Notes

Glycosylation Reactions with a (4-Alkoxypentadienyl)oxy Leaving Group Linking the Glycosyl Donor and the Acceptor Moiety

Götz Scheffler and Richard R. Schmidt*

Fakultät Chemie, Universität Konstanz, Fach M 725, D-78457 Konstanz, Germany

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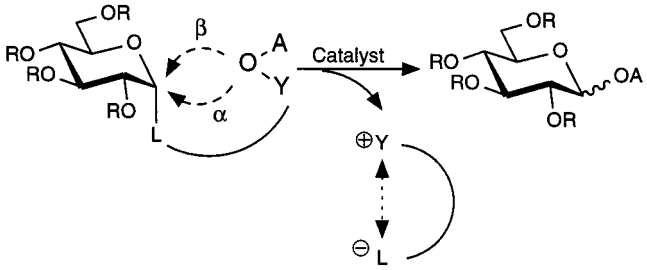
Introduction

Glycosyl transfer within the active site of an enzyme can be regarded as an intramolecular process in which the anomeric center of the glycosyl donor and the accepting moiety are held in close proximity to ensure regio- and diastereoselective glycoside bond formation.[1,2] To enforce a related reaction course, various approaches to intramolecular glycoside bond formation have been recently proposed;[3−14] they are based on attachment of the acceptor to the donor moiety via the 2-hydroxy group at the donor or, alternatively, as exhibited in Scheme 1, attachment through the spacer Y via the leaving group L.[3−14] Varying results have been obtained, and for some cases even an intermolecular reaction course could be verified, though model considerations favored intramolecularity of the process.[13]

Particularly suitable for connecting the acceptor moiety to the leaving group at the glycosyl donor seems to be

Scheme 1



modification of the known 4-pentenyloxy leaving group.[15] As shown in Scheme 2, selection of a cis-configured 2,4-pentadienyloxy group and attachment of the acceptor moiety at C-4 via an enol ether linkage (→ **A**) would not only facilitate activation of the C-4−C-5 double bond by an electrophilic reagent (E^+X^-) but also generate close proximity of the anomeric carbon with the acceptor moiety in intermediate **B**. Thus, ensuing bond reorganization in a cage, i.e., cleavage of the bond between the anomeric carbon and the oxonium oxygen (→ **C** and **D**) and then immediate attack of the electrophilic carbon of **C** at the nucleophilic oxygen of **D** will readily generate glycoside **F** and, due to the presence of the benzene ring, resonance-stabilized species **E**. A face-selective 1,3-shift in this cage should favor retention of configuration in this process (→ **F**α in Scheme 2). However, solvent separation of intermediates **C** and **D** or, alternatively, direct disintegration of **B** into independent fragments **C** and **D** could result in an intermolecular reaction course and then ultimately to loss of anomeric diastereocontrol (**F**α + **F**β). On the basis of previous findings in *O*-glycosyl ortho ester rearrangement[11] success in this internal reorganization of *O*-glycosyl acetal **B** leading to glycoside bond formation was envisaged.

Results and Discussion

To test the concept detailed in the Introduction, mannopyranoside and glucopyranoside formation were investigated. Toward this aim, 2-bromobenzyl alcohol was mannosylated with known glycosyl donor **1**[16] (Scheme 3); ensuing removal of *O*-acetyl groups with NaOMe/MeOH (Zemplén conditions)[17] and *O*-benzylation with BnBr/NaH in DMF afforded α-mannopyranoside **2**. Bromo/lithium exchange with *n*-butyllithium in THF at −100 °C and then CO_2 addition furnished after workup benzoic acid derivative **3**. As glycosyl acceptors the known 6-O-unprotected and 4-O-unprotected methyl glucopyranosides **4**[18] and **5**[19] were employed. Ester formation with **3**

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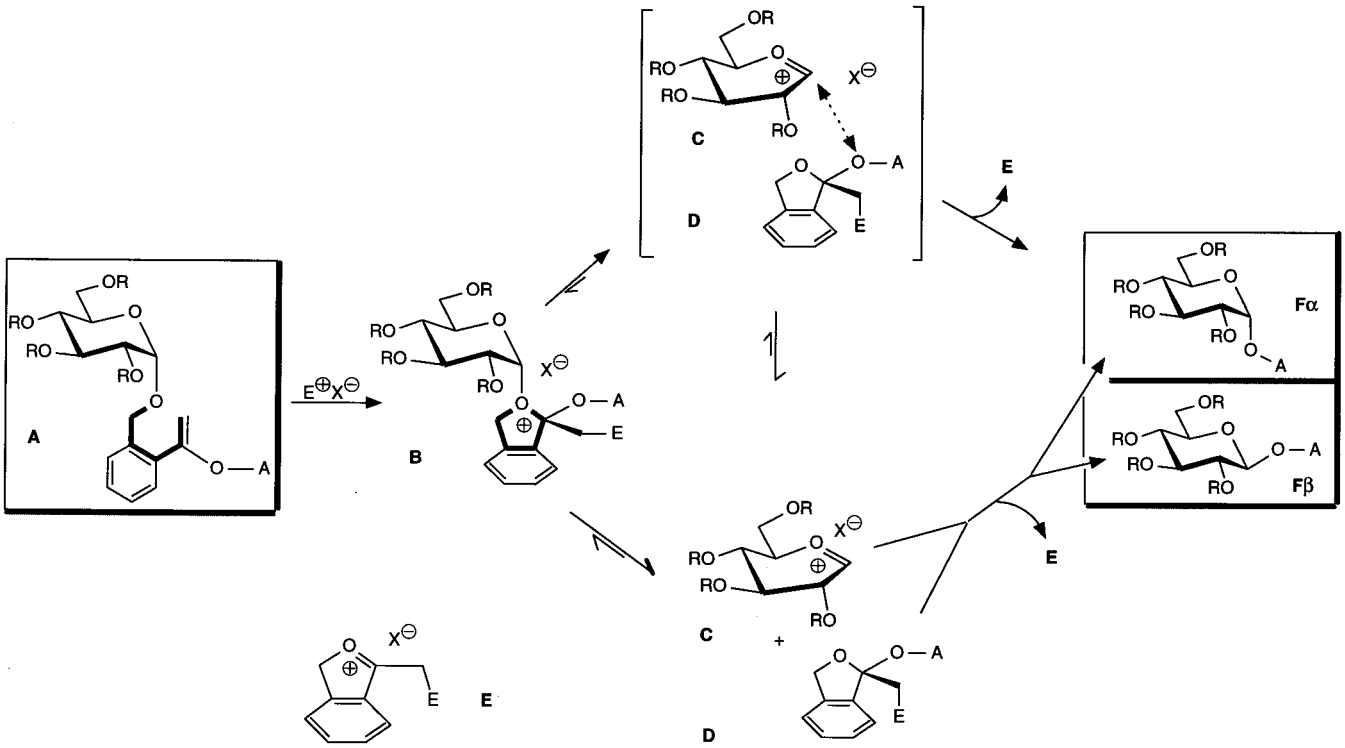
Scheme 2



