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The 4-(*tert*-Butyldiphenylsiloxy)-3-fluorobenzyl Group: A New Alcohol Protecting Group, Fully Orthogonal with the *p*-Methoxybenzyl Group and Removable under Desilylation Conditions

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Abstract

A new benzyl ether-type protecting group for alcohols, the 4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl group, is introduced. The protecting group is introduced by means of the readily prepared benzyl bromide and is cleaved with tetrabutylammonium fluoride in dimethylformamide around 90 °C. The fluoride substituent provides stability to oxidizing conditions, such that the new protecting group is fully compatible with the removal of *p*-methoxybenzyl ethers with DDQ. Applications of the new protecting group in the direct stereocontrolled synthesis of β -mannopyranosides are presented.

Introduction

Benzyl and silyl ethers are some of the most widely used alcohol protecting groups.¹ The high degree of mutual orthogonality which they display makes combinations of them attractive protecting systems for complex polyols, whether in the context of total synthesis, combinatorial library synthesis, or oligosaccharide synthesis. In addition to their differing reactivity patterns, the two types of protecting group differ significantly in their steric properties. The appreciably greater bulk of the silyl ethers leads to the much reduced chelating ability of α -siloxy carbonyl systems,² and contributes to the inverted conformations adopted by some polysilylated six-membered ring systems.³ In the course of a study targeted at the synthesis of the common core pentasaccharide of the *N*-linked glycoproteins we uncovered an unanticipated consequence of the steric bulk of silyl ether protecting groups.⁴ Thus, while 4,6-*O*-benzylidene protected thiomannopyranosides, and their sulfoxides, carrying benzyl ethers at positions 2 and 3 are known to be superb donors in the direct stereocontrolled formation of β -mannopyranoside linkages,⁵ an analogous system **1** carrying a 3-*O*-*tert*-butyldimethylsilyl group in place of a benzyl ether was found to favor the formation of α -mannosides. This result was even more surprising in view of the fact that the regioisomeric 3-*O*-benzyl-2-*O*-*tert*-butyldimethylsilyl system **2** showed adequate β -selectivity. Thus, the more remote 3-*O*-silyl group in **1** had a greater influence on the

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stereochemical outcome of the glycosylation than the 2-*O*-silyl ether adjacent to the reactive site in **2**. We rationalized this effect in terms of a buttressing interaction between the 3-*O*-silyl and 2-*O*-benzyl ethers in **1**, which forces the benzyl closer to the anomeric center leading ultimately to the reduced stereoselectivity.^{6,7}

This interesting reactivity pattern alerted us to the need for a protecting group having the steric characteristics of a benzyl ether but which is removable under typical desilylation conditions. We report here on the design and successful implementation of such a system.⁸

Results and Discussion

A significant range of substituted benzyl ether protecting groups is reported in the literature,^{1,9} many of which have been applied in carbohydrate chemistry.¹⁰ However, until the description of the *p*-silytanylbzyl ether,¹¹ none could be considered to be cleavable under typical desilylation conditions.¹² In designing such a protecting group we first considered the obvious simple *p*-siloxybenzyl type systems, but dismissed them on the grounds that they would be too acid sensitive and subject to cleavage under the same oxidative conditions commonly used for the removal of *p*-methoxybenzyl^{1,13} and naphthylmethyl ethers.¹⁴ Rather, we focused on *p*-siloxybenzyl systems bearing an electron-withdrawing substituent intended to provide enhanced stability under acidic and oxidative conditions, in much the same way that a 3-chloro substituent enhances the stability of the 4-azidobenzyl ethers.¹⁵ In view of our requirement for a system with the steric properties of a simple benzyl ether we targeted therefore the 3-fluoro-4-siloxybenzyl groups.

Starting from commercially available 4-carboxy-2-fluorophenol (**3**), 4-(*tert*-Butyldiphenylsiloxy)-3-fluorobenzyl bromide (**5**) was assembled in three convenient steps (Scheme 1).

Before proceeding to applications in oligosaccharide synthesis, the orthogonality of the new protecting group with *p*-methoxybenzyl ethers was tested. Thus, monoalkylation of 2,2-dibenzyl-1,3-propanediol **6** with *p*-methoxybenzyl chloride gave **7**, which was converted to the fully protected **8** on treatment with sodium hydride in THF in the presence of HMPA, followed by the addition of **5** (Scheme 2). Exposure of **8** to DDQ in wet dichloromethane at room temperature resulted in cleavage of the *p*-PMB ether in 95% yield. On the other hand, exposure of **8** to tetrabutylammonium fluoride in a variety of solvents, including DMF, at room temperature resulted only in the removal of the silyl ether, giving phenol **10**. This result was not totally unexpected in view of similar observations reported in the literature on saponification of *p*-acetoxybenzyl ethers.^{9b} Fortunately, when desilylation was conducted under microwave irradiation at 90 °C, a satisfactory 85% yield of the desired alcohol **7** was obtained (Scheme 2). The complete orthogonality of the new protecting group with *p*-methoxybenzyl ethers, for which the system had been designed, was thus established.

