^{21}_D$ −33.8 (c 1.03, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50−7.46 (m, 2H), 7.46−7.25 (m, 8H), 5.58 (s, 1H), 4.86−4.78 (m, 2H), 4.76 (d, J = 0.9 Hz, 1H), 4.58−4.50 (m, 2H), 4.24 (dd, J = 10.4, 4.8 Hz, 1H), 4.18 (t, J = 9.6 Hz, 1H), 3.92−3.87 (m, 2H), 3.70 (s, 3H), 3.62 (dd, J = 9.9, 3.1 Hz, 1H), 3.30 (td, J = 9.7, 4.8 Hz, 1H), 2.14 (p, J = 3.3 Hz, 3H), 1.84−1.71 (m, 6H), 1.66−1.55 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 138.5, 137.7, 128.8, 128.24, 128.15, 127.6, 127.4, 126.0, 101.4, 94.8, 79.2, 78.1, 77.5, 75.5, 72.2, 70.0, 68.8, 67.4, 51.6, 42.3, 36.1, 30.6. HRMS (ESI-TOF) m/z: calcd for $C_{33}H_{40}O_8Na$ ([M + Na]$^+$), 587.2621; found, 587.2597.

*1,2-O-(2-Benzenesulfenyl-1-phenyl-1,2-ethenediyl)-3-O-benzyl-4,6-O-benzylidene-β-D-mannopyranose (**22**).* **22** was obtained from **5** by following general procedure I using DPSO as activation agent, 8% ethyl acetate/hexanes, colorless oil (7.8 mg, 33%): $[\alpha]^{21}_D$ −83.8 (c 0.185, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57−7.53 (m, 2H), 7.49−7.45 (m, 2H), 7.39−7.33 (m, 5H), 7.32−7.25 (m, 10H), 7.21−7.16 (m, 1H), 5.55 (s, 1H), 5.33 (d, J = 0.8 Hz, 1H), 4.76 (d, J = 12.3 Hz, 1H), 4.69 (d, J = 12.3 Hz, 1H), 4.43 (dd, J = 10.4, 4.8 Hz, 1H), 4.35 (d, J = 2.8 Hz, 1H), 4.17 (t, J = 9.5 Hz, 1H), 3.90 (t, J = 10.3 Hz, 1H), 3.81 (dd, J = 9.6, 2.9 Hz, 1H), 3.54 (td, J = 9.7, 4.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 140.1, 137.7, 137.2, 135.7, 132.9, 128.99, 128.96, 128.7, 128.6, 128.4, 128.2, 127.74, 127.71, 127.7, 127.4, 127.2, 126.04, 125.99, 101.6, 93.1, 77.8, 75.6, 72.7, 72.0, 68.4, 67.8. HRMS (ESI-TOF) m/z: calcd for $C_{34}H_{30}O_6SNa$ ([M + Na]$^+$), 589.1661; found, 589.1645.

*Methyl 4-O-[4,6-O-Benzylidene-2-O-(2′,4′-bis-trifluoromethylphenacyl)-3-O-benzyl-β-D-mannopyranosyl]-(1→4)-2,3-O-isopropylidene-α-L-rhamanopyranoside (**23β**).* **23β** was obtained from **10** by following general procedure II, 17% ethyl acetate/hexanes, colorless oil (19.3 mg, 57%): $[\alpha]^{21}_D$ −73.4 (c 0.535, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.49−7.44 (m, 2H), 7.40−7.26 (m, 8H), 5.50 (s, 1H), 4.96 (d, J = 0.8 Hz, 1H), 4.83 (s, 1H), 4.81−4.75 (m, 2H), 4.78 (d, J = 12.2 Hz, 1H), 4.70 (d, J = 12.1 Hz, 1H), 4.24 (dd, J = 10.4, 4.8 Hz, 1H), 4.11 (dd, J = 7.4, 5.5 Hz, 1H), 4.07 (d, J = 5.5 Hz, 1H), 3.97 (d, J = 3.0 Hz, 1H), 3.88 (t, J = 9.6 Hz, 1H), 3.80 (t, J = 10.3 Hz, 1H), 3.65 (dd, J = 9.8, 3.0 Hz, 1H), 3.58 (dd, J = 10.0, 7.4 Hz, 1H), 3.55−3.48 (m, 1H), 3.36 (s, 3H), 3.26 (td, J = 9.8, 4.9 Hz, 1H), 1.47 (s, 3H), 1.32 (s, 3H), 1.17 (d, J = 6.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 200.5, 140.9, 138.1, 137.3, 132.3 (q, J = 33.8 Hz), 129.1, 128.9, 128.7 (q, J = 33.4 Hz), 128.4, 128.20, 128.18, 127.8, 127.7, 126.0, 123.7−123.5 (m), 122.9 (q, J = 272.9 Hz), 122.8 (q, J = 273.9 Hz), 109.4, 101.4, 99.7, 97.8, 78.81, 78.79, 78.21, 78.17, 77.7, 77.3, 76.1, 72.9, 68.6, 67.4, 63.9, 54.8, 27.8, 26.4, 17.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.27, −63.10. HRMS (ESI-TOF) m/z: calcd for $C_{40}H_{42}F_6O_{11}Na$ ([M + Na]$^+$), 835.2529; found, 835.2495.