in the presence of DCC/DMAP as condensing agents and then methylenation with Tebbe's reagent[20] in THF at 0 °C afforded the desired enol ethers **6** and **7**, respectively, in high overall yields. Among the various promoter systems investigated for glycoside bond formation with **6** and **7**, phenylselenyl trifluoromethanesulfonate (PhSeOTf was generated in situ from PhSeCl/AgOTf) in toluene at 0 °C proved to be particularly successful. Thus, **6** and **7** afforded the desired disaccharides **8**[21] and **9**,[21] respectively, in high yields and, in this case where kinetic and thermodynamic effects favor α-product formation, expectedly only α-products were obtained.

For the glucosylation studies, the required glucopyranosyl precursors **13**α and **13**β were readily obtained via the same route; thus, from 2-bromobenzyl alcohol and known glucosyl donor **10**[22] glycoside **11**β[13] was obtained (Scheme 4). Anomeric O-alkylation of 2,3,4,6-tetra-*O*-benzyl-D-glucose[23] (**12**) with 2-bromobenzyl bromide as alkylating agent and NaH as base in DMF at room temperature afforded a separable 1:1 mixture of **11**α and **11**β in practically quantitative yield. Transformation of **11**α,β into benzoic acid derivatives **13**α,β and then into enol ethers **14**α, **14**β, and **15**β, respectively, was performed as described above. For the generation of disaccharides, PhSeOTf and TMSOTf were employed as promoter systems; thus, **14**α and **14**β gave disaccharides **16**[27] in high yield. Surprisingly, however, at 0 °C the anomer ratio of the product **16** was practically independent of the configuration of the starting material **14** and independent of the two promotor systems selected; preferentially the β-isomer **16**β was obtained (Table 1). At lower temperatures (−40 °C) the β-anomer **16**β predominated with a ratio between 1:5 and 1:20. This result could be due to competing reaction of glycosyl cation intermediate **C** with counterion X^- (Scheme 2, X^- = trifluoromethanesulfonate) from the α-side,[11,24−26] thus providing in an ensuing slow S_N2-type reaction with **D** the β-glycoside. A similar result was obtained for the transformation of **15**β; though (1−4)-linkage between two glucose residues is frequently less efficient, disaccharide **17**[27] was obtained in good yield, yet also some α-anomer **17**α was generated (α:β = 1:2).

This result prompted us to perform competition studies in order to further elucidate the reaction course. Toward this aim, a 1:1 mixture of **14**β and **20**α,β (α:β = 1:1; Scheme 5), prepared via anomeric O-alkylation as described above, was treated with different promoter systems (see Table 2). Obviously, intramolecular reaction in a cage (**C** + **D** in Scheme 2) should exclusively result in formation of disaccharides **16** and **18**.[13] However, under all reaction conditions (see entries 1−5) scrambling of donors and acceptors is observed, thus leading also to crossover products **21**α,β[13] and **11**α,β, respectively, in practically equal amounts. Yet, as found above, at low temperatures (−40 °C) the β-selectivity observed in the direct product **16** from **14**β is increased, whereas for the 1:1 ratio of **20**α,β the same ratio is also found in the products **11** and **18**. From these results it can be reasoned that intermediate **B** disintegrates even in toluene as

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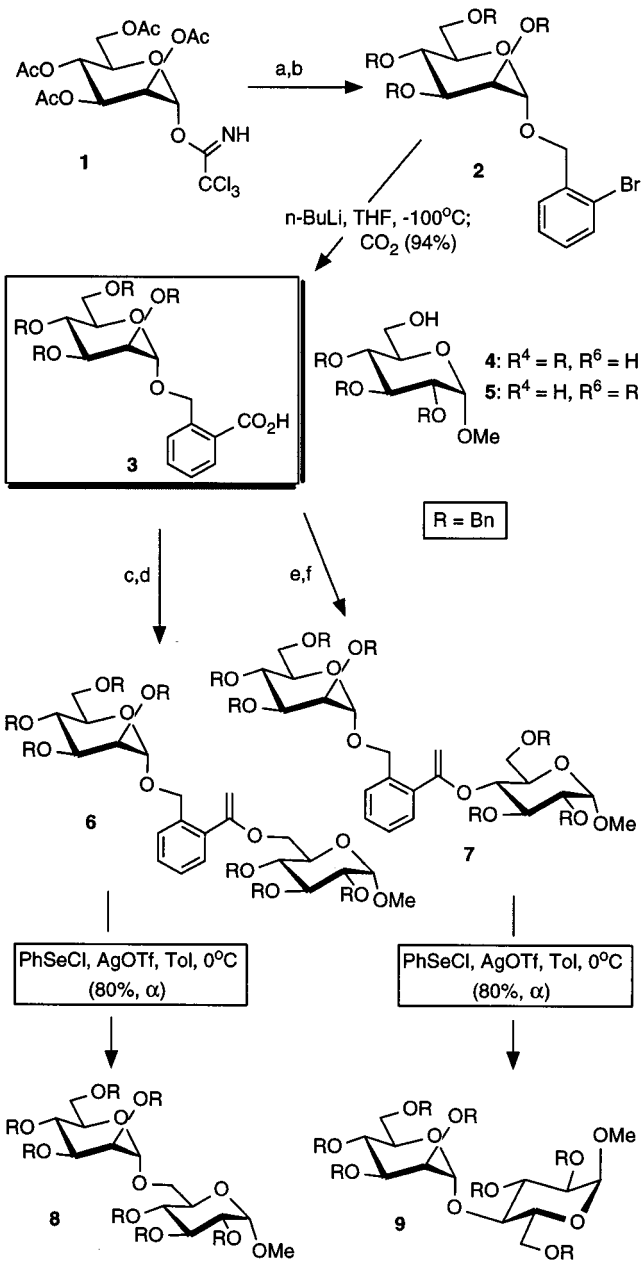
Scheme 3



(a) $BF_3{\cdot}OEt_2$. CH_2Cl_2 (67%); (b) NaOMe, MeOH; BnBr, NaH, DMF (79%)
(c) **4**, DCC, DMAP, CH_2Cl_2 (89%); (d) Tebbe, THF, 0°C (78%);
(e) **5**, DCC, DMAP, CH_2Cl_2 (77%); (f) Teppe, THF, 0°C (80%)

solvent, either by direct means or via a cage, into donor and acceptor species **C** and **D**, which leads to practically complete scrambling in the product formation.