Turning to applications in glycosidic bond formation, treatment of Phenyl 4,6-*O*-benzylidene-1-thio- α -D-mannopyranoside **11** with *p*-methoxybenzyl chloride under phase transfer conditions¹⁶ afforded the 2-*O*-PMB ether **12**. Benzylolation with **5** and sodium hydride in DMF then provided the orthogonally protected glycosyl donor **13** (Scheme 3).

With acceptor **13** in hand, the glycosylation of a series of four acceptor alcohols was undertaken. These reactions were carried out in dichloromethane at $-60\text{ }^{\circ}\text{C}$, with prior activation of the thioglycoside with a combination of 1-benzenesulfinyl piperidine (BSP),^{5c,d,f} and trifluoromethanesulfonic anhydride in the presence of the convenient non-nucleophilic base 2,4,6-tri-*tert*-butylpyrimidine (TTBP),¹⁷ before addition of the alcohol. Like the action of trifluoromethanesulfonic anhydride on glycosyl sulfoxides,¹⁸ this activation protocol converts the thioglycoside to a covalent α -glycosyl trifluoromethanesulfonate,^{5c} which then undergoes $\text{S}_{\text{N}}2$ -like reaction with the alcohol with the intermediacy of a transient contact ion pair.¹⁹ As is clear from Table 1, all couplings proceeded in high yield and with excellent β -selectivity.²⁰

Glycosides **14-17** were then subjected to partial deprotection by exposure to DDQ at room temperature and by treatment with TBAF in THF at $90\text{ }^{\circ}\text{C}$ with the results set out in Table 2. As in the model experiments (Scheme 2), all attempts at debenzylation with TBAF at lower temperatures resulted only in the cleavage of the silyl group.

In a final demonstration of the ability of the new protecting group to support β -mannosylation reactions, donor **13** was coupled to alcohols **18** and **22** to generate the disaccharides **25** and **26**, both with excellent β -selectivity (Scheme 4), thereby establishing the viability of this new protecting group for use in the synthesis of mannans containing both the β -(1 $\rightarrow$ 2)^{5g} and β -(1 $\rightarrow$ 3)^{16d} linkages.

While the focus of this project has been on the application of the new benzyl protecting group in glycosylation reactions, we anticipate that it will also find use in the broader context of organic synthesis. In particular, we anticipate that the new protecting group will find application in situations requiring chelation control and the subsequent cleavage of the protecting group under desilylation conditions. Finally, we note that while we have concentrated here on benzyl ethers derived from bromide **5** base on the *tert*-butyldiphenylsilyl ether moiety, we expect that analogous chemistry was displayed by the corresponding 4-(*tert*-butyldimethylsiloxy)-3-fluorobenzyl and 4-(triisopropylsiloxy)-3-fluorobenzyl systems whose preparation is described in the supporting information.

Experimental Section

4-(*tert*-Butyldiphenylsiloxy)-3-fluorobenzyl alcohol (**4**)

To a stirred solution of 3-fluoro-4-hydroxybenzoic acid (2.0 g, 12.8 mmol) and Et_3N (10.7 ml, 76.8 mmol) in CH_2Cl_2 (30 ml) was added TBDPSCl (8.4 ml, 32.0 mmol) dropwise at room temperature. The reaction mixture was stirred at rt overnight and then diluted with CH_2Cl_2 , washed with brine. The organic layer was separated, dried over Na_2SO_4 and concentrated. The residue was then dissolved in dry THF (30 ml) at $0\text{ }^{\circ}\text{C}$ and LiAlH_4 (947 mg, 25.6 mmol) was added portion wise. After 10 min, the cooling bath was removed, the reaction mixture was stirred under reflux for 4 h. The reaction mixture was cooled to room temperature, and then water was added dropwise until a white solid precipitated. To

this mixture was added Na_2SO_4 and the mixture was filtered through Celite. The filter cake was washed with CH_2Cl_2 and the filtrate was concentrated and the residue was purified by flash chromatography over silica gel (15% ethyl acetate in hexane) afforded **4** (2.25 g, 46%). Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.79–7.77 (m, 4H), 7.46–7.40 (m, 6H), 7.06–7.04 (dd, J = 2.0, 11.0 Hz, 1H), 6.72 (d, J = 9.0 Hz, 1H), 6.65 (t, J = 8.5 Hz, 1H), 4.46 (s, 2H), 2.30 (s, 1H), 1.19 (s, 9H); ^{13}C NMR (125.9 MHz, CDCl_3) δ 153.7 (d, J = 246.7 Hz), 142.8 (d, J = 12.9 Hz), 135.5, 134.6 (d, J = 5.0 Hz), 132.6, 130.1, 127.9, 122.5 (d, J = 2.5 Hz), 121.3, 115.2 (d, J = 18.9 Hz), 64.3, 26.6, 19.8; HRESIMS calcd for $\text{C}_{23}\text{H}_{25}\text{O}_2\text{FSiNa}$ $[\text{M} + \text{Na}]^+$, 403.1506; found, 403.1496.

