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β-Directing Effect of Electron-Withdrawing Groups at *O*-3, *O*-4, and *O*-6 Positions and α-Directing Effect by Remote Participation of 3-*O*-Acyl and 6-*O*-Acetyl Groups of Donors in Mannopyranosylations

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Abstract: Mannosylations of various acceptors with donors possessing an electron-withdrawing *o*-trifluoromethylbenzenesulfonyl, benzylsulfonyl, *p*-nitrobenzoyl, benzoyl, or acetyl group at *O*-3, *O*-4, or *O*-6 positions were found to be β-selective except when donors had 3-*O*-acyl and 6-*O*-acetyl groups, which afforded α-mannosides as major products. The α-directing effect of 3-*O*-acyl and 6-*O*-acetyl groups was attributed to their remote participation, and the isolation of a stable bicyclic trichlorooxazine ring resulting from the intramolecular trapping of the anomeric oxocarbenium ion by 3-*O*-trichloroacetimidoyl group provided evidence for this remote participation. The triflate anion, counteranion of the mannosyl oxocarbenium ion, was essential for the β-selectivity, and covalent α-mannosyl triflates with an electron-withdrawing group at *O*-3, *O*-4, or *O*-6 were detected by low-temperature NMR. The strongly electron-withdrawing sulfonyl groups, which exhibited a higher β-directing effect in the mannosylation, made the α-mannosyl triflates more stable than the weakly electron-withdrawing acyl groups. We therefore proposed the mechanism for the β-mannosylation and the origin of the β-directing effect: the electron-withdrawing groups would stabilize the α-mannosyl triflate intermediate, and the subsequent reaction of the α-triflate (or its contact ion pair) with the acceptor would afford the β-mannoside. The β-selective mannosylation of a sterically demanding acceptor was achieved by employing a donor possessing two strongly electron-withdrawing benzylsulfonyl groups at *O*-4 and *O*-6 positions.

Introduction

The development of stereoselective glycosylation methodologies has attracted a great deal of attention over the past decade due to the important roles of complex oligosaccharides in many fundamental life-sustaining processes.[1] Although there are many methods for the stereoselective formation of glycosyl linkages,[2] the stereoselective construction of the 1,2-*cis*-β-D-mannopyranosyl linkage still poses a great challenge, while the formation of the 1,2-*trans*-α-mannosyl bond is relatively straightforward, utilizing neighboring group participation.[3] Several innovative strategies for β-mannopyranosylation have been developed,[4] including a method using mannosyl halides with silver salt promoters[5] and the indirect intramolecular aglycon delivery approach.[6] Recently, Crich and co-workers have made a significant breakthrough in β-mannoside synthesis by employing 4,6-*O*-benzylidene-protected mannopyranosyl sulfoxides or thiomannopyranosides as mannosyl donors.[7] The 4,6-*O*-acetal effect on the construction of β-mannosyl linkages was further demonstrated with other mannosyl donors by us[8,9] and other

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workers.[10] A combination of torsional and electronic disarming effects was ascribed to the stereoselectivity in the 4,6-*O*-benzylidene directed β-mannosylation: the benzylidene acetal disarms the donor not only by raising the activation barrier by opposing the flattening that is required in the oxocarbenium ion[11] but also by restricting the C5−C6 bond to the most electron-withdrawing *tg* conformer.[12] On the other hand, Schuerch and co-workers reported earlier that a nonparticipating, strongly electron-withdrawing group such as the alky or aryl sulfonyl group at *O*-2 in the mannosyl donor led to the preferential formation of the β-mannopyranoside.[13] Recently, the scope and limitation of Schuerch's selective β-mannosylation were further investigated, and explanations for the β-selectivity were provided by Schmidt and Crich. Schmidt and co-workers reported that mannosylations of one acceptor with three 2-*O*-benzylsulfonly mannosyl donors were β-selective and proposed that the strong dipole produced by the *O*-2 sulfonyl group would favor the formation of the mannosyl oxocarbenium ion in a twist-boat conformation over the half-chair conformation, and that the twist-boat oxocarbenium ion intermediate would be preferentially attacked by the acceptor from the β-side.[14] Crich and colleagues reported that with 2-*O*-sulfonyl-thiomannosides as donors, mannosylations of less hindered alcohols were β-selective, but those of sterically demanding glucose 4-OH gave α-mannosides as major products. They reasoned that the electron-withdrawing effect of the *O*-2 sulfonyl group would destabilize the oxocarbenium ion, thereby shifting the equilibrium toward a covalent α-mannosyl triflate, which would react with an acceptor to generate the β-mannoside.[15] However, the effect on the mannosylation stereochemistry of nonparticipating, strongly electron-withdrawing protective groups at the *O*-3, *O*-4, or *O*-6 positions of the donors has not been addressed. However, the β-directing effects of the *O*-4-benzylsulfonyl group in D-olivose (2,6-dideoxy-D-*arabino*-hexose) and D-oliose (2,6-dideoxy-D-*lyxo*-hexose) donors,[16] of the *C*-5-carboxylate ester group in D-mannuronate donors,[17] and of the *C*-6-fluorine in 6-fluoro-D-rhamnose donors[18] have been investigated. The origin of the β-selectivity was ascribed to the reaction of the glycosyl oxocarbenium ion intermediate of the $^3H_4$ conformation with the acceptor, in the case of the mannuronates,[19] and to the reaction of the α-glycosyl triflate intermediates with the acceptor, in the case of the fluoro sugars.[18] In this study, we investigated the directing effect of electron-withdrawing protecting groups at *O*-3, *O*-4, and *O*-6 positions of mannosyl donors on the outcome of the stereochemistry in mannosylations. We were also interested in the magnitude of the directing effect by each of the groups at *O*-3, *O*-4, and *O*-6 of mannosyl donors, because their distances from the anomeric center are different and all of them are in remote position from the anomeric center as compared to groups at *O*-2. Ley's work on quantification of the deactivating effect of electron-withdrawing protective groups at each position of thiomannoside donors in mannosylations indicates that the electron-withdrawing benzoyl group at *O*-2 is more deactivating than benzoyl groups at other positions, and thus the influence of the positions is in the order of 2 > 6 > 4 > 3.[20]

When the electron-withdrawing, potentially participating protective groups are present at *O*-3, *O*-4, and *O*-6 of mannosyl donors, it is difficult to distinguish the electron-withdrawing effect from the effect of remote participation of the protective groups on the outcome of the stereochemistry in the mannosylation. In mannosylations with donors possessing electron-withdrawing, participating groups at *O*-3 and *O*-6, remote participation and electron-withdrawing would have opposite effects on the outcome of the stereochemistry: the α-mannoside would be favored by the remote participation, while the β-mannoside might be formed preferentially by the electron-withdrawing effect, if the electron-withdrawing effect is β-directing. On the other hand, in mannosylations with donors possessing electron-withdrawing, participating groups at *O*-4, both effects would contribute to the generation of the β-mannoside if the electron-withdrawing effect is β-directing. Although numerous examples for mannosylations with electron-withdrawing, potentially participating groups at *O*-3, *O*-4, and *O*-6 of donors can be found in the literature, most of them do not provide any information on remote participation, and only a handful of reports discuss the remote participation of the protective groups in mannosylations. There have been reports both opposed to and in favor of the remote participation by *O*-3 acyl groups of mannosyl donors. Thus, van Boeckel and colleagues oppose the remote participation of the 3-*O*-acetyl group in mannosylations, even though mannosylation with a donor bearing the 3-*O*-acetyl group afforded more α-mannoside than that with the corresponding donor bearing the 3-*O*-benzyl group. Their reasoning was that mannosylations with donors with the 3-*O*-acetyl group afforded almost the same ratio of the α- and β-mannosides as mannosylations with donors with the 3-*O*-trichloroacetyl group, which they believed to be a poor participating group.[21] Reports by Crich and co-workers supported the participation by the 3-*O*-benzoyl and 3-*O*-chloroactyl groups of mannosyl donors, because mannosylation with them resulted in predominantly α-anomers.[22] Contradictory views are also found in discussions of the remote participation by the 4-*O*-acyl and 4-*O*-thiocarbamoyl groups of mannosyl donors. Thus, van Boeckel and colleagues are opposed to the remote participation of 4-*O*-acetyl group based on the same argument as that for the 3-*O*-acetyl group.[21] Demchenko and co-workers, on the