Conclusion

In conclusion, activated pentadienyloxy systems offer high glycosyl donor properties. Their combination with an appropriately attached glycosyl acceptor leads in the α-mannopyranosyl donor case to complete α-selectivity. In the glucopyranosyl donor series of experiments, independent of the configuration of the starting material, similar α:*β*-ratios in the products were obtained and at low temperatures preferentially the *β*-linked disaccharides were formed. On the basis of crossover experiments essentially an intermolecular reaction course could be verified. However, it can be presumed that extension of this concept to systems with less translational and rotational freedom will eventually lead to a highly efficient methodology for glycoside bond formation.

Experimental Section

Materials were obtained from Aldrich Chemical Co. All reactions were conducted under a positive pressure of dry argon. THF was distilled from sodium benzophenone ketyl. All reactions were monitored by TLC (Merck Kieselgel 60 F_{254} plates); flash chromatography was performed over silica 40 (Baker). Petroleum ether was used in the boiling range of 35−65 °C; EtOAc and toluene were distilled. Melting points were uncorrected. ^{1}H NMR spectra were recorded with TMS as internal standard; NMR peak assignments are derived from 2-D NMR techniques (600 MHz). FAB mass spectra were recorded using a *m*-nitrobenzyl alcohol matrix with NaI.

2-Bromobenzyl 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranoside (2). To a slurry of **1**[16] (9.80 g, 19.7 mmol) and 2-bromobenzyl alcohol (5.80 g, 31 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C was added distilled $BF_3{\cdot}OEt_2$ (0.23 mL, 1.9 mmol). After the mixture was stirred for 20 min, saturated aqueous $NaHCO_3$ (50 mL) and water (50 mL) were added and the mixture was extracted with EtOAc (2 × 200 mL). The combined organic phases were washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc 2:1) was done twice and yielded a white solid (6.85 g, 13.3 mmol, 67%). The solid was dissolved in dry MeOH (70 mL), NaOMe (1 M in MeOH, 3 mL, 3 mmol) was added, and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was then neutralized with Amberlite IR120 (H^+ mode) and concentrated in vacuo. After it was dried under high vacuum, the residue was dissolved in DMF (30 mL) and benzyl bromide (7.7 mL, 66 mmol) was added. NaH (1.58 g, 66 mmol) was added at 0 °C in portions. After addition of tetra-*n*-butylammonium iodide (200 mg, 0.54 mmol), ice-cooling was removed. The reaction mixture was stirred for 16 h at room temperature with exclusion of light. Addition of MeOH (2 mL), followed after some minutes by saturated aqueous $NaHCO_3$ (80 mL) and water (80 mL), quenched the reaction. The mixture was extracted with Et_2O (2 × 200 mL). The combined organic layers were washed with water (80 mL) and brine (200 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc 8:1) yielded **2** (7.41 g, 79%) as a colorless syrup: R_f 0.67 (toluene/EtOAc 10:1); $[\alpha]_D$ 48.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) *δ* 3.72−4.08 (m, 6 H), 4.50−4.80 (m, 9 H), 4.89 (d, *J* = 10.7 Hz, 1 H), 5.03 (d, *J* = 1.6 Hz, 1 H), 7.11−7.37 (m, 23 H), 7.52 (dd, 1 H). Anal. Calcd for $C_{41}H_{41}BrO_6$: C, 69.39; H, 5.82. Found: C, 69.41; H, 5.87.

2-{[(2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl)oxy]-methyl}benzoic Acid (3). To **2** (3.00 g, 4.23 mmol) in a mixture of dry THF (60 mL) and dry *n*-hexane (16 mL) at −100 °C was added *n*-butyllithium (1.6 M in hexane, 2.9 mL, 4.6 mmol). After the mixture was stirred for 20 min, dry CO_2 (developed from dry ice) was bubbled through the solution for 30 min at −100 °C. The reaction mixture was warmed to room temperature and poured on a Et_2O (200 mL)/ice (75 mL)/concentrated hydrochloric acid (30 mL) mixture. After separation, the aqueous layer was extracted with Et_2O (3 × 75 mL). The combined organic layers were washed with water (30 mL) and brine (3 × 100 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc 2:1) yielded **3** (2.68 g, 94%) as a colorless, viscous syrup: R_f 0.0−0.2 (petroleum ether/EtOAc 3:1); $[\alpha]_D$ 52.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) *δ* 3.71−3.86 (m, 4 H), 3.96−4.09 (m, 2 H), 4.52 (d, *J* = 10.7 Hz, 1 H), 4.54 (d, *J* = 12.1 Hz, 1 H), 4.65 (s, 2 H), 4.68 (d, *J* = 12.1 Hz, 1 H), 4.74 (s, 2 H), 4.88 (d, *J* = 10.7 Hz, 1 H), 4.91 (d, *J* = 14.3 Hz, 1 H), 5.06 (d, *J* = 1.8 Hz, 1 H), 5.13 (d, *J* = 14.3 Hz, 1 H), 7.14−7.39 (m, 21 H), 7.46−7.56 (m, 2 H), 8.03 (dd, 1 H). Anal. Calcd for $C_{42}H_{42}O_8$: C, 74.76; H, 6.27. Found: C, 74.85; H, 6.38.

Methyl 6-{1-[2-(((2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl)oxy)methyl)phen-1-yl]vinyl}-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (6). To **3** (709 mg, 1.05 mmol), **4**[18] (488 mg,