4-(*tert*-Butyldiphenylsiloxy)-3-fluorobenzyl bromide (**5**)

To a stirred solution of **4** (2.20 g, 5.78 mmol) and PPh_3 (2.27 g, 8.67 mmol) in CH_2Cl_2 (10 mL) was added CBr_4 portion wise and the resulting solution was stirred for 1 h at rt. The reaction mixture was concentrated and the residue was purified by chromatographic purification over silica gel (1% ethyl acetate in hexane) afforded **5** (2.32 g, 92%). Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.76–7.74 (m, 4H), 7.48–7.44 (m, 2H), 7.42–7.38 (m, 4H), 7.12–7.09 (dd, J = 2.0, 11.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.59 (t, J = 8.5 Hz, 1H), 4.37 (s, 2H), 1.16 (s, 9H); ^{13}C NMR (125.9 MHz, CDCl_3) δ 153.5 (d, J = 246.7 Hz), 143.7 (d, J = 12.9 Hz), 135.5, 132.3, 131.2 (d, J = 6.3 Hz), 130.2, 127.9, 124.7 (d, J = 2.5 Hz), 121.4, 117.2 (d, J = 18.9 Hz), 33.0, 26.5, 19.7; HRESIMS calcd for $\text{C}_{23}\text{H}_{24}\text{OBrFSiNa}$ $[\text{M} + \text{Na}]^+$, 465.0662; found, 465.0654.

General procedure for the removal of 4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl group using microwave reactor (method A)

To a stirred solution of the substrate and 4 Å molecular sieves in THF (0.05 M) was added TBAF (2 equiv, 1.0 M in THF). The reaction mixture was heated to 90 °C in microwave reactor for 2 h and cooled to rt. The reaction mixture was filtered through Celite. Purification by column chromatography on silica gel, eluting with hexane/ethyl acetate mixtures, afforded the corresponding alcohols.

General procedure for the removal of 4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl group with conventional heating (method B)

To a stirred solution of the substrate and 4 Å molecular sieves in DMF (0.05 M) was added TBAF (2 equiv, 1.0 M in THF). The reaction mixture was heated to 90 °C for 3 h and cooled to rt. The reaction mixture was filtered through Celite filtered and washed with EtOAc. The filtrate was diluted with EtOAc, washed with H_2O . The aqueous phase was extracted with EtOAc three times, and the combined organic phase was dried and concentrated. Purification by column chromatography on silica gel, eluting with hexane/ethyl acetate mixtures, afforded the corresponding alcohols.

General procedure for the removal of *para*-methoxybenzyl group

To a stirred solution of the substrate in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (9/1, 0.05 M) was added DDQ (2 equiv) in one portion. The reaction mixture was stirred at rt for 2 h and then diluted with CH_2Cl_2 , washed with brine. The organic layer was separated, dried over Na_2SO_4 and concentrated. Chromatographic purification on silica gel, eluting with hexane/ethyl acetate mixtures, afforded the corresponding alcohols.

2,2-Dibenzyl-3-(4-methoxybenzyloxy)propan-1-ol (**7**). From 2,2-Dibenzylpropane-1,3-diol **6**

To a stirred solution of 2,2-dibenzylpropane-1,3-diol (309 mg, 1.21 mmol) in THF (5 mL) at 0 °C was added sodium hydride (60%, 63 mg, 1.57 mmol). After 10 min, PMBCl (213 μL , 1.57 mmol) was added and the reaction mixture stirred under reflux for 6 h. The reaction

mixture was concentrated, dissolved in CH_2Cl_2 , washed with saturated NH_4Cl and brine. The organic layer was separated, dried over Na_2SO_4 and concentrated. Chromatographic purification (7.5 % ethyl acetate in hexane) on silica gel gave **7** (369 mg, 81%). **From 8:** Prepared by the general procedure for the removal of 4-(*tert*-butyldiphenylsilyloxy)-3-fluorobenzyl group using microwave reactor (method A) with a yield of 25.4 mg (85%). Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.32–7.20 (m, 12H), 6.94–6.92 (m, 2H), 4.43 (s, 2H), 3.83 (s, 3H), 3.47 (d, $J = 5.5$ Hz, 2H), 3.25 (s, 2H), 2.82 (d, $J = 13.5$ Hz, 1H), 2.78 (d, $J = 13.5$ Hz, 1H), 2.37 (t, $J = 5.5$ Hz, 1H); ^{13}C NMR (125.9 MHz, CDCl_3) δ 159.3, 137.9, 130.7, 130.1, 129.5, 128.1, 126.2, 113.9, 73.7, 73.1, 66.5, 55.4, 43.4, 39.4; HRESIMS calcd for $\text{C}_{25}\text{H}_{28}\text{O}_3\text{Na}$ $[\text{M} + \text{Na}]^+$, 399.1931; found, 399.1930.