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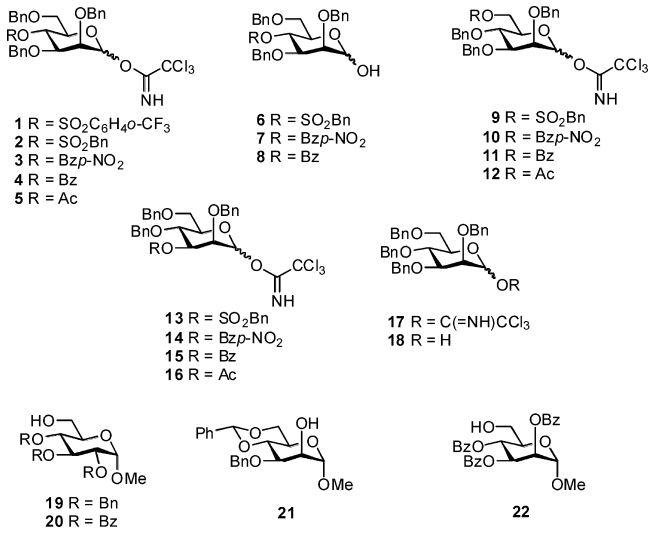

Figure 1. Mannosyl donors and acceptors.

other hand, argued that β-selective mannosylations with donors bearing a *p*-methoxybenzoyl and a thiocarbamoyl groups at *O*-4 could be attributed to the remote participation of the groups at *O*-4.[23] Reports on the potential participation by *O*-6 protective groups of mannosyl donors are rare, but there have been reports both in favor of and opposed to the participation by *O*-6 protective groups of glucosyl and galactosyl donors.[24] Recently, Crich and co-workers performed a trapping experiment of the bridging dioxocarbenium ion intermediates resulting from possible neighboring group participation by nonvicinal esters of donors in glycosylations and concluded that neighboring group participation from 3-*O*-equatorial, 4-*O*-axial and -equatorial, and 6-*O*-positions does not occur under typical glycosylation conditions.[25] This result suggests that no remote participations occur by acyl groups at *O*-3, *O*-4, and *O*-6 of donors in mannosylations. These results and evidence on the potential remote participation by the electron-withdrawing groups in mannosyl donors are contradictory, somewhat confusing, and not at all conclusive.

The earlier reports on the β-directing effect and the potential remote participation by electron-withdrawing groups of donors on the mannosylation stereochemistry suggest the following questions: (1) Do electron-withdrawing protective groups at *O*-3, *O*-4, and *O*-6 of donors also enhance the β-selectivity in the mannosylation like those at *O*-2? (2) If so, what makes the electron-withdrawing groups facilitate the formation of β-mannosides and what is the reactive intermediate? (3) Are acyl protective groups at *O*-3, *O*-4, and *O*-6 of donors involved in the remote participation in mannosylations? To address these questions, a systematic study was required, which could also lead to the development of a new method for the synthesis of β-mannosides. Therefore, we designed mannosyl donors **1**−**16**, bearing a nonparticipating or potentially participating, electron-withdrawing protective group at the *O*-3, *O*-4, or *O*-6 positions, as shown in Figure 1. *o*-Trifluoromethylbenzenesulfonyl and benzylsulfonyl groups were selected as nonparticipating, strongly electron-withdrawing protective groups, and *p*-nitrobenzoyl, benzoyl, and acetyl groups were chosen as potentially participating, weakly electron-withdrawing protective groups. For comparison purposes, tetra-*O*-benzyl-mannosyl trichloroacetimidate **17** and tetra-*O*-benzyl-mannose **18** were selected as standard donors bearing no electron-withdrawing groups. Primary hydroxy sugars **19**, **20**, and **22** and a secondary hydroxy sugar **21** were chosen as acceptors as shown in Figure 1. Mannosylations were carried out with mannosyl trichloroacetimidates **1**−**5** and **9**−**16** using TMSOTf as a promoter[26] and with anomeric hydroxy sugars **6**−**8** using phthalic anhydride/Tf_2O as promoters.[9] Here, we report the results of mannosylations of various acceptors with donors **1**−**18**, which support the β-directing effect of nonparticipating, electron-withdrawing groups and the α-directing effect by the remote participation of some acyl groups at *O*-3 and *O*-6 of donors. We also detected α-mannosyl triflate intermediates by low-temperature NMR and isolated a bridging bicyclic compound as evidence for remote participation.

Results and Discussion

Synthesis of Mannosyl Donors and Mannosylation Conditions. Introduction of electron-withdrawing groups (EWGs) to donors was achieved by sulfonylation and acylation of the hydroxy group at the *O*-3, *O*-4, or *O*-6 position of allyl tri-*O*-benzyl-mannosides. The resulting fully protected allyl mannosides were converted into mannosyl trichloroacetimidates **1**−**5** and **9**−**16** by deallylation with $PdCl_2$ in methanol, followed by the reaction of the resultant anomeric hydroxy sugars with trichloroacetonitrile in the presence of a base. Anomeric hydroxy sugar donors **6**−**8** were obtained by deallylation of the corresponding fully protected ally mannosides with $PdCl_2$ in methanol (see the Supporting Information).

For mannosylation with trichloroacetimidate donors, the coupling was carried out by addition of TMSOTf (0.15 equiv) to a solution of the acceptor (1.0 equiv) and of the donor (1.5 equiv) in CH_2Cl_2 at −78 °C, followed by stirring the solution for 2 h at −78 °C. The reaction was quenched by addition of triethylamine at −78 °C. The amount of TMSOTf (0.15 or 1.0 equiv) did not significantly affect the yield and the β/α ratio of the mannosylation product, although the reaction was a little faster with 1.0 equiv of TMSOTf.

Mannosylation with anomeric hydroxy sugar donors was carried out in the following one-pot sequence: (i) reaction of the donor (1.0 equiv), phthalic anhydride (1.1 equiv), and 1,8-diazobicyclo[5,4,0]undec-7-ene (DBU, 1.2 equiv) in the presence of 4A molecular sieves for 15 min at room temperature in CH_2Cl_2; (ii) addition of Tf_2O (1.5 equiv) to this solution at −78 °C and stirring for further 15 min; and (iii) addition of the acceptor (1.5 equiv) at −78 °C and allowing the reaction mixture to warm over 1 h to 0 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C.