*Methyl 4-O-[4,6-O-Benzylidene-2-O-(methoxycarbonylmethyl)-3-O-benzyl-β-D-mannopyranosyl]-(1→4)-2,3-O-isopropylidene-α-L-rhamnopyranoside (**24β**).* **24β** was obtained from **11** by following general procedure I (50.1 mg, 83%) and from **13** by following general procedure II (26.8 mg, 85%), 20% ethyl acetate/hexanes, colorless oil: $[\alpha]^{21}_D$ −60.7 (c 1.045, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50−7.46 (m, 2H), 7.41−7.25 (m, 8H), 5.60 (s, 1H), 4.98 (s, 1H), 4.84 (s, 1H), 4.84−4.78 (m, 2H), 4.48−4.39 (m, 2H), 4.25 (dd, J = 10.4, 4.8 Hz, 1H), 4.18 (t, J = 9.6 Hz, 1H), 4.14 (dd, J = 7.0, 5.5 Hz, 1H), 4.07 (d, J = 5.5 Hz, 1H), 4.03 (d, J = 3.0 Hz, 1H), 3.94 (t, J = 10.3 Hz, 1H), 3.70 (s, 3H), 3.67−3.58 (m, 3H), 3.36 (s, 3H), 3.30 (td, J = 9.8, 4.9 Hz, 1H), 1.48 (s, 3H), 1.31 (s, 3H), 1.30 (d, J = 5.8 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.7, 138.4, 137.5, 128.8, 128.3, 128.2, 127.6, 127.5, 126.0, 109.4, 101.4, 99.8, 97.8, 78.3, 78.2, 77.9, 77.8, 77.5, 76.1, 72.3, 69.8, 68.5, 67.7, 64.0, 54.8, 51.7, 27.8, 26.4, 17.6. HRMS (ESI-TOF) m/z: calcd for $C_{33}H_{42}O_{12}Na$ ([M + Na]$^+$), 653.2574; found, 653.2559.

*Methyl 4-O-[4,6-O-Benzylidene-2-O-(t-butoxycarbonylmethyl)-3-O-benzyl-β-D-mannopyranosyl]-(1→4)-2,3-O-isopropylidene-α-L-rhamnopyranoside (**25β**).* To a stirred solution of **28** (15.3 mg, 0.027 mmol) in THF (0.4 mL) at 0 °C was added sodium hydride (1.7 mg, 60% suspension in mineral oil, 0.04 mmol). After being stirred at 0 °C for 25 min, a solution of *tert*-butyl bromoacetate (8.0 mg, 0.04 mmol) in THF (0.2 mL) was added dropwise. The resulting mixture was stirred at rt for 3 h. After the completion of reaction, ethyl acetate was added, and the reaction mixture was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification (17% ethyl acetate/hexanes) afforded the title compound as a colorless oil (11.6 mg, 63%): $[\alpha]^{21}_D$ −56.6 (c 0.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.47 (m, 2H), 7.45−7.23 (m, 8H), 5.61 (s, 1H), 4.97 (s, 1H), 4.86 (s, 1H), 4.83 (s, 2H), 4.35−4.26 (m, 2H), 4.28−4.18 (m, 2H), 4.16 (dd, J = 7.1, 5.4 Hz, 1H), 4.08 (dd, J = 5.5, 0.7 Hz, 1H), 4.06 (d, J = 3.0 Hz, 1H), 3.94 (t, J = 10.3 Hz, 1H), 3.70−3.59 (m, 3H), 3.37 (s, 3H), 3.30 (td, J = 9.8, 4.8 Hz, 1H), 1.49 (s, 3H), 1.47 (s, 9H), 1.33 (s, 3H), 1.31 (d, J = 5.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 138.6, 137.6, 128.8, 128.3, 128.2, 127.6, 127.4, 126.0, 109.4, 101.3, 100.0, 97.8, 81.1, 78.30, 78.25, 77.8, 77.6, 77.5, 76.1, 72.1, 70.0, 68.6, 67.7, 64.1, 54.9, 28.1, 27.8, 26.4, 17.6. HRMS (ESI-TOF) m/z: calcd for $C_{36}H_{48}O_{12}Na$ ([M + Na]$^+$), 695.3043; found, 695.3026. Compound **25β** was also obtained from **14** by following general procedure II (1.2 mg, 3%).