2,2-Dibenzyl-1-[4-(*tert*-butyldiphenylsilyloxy)-3-fluorobenzoyloxy]-3-(4-methoxybenzoyloxy)propane (**8**)

To a stirred solution of **7** (157 mg, 0.417 mmol) in HMPA (404 μL , 0.417 mmol) and anhydrous THF (4 ml) at 0 °C was added *n*-BuLi (184 μL , 0.459 mmol). The reaction mixture was stirred at 0 °C for 5 min and then bromide **5** (222 mg, 0.500 mmol) in 1 ml THF was added. The ice bath was removed and the stirring continued for 10 h at rt. The reaction mixture was diluted with CH_2Cl_2 , washed with saturated NaHCO_3 and brine. The organic layer was separated, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (2.5% ethyl acetate in hexane) to give **8** (219 mg, 71%). Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.78–7.76 (m, 4H), 7.48–7.35 (m, 8H), 7.26–7.16 (m, 10H), 7.12–7.10 (dd, $J = 2.0$, 11.0 Hz, 1H), 6.96–6.94 (m, 2H), 6.78 (d, $J = 8.5$ Hz, 1H), 6.65 (t, $J = 8.5$ Hz, 1H), 4.42 (s, 2H), 4.32 (s, 2H), 3.85 (s, 3H), 2.93 (s, 2H), 2.89 (s, 2H), 2.853 (s, 2H), 2.849 (s, 2H), 1.18 (s, 9H); ^{13}C NMR (125.9 MHz, CDCl_3) δ 159.2, 153.6 (d, $J = 245.5$ Hz), 142.7 (d, $J = 11.3$ Hz), 138.4, 135.5, 132.6, 132.2 (d, $J = 5.0$ Hz), 130.7, 130.6, 130.1, 129.5, 127.8, 126.0, 123.2 (d, $J = 2.6$ Hz), 121.0, 115.9 (d, $J = 17.6$ Hz), 113.8, 72.7, 72.2, 70.0, 69.7, 55.4, 43.9, 39.0, 26.6, 19.7; HRESIMS calcd for $\text{C}_{48}\text{H}_{51}\text{O}_4\text{FSiNa}$ $[\text{M} + \text{Na}]^+$, 761.3438; found, 761.3400.

2,2-Dibenzyl-3-[4-(*tert*-butyldiphenylsilyloxy)-3-fluorobenzoyloxy]-propan-1-ol (**9**)

Prepared by the general procedure for the removal of *para*-methoxybenzyl group from **8** with a yield of 29.6 mg (89%). Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.74–7.72 (m, 4H), 7.46–7.35 (m, 6H), 7.26–7.16 (m, 10H), 7.05–7.02 (dd, $J = 2.0$, 11.5 Hz, 1H), 6.72 (d, $J = 8.5$ Hz, 1H), 6.60 (t, $J = 8.5$ Hz, 1H), 4.30 (s, 2H), 3.43 (d, $J = 5.5$ Hz, 2H), 3.16 (s, 2H), 2.77 (d, $J = 13.5$ Hz, 1H), 2.73 (d, $J = 13.5$ Hz, 1H), 2.12 (t, $J = 5.5$ Hz, 1H), 1.14 (s, 9H); ^{13}C NMR (125.9 MHz, CDCl_3) δ 153.4 (d, $J = 246.7$ Hz), 142.9 (d, $J = 11.3$ Hz), 137.8, 135.5, 132.6, 131.5 (d, $J = 5.0$ Hz), 130.6, 130.1, 128.0, 127.8, 126.2, 123.2, 121.1 (d, $J = 2.6$ Hz), 115.9 (d, $J = 18.8$ Hz), 73.7, 72.7, 66.2, 43.4, 39.4, 26.5, 19.7; HRESIMS calcd for $\text{C}_{40}\text{H}_{43}\text{O}_3\text{FSiNa}$ $[\text{M} + \text{Na}]^+$, 641.2858; found, 641.2854.

2,2-Dibenzyl-1-(4-hydroxy-3-fluorobenzoyloxy)-3-(4-methoxybenzoyloxy)propane (**10**)

To a stirred solution of **8** (16.2 mg, 21.9 μmol) in THF (1 ml) was added TBAF (33.0 μL , 1.0 M in THF). The reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated and chromatographic purification (10% ethyl acetate in hexane) on silica gel afforded **10** (12.5 mg, 92%). Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.34–7.32 (m, 2H), 7.23–7.13 (m, 10H), 7.05–6.97 (m, 2H), 6.94–6.91 (m, 2H), 5.18 (s, 1H), 4.40 (s, 2H), 4.36 (s, 2H), 3.84 (s, 3H), 2.93 (s, 2H), 2.92 (s, 2H), 2.84 (s, 4H); ^{13}C NMR (125.9 MHz, CDCl_3) δ 159.2, 150.9 (d, $J = 236.6$ Hz), 142.9 (d, $J = 13.8$ Hz), 138.4, 131.6 (d, $J = 5.0$ Hz), 130.7, 130.6, 129.5, 127.8, 125.9, 124.3 (d, $J = 2.6$ Hz), 117.0, 115.1 (d, $J = 17.6$ Hz), 113.8, 72.7, 72.1, 69.6, 55.3, 43.9, 39.0; HRESIMS calcd for $\text{C}_{32}\text{H}_{33}\text{O}_4\text{FNa}$ $[\text{M} + \text{Na}]^+$, 523.2255; found, 523.2252.