Scheme 4

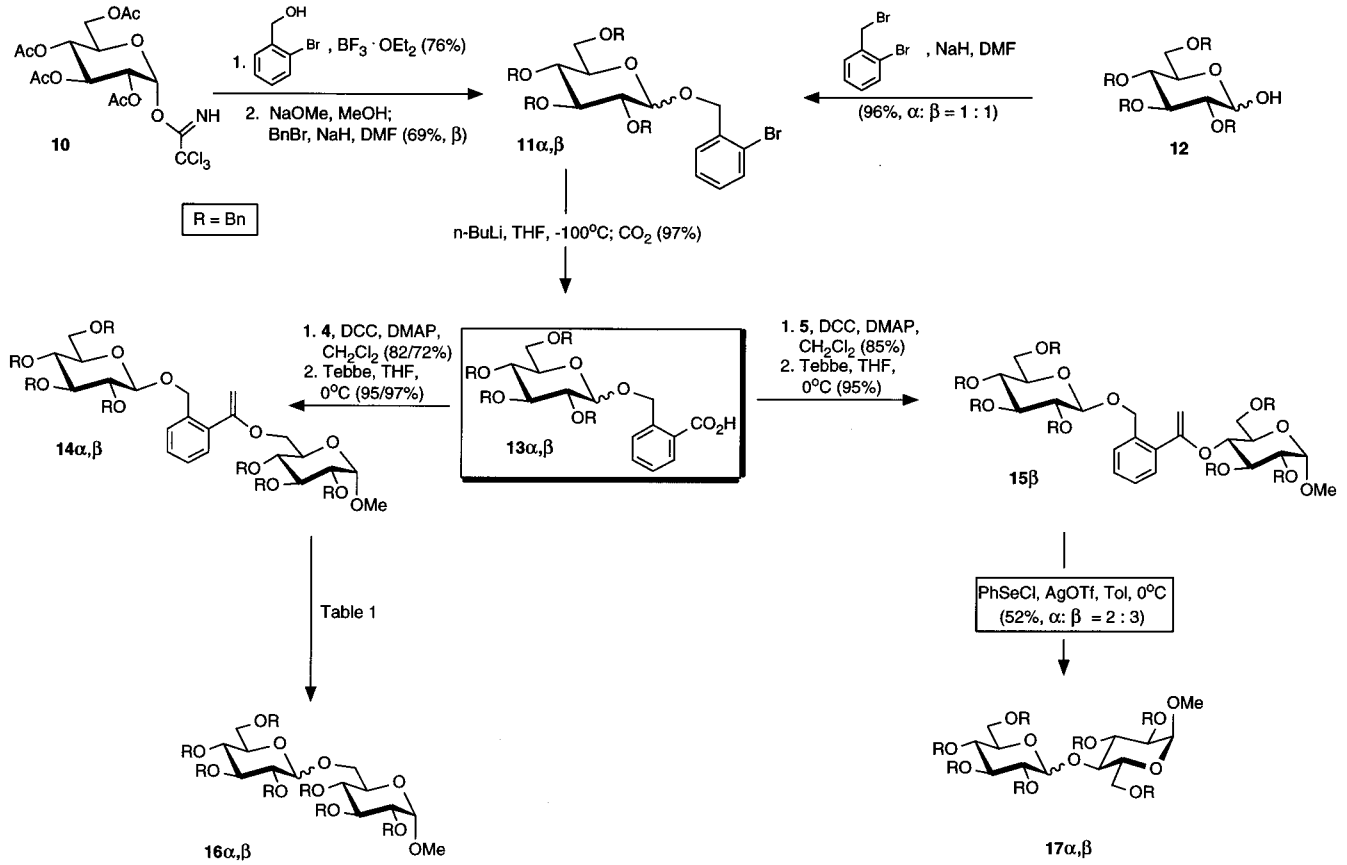


Table 1. Disaccharide Formation from Compounds 14α and 14*β*

	reaction conditions			product **16**α,*β*	
educt	solvent	promoter (amt, equiv)	temp (°C)	yield (%)	α:*β*
14α	Tol	PhSeCl (1.5), AgOTf (1.5)	0	82	1:2
14α	Tol	PhSeCl (1.5), AgOTf (1.5)	−40	41	1:5
14α	Tol	TMSOTf (1.0)	0	77	2:3
14α	Tol	TMSOTf (1.0)	−40	75	1:8
14*β*	Tol	PhSeCl (1.5), AgOTf (1.5)	0	70	1:3
14*β*	Tol	PhSeCl (1.5), AgOTf (1.5)	−40	75	1:20
14*β*	Tol	TMSOTf (1.0)	0	81	1:2
14*β*	Tol	TMSOTf (1.0)	−40	70	1:12

1.05 mmol), and DMAP (26 mg, 0.21 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C was added DCC (433 mg, 2.10 mmol). Ice-cooling was removed after 10 min, and the reaction mixture was stirred for 16 h at room temperature. Concentration in vacuo was followed by coevaporation with toluene. Flash chromatography (toluene/EtOAc 12:1) was done twice and yielded a colorless syrup (1.05 g, 0.937 mmol, 89%). To the syrup (500 mg, 0.446 mmol) in dry THF (5 mL) at 0 °C was added commercially available Tebbe's reagent (0.5 M in toluene, 1.3 mL, 0.65 mmol). Ice-cooling was removed after 40 min, and stirring at room temperature was continued for 2 h. The black reaction mixture was diluted with Et_2O (10 mL), and aqueous NaOH (2.5 M, 1 mL) was added cautiously over 25 min in portions. After it was stirred for 2 h at room temperature, the deep orange reaction-mixture was filtered with a 1:1 mixture of Celite and $MgSO_4$ and concentrated in vacuo (bath temperature below 30 °C). Flash chromatography (petroleum ether/EtOAc 4:1, 1 vol % triethylamine) yielded **6** (388 mg, 78%) as a colorless oil: R_f 0.41 (petroleum ether/EtOAc 3:1); $[\alpha]_D$ 50.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$ + 1 vol % d_6-pyridine) δ 3.33 (s, 3 H, OMe), 3.50 (2b-H), 3.54 (4b-H-H), 3.68 (6a-H), 3.77 (2a-H), 3.77 (6′a-H), 3.80 (5a-H), 3.88 (5b-H), 3.89 (m, 2 H, 6b-, 6′b-H), 3.94 (3a-H), 3.99 (3b-H), 4.03 (4a-H), 4.20 (d, 1 H, vinyl-H), 4.21 (d, 1 H, vinyl-H), 4.48 (d, ^2J = 12.1 Hz, 1 H, PhCH), 4.51 (d, ^2J = 10.9 Hz, 1 H, PhCH), 4.55 (d, ^2J = 11.2 Hz, 1 H, PhCH), 4.56−4.82 (m, 11 H, 8 PhCH, styrene-CH_2, 1b-H), 4.85 (d, ^2J = 10.9 Hz, 1 H, PhCH), 4.88 (d, ^2J = 10.8 Hz, 1 H, PhCH), 4.94 (d, 1 H, 1a-H), 4.95 (d, ^2J = 11.2 Hz, 1 H, PhCH), 7.17 (m, 2 H), 7.24−7.33 (m, 37 H); ^{13}C NMR (150.9 MHz, $CDCl_3$ + 1 vol % d_6-pyridine, extract of data) δ 55.17 (OMe), 66.63 (6b-C), 68.87 (5b-C), 69.21 (6a-C), 72.08 (5a-C), 74.72 (2a-C), 74.91 (4a-C), 77.73 (4b-C), 80.06 (3a-C), 80.09 (2b-C), 82.00 (3b-C), 86.67 (vinyl-CH_2), 97.33 (1a-C), 97.88 (1b-C); INEPT $^1J_{1a-H,1a-C}$ = 169 Hz, $^1J_{1b-H,1b-C}$ = 168 Hz; MS (FAB, 3-NBOH, NaI) *m/e* 1293 (3%, [M + NaI]Na^+), 1158 (7%, MK^+), 1142 (100%, MNa^+).