Mannosylations with Donors Possessing an Electron-Withdrawing Group at *O*-4. Mannosylations of benzyl-protected primary hydroxy sugar **19** with mannosyl donors with strongly electron-withdrawing sulfonyl groups at *O*-4, including 4-*O*-(*o*-trifluo-

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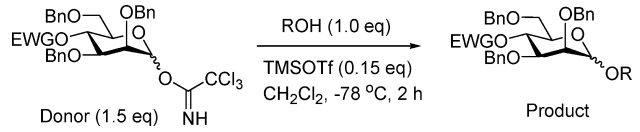
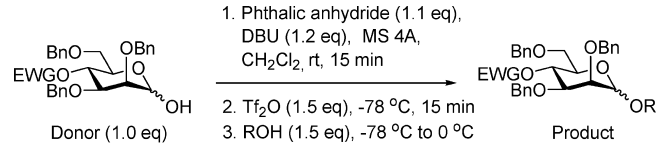
Table 1. Mannosylations with Trichloroacetimidate Donors **1**−**5** Having EWGs at *O*-4



entry	acceptor ROH	donor	EWG	product (yield, %)[a]	ratio[b] β/α
1	**19**	**1**	$SO_2C_6H_4o$-CF_3	**23** (81)	15.5/1
2	**19**	**2**	SO_2Bn	**24** (80)	10.7/1
3	**19**	**3**	Bz*p*-NO_2	**25** (91)	7.2/1
4	**19**	**4**	Bz	**26** (73)	7.1/1
5	**19**	**5**	Ac	**27** (85)	4.0/1
6	**19**	**17**	(Bn)[c]	**28** (91)	2.7/1
7	**20**	**1**	$SO_2C_6H_4o$-CF_3	**29** (81)	7.2/1
8	**20**	**2**	SO_2Bn	**30** (86)	5.0/1
9	**20**	**3**	Bz*p*-NO_2	**31** (95)	5.0/1
10	**20**	**4**	Bz	**32** (79)	4.6/1
11	**20**	**5**	Ac	**33** (87)	4.1/1
12	**20**	**17**	(Bn)[c]	**34** (96)	2.5/1
13	**21**	**2**	SO_2Bn	**35** (80)	3.5/1
14	**21**	**3**	Bz*p*-NO_2	**36** (82)	2.9/1
15	**21**	**4**	Bz	**37** (85)	2.3/1
16	**21**	**5**	Ac	**38** (81)	2.1/1[a]
17	**21**	**17**	(Bn)[c]	**39** (87)	1/2.7

[a] Determined after isolation. [b] The ratio was determined by LC−mass. [c] A standard donor for comparison.

Table 2. Mannosylations with Anomeric Hydroxy Sugar Donors **6**−**8** Having EWGs at *O*-4



entry	acceptor ROH	donor	EWG	product (yield, %)[a]	ratio[b] β/α
1	**19**	**6**	SO_2Bn	**24** (85)	9.2/1
2	**19**	**7**	Bz*p*-NO_2	**25** (88)	4.7/1
3	**19**	**8**	Bz	**26** (89)	6.1/1
4	**20**	**6**	SO_2Bn	**30** (88)	4.9/1
5	**20**	**7**	Bz*p*-NO_2	**31** (89)	3.0/1
6	**20**	**8**	Bz	**32** (88)	3.6/1
7	**20**	**18**	(Bn)[c]	**34** (86)	1.6/1
8	**21**	**6**	SO_2Bn	**35** (87)	3.1/1
9	**21**	**7**	Bz*p*-NO_2	**36** (88)	1.5/1
10	**21**	**8**	Bz	**37** (85)	1.3/1
11	**21**	**18**	(Bn)[c]	**39** (81)	α only[a]
12	**22**	**6**	SO_2Bn	**40** (90)	7.3/1
13	**22**	**7**	Bz*p*-NO_2	**41** (85)	2.8/1
14	**22**	**8**	Bz	**42** (89)	3.0/1

[a] Determined after isolation. [b] The ratio was determined by LC−mass. [c] A standard donor for comparison.

romethylbenzenesulfonyl)-tri-*O*-benzyl-mannosyl trichloroacetimidate, **1**, and 4-*O*-benzylsulfonyl-tri-*O*-benzyl-mannosyl trichloroacetimidate, **2**, were highly β-selective, yielding mannosyl disaccharides **23** (β/α = 15.5:1) and **24** (β/α = 10.7:1), respectively, with a large excess of β-anomers in high yields (entries 1 and 2 in Table 1). The acyl groups at *O*-4 of mannosyl trichloroacetimidate donors **3**−**5** also made the mannosylation of **19** highly β-selective, although less pronounced than the 4-*O*-sulfonyl groups. Thus, mannosylations of **19** with 4-*O*-*p*-nitrobenzoyl-mannosyl imidate, **3**, 4-*O*-benzoyl-mannosyl imidate, **4**, and 4-*O*-acetyl-mannosyl imidate, **5**, provided mannosyl disaccharides, **25** (β/α = 7.2:1), **26** (β/α = 7.1:1), and **27** (β/α = 4.0:1), respectively, favoring β-anomers (entries 3−5). For comparison, we carried out the mannosylation of **19** with 2,3,4,6-tetra-*O*-benzyl-mannosyl trichloroacetimidate, **17**, possessing no electron-withdrawing protective groups, and obtained a mixture of α- and β-mannosyl disaccharide, **28** (β/α = 2.7:1) (entry 6). The β-directing effect of the 4-*O*-sulfonyl group was confirmed in the mannosylation of a different acceptor, benzoyl-protected glucose acceptor, **20**. Thus, mannosylations of **20** with **1** and **2** provided mannosyl disaccharides **29** (β/α = 7.2:1) and **30** (β/α = 5.0:1), respectively, with an excess of β-anomers (entries 7 and 8). With 4-*O*-acyl-mannosyl imidate donors **3**−**5**, mannosylations of **20** were also β-selective, giving **31** (EWG = *p*-NO_2Bz, β/α = 5.0:1), **32** (EWG = Bz, β/α = 4.6:1), and **33** (EWG = Ac, β/α = 4.1:1), respectively, in high yields (entries 9−11). In the mannosylation of secondary hydroxy acceptor **21** with mannosyl imidate donors **2**−**5**, the β/α ratios of the products decreased (entries 13−16) as compared to those in the mannosylations of primary hydroxy acceptors. Nevertheless, when their β/α ratios were compared to the β/α ratio, 1/2.7, of product **39** (no EWG) from the mannosylation of **21** with fully benzyl-protected acceptor **17** (entry 17), the β-directing effect by the sulfonyl group of **2** and acyl groups of **3**, **4**, and **5** appeared quite substantial.

To examine the leaving group effect in the present mannosylation, we carried out mannosylations of acceptors **19**−**22** with anomeric hydroxy sugar donors **6**−**8** with electron-withdrawing groups at *O*-4. The results shown in Table 2 were quite similar to those with the trichloroacetimidate donors **2**−**4**. Thus, the benzylsulfonyl and acyl groups of donors **6**−**8** exhibited the β-directing effect in mannosylations of primary hydroxy sugar acceptors **19** and **20**, and the effect of the benzylsulfonyl group was stronger than those of acyl groups (entries 1−7 in Table 2). Although mannosylations of secondary hydroxy sugar acceptor **21** with **6**−**8**, on the other hand, exhibited poor β-selectivity (entries 8−10), the β-directing effects of the sulfonyl and acyl groups contrasted to the α only yield of disaccharide **39** obtained from the mannosylation of **21** with tetra-*O*-benzyl-mannose **18** (entry 11). Mannosylations of benzoyl-protected primary hydroxy sugar acceptor **22** with donors **6**−**8** were also β-selective (entries 12−14).

All electron-withdrawing protecting groups, $SO_2C_6H_4o$-CF_3, SO_2Bn, *p*-NO_2Bz, Bz, and Ac, at *O*-4 of donors promoted β-selective mannosylation, and the magnitude and the trend of their β-directing effect were not much affected by different leaving groups at the anomeric center. It was also noteworthy that the more strongly electron-withdrawing groups, $SO_2C_6H_4o$-CF_3 and SO_2Bn, exhibited a somewhat higher β-directing effect than did the weakly electron-withdrawing acyl groups, *p*-NO_2Bz, Bz, and Ac.[27] As compared to the β-directing effect of electron-withdrawing groups at *O*-2,[13−15] the β-directing effect of those at *O*-4 was not smaller and even greater in certain cases. The stereochemistries at the newly generated anomeric centers of the product disaccharides were unequivocally determined on the basis of characteristic one-bond C1′−H1′ coupling constants.[28]

Mannosylations with Donors Possessing an Electron-Withdrawing Group at *O*-6. The mannosylation of benzyl-protected primary hydroxy acceptor **19** with 6-*O*-benzylsulfonyl-tri-*O*-

(27) The field/inductive parameter *F* of SO_2Ph is +0.58, and that of SO_2Me is +0.53, whereas those of Bz and Ac are +0.31 and +0.33, respectively. On the other hand, the parameter *F* of Bn is known to be−0.04. See: Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195.