Phenyl 4,6-*O*-Benzylidene-2-*O*-(4-methoxybenzyl)-1-thio- α -D-mannopyranoside (**12**)

To a mixture of **11** (1.25 g, 3.46 mmol), tetrabutylammonium hydrogensulfate (235 mg, 0.692 mmol) and PMBCl (0.565 mL, 4.16 mmol) in CH₂Cl₂ (50 mL) was added 1 M aq. NaOH (17 mL). The reaction mixture was stirred under reflux for 24 h, then allowed to cool to room temperature, and diluted with CH₂Cl₂. The organic layer was separated. The aqueous phase was extracted twice with CH₂Cl₂. The combined organic layer was washed with saturated NaHCO₃, brine, dried over Na₂SO₄, and concentrated. Chromatographic purification (50% hexane in CH₂Cl₂) afforded **12** (1.16 g, 70%) as white crystalline solid. M.p. 113 °C. $[\alpha]_{\text{D}}^{22}$: +124.7 (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.53–7.25 m, 10H), 6.91–6.88 (m, 2H), 5.57 (s, 1H), 5.53 (s, 1H), 4.68 (d, *J* = 11.2 Hz, 1H), 4.58 (d, *J* = 11.2 Hz, 1H), 4.32–4.26 (dt, *J* = 4.8, 9.6 Hz, 1H), 4.24–4.20 (dd, *J* = 4.8, 10.4 Hz, 1H), 4.12–4.07 (m, 2H), 3.97 (t, *J* = 9.6 Hz, 1H), 3.83 (t, *J* = 10.4 Hz, 1H), 3.80 (s, 3H), 2.47 (d, *J* = 8.0 Hz, 1H); ¹³C NMR (100.7 MHz, CDCl₃) δ 159.9, 137.5, 133.9, 132.0, 130.0, 129.5, 129.4, 128.5, 128.0, 126.6, 114.3, 102.4, 86.6, 79.9, 79.8, 73.1, 69.2, 68.7, 64.9, 55.5. HRESIMS calcd for C₂₇H₂₈O₆SNa [M + Na]⁺, 503.1504; found, 503.1500.

Phenyl 4,6-*O*-Benzylidene-3-*O*-[4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl]-2-*O*-(4-methoxybenzyl)-1-thio- α -D-mannopyranoside (**13**)

To a stirred solution of **12** (700 mg, 1.61 mmol) in DMF (8 mL) at 0 °C was added NaH (60% in mineral oil, 70.8 mg, 1.77 mmol). After 15 min, **5** (857 mg, 1.93 mmol) in DMF (2 mL) was added and the reaction mixture stirred at rt for 10 h. The reaction mixture was diluted with EtOAc, washed with H₂O. The aqueous phase was extracted with EtOAc three times, and the combined organic phase was dried and concentrated. Chromatographic purification (7.5 % ethyl acetate in hexane) on silica gel gave **13** (947 mg, 74%). Colorless oil; $[\alpha]_{\text{D}}^{23}$: +51.8 (*c* 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.75–7.73 (m, 4H), 7.50–7.24 (m, 18H), 7.06–7.03 (dd, *J* = 2.0, 11.5 Hz, 1H), 6.85 (s, 1H), 6.83 (s, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.60 (t, *J* = 8.5 Hz, 1H), 5.62 (s, 1H), 5.47 (s, 1H), 4.66–4.58 (m, 3H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.27–4.20 (m, 3H), 3.97–3.96 (dd, *J* = 1.0, 3.0 Hz, 1H), 3.90–3.85 (m, 2H), 3.78 (s, 3H), 1.15 (s, 9H); ¹³C NMR (125.6 MHz, CDCl₃) δ 159.7, 153.9 (d, *J* = 245.6 Hz), 143.0 (d, *J* = 12.0 Hz), 137.7, 135.7, 134.1, 132.8, 132.2 (d, *J* = 6.5 Hz), 131.9, 130.3, 130.1, 129.8, 129.4, 129.1, 128.4, 128.0, 127.9, 126.3, 123.3 (d, *J* = 3.8 Hz), 121.2 (d, *J* = 1.9 Hz), 116.0 (d, *J* = 18.6 Hz), 114.1, 101.7, 87.3, 79.2, 77.5, 76.1, 72.7, 72.4, 68.7, 65.7, 55.5, 26.7, 19.9. HRESIMS calcd for C₅₀H₅₁O₇FSSiNa [M + Na]⁺, 865.3007; found, 865.2997.