*Methyl 2,3,6-Tri-O-benzyl-4-O-[4,6-O-benzylidene-2-O-(methoxycarbonylmethyl)-3-O-benzyl-α-D-mannopyranosyl]-(1→4)-α-D-glucopyranoside (**26α**).* **26α** was obtained from **11** by following general procedure I, 20% ethyl acetate/hexanes, colorless oil (23.9 mg, 24%): $[\alpha]^{21}_D$ +26.7 (c 0.375, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50−7.44 (m, 2H), 7.40−7.21 (m, 23H), 5.60 (s, 1H), 5.38 (d, J = 1.8 Hz, 1H), 5.06 (d, J = 11.4 Hz, 1H), 4.78 (d, J = 12.0 Hz, 1H), 4.69 (d, J = 12.1 Hz, 1H), 4.63−4.57 (m, 4H), 4.56 (d, J = 12.1 Hz, 1H), 4.50 (d, J = 11.9 Hz, 1H), 4.23 (t, J = 9.3 Hz, 1H), 4.13 (d, J = 16.6 Hz, 1H), 4.09 (dd, J = 9.2, 3.6 Hz, 1H), 3.92−3.77 (m, 6H), 3.73 (t, J = 2.4 Hz, 1H), 3.70 (m, 3H), 3.57 (s, 3H), 3.55 (dd, J = 9.1, 3.4 Hz, 1H), 3.38 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 138.7, 138.4, 137.9, 137.8, 137.6, 128.8, 128.5, 128.4, 128.3 (2 carbons), 128.14, 128.13, 128.0, 127.7, 127.59, 127.56, 127.55, 127.45, 126.9, 126.0, 102.2, 101.4, 97.8, 81.2, 80.0, 79.3, 79.2, 77.9, 76.2, 75.2, 73.6, 73.5, 73.2, 69.7, 69.3, 68.8, 68.7, 64.9, 55.3, 51.6. HRMS (ESI-TOF) m/z: calcd for $C_{51}H_{56}O_{13}Na$ ([M + Na]$^+$), 899.3619; found, 899.3608.

*Methyl 2,3,6-Tri-O-benzyl-4-O-[4,6-O-benzylidene-2-O-(methoxycarbonylmethyl)-3-O-benzyl-β-D-mannopyranosyl]-(1→4)-α-D-glucopyranoside (**26β**).* **26β** was obtained from **11** by following general procedure I (35.6 mg, 42%) and from **13** by following general procedure II (30.3 mg, 59%), 25% ethyl acetate/hexanes, colorless oil: $[\alpha]^{21}_D$ −14.7 (c 0.32, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51−7.47 (m, 2H), 7.47−7.42 (m, 2H), 7.42−7.23 (m, 20H), 7.19 (ddd, J = 8.8, 6.0, 3.1 Hz, 1H), 5.53 (s, 1H), 5.01 (d, J = 10.6 Hz, 1H), 4.85−4.76 (m, 3H), 4.72−4.63 (m, 3H), 4.62 (d, J = 3.7 Hz, 1H), 4.46−4.31 (m, 4H), 4.11 (t, J = 9.6 Hz, 1H), 4.03 (dd, J = 10.4, 4.8 Hz, 1H), 3.92 (t, J = 9.2 Hz, 1H), 3.87 (t, J = 9.1 Hz, 1H), 3.75 (d, J = 3.0 Hz, 1H), 3.74−3.60 (m, 6H), 3.58−3.50 (m, 2H), 3.40 (s, 3H), 3.33 (dd, J = 9.9, 3.0 Hz, 1H), 3.03 (td, J = 9.7, 4.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 139.3, 138.5, 138.3, 137.6, 137.5, 128.9, 128.6, 128.4, 128.3, 128.2, 128.14, 128.12, 128.07, 128.05, 127.82, 127.76, 127.6,

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127.4, 127.3, 126.1, 101.33, 101.26, 98.4, 80.2, 79.1, 78.3, 78.1, 77.8, 77.3, 75.3, 73.63, 73.60, 72.5, 69.9, 69.5, 68.5, 68.4, 67.4, 55.4, 51.6. HRMS (ESI-TOF) m/z: calcd for $C_{51}H_{56}O_{13}Na$ ([M + Na]$^+$), 899.3619; found, 899.3586.