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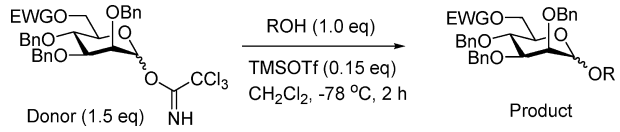
Table 3. Mannosylations with Trichloroacetimidate Donors **9**−**12** Having EWGs at *O*-6



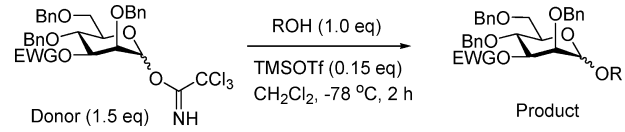
entry	acceptor ROH	donor	EWG	product (yield, %)[a]	ratio[b] β/α
1	**19**	**9**	SO_2Bn	**43** (76)	13.8/1
2	**19**	**10**	Bz*p*-NO_2	**44** (83)	5.2/1
3	**19**	**11**	Bz	**45** (83)	6.8/1[a]
4	**19**	**12**	Ac	**46** (84)	α only[a]
5	**19**	**17**	(Bn)[c]	**27** (91)	2.7/1
6	**20**	**9**	SO_2Bn	**47** (85)	9.1/1
7	**20**	**10**	Bz*p*-NO_2	**48** (85)	3.5/1
8	**20**	**11**	Bz	**49** (85)	4.0/1[a]
9	**20**	**12**	Ac	**50** (85)	1/2.2
10	**20**	**17**	(Bn)[c]	**34** (96)	2.5/1
11	**21**	**9**	SO_2Bn	**51** (70)	5.6/1
12	**21**	**10**	Bz*p*-NO_2	**52** (85)	2.5/1
13	**21**	**11**	Bz	**53** (85)	2.5/1[a]
14	**21**	**12**	Ac	**54** (82)	α only[a]
15	**21**	**17**	(Bn)[c]	**39** (87)	1/2.7

[a] Determined after isolation. [b] The ratio was determined by LC−mass. [c] A standard donor for comparison.

benzyl-mannsoyl trichloroacetimidate **9**, a mannosyl donor having a strongly electron-withdrawing group at *O*-6, was highly β-selective, yielding mannosyl disaccharide **43** (entry 1 in Table 3). The *p*-nitrobenzoyl and benzoyl groups at *O*-6 of mannosyl donors **10** and **11** also exhibited a β-directing effect in the mannosylation of **19** (entries 2 and 3 in Table 3). Surprisingly, however, the acetyl group at *O*-6 of mannosyl donor **12** in the mannosylation of **19** exhibited a strong α-directing effect, yielding α-mannosyl disaccharide **46** exclusively (entry 4), whereas the mannosylation of **19** with the standard compound **17** with all benzyl-protecting groups gave an anomeric mixture of disaccharide **27** (entry 5). Mannosylations of benzoyl-protected primary hydroxy acceptor **20** with donors **9**−**12**, possessing electron-withdrawing groups at *O*-6, showed a trend (entries 6−8) similar to mannosylations of **19** with **9**−**12**. However, the mannosylation of **20** with **12**, possessing the 6-*O*-acetyl group, was α-selective, affording mannoside **50** (β/α = 1:2.2) with a slight excess of the α-anomer (entry 9), while the mannosylation of **20** with the standard compound **17** was β-selective, giving **34** (β/α = 2.5:1) (entry 10). The mannosylations of the secondary hydroxy acceptor **21** with **9**−**11** also exhibited the β-directing effect, giving disaccharides **51**, **52**, and **53**, respectively, favoring β-anomers (entries 11−13). However, the acetyl group at *O*-6 of donor **12** exhibited a strong α-directing effect in the mannosylation of **21**, so that the mannosylation product was exclusively α-disaccharide **54** (entry 14).

The electron-withdrawing benzylsulfonyl, *p*-nitrobenzoyl, and benzoyl groups at *O*-6 of mannosyl donors exerted the β-directing effect, and this was more pronounced in the strongly electron-withdrawing benzylsulfonyl group than in the weakly electron-withdrawing *p*-nitrobenzoyl and benzoyl groups. It was also noteworthy that the β-directing effect of electron-withdrawing groups at *O*-6 was not smaller or even greater than the β-directing effect of those at *O*-2.[13−15] A surprising result was that the acetyl group at *O*-6 of mannosyl donors exhibited an α-directing effect, to give exclusively or predominantly α-disaccharides. The remote participation of the 6-*O*-acetyl group of donors would be a possible explanation for its α-directing effect.

Table 4. Mannosylations with Trichloroacetimidate Donors **13**−**16** Possessing EWGs at *O*-3



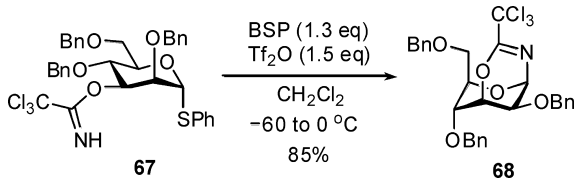
entry	acceptor ROH	donor	EWG	product (yield, %)[a]	ratio[b] β/α
1	**19**	**13**	SO_2Bn	**55** (95)	15.9/1
2	**19**	**14**	Bz*p*-NO_2	**56** (92)	1/1.7
3	**19**	**15**	Bz	**57** (81)	1/9.8
4	**19**	**16**	Ac	**58** (91)	1/25.9
5	**19**	**17**	(Bn)[c]	**27** (91)	2.7/1
6	**20**	**13**	SO_2Bn	**59** (93)	10.2/1
7	**20**	**14**	Bz*p*-NO_2	**60** (89)	1/2.3
8	**20**	**15**	Bz	**61** (88)	1/29.6
9	**20**	**16**	Ac	**62** (94)	1/39.0
10	**20**	**17**	(Bn)[c]	**34** (96)	2.5/1
11	**21**	**13**	SO_2Bn	**63** (85)	11.8/1
12	**21**	**14**	Bz*p*-NO_2	**64** (80)	1/3.8
13	**21**	**15**	Bz	**65** (91)	1/19.8
14	**21**	**16**	Ac	**66** (92)	1/40.4
15	**21**	**17**	(Bn)[c]	**39** (87)	1/2.7

[a] Determined after isolation. [b] The ratio was determined by LC−mass. [c] A standard donor for comparison.