Methyl 4-{1-[2-(((2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl)oxy)methyl)phen-1-yl]vinyl}-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (7). To **3** (715 mg, 1.06 mmol), **5**[19] (492 mg, 1.06 mmol), and DMAP (26 mg, 0.21 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C was added DCC (437 mg, 2.12 mmol). Ice-cooling was removed after 10 min, and the reaction mixture was stirred for 16 h at room temperature. Concentration in vacuo was followed by coevaporation with toluene. Flash chromatography (toluene/EtOAc 12:1) was done twice and yielded a colorless syrup (916 mg, 77%). To the syrup (500 mg, 0.446 mmol) in dry THF (5 mL) at 0 °C was added Tebbe's reagent (0.5 M in toluene, 1.3 mL, 0.65 mmol). Ice-cooling was removed after 30 min, and stirring at room temperature was continued for 3 h. Workup was carried out as described for **6**. Flash chromatography (petroleum ether/EtOAc 6:1, 1 vol % triethylamine) yielded **7** (400 mg, 80%) as a colorless oil: R_f 0.43 (petroleum ether/EtOAc 3:1); $[\alpha]_D$ 39.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.38 (s, 3 H), 3.58−4.10 (m, 12 H), 4.36−4.85 (m, 19 H), 4.90 (d, *J* = 1.9 Hz, 1 H), 7.13−7.37 (m, 39 H); MS (FAB, 3-NBOH, NaI) *m/e* 1293 (3%, [M + NaI]Na^+), 1158 (6%, MK^+), 1142 (100%, MNa^+).

Methyl *O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (8). General Procedure for the Glycoside Syntheses. To dry toluene (1.5 mL) and activated molecular sieves 4 Å (0.3 g) at 0 °C were added phenylselenyl chloride (28 mg, 0.15 mmol) and dried Ag^I-OTf (38 mg, 0.15 mmol). After the reaction mixture was stirred for 10 min at 0 °C under exclusion of light, a solution of **6** (110 mg, 0.098 mmol) in dry toluene (1.0 mL) was added dropwise over 2 min. The reaction mixture was stirred for 40 min at 0 °C

Scheme 5

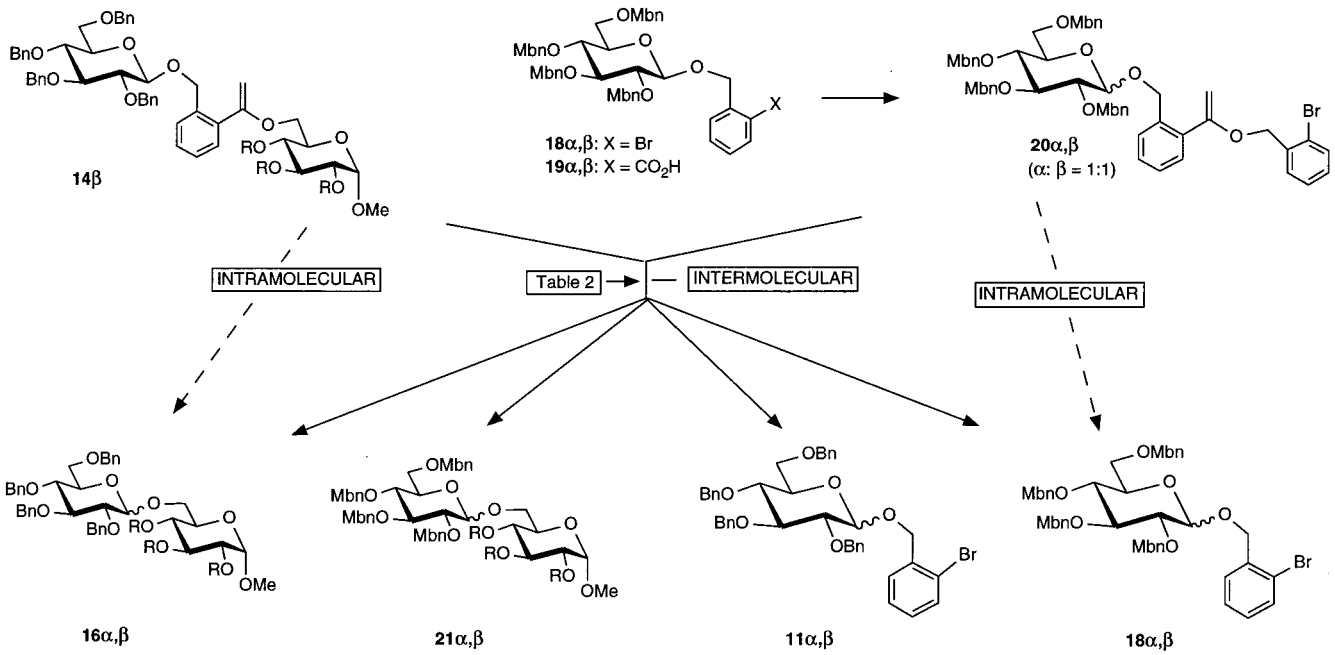


Table 2. Competition Experiments with Compounds 14*β* and 20α,*β*

entry no.	reaction conditions: solvent	promoter (amt, equiv)	temp (°C)	concn (10^{-2} M)	yield (%) (α:*β*): **16α,*β***	**21α,*β***	**11α,*β***	**18α,*β***
1	Tol	$BF_3.OEt_2$ (0.8)	0	2	11 (1:1)	11 (1:1)	33 (1:1)	29 (1:1)
2	Tol	TMSOTf (1)	0	2	38 (1:2)	38 (1:2)	26 (1:1)	26 (1:1)
3	Tol	TMSOTf (1.1)	−40	2	17 (1:4)	17 (1:4)	6 (1:1)	6 (1:1)
4	Tol	PhSeCl (1.5), AgOTf (1.5)	−40	1	36 (1:5)	28 (1:4)	27 (1:1)	27 (1:1)
5	Tol	PhSeCl (1.5), AgOTf (1.5)	0	5	41 (1:2)	41 (1:2)	41 (1:1)	41 (1:1)

and then diluted with EtOAc (4 mL) and, after addition of saturated aqueous $Na_2S_2O_3$ (3 mL), was again stirred for 2 h at room temperature. Water (10 mL) and EtOAc (50 mL) were added, and the layers were separated. The organic layer was washed with water (20 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (toluene/EtOAc 12:1) yielded the known **8**[21] (77 mg, 80%).