General glycosylation procedure using the BSP/TTBP/Tf₂O system

To a stirred solution of donor (1 equiv.), BSP (1.2 equiv.), TTBP (1.5 equiv.), and 4 Å molecular sieves in CH₂Cl₂ (0.05 M in donor) at –60 °C, was added Tf₂O (1.2 equiv.). After 30 min of stirring at –60 °C, a 0.15 M solution of the glycosyl acceptor (1.5 equiv.) in CH₂Cl₂ was slowly added. The reaction mixture was stirred for a further 2 h at –60 °C, before saturated NaHCO₃ was added to quench the reaction. The reaction mixture was allowed to reach room temperature and then filtered through a pad of Celite and washed with CH₂Cl₂, after which the filtrate was washed with saturated NaHCO₃ and brine. The organic layer was separated, dried over Na₂SO₄, and concentrated. Purification by column chromatography on silica gel, eluting with hexane/ethyl acetate mixtures, afforded the corresponding coupled products.

1-Adamantanyl 4,6-*O*-Benzylidene-3-*O*-[4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl]-2-*O*-(4-methoxybenzyl)- β -D-mannopyranoside (**14 β**) and 1-Adamantanyl 4,6-*O*-Benzylidene-3-*O*-[4-

(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl]-2-O-(4-methoxybenzyl)- α -D-mannopyranoside (14 α)

Prepared by the general glycosylation procedure with a yield of 419 mg (85%, β : α = 11.7:1). **14 β** : white crystalline solid. M.p. 139 °C. $[\alpha]_{\text{D}}^{23}$: -19.8 (*c* 2.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.75–7.73 (m, 4H), 7.48–7.27 (m, 13H), 7.00 (d, *J* = 12.0 Hz, 1H), 6.85 (s, 1H), 6.83 (s, 1H), 6.63 (d, *J* = 8.5 Hz, 1H), 6.56 (t, *J* = 8.5 Hz, 1H), 5.59 (s, 1H), 4.92 (d, *J* = 12.5 Hz, 1H), 4.87 (d, *J* = 12.5 Hz, 1H), 4.76 (s, 1H), 4.48 (d, *J* = 12.5 Hz, 1H), 4.36 (d, *J* = 12.0 Hz, 1H), 4.28–4.25 (dd, *J* = 5.0, 10.5 Hz, 1H), 4.16 (t, *J* = 9.5 Hz, 1H), 3.93 (t, *J* = 10.0 Hz, 1H), 3.77 (s, 3H), 3.72 (d, *J* = 3.0 Hz, 1H), 3.52–3.49 (dd, *J* = 3.0, 10.0 Hz, 1H), 3.33–3.28 (dt, *J* = 4.5, 9.5 Hz, 1H), 2.19 (s, 3H), 1.88 (d, *J* = 11.0 Hz, 3H), 1.78 (d, *J* = 11.5 Hz, 3H), 1.68 (d, *J* = 12.5 Hz, 3H), 1.63 (d, *J* = 12.5 Hz, 3H), 1.15 (s, 9H); ¹³C NMR (125.6 MHz, CDCl₃) δ 159.4, 153.8 (d, *J* = 245.6 Hz), 142.9 (d, *J* = 12.1 Hz), 137.9, 135.7, 132.8, 132.4 (d, *J* = 6.5 Hz), 130.8, 130.7, 130.3, 129.0, 128.4, 128.0, 126.3, 123.1 (d, *J* = 2.8 Hz), 121.1 (d, *J* = 1.9 Hz), 115.9 (d, *J* = 19.5 Hz), 113.7, 101.6, 95.2 (¹*J*_{CH} = 153.6 Hz), 78.7, 78.5, 76.1, 75.5, 74.2, 71.7, 69.1, 67.5, 55.5, 42.7, 36.5, 30.9, 26.8. HRESIMS calcd for C₅₄H₆₁O₈FSiNa [M + Na]⁺, 907.4017; found, 907.4018. **14 α** : colorless oil; $[\alpha]_{\text{D}}^{22}$: +37.6 (*c* 0.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.74–7.72 (m, 4H), 7.49–7.27 (m, 13H), 7.08–7.05 (dd, *J* = 2.0, 11.5 Hz, 1H), 6.87 (s, 1H), 6.85 (s, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 6.58 (t, *J* = 8.5 Hz, 1H), 5.62 (s, 1H), 5.09 (d, *J* = 2.0 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.21–4.18 (dd, *J* = 5.0, 10.0 Hz, 1H), 4.15 (t, *J* = 9.5 Hz, 1H), 3.99–3.93 (dt, *J* = 5.0, 10.5 Hz, 1H), 3.94–3.91 (dd, *J* = 3.0, 9.5 Hz, 1H), 3.82 (t, *J* = 10.0 Hz, 1H), 3.79 (s, 3H), 3.60–3.59 (dd, *J* = 2.0, 3.0 Hz, 1H), 2.11 (s, 3H), 1.70–1.55 (m, 12H), 1.14 (s, 9H); ¹³C NMR (125.6 MHz, CDCl₃) δ 159.6, 153.8 (d, *J* = 244.7 Hz), 142.8 (d, *J* = 12.3 Hz), 134.0, 135.7, 132.9, 132.7 (d, *J* = 6.5 Hz), 130.5, 130.2, 130.1, 129.0, 128.4, 128.0, 126.2, 123.1 (d, *J* = 2.6 Hz), 121.1, 115.8 (d, *J* = 19.6 Hz), 114.0, 101.5, 92.7 (¹*J*_{CH} = 167.9 Hz), 79.8, 77.3, 76.6, 74.9, 73.1, 72.5, 69.2, 64.0, 55.5, 42.5, 36.4, 30.8, 26.7, 19.9. HRESIMS calcd for C₅₄H₆₁O₈FSiNa [M + Na]⁺, 907.4017; found, 907.4019.