Mannosylations with Donors Possessing an Electron-Withdrawing Group at *O*-3. The mannosylation of the benzyl-protected primary hydroxy acceptor **19** with mannosyl trichloroacetimidate donor **13**, possessing the benzylsulfonyl group at *O*-3, yielded mannosyl disaccharide **55** (β/α = 15.9:1) with a large excess of the β-anomer (entry 1 in Table 4). However, the mannosylation of **19** with donor **14**, having *p*-nitrobenzoyl group at *O*-3, was not β-selective, giving disaccharide **56** (β/α = 1:1.7) with a slight excess of α-anomer (entry 2). The benzoyl group at *O*-3 of donor **15** exhibited a stronger α-directing effect than the *p*-nitrobenzoyl group in the mannosylation of **19**, and product disaccharide **57** (β/α = 1:9.8) contained predominantly the α-anomer (entry 3). In the mannosylation of **19**, the strongest α-directing effect was obtained when there was an acetyl group at *O*-3. Thus, the mannosylation of **19** with **16**, with an acetyl group at *O*-3, afforded almost exclusively α-disaccharide **58** (β/α = 1:25.9) (entry 4). It is noteworthy that the mannosylation of **19** with the standard donor **17**, with a benzyl group at *O*-3, gave mannoside **27** (β/α = 2.7:1) with a little excess of the β-anomer (entry 5). The high β-directing effect of the benzylsulfonyl group was also observed in the mannosylation of benzoyl-protected primary hydroxy acceptor **20** with donor **13**, with the benzylsulfonyl group at *O*-3, providing disaccharide **59** (β/α = 10.2:1) with a large excess of the β-anomer (entry 6 in Table 4). In contrast, all three acyl groups showed an α-directing effect in the mannosylation of **20**. Thus, mannosylations of **20** with donors **14**−**16**, possessing an acyl group at *O*-3, provided disaccharides favoring α-anomers, **60**, **61**, and **62**, respectively (entries 7−9). Mannosylations of the secondary hydroxy acceptor **21** with donors **13**−**16** also indicated that the benzylsulfonyl group at *O*-3 was β-directing, giving **63** (β/α = 11.8:1) (entry 11), whereas the *p*-nitrobenzoyl group was weakly α-directing, yielding **64** (β/α = 1:3.8) (entry 12), and the benzoyl and acetyl groups at *O*-3 were strongly α-directing, giving **65** (β/α = 1:19.8) and **66** (β/α = 1:40.4), respectively (entries 13 and 14).

We observed that nonparticipating, strongly electron-withdrawing benzylsulfonyl groups at *O*-3 of mannosyl donors were highly β-directing, while all acyl groups at *O*-3 were α-directing

Scheme 1. Formation of **68** by Intramolecular Trapping of the Anomeric Oxocarbenium Ion Intermediate Resulting from the Activation of **67**



in mannosylations. Among three acyl groups, the acetyl group exhibited the strongest α-directing effect, whereas the *p*-nitrobenzoyl group at *O*-3 showed the weakest α-directing effect. Mannosylations with donors having the *O*-3 acetyl group probably proceeded almost exclusively through the six-membered ring 2-methyl-1,3-dioxanium ion intermediate, in which the sugar ring is in the $^1C_4$ conformation, resulting from the remote participation of the acetyl group. Mannosylations with donors having the 3-*O*-benzoyl group might also have proceeded through the 1,3-dioxanium ion pathway by the remote participation of the benzoyl group, whereas the 3-*O*-*p*-nitrobenzoyl group might have participated only partially during the mannosylation.

Further Evidence for the Participation of 3-*O*-Acyl and 6-*O*-Acetyl Groups in Mannosylations. To obtain more support for the remote participation of 3-*O*-acyl and 6-*O*-acetyl groups in mannosyl donors, we carried out experiments to trap anomeric oxocarbenium ion intermediates by the intramolecular nucleophilic attack of the *tert*-butoxycarbonyl (Boc) group or the trichloroacetimidoyl group at the *O*-3, *O*-4, or *O*-6 positions of mannosyl donors. The trapping of nearby electrophilic centers by the Boc group, leading to the formation of cyclic carbonates,[25,29] and by the trichloroacetimidoyl group, leading to the formation of cyclic oxazolines or oxazines,[30] is quite well established. In the present trapping experiment, although there was no sign of the generation of cyclic products in the reaction of phenyl 1-thio-3-Boc-mannoside with 1-benzenesulfinyl piperidine (BSP) and Tf_2O,[31] we were able to obtain stable bicyclic product **68**, having a six-membered trichlorooxazine ring, in 85% yield by activation of phenyl 1-thio-3-*O*-trichloroacetimidoyl- mannoside **67** with BSP and Tf_2O, as shown in Scheme 1. ^{1}H NMR spectral data clearly indicated that the 3-trichloroacetimidate **67** was in the $^4C_1$ conformation, while the sugar ring of the bicyclic product **68** was in the $^1C_4$ conformation. Two vicinal diaxial coupling constants, $J_{H3-H4} = 9.7$ Hz and $J_{H4-H5} = 9.7$ Hz, were observed in **67**, whereas the two coupling constants, J_{H3-H4} and J_{H4-H5}, of product **68** were both found to be 2.8 Hz. In contrast, no bicyclic products were isolated at all when phenyl 1-thio-mannosides possessing either the trichloroacetimidoyl group or the Boc group at one of the 4- and 6-positions were activated with BSP and Tf_2O. Nevertheless, a small amount of a bicyclic product with a seven-membered trichlorooxazepine ring was detected in the product mixture by mass spectrometry, resulting from the activation of phenyl 1-thio-6-trichloroacetimidoyl-mannoside with BSP and Tf_2O. The result of our trapping experiment was consistent with our mannosylation results. The

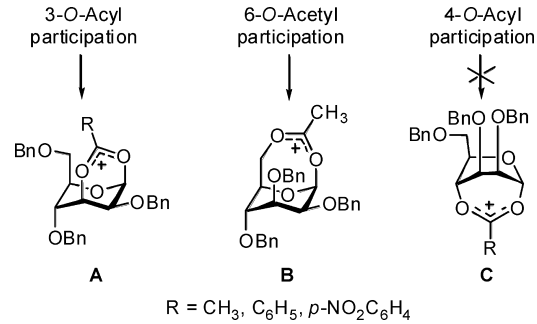


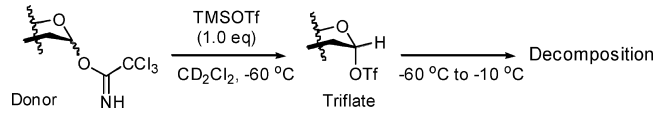
Figure 2. Dioxocarbenium ions **A** and **B** are possible intermediates for the formation of α-mannosides, but **C** might not be involved in mannosylation pathways.

remote participation by 3-*O*-acyl and 6-*O*-acetyl groups, but no participation by 4-*O*-acyl groups, could be explained by comparing the relative stabilities of dioxocarbenium ion intermediates resulting from possible remote participation of the acyl groups. The participation of 3-*O*-acyl groups would generate relatively stable bicyclic six-membered ring dioxocarbenium ion intermediate **A**, in which the sugar ring is in a chair, $^1C_4$, conformation, and mannosylations with 3-*O*-acyl-mannosyl donors would occur exclusively or predominantly through intermediate **A**, as shown in Figure 2. The 6-*O*-acyl group participation would generate the less stable seven-membered dioxocarbenium ion **B**, having the sugar ring in a chair conformation, and mannosylation with only the 6-*O*-acetyl-mannosyl donor might occur through the bridging dioxocarbenium ion **B** pathway. Nevertheless, the possibility cannot be excluded that a small portion of the α-mannosyl products were produced by the partial remote participation of the 6-*O*-benzoyl and the 6-*O*-*p*-nitrobenzoyl groups. Participation of the 4-*O*-acyl group would give the least stable seven-membered ring dioxocarbenium ion **C**, with the sugar ring in a boat conformation, so that mannosylations with 4-*O*-acyl-mannosyl donors would not occur through the pathway involving the intermediate **C**.