Via the same route the known **9**,[21] the known **16**α/*β*[27] and the known **17**α/*β*[27] were prepared.

2-Bromobenzyl 2,3,4,6-Tetra-*O*-benzyl-α/*β*-D-glucopyranoside (11α/*β*). (a) From 12. To **12**[23] (1.05 g, 1.94 mmol) in 5 mL of DMF at 0 °C was added 2-bromobenzyl bromide (0.73 g, 2.96 mmol) and then NaH (67 mg, 2.8 mmol). Ice-cooling was removed after 10 min, and stirring under exclusion of light was continued for 2 h at room temperature. The reaction mixture was diluted with Et_2O (50 mL) and quenched with saturated aqueous $NaHCO_3$ (20 mL) and water (20 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (2 × 75 mL). The combined organic layers were washed with water (2 × 50 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc 6:1) yielded **11**α,*β*[13] (1.32 g, 96%, α:*β* = 1:1) as a colorless solid. Separation was performed by column chromatography ($CHCl_3/Et_2O$ 60:1). **11**α/*β*: R_f 0.65 (toluene/EtOAc 10:1). **11**α: R_f 0.60 ($CHCl_3/Et_2O$ 30:1). **11***β*: R_f 0.57 ($CHCl_3/Et_2O$ 30:1).

(b) From 10. To a slurry of **10**[22] (3.20 g, 6.48 mmol) and 2-bromobenzyl alcohol (1.82 g, 9.72 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C was added distilled $BF_3 \cdot OEt_2$ (80 μL, 0.65 mmol). After 20 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL). Water (40 mL) and EtOAc (100 mL) were added, and the separated aqueous layer was extracted with EtOAc (2 × 50 mL). The resulting organic layers were combined and washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified via flash chromatography (petroleum ether/EtOAc 1.3:1). The eluted white solid (2.54 g, 4.92 mmol, 76%) was dissolved in dry MeOH (32 mL), and NaOMe (1 M in MeOH, 0.48 mL, 0.48 mmol) was added. After it was stirred for 1 h at room temperature, the reaction mixture was neutralized by addition of Amberlite IR120 (H^+-mode), concentrated in vacuo, and dried under high vacuum. The residue was dissolved in DMF (16 mL); at 0 °C benzyl bromide (2.8 mL, 24.0 mmol), NaH (576 mg, 24.0 mmol), and a catalytic amount of tetra-*n*-butylammonium iodide (100 mg, 0.27 mmol) were added, and the reaction was carried out and the mixture worked up as described for **2**. Flash chromatography (petroleum ether/EtOAc 8:1) yielded **11***β* (2.41 g, 69%) as a white solid: mp 92 °C; R_f 0.65 (toluene/EtOAc 10:1); $[\alpha]_D$ −7.2 (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 3.47−3.81 (m, 6 H), 4.53−5.05 (m, 9 H), 7.12−7.37 (m, 22 H), 7.53−7.57 (m, 2 H). Anal. Calcd for $C_{41}H_{41}BrO_6$: C, 69.39; H, 5.82. Found: C, 69.77; H 5.88.

2-{[(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)oxy]-methyl}benzoic Acid (13α). To **11**α (0.25 g, 0.37 mmol) in a mixture of dry THF (5 mL) and dry *n*-hexane (1.5 mL) at −100 °C was added *n*-butyllithium (1.6 M in hexane, 0.24 mL, 0.38 mmol). The reaction was carried out and the mixture worked up as described for **3**. Concentration in vacuo gave a solid, which was crystallized in Et_2O/petroleum ether at 4 °C (**13**α, 122 mg, 51%). Crystallization of the concentrated mother liquor from Et_2O/petroleum ether at 4 °C gave again **13***β* (105 mg, 42%): mp 104 °C; R_f 0.45−0.65 (toluene/EtOAc 1:1); $[\alpha]_D$ 57.3 (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 3.60−3.76 (m, 4 H), 3.85 (m, 1 H), 4.07 (dd, 1 H), 4.44 (d, *J* = 12.1 Hz, 1 H), 4.47 (d, *J* = 10.8 Hz, 1 H), 4.60 (d, *J* = 12.1 Hz, 1 H), 4.63 (d, *J* = 11.9 Hz, 1 H), 4.75 (d, *J* = 11.9 Hz, 1 H), 4.82 (d, *J* = 10.8 Hz, 1 H), 4.84 (d, *J* = 10.8 Hz, 1 H), 4.91−5.01 (m, 3 H), 5.10 (d, *J* = 14.7 Hz, 1 H), 6.97−7.13 (m, 2 H), 7.20−7.40 (m, 19 H), 7.51 (ddd, 1 H), 7.77 (d, 1 H), 8.03 (dd, 1 H).

2-{[(2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranosyl)oxy]-methyl}benzoic Acid (13*β*). To **11***β* (1.96 g, 2.75 mmol) in a mixture of dry THF (40 mL) and dry *n*-hexane (12 mL) at −100 °C was added *n*-butyllithium (1.6 M in hexane, 1.9 mL, 3.0 mmol). The reaction was carried out and the mixture worked up as described for **3**. Concentration in vacuo gave a solid, which

was dissolved in EtOAc (6 mL) at 70 °C. Crystallization with addition of petroleum ether yielded **13**β (1.28 g, 69%) as white crystals. Crystallization of the concentrated mother liquor from Et_2O/petroleum ether at room temperature gave again **13**β (0.48 g, 26%): mp 144 °C (EtOAc/petroleum ether); R_f 0.45−0.65 (toluene/EtOAc 1:1); $[\alpha]_D$ − 2.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.50 (m, 1 H), 3.56−3.80 (m, 5 H), 4.51−4.56 (m, 2 H), 4.58 (d, $J \approx 8$ Hz, 1 H), 4.63 (d, $J = 12.2$ Hz, 1 H), 4.80 (d, $J = 10.9$ Hz, 1 H), 4.81 (d, $J = 11.0$ Hz, 1 H), 4.83 (d, $J = 10.7$ Hz, 1 H), 4.94 (d, $J = 10.9$ Hz, 1 H), 5.00 (d, $J = 11.0$ Hz, 1 H), 5.18 (d, $J = 14.9$ Hz, 1 H), 5.37 (d, $J = 14.9$ Hz, 1 H), 7.14−7.38 (m, 21 H), 7.50 (ddd, 1 H), 7.80 (dd, 1 H), 8.06 (dd, 1 H). Anal. Calcd for $C_{42}H_{42}O_8$: C, 74.46; H, 6.27. Found: C, 74.77; H, 6.28.