4,6-O-Benzylidene-3-O-[4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl]-2-O-(4-methoxybenzyl)- β -D-mannopyranosyl-(1 $\rightarrow$ 3)-1,2:5,6-di-isopropylidene- α -D-glucofuranose (15)

Prepared by the general glycosylation procedure with a yield of 120.6 mg (82%). Colorless oil; $[\alpha]_{\text{D}}^{23}$: -31.6 (*c* 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.74–7.72 (m, 4H), 7.48–7.27 (m, 13H), 7.02–6.99 (dd, *J* = 2.0, 11.5 Hz, 1H), 6.85 (s, 1H), 6.83 (s, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.57 (t, *J* = 8.5 Hz, 1H), 5.92 (d, *J* = 3.5 Hz, 1H), 5.59 (s, 1H), 4.78 (d, *J* = 11.5 Hz, 1H), 4.70 (d, *J* = 11.5 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.54 (s, 1H), 4.45–4.41 (m, 3H), 4.33–4.27 (m, 3H), 4.18–4.13 (m, 2H), 4.09–4.06 (dd, *J* = 6.0, 8.5 Hz, 1H), 3.91 (t, *J* = 10.0 Hz, 1H), 3.81 (d, *J* = 3.0 Hz, 1H), 3.78 (s, 3H), 3.53–3.50 (dd, *J* = 3.0, 10.0 Hz, 1H), 3.32–3.27 (dt, *J* = 4.5, 10.0 Hz, 1H), 1.52 (s, 3H), 1.45 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 1.15 (s, 9H); ¹³C NMR (125.6 MHz, CDCl₃) δ 159.6, 153.9 (d, *J* = 245.5 Hz), 143.0 (d, *J* = 12.2 Hz), 137.6, 135.7, 132.8, 132.1 (d, *J* = 5.5 Hz), 130.4, 130.3, 129.1, 128.5, 128.0, 126.2, 123.3 (d, *J* = 3.8 Hz), 121.2, 115.9 (d, *J* = 18.6 Hz), 113.9, 112.2, 108.9, 105.2 (d, *J* = 183.8 Hz), 101.6, 100.6 (¹*J*_{CH} = 155.7 Hz), 83.1, 81.2, 80.7, 78.7, 78.1, 75.7, 74.6, 73.3, 72.0, 68.7, 68.0, 66.4, 55.5, 27.0, 26.9, 26.7, 26.5, 25.7, 19.9. HRESIMS calcd for C₅₆H₆₅O₁₃FSiNa [M + Na]⁺, 1015.4076; found, 1015.4038.

Methyl 4,6-O-Benzylidene-3-O-[4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl]-2-O-(4-methoxybenzyl)- β -D-mannopyranosyl-(1 $\rightarrow$ 6)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (16 β) and Methyl 4,6-O-Benzylidene-3-O-[4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl]-2-O-(4-methoxybenzyl)- α -D-mannopyranosyl-(1 $\rightarrow$ 6)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (16 α)

Prepared by the general glycosylation procedure with a yield of 133.8 mg (79%, β : α = 8.2:1). **16 β** : colorless oil; $[\alpha]_{\text{D}}^{23}$: -1.1 (*c* 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.74–7.71