Detection of α-Mannopyranosyl Triflate Intermediates and Their Relationship with the *β*-Directing Effect. Activation of the trichloroacetimidate donors by TMSOTf, and of the anomeric hydroxy sugar donors by phthalic anhydride/Tf_2O, would lead to mannosyl oxocarbenium ions with triflate counteranions, which might be in equilibrium with covalent α-mannopyranosyl triflates. Since the first detection of α-mannopyranosyl triflates by Crich and colleagues,[32] they have been quite well characterized by low-temperature NMR experiments.[9,15,18,22a,33] In some stereoselective *β*-mannosylations, the S_N2-like reaction between the α-mannopyranosyl triflate intermediate and the acceptor alcohol is attributed to the generation of the *β*-mannoside.[9,15,18,30,34] In the present study, we performed a low-temperature NMR study to detect mannosyl triflates intermediates and determine their stabilities, to better understand the *β*-directing effect of the electron-withdrawing groups. When trichloroacetimidate donors **2**, **9**, and **13**, possessing the benzylsulfonyl group, and trichloroacetimidate donors **4**, **11**, and **15**, possessing the benzoyl group, were activated with 1.0 equiv

(29) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013–4018.
(30) (a) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *J. Org. Chem.* **1986**, *51*, 4905–4910. (b) Sammes, P. G.; Thetford, D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 111–123.
(31) For activation of thioglycosides with BSP/Tf_2O, see: Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015–9020.
(32) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217–11223.
(33) (a) Nokami, T.; Shibuya, A.; Tsuyama, H.; Suga, S.; Bowers, A. A.; Crich, D.; Yoshida, J. *J. Am. Chem. Soc.* **2007**, *129*, 10922–10928. (b) Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926–4930.
(34) Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5386–5389.

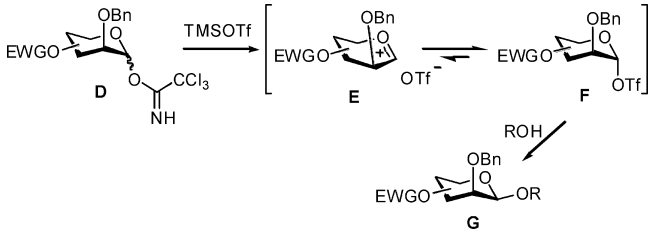
Table 5. α-Mannopyranosyl Triflates in Low-Temperature NMR Experiments



donor	triflate	δ_{H1}, ppm ($J_{1,2}$, Hz)	δ_{C13}, ppm	relative intensity of H1[a]	decomp. temp, °C
2 (4-*O*-SO_2Bn)	**69**	6.09 (d, 1.9)	105.2	0.60	−30 to −20
4 (4-*O*-Bz)	**70**	6.16 (s)	106.3	0.16	−40 to −30
9 (6-*O*-SO_2Bn)	**71**	6.11 (s)	105.4	0.47	−20 to −10
11 (6-*O*-Bz)	**72**	6.21 (d, 1.6)	105.2	0.05	−40 to −30
13 (3-*O*-SO_2Bn)	**73**	6.04 (s)	105.2	0.30	−30 to −20
15 (3-*O*-Bz)	**74**	6.21 (d, 1.5)	105.6	0.07	−50 to −40
17 (tetra-*O*-Bn)	not detected				

[a] The ratio of the H1 signal integration of the triflate and that of the corresponding donor.

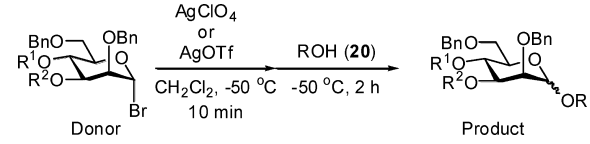
Scheme 2. Mechanism for the Stereoselective β-Mannosylation with Donors Possessing Electron-Withdrawing Group (EWG)



of TMSOTf in CD_2Cl_2 at −60 °C, NMR spectra showed generation of corresponding α-mannosyl triflates **69**−**74**, although their signal intensities and thermal stabilities differed, as shown in Table 5. Their ^{1}H and ^{13}C chemical shift values and the zero or small H1−H2 coupling constants indicated that mannosyl triflates **69**−**74** all have α-configurations at their anomeric centers. Stabilities of the triflates were determined by measuring their relative H1 signal intensities at −60 °C and their decomposition temperatures. Each of the relative H1 signal intensities given in Table 5 is the ratio of the H1 signal integration of the triflate and that of the corresponding trichloroacetimidate donor at −60 °C. The decomposition temperature was determined by observing the disappearance of the H1 signal of the triflates while the temperature was raised from −60 to −10 °C. In contrast, the NMR spectra showed no sign of the generation of the triflate intermediate when tetra-*O*-benzylmannosyl donor **17** was activated with TMSOTf. Triflates **69**, **71**, and **73**, possessing the benzylsulfonyl group, were found to be consistently more stable than triflates **70**, **72**, and **74**, possessing the benzoyl group. The results clearly indicated that the strongly electron-withdrawing benzylsulfonyl group, which exhibited the stronger β-directing effect in the mannosylation, also made the α-mannosyl triflate intermediate more stable than the weakly electron-withdrawing benzoyl group.

We therefore propose the following mechanism of the present β-mannosylation and the origin of the β-directing effect of the electron-withdrawing groups. Activation of donor **D** with TMSOTf would generate mannosyl oxocarbenium ion **E**, which is in equilibrium with α-mannosyl triflate **F** as shown in Scheme 2. The electron-withdrawing group on the sugar ring would stabilize **F**, but might destabilize **E** so that the equilibrium would shift toward the α-mannosyl triflate **F**. Next, **F**, or its contact ion pair, would react with acceptor alcohol ROH in a S_N2-like fashion to give β-mannoside **G**.

Table 6. Mannosylations of **20** with **75** and **76** Employing $AgClO_4$ or AgOTf as Promoter

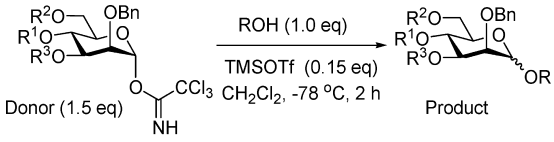


donor	R^1	R^2	promoter	product (yield %)[a]	ratio[b] β/α
75	SO_2Bn	Bn	$AgClO_4$	**30** (53)	1/2.1
75	SO_2Bn	Bn	AgOTf	**30** (55)	2.7/1
76	Bn	SO_2Bn	$AgClO_4$	**59** (51)	1/2.1
76	Bn	SO_2Bn	AgOTf	**59** (55)	3.9/1

[a] Determined after isolation. [b] The ratio was determined by LC−mass.

In this mechanism, one of the crucial factors for the β-selectivity is the triflate counteranion of the mannosyl oxocarbenium ion **E**, which could produce the very reactive but reasonably stable covalent α-mannosyl triflate **F**. We therefore performed mannosylations of **20** with mannosyl bromides **75** and **76**, by employing either $AgClO_4$ or AgOTf as the promoter, to examine the counteranion effect of the mannosyl oxocarbenium ion on the stereochemical outcome in the present mannosylation. With $AgClO_4$ as the promoter, the mannosylation of **20** with the donor **75** bearing the *O*-4-benzylsulfonyl group, in CH_2Cl_2 at −50 °C was α-selective and gave disaccharide **30** (β/α = 1:2.1), while the same mannosylation with AgOTf as the promoter was β-selective and gave **30** (β/α = 2.7:1) as shown in Table 6. Similarly, in the mannosylation of **20** with **76**, bearing the 3-*O*-benzylsulfonyl group, employing $AgClO_4$ as the promoter, product mannoside **59** had more α-anomer (β/α = 1:2.1), whereas the β-mannoside was found to be the major anomer in product **59** (β/α = 3.9:1), produced from the reaction of **20** with **76** employing AgOTf as the promoter. The results clearly indicate that the counteranion of the mannosyl oxocarbenium ion profoundly affects the outcome of the stereochemistry of mannosylations. The activation of mannosyl bromide with AgOTf would generate the mannosyl oxocarbenium ion, having the triflate counteranion, which could form the covalent α-mannosyl triflate at equilib-