Methyl 6-{1-[2-(((2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)oxy)methyl)phen-1-yl]vinyl}-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (14α). To **13**α (340 mg, 0.50 mmol), **4**[18] (234 mg, 0.50 mmol), and DMAP (12 mg, 0.010 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C was added DCC (268 mg, 1.01 mmol). Ice-cooling was removed after 10 min, and the reaction mixture was stirred for 16 h at room temperature. Concentration in vacuo was followed by coevaporation with toluene. Flash chromatography (petroleum ether/EtOAc 4:1) eluted a residue that was purified via a second flash chromatography (toluene/EtOAc 10:1), which gave a white solid (465 mg, 0.41 mmol, 82%; R_f 0.14 ($CHCl_3$/Et_2O 30:1), R_f 0.42 (petroleum ether/EtOAc 3:1)). To the solid (403 mg, 0.359 mmol) in dry THF (2.8 mL) at 0 °C was added Tebbe's reagent (0.5 M in toluene, 0.95 mL, 0.48 mmol). The reaction was carried out and the mixture worked up as described for **6**. Flash chromatography (petroleum ether/EtOAc 4.5:1, 1 vol % triethylamine) yielded **14**α (380 mg, 95%) as a colorless syrup: R_f 0.51 (petroleum ether/EtOAc 3:1); $[\alpha]_D$ 56.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.34 (s, 3 H, OMe), 3.50 (2b-H), 3.52 (6b-H), 3.54 (2a-H), 3.56 (4b-H), 3.67 (4a-H), 3.68 (6′b-H), 3.80 (5a-H), 3.89 (5b-H), 3.90 (6a-H), 3.94 (6′a-H), 4.00 (3b-H), 4.04 (3a-H), 4.27 (d, 1 H, vinyl-H), 4.36 (d, 1 H, vinyl-H), 4.40 (d, $^2J = 12.1$ Hz, 1 H), 4.48 (d, $^2J = 10.8$ Hz, 1 H), 4.55−4.59 (m, 3 H), 4.62 (d, 1 H, 1b-H), 4.64−4.67 (m, 3 H), 4.74 (d, $^2J = 12.1$ Hz, 1 H), 4.78−4.87 (m, 5 H), 4.88 (d, $^3J = 3.4$ Hz, 1 H, 1a-H), 4.97 (m, 2 H), 7.14 (m, 2 H), 7.23−7.34 (m, 36 H), 7.59 (d, 1 H); ^{13}C NMR (150.9 MHz, $CDCl_3$, extract of data) δ 55.2 (OMe), 66.7 (6a-C), 68.4 (6b-C), 68.9 (5b-C), 70.4 (5a-C), 77.7 (4a-C), 77.8 (2a-C), 80.0 (2b-C), 80.2 (4b-C), 82.0 (3b-C), 82.0 (3a-C), 87.1 (vinyl-CH_2), 96.3 (1a-C), 97.9 (1b-C); MS (FAB, 3-NBOH, NaI) *m*/*e* 1293 (5%, $[M + NaI]Na^+$), 1158 (9%, MK^+), 1142 (100%, MNa^+).

Methyl 6-{1-[2-(((2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)oxy)methyl)phen-1-yl]vinyl}-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (14β). To **13**β (800 mg, 1.19 mmol), **4**[18] (553 mg, 1.19 mmol), and DMAP (29 mg, 0.24 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C was added DCC (490 mg, 2.38 mmol). Ice-cooling was removed after 10 min, and the reaction mixture was stirred for 16 h at room temperature. Concentration in vacuo was followed by coevaporation with toluene. Flash chromatography (toluene/EtOAc 10:1) eluted a residue that was purified via a second flash chromatography (petroleum ether/EtOAc 3.5:1), which gave a white solid (1.05 g, 0.857 mmol, 72%; R_f 0.09 ($CHCl_3$/Et_2O 30:1), R_f 0.42 (petroleum ether/EtOAc 3:1)). To the solid (555 mg, 0.495 mmol) in dry THF (5 mL) at 0 °C was added Tebbe's reagent (0.5 M in toluene, 1.3 mL, 0.65 mmol). The reaction was carried out and the mixture worked up as described for **6**. Flash chromatography (petroleum ether/EtOAc 5:1, 1 vol % triethylamine) yielded **14**β (535 mg, 97%) as a white solid, which crystallized from EtOAc/petroleum ether at room temperature: mp 110 °C (EtOAc/petroleum ether); R_f 0.51 (petroleum ether/EtOAc 3:1); $[\alpha]_D$ 19.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.34 (s, 3 H), 3.41 (m, 1 H), 3.49−3.68 (m, 7 H), 3.87−3.93 (m, 3 H), 4.00 (dd, 1 H), 4.26 (d, $J = 2.4$ Hz, 1 H), 4.33 (d, $J = 2.4$ Hz, 1 H), 4.47 (d, $J = 7.5$ Hz, 1 H), 4.47−5.00 (m, 17 H), 7.14−7.38 (m, 38 H), 7.58 (dd, 1 H). Anal. Calcd for $C_{71}H_{74}O_{12}$: C, 76.18; H, 6.66. Found: C, 76.14; H, 6.67.

Methyl 4-{1-[2-(((2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)oxy)methyl)phen-1-yl]vinyl}-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (15β). To **13**β (915 mg, 1.36 mmol), **5**[19] (630 mg, 1.36 mmol), and DMAP (33 mg, 0.27 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C was added DCC (536 mg, 2.60 mmol). Ice-cooling was removed after 10 min, and the reaction mixture was stirred for 16 h at room temperature. Concentration in vacuo was followed by coevaporation with toluene. Flash chromatography (toluene/EtOAc 10:1) was done twice and yielded a white solid (1.30 g, 85%). To the solid (720 mg, 0.642 mmol) in dry THF (8 mL) at 0 °C was added Tebbe's reagent (0.5 M in toluene, 1.6 mL, 0.80 mmol). The reaction was carried out and the mixture worked up as described for **7**. Flash chromatography (petroleum ether/EtOAc 3.5:1, 1 vol % triethylamine) yielded **15**β (689 mg, 96%) as a colorless oil: R_f 0.27 (petroleum ether/EtOAc 3:1); $[\alpha]_D$ 11.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.27 (m, 1 H), 3.37 (s, 3 H), 3.43−3.73 (m, 7 H), 3.82 (m, 1 H), 4.02 (dd, 1 H), 4.35−4.93 (m, 21 H), 5.08 (d, $J = 12.5$ Hz, 1 H), 7.12−7.30 (m, 38 H), 7.59 (dd, 1 H); MS (FAB, 3-NBOH, NaI) *m*/*e* 1158 (5%, MK^+), 1142 (100%, MNa^+).