1,2-O-(1-Oxo-ethanediyl)-3-O-benzyl-4,6-O-benzylidene β-D-Mannopyranose (27). **27** was obtained from **14** by following general procedure II (18.1 mg, 70%), 20% ethyl acetate/hexanes, colorless oil: $[\alpha]^{21}_D$ −24.8 (c 0.31, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.44−7.28 (m, 8H), 5.62 (s, 1H), 5.28 (s, 1H), 4.92 (d, J = 12.4 Hz, 1H), 4.76 (d, J = 12.4 Hz, 1H), 4.60 (d, J = 17.8 Hz, 1H), 4.37 (dd, J = 10.5, 4.9 Hz, 1H), 4.30 (d, J = 17.8 Hz, 1H), 4.16 (t, J = 9.6 Hz, 1H), 3.98 (d, J = 3.2 Hz, 1H), 3.90 (t, J = 10.3 Hz, 1H), 3.80 (dd, J = 9.7, 3.2 Hz, 1H), 3.44 (td, J = 9.7, 4.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 137.4, 137.0, 129.1, 128.6, 128.3, 128.2, 128.1, 126.0, 101.7, 96.2, 77.6, 75.1, 73.4, 71.4, 68.1, 67.6, 65.3. HRMS (ESI-TOF) m/z: calcd for $C_{22}H_{22}O_7Na$ ([M + Na]$^+$), 421.1263; found, 421.1280.

Reductive Removal of Phenacyl-Type Protecting Groups Using SmI_2. *Methyl 4-O-[4,6-O-Benzylidene-3-O-benzyl-β-D-mannopyranosyl]-(1→4)-2,3-O-isopropylidene-α-L-rhamnopyranoside (28).* A solution of SmI_2 in THF (0.1 M in THF, 0.66 mL, 0.07 mmol) was added to a round-bottom flask containing **23β** (10.7 mg, 0.01 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C for 10 min before it was quenched by adding saturated $NaHCO_3$ solution (1 mL) at 0 °C. The resulting mixture was diluted with ethyl acetate and washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification (33% ethyl acetate/hexanes) afforded the title compound as a colorless oil (5.5 mg, 75%), whose spectral data were identical to the literature values.[74] $[\alpha]^{21}_D$ −40.7 (c 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, J = 7.6, 2.1 Hz, 2H), 7.42−7.27 (m, 8H), 5.61 (s, 1H), 5.02 (d, J = 1.1 Hz, 1H), 4.86 (s, 1H), 4.85 (d, J = 12.4 Hz, 1H), 4.79 (d, J = 12.4 Hz, 1H), 4.29 (dd, J = 10.5, 4.9 Hz, 1H), 4.22−4.11 (m, 3H), 4.10 (t, J = 5.5 Hz, 1H), 3.90 (t, J = 10.3 Hz, 1H), 3.73−3.62 (m, 3H), 3.36 (s, 3H), 3.33 (dt, J = 9.8, 4.9 Hz, 1H), 1.51 (s, 3H), 1.33 (s, 3H), 1.30 (d, J = 5.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9, 137.4, 128.9, 128.4, 128.2, 127.8 (2 carbons), 126.0, 109.4, 101.5, 98.7, 97.8, 78.5, 78.23, 78.20, 76.8, 76.1, 72.4, 70.0, 68.6, 67.0, 63.9, 54.8, 27.8, 26.4, 17.5. HRMS (ESI-TOF) m/z: calcd for $C_{30}H_{38}O_{10}Na$ ([M + Na]$^+$), 581.2363; found, 581.2370.

Oxidative Removal of the Methoxycarbonylmethyl Protecting Group Using (1*S*)-(+)-(10-Camphorsulfonyl)oxaziridine. THF (0.3 mL) was added to a solution of KHMDS in toluene (0.5 M, 0.17 mL, 0.09 mmol) at −78 °C under argon. To the resulting mixture was added a solution of **24β** (34.4 mg, 0.06 mmol) in THF (0.45 mL) dropwise over 15 min. After the mixture was stirred at the same temperature for 30 min, (1*S*)-(+)-(10-camphorsulfonyl)-oxaziridine (39.3 mg, 0.17 mmol) was added in one portion, and the reaction mixture was stirred at −78 °C for another 1 h before it was quenched with saturated $NaHCO_3$ solution (1 mL). After being warmed to rt, the mixture was diluted with ethyl acetate and washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification (33% ethyl acetate/hexanes) afforded the title compound as a colorless oil (19.6 mg, 64%).

COMPUTATIONAL METHODS

Geometry optimization of all four structures was performed using density functional theory (DFT) Becke's three-parameter hybrid function with the nonlocal correlation of Lee−Yang−Parr (B3LYP) method in the gas phase.[66−69] The corresponding harmonic vibrational frequencies were computed at the same level of theory to characterize them as minima (no imaginary frequencies) with the help of the Gaussian 09W package program.[70] All of the above calculations were done using the 6-31+G(d,p) basis set.[75−78] The Gibbs free energy differences reported include thermal correction at the B3LYP/6-31+G(d,p) level of theory. All of the structures were built using GaussView 5.0.9.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02203.

Full experimental details, copies of ^{1}H and ^{13}C NMR spectra for all new compounds, and Cartesian coordinates and total electronic energies for computed structures (PDF)

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Notes

The authors declare no competing financial interest.

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