Table 7. Mannosylations of **77** with Donors Bearing One Benzylsulfonyl and Two Benzylsulfonyl Groups



entry	donor	R^1	R^2	R^3	product (yield, %)[a]	ratio[b] β/α
1	**2**	SO_2Bn	Bn	Bn	**78** (70)	α only
2	**9**	Bn	SO_2Bn	Bn	**79** (86)	3.8/1
3	**13**	Bn	Bn	SO_2Bn	**80** (78)	1/3.7
4	**81**	SO_2Bn	SO_2Bn	Bn	**82** (84)	6/1

[a] Determined after isolation. [b] The ratio was determined by ^{1}H NMR.

rium; then the reaction of the α-triflate with the acceptor would provide the β-mannoside. In contrast, the activation of the mannosyl bromide with $AgClO_4$ would form the mannosyl oxocarbenium ion, having the noncoordinating (or weakly coordinating) perchlorate counteranion, so that the reaction of the oxocarbenium ion with the acceptor would be the major pathway to provide the α-mannoside as the major product.[35]

Mannosylation of a Sterically Demanding Secondary Hydroxy Sugar with the Donor Bearing Two Benzylsulfonyl Groups at *O*-4 and *O*-6 Positions. Mannosylations of the secondary hydroxy acceptor **21** were found to be less β-selective than those of the primary hydroxy acceptors **19**, **20**, and **22**. We examined the β-selectivity of the mannosylation of another secondary hydroxy sugar acceptor, **77**, the mannosylation of which with the donor bearing the strongly electron-withdrawing *o*-trifluoromethylbenzenesulfonyl group at the *O*-2 position was previously reported to be not β-selective, possibly because of steric hindrance.[15] In the present study, mannosylations of **77** with **2**, possessing the 4-*O*-benzylsulfonyl group, and with **13**, possessing 3-*O*-benzylsulfonyl groups, were not β-selective, either, yielding disaccharides **78** (α only) and **80** (β/α = 1:3.7), respectively (entries 1 and 3 in Table 7), while the reaction of **77** with **9**, bearing the 6-*O*-benzylsulfonyl group, was β-selective, giving **79** (β/α = 3.8:1) (entry 2). To improve the β-selectivity of the mannosylation of the sterically demanding **77**, we prepared mannosyl donor **81**, possessing two benzylsulfonyl groups, both at *O*-4 and *O*-6 positions. The mannosylation of **77** with **81**, with two benzylsulfonyl groups, exhibited a substantially improved β-selectivity, giving disaccharide **82** (β/α = 6.0:1) in 84% yield (entry 4 in Table 7). Comparison of their one-bond C1′−H1′ coupling constants and C1′ chemical shifts led us to assign tentatively the major product as the β-anomer **82*β*** and the minor product as the α-anomer **82α**. However, we conducted more NMR studies for the unambiguous assignment because C1′−H1′ coupling constant values, 171 Hz at 99.5 ppm for the major product and 174 Hz at 98.9 ppm for the minor product, both fall into the range of those for the α-anomer of hexopyranosides.[28] At first, the possibility that the unusual C1′−H1′ coupling constant for the β-anomer of **82** might be attributed to a non-$^4C_1$ conformation, maybe the $^1C_4$ conformation, of the sugar ring at the nonreducing end was excluded by the measurement of exact values of all proton vicinal coupling constants of the sugar ring.[36] Finally, the NOE experiments, in which the strong NOE interaction between H1′ and H2′ of the major product was observed, confirmed our tentative assignment and thus enable us to unequivocally assign the major product ($J_{C1'-H1'}$ = 171 Hz) as β-disaccharide **82*β*** and the minor product ($J_{C1'-H1'}$ = 174 Hz) as α-disaccharide **82α**.

Conclusion

Through a systematic study on mannosylations with donors possessing an electron-withdrawing group at *O*-3, *O*-4, or *O*-6 positions, we clearly observed the β-directing effect of these electron-withdrawing groups, except for 3-*O*-acyl and 6-*O*-acetyl groups, which exhibited the α-directing effect in mannosylations. The α-directing effect was ascribed to the remote participation of 3-*O*-acyl and 6-*O*-acetyl groups, whereas the β-directing effect was explained by the reaction between the acceptor and the α-mannosyl triflate intermediate, which is stabilized by electron-withdrawing groups. Evidence for the remote participation was provided, and the stability of the α-mannosyl triflates was determined by a low-temperature NMR study. With a donor possessing two benzylsulfonyl groups at *O*-4 and *O*-6 positions, the β-selective mannosylation of a sterically demanding acceptor was achieved.

Experimental Section

General Procedure for Mannosylations with Mannosyl Trichloroacetimidate Donors. A solution of a mannosyl trichloroacetimidate donor (0.15 mmol, 1.5 equiv) and a mannosyl acceptor (0.10 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was stirred for 5 min at room temperature and cooled to −78 °C. After the addition of TMSOTf (0.015 mmol, 0.15 equiv), the reaction mixture was stirred at −78 °C for 2 h, quenched with triethylamine, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography.

General Procedure for Mannosylations with Anomeric Hydroxy Mannose Donors. A solution of an anomeric hydroxy mannose donor (0.1 mmol, 1.0 equiv), phthalic anhydride (1.1 equiv), and 1,8-diazobicyclo[5,4,0]undec-7-ene (DBU, 1.2 equiv) in CH_2Cl_2 (4 mL) in the presence of 4A molecular sieves was stirred for 15 min at room temperature and cooled to −78 °C. Next, Tf_2O (1.5 equiv) was added, and the resulting solution was stirred for further 15 min at −78 °C. After addition of a mannosyl acceptor (1.5 equiv) in CH_2Cl_2 (2 mL) to the above solution via cannula, the reaction mixture was stirred at −78 °C for 15 min, allowed to warm over 1 h to 0 °C, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography.

Formation of Bicyclic Trichlorooxazine 68 by Intramolecular Trapping of the Anomeric Oxocarbenium Ion Intermediate Resulting from the Activation of 67. A solution of **67** (118 mg, 0.172 mmol) and BSP (43.1 mg, 0.206 mmol) in CH_2Cl_2 (5 mL) in the presence of 4A molecular sieves was stirred for 15 min at −60 °C. After addition of Tf_2O (43.3 μL, 0.258 mmol), the reaction mixture was stirred at −60 °C for 1 h, allowed to warm over 1 h to 0 °C, quenched with saturated aqueous $NaHCO_3$, and extracted

(35) For discussions on preferred conformations and stereoselective reactions of pyranosyl oxocarbenium ions, see: (a) Yang, M. T.; Woerpel, K. A. *J. Org. Chem.* **2009**, *74*, 545–553. (b) Lucero, C. G.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 2641–2647. (c) Chamberland, S.; Ziller, J. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5322–5323. (d) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521–15528.

(36) Because of the extensive overlap of sugar ring protons of **82*β***, the assignment of proton signals and the measurement of proton vicinal coupling constants in the sugar ring at the nonreducing end of **82*β*** were only possible after the selective COSY and TOCSY: $J_{H1'-H2'}$ = 1.8 Hz, $J_{H2'-H3'}$ = 3.1 Hz, $J_{H3'-H4'}$ = 9.7 Hz, and $J_{H4'-H5'}$ = 9.7 Hz.

with CH_2Cl_2. The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (hexane/EtOAc, 6:1) to afford compound **68** (84.6 mg, 85%): colorless oil, R_f = 0.35 (hexane/EtOAc, 5:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.38 (dd, J = 9.6, 8.3 Hz, 1H, H-6), 3.45 (dd, J = 9.7, 4.8 Hz, 1H, H-6′), 3.96 (t, J = 2.8 Hz, 1H, H-4), 3.98−4.04 (m, 1H, H-5), 4.08 (t, J = 2.4 Hz, 1H, H-2), 4.44 and 4.50 (ABq, J = 12.0 Hz, 2H), 4.55 and 4.62 (ABq, J = 12.0 Hz, 2H), 4.59 and 4.61 (ABq, J = 12.0 Hz, 2H), 4.85 (dd, J = 2.8, 2.4 Hz, 1H, H-3), 5.35 (t, J = 2.4 Hz, 1H, H-1), 7.21−7.35 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.7, 70.7, 70.8, 71.7, 72.0, 73.47, 73.52, 75.6, 76.5, 127.8, 127.85, 127.88, 128.1, 128.2, 128.3, 128.5, 128.65, 128.69, 137.0, 137.2, 138.0, 155.8. HRMS calcd for $C_{29}H_{28}Cl_3NO_5Na$ [M + Na]$^+$, 598.0931; found, 598.0934.