2-[2,3,4,6-Tetra-*O*-(3-methylbenzyl)-α/β-D-glucopyranosyloxymethyl]benzoic Acid (19α/β). To an anomeric mixture of **18**α/β[13] (2.80 g, 3.66 mmol, α:β = 1:1) in a mixture of dry THF (60 mL) and dry *n*-hexane (18 mL) at −100 °C was added *n*-butyllithium (1.6 M in hexane, 2.5 mL, 4.0 mmol). The reaction was carried out and the mixture worked up as described for **3**. Concentration in vacuo gave a syrup, which was purified by flash chromatography (petroleum ether/EtOAc 2:1). **19**α/β (2.30 g, 86%, α:β = 1:1) was obtained as a colorless, waxy solid: R_f 0.05−0.19 (petroleum ether/EtOAc 3:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.25−2.32 (m, 12 H), 3.50 (m, 0.5 H), 3.57−3.87 (m, 5 H), 4.08 (dd, 0.5 H), 4.39−5.14 (m, 10 H), 5.19 (d, $J = 15.0$ Hz, 0.5 H), 5.38 (d, $J = 15.0$ Hz, 0.5 H), 6.96 (m, 2 H), 7.06−7.24 (m, 14 H), 7.36 (m, 1 H), 7.52 (m, 1 H), 7.82 (m, 1 H), 8.06 (m, 1 H). Anal. Calcd for $C_{46}H_{50}O_8$: C, 75.59; H, 6.90. Found: C, 75.37; H, 6.89.

{1-[2-(((2,3,4,6-Tetra-*O*-(3-methylbenzyl)-α/β-D-glucopyranosyl)oxy)methyl)phen-1-yl]vinyl}-2-bromobenzyl Ether (20α/β). To an anomeric mixture of **19**α/β (1.20 g, 1.64 mmol, α:β = 1:1), 2-bromobenzyl alcohol (0.38 g, 2.03 mmol), and 4-(dimethylamino)pyridine (33 mg, 0.27 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C was added DCC (0.56 g, 2.7 mmol). Ice-cooling was removed after 10 min, and the reaction mixture was stirred for 16 h at room temperature. Concentration in vacuo was followed by coevaporation with toluene. Flash chromatography (petroleum ether/EtOAc 7:1) was done twice and yielded a colorless, waxy solid (1.41 g, 96%, α:β = 1:1; R_f 0.63 (toluene/EtOAc 10:1)). To the solid (440 mg, 0.489 mmol, α:β = 1:1) in dry THF (4 mL) at 0 °C was added Tebbe's reagent (0.5 M in toluene, 1.4 mL, 0.70 mmol). The reaction mixture was stirred at 0 °C for 90 min. Workup was carried out as described for **6**. Flash chromatography (petroleum/EtOAc 10:1, 1 vol % triethylamine) yielded **20**α/β (435 mg, 99%, α:β = 1:1) as a colorless oil: R_f 0.66 (toluene/EtOAc 10:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.25−2.30 (m, 12 H), 3.44 (m, 0.5 H), 3.49−3.73 (m, 4.5 H), 3.81 (m, 0.5 H), 4.04 (dd, 0.5 H), 4.36−4.98 (m, 14.5 H), 5.13 (d, $J = 12.9$ Hz, 0.5 H), 6.94−6.98 (m, 2 H), 7.05−7.67 (m, 22 H); MS (FAB, 3-NBOH, NaI): *m*/*e* 921 (17%, MNa^+), 303 (11%), 209 (93%), 169 (100%, $[BrPhCH_2]^+$).

Competition Experiments. (a) PhSeOTf Activation. To dry toluene (2.0 mL) and activated molecular sieves 4A (0.5 g) at 0 °C were added phenylselenyl chloride (63 mg, 0.33 mmol) and dried Ag^IOTf (85 mg, 0.33 mmol). After the mixture was stirred for 10 min at 0 °C with exclusion of light, a solution of **14**β (110 mg, 0.098 mmol) and **20**α,β (99 mg, 0.110 mmol, α:β = 1:1) in dry toluene (2.6 mL), cooled to 0 °C, was added by syringe dropwise over 2 min. The reaction mixture was stirred for 90 min at 0 °C and then diluted with EtOAc (8 mL) and after addition of saturated aqueous $Na_2S_2O_3$ (6 mL) again stirred for 2 h at room temperature. Water (20 mL) and EtOAc (80 mL) were added, and the layers were separated. The organic layer was washed with water (40 mL) and brine (60 mL), dried over $MgSO_4$, concentrated in vacuo, and coevaporated twice with toluene. Flash chromatography (22 g of SiO_2) was started with toluene/EtOAc (60:1, 450 mL). The fractions, which contained **18**α,β and **11**α,β, partially separated, were combined. The second solvent system (toluene/EtOAc 15:1, 450 mL) eluted **21**α,β followed by **16**α,β, which were again partially separated. These fractions were also combined. The total anomeric ratio could be determined with the help of the ^{1}H NMR signals by employing the following equations for the **16**α/β + **21**α/β mixture: (i) **16**α + **16**β + **21**α + **21**β = 1; (ii) (**16**α + **16**β)/(**21**α + **21**β) = *x*, which was determined from the integration of 3-methylbenzyl signals at δ ∼2.3; (iii) (**16**α + **21**α)/(**16**β + **21**β) = *y*, which was

determined from the integration of the α-OMe signal at δ 3.35 and the β-OMe signal at δ 3.32; (iv) **16**β/**21**β = z, which was determined from the integration of **16**β 1-H at δ 4.33 and **21**β 1-H at δ 4.34. Similar equations were employed for the **11**α/β + **18**α/β mixture: (i) **11**α + **11**β + **18**α + **18**β = 1; (ii) (**11**α + **11**β)/(**18**α + **18**β) = x, taken from the 3-methylbenzyl signal at δ ~2.3; (iii) (**11**α + **18**α)/(**11**β + **18**β) = y, taken from the 3α-H signal of the α-anomers at δ 4.06, 4.07; (iv) **11**α/**18**α = z, taken from 3α-H of **11**α at δ 4.07 and **18**α at δ 4.06. In the described experiment, the resulting yields were as follows: **18**α,β,[13] 37 mg, 44%, α:β = 1:1; **11**α,β,[13] 34 mg, 44%, α:β = 1:1; **21**α,β,[13] 47 mg, 41%; **16**α,β,[27] 45 mg, 41%; Σα:β = 1:2.

(b) TMSOTf Activation. The activating reagent was added to a solution of **14**β and **20**α,β at the corresponding temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ instead of saturated aqueous $Na_2S_2O_3$.

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