Procedure for the Detection and Thermal Decomposition of α-Mannosyl Triflates 69−74 in CD_2Cl_2 by Low-Temperature NMR Analysis. A 5 mm NMR tube containing a solution of a mannosyl trichloroacetimidate **2**, **4**, **9**, **11**, **13**, **15**, or **17** (0.05−0.10 mmol) in CD_2Cl_2 (500 μL) was placed in the NMR probe at room temperature, cooled to −60 °C, and then the reference ^{1}H NMR spectrum was obtained. The NMR tube was removed from the NMR probe, and TMSOTf (1.2 equiv) was added to the tube at −78 °C in an acetone/dry ice bath. After being briefly agitated, the NMR tube was placed in the precooled NMR probe at −60 °C, and the ^{1}H NMR spectrum was recorded again. The conversion of the mannosyl trichloroacetimidate into the α-mannosyl triflate was almost instantaneous, and the ^{1}H NMR spectrum showed the anomeric proton signal of the α-mannosyl triflate. Also, then the ^{1}H−^{13}C HSQC spectrum was recorded to assign ^{13}C chemical shifts and to confirm the anomeric proton signal. The NMR probe temperature was increased by 10 °C increments, and ^{1}H NMR spectra were acquired at each temperature until the thermal decomposition of the α-mannosyl triflate was completed.

General Procedure for Mannosylations of 20 with Mannosyl Bromides 75 and 76 Employing $AgClO_4$ or AgOTf as the Promoter. A solution of a mannosyl bromide (70 mg, 0.105 mmol) and a promoter ($AgClO_4$ or AgOTf, 0.157 mmol) in CH_2Cl_2 (3 mL) in the presence of 4A molecular sieves was stirred for 10 min at −50 °C. After addition of acceptor **20** (63.7 mg, 0.126 mmol) to the above solution, the reaction mixture was stirred at −50 °C for 2 h, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography.

Methyl (2,3-Di-*O*-benzyl-4,6-di-*O*-benzylsulfonyl-α-D-mannopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-mannopyranoside (82α) and Methyl (2,3-Di-*O*-benzyl-*O*-4,6-di-*O*-benzylsulfonyl-*β*-D-mannopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-mannopyranoside (82*β*). A solution of 2,3-di-*O*-benzyl-4,6-di-*O*-benzylsulfonyl-α-D-mannopyranosyl trichloroacetimidate (**81**, 183 mg, 0.226 mmol) and acceptor **77** (70 mg, 0.151 mmol) in CH_2Cl_2 (5 mL) was stirred for 5 min at room temperature and cooled to −78 °C. After the addition of TMSOTf (4.1 μL, 0.0226 mmol), the reaction mixture was stirred at −78 °C for 2 h, quenched with triethylamine, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (hexane/EtOAc/CH_2Cl_2, 3:1:1) to afford compound **82α** (20 mg, 12%): colorless oil, R_f = 0.38 (hexane/EtOAc/CH_2Cl_2, 3:1:1, v/v/v); $[\alpha]^{20}_D$ = 20.7 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36 (s, 3H), 3.38−3.44 (m, 2H), 3.51 (dd, J = 11.2, 3.6 Hz, 1H), 3.55 (dd, J = 11.2, 3.6 Hz, 1H), 3.65−3.71 (m, 2H), 3.78−3.91 (m, 2H), 3.93 (d, J = 9.2 Hz, 1H), 4.01 (d, J = 14.0 Hz, 1H), 4.13 (d, J = 14.4 Hz, 1H), 4.22 (d, J = 14.4 Hz, 1H), 4.24 (d, J = 10.4 Hz, 1H), 4.33−4.39 (m, 2H), 4.46−4.58 (m, 6H), 4.65 (d, J = 12.0 Hz, 1H), 4.86 (d, J = 11.6 Hz, 1H), 5.01 (d, J = 11.6 Hz, 1H), 5.02−5.08 (m, 2H), 5.41 (d, J = 1.2 Hz, 1H, H-1′), 7.12−7.41 (m, 35H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 57.6, 57.7, 68.4, 69.0, 69.5, 72.4, 72.8, 73.3, 73.4, 73.7, 74.9, 76.7, 77.12, 77.13, 80.4, 81.1, 97.9, 98.9 (C-1′, $J_{C1'-H1'}$ = 174 Hz), 127.4, 127.5, 127.6, 127.9, 128.0, 128.1, 128.3, 128.4, 128.52, 128.53, 128.6, 128.90, 128.92, 129.1, 129.3, 130.7, 131.0, 131.1, 137.6, 138.0, 138.3, 139.0. HRMS calcd for $C_{62}H_{66}O_{15}S_2Na$ [M + Na]$^+$, 1137.3741; found, 1137.3740.

Further elution provided compound **82*β*** (118 mg, 70%): colorless oil, R_f = 0.35 (hexane/EtOAc/CH_2Cl_2, 3:1:1, v/v/v); $[\alpha]^{20}_D$ = 8.9 (*c* 5.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 (s, 3H), 3.56 (dd, J = 9.6, 3.6 Hz, 1H), 3.63 (d, J = 5.6 Hz, 1H), 3.68 (d, J = 5.6 Hz, 1H), 3.72−3.76 (m, 3H), 3.84−3.88 (m, 2H, H-3′, H-5′), 3.90 (dd, J = 9.6, 2.8 Hz, 1H), 4.10 (dd, J = 11.4, 4.4 Hz, 1H), 4.11 (d, J = 11.6 Hz, 1H), 4.17 (d, J = 9.2 Hz, 1H), 4.18 (d, J = 14.4 Hz, 1H), 4.20−4.28 (m, 2H), 4.29 (d, J = 14.4 Hz, 1H), 4.34 (d, J = 14.0 Hz, 1H), 4.41 and 4.44 (ABq, J = 11.2 Hz, 2H), 4.48 (d, J = 12.2 Hz, 1H), 4.53−4.65 (m, 4H), 4.68 (d, J = 12.0 Hz, 1H), 4.95 (t, J = 9.7 Hz, 1H, H-4′), 5.16 (d, J = 12.0 Hz, 1H), 5.32 (d, J = 1.8 Hz, 1H, H-1′), 7.02−7.38 (m, 35H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 68.8, 69.2, 69.8, 70.0, 71.6, 72.5, 73.3, 73.5, 75.0, 75.1, 76.1, 76.7, 77.4, 80.1, 81.5, 97.8, 99.5 (C-1′, $J_{C1'-H1'}$ = 171 Hz), 126.6, 127.4, 127.66, 127.73, 127.80, 127.84, 128.0, 128.2, 128.3, 128.4, 128.56, 128.60, 128.64, 128.7, 128.89, 128.93, 129.0, 130.7, 130.9, 137.3, 137.8, 137.9, 138.2, 138.8. HRMS calcd for $C_{62}H_{66}O_{15}S_2Na$ [M + Na]$^+$, 1137.3741; found, 1137.3743.

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Supporting Information Available: Experimental procedure, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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