(m, 4H), 7.48–7.17 (m, 28H), 7.02–7.00 (dd, $J = 2.0, 11.5$ Hz, 1H), 6.84 (s, 1H), 6.82 (s, 1H), 6.65 (d, $J = 8.5$ Hz, 1H), 6.57 (t, $J = 8.5$ Hz, 1H), 5.57 (s, 1H), 5.04 (d, $J = 11.0$ Hz, 1H), 4.87–4.80 (m, 4H), 4.71 (d, $J = 12.0$ Hz, 1H), 4.69 (d, $J = 12.0$ Hz, 1H), 4.61 (d, $J = 4.0$ Hz, 1H), 4.55 (d, $J = 12.0$ Hz, 1H), 4.51 (d, $J = 12.5$ Hz, 1H), 4.40 (d, $J = 12.5$ Hz, 1H), 4.28–4.24 (dd, $J = 5.0, 10.5$ Hz, 1H), 4.16–4.03 (m, 4H), 3.90 (t, $J = 10.0$ Hz, 1H), 3.80–3.77 (dd, $J = 5.0, 12.0$ Hz, 1H), 3.69 (s, 3H), 3.65 (d, $J = 3.0$ Hz, 1H), 3.55–3.52 (dd, $J = 4.0, 10.0$ Hz, 1H), 3.50–3.45 (m, 2H), 3.41–3.39 (dd, $J = 3.0, 9.5$ Hz, 1H), 3.36 (s, 3H), 3.23–3.18 (dt, $J = 5.0, 10.0$ Hz, 1H), 1.14 (s, 9H); ^{13}C NMR (125.6 MHz, CDCl_3) δ 159.5, 153.9 (d, $J = 245.5$ Hz), 143.0 (d, $J = 12.1$ Hz), 139.0, 138.6, 138.2, 137.7, 135.7, 132.8, 132.2 (d, $J = 5.5$ Hz), 130.5, 130.4, 130.3, 129.1, 128.74, 128.67, 128.6, 128.47, 128.45, 128.4, 128.2, 128.0, 127.9, 126.2, 123.2 (d, $J = 1.8$ Hz), 121.2, 115.9 (d, $J = 18.6$ Hz), 113.8, 102.2 ($^1J_{\text{CH}} = 156.7$ Hz), 101.6, 98.0 ($^1J_{\text{CH}} = 169.3$ Hz), 82.5, 80.1, 78.8, 78.1, 76.1, 75.0, 74.6, 74.1, 73.6, 71.8, 69.9, 68.8, 68.4, 67.7, 55.40, 55.36, 26.7, 19.9. HRESIMS calcd for $\text{C}_{72}\text{H}_{77}\text{O}_{13}\text{FSiNa}$ $[\text{M} + \text{Na}]^+$, 1219.5015; found, 1219.4989. **16a**: colorless oil; $[\alpha]_{\text{D}}^{23}$: +25.5 (c 0.4, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ 7.73–7.71 (m, 4H), 7.46–7.23 (m, 28H), 7.06–7.03 (dd, $J = 2.0, 12.0$ Hz, 1H), 6.83 (s, 1H), 6.81 (s, 1H), 6.68 (d, $J = 8.0$ Hz, 1H), 6.55 (t, $J = 8.5$ Hz, 1H), 5.59 (s, 1H), 5.00 (d, $J = 10.5$ Hz, 1H), 4.92 (d, $J = 11.0$ Hz, 1H), 4.83–4.77 (m, 3H), 4.69–4.56 (m, 6H), 4.43 (d, $J = 12.0$ Hz, 1H), 4.19–4.15 (m, 2H), 4.00 (t, $J = 10.0$ Hz, 1H), 3.84–3.62 (m, 10H), 3.50–3.47 (dd, $J = 3.5, 10.0$ Hz, 1H), 3.40 (t, $J = 9.5$ Hz, 1H), 3.31 (s, 3H), 1.13 (s, 9H); ^{13}C NMR (125.6 MHz, CDCl_3) δ 159.5, 153.7 (d, $J = 245.6$ Hz), 142.9 (d, $J = 12.2$ Hz), 138.8, 138.30, 138.25, 137.9, 135.7, 132.8, 132.6 (d, $J = 5.7$ Hz), 130.2, 129.9, 129.0, 128.73, 128.71, 128.69, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 126.3, 123.1 (d, $J = 1.8$ Hz), 121.1, 115.8 (d, $J = 19.4$ Hz), 114.0, 101.7, 99.7 ($^1J_{\text{CH}} = 171.7$ Hz), 98.0 ($^1J_{\text{CH}} = 169.5$ Hz), 82.3, 80.3, 79.3, 78.0, 76.6, 76.1, 75.8, 75.2, 73.5, 73.2, 69.9, 66.4, 64.4, 55.5, 55.3, 26.7, 19.9. HRESIMS calcd for $\text{C}_{72}\text{H}_{77}\text{O}_{13}\text{FSiNa}$ $[\text{M} + \text{Na}]^+$, 1219.5015; found, 1219.5043.

Methyl 4,6-O-Benzylidene-3-O-[4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl]-2-O-(4-methoxybenzyl)- β -D-mannopyranosyl-(1 $\rightarrow$ 4)-2-azido-3,6-di-O-benzyl-2-deoxy- α -D-glucopyranoside (17)

Prepared by the general glycosylation procedure with a yield of 126.4 mg (62%). Colorless oil; $[\alpha]_{\text{D}}^{24}$: -7.2 (c 2.0, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.76–7.74 (m, 4H), 7.47–7.18 (m, 23H), 7.07–7.05 (dd, $J = 2.0, 11.0$ Hz, 1H), 6.84–6.82 (m, 2H), 6.70 (d, $J = 8.0$ Hz, 1H), 6.62 (t, $J = 8.5$ Hz, 1H), 5.49 (s, 1H), 5.21 (d, $J = 10.5$ Hz, 1H), 4.82–4.67 (m, 5H), 4.40 (d, $J = 12.5$ Hz, 1H), 4.42–4.37 (m, 3H), 4.07–4.01 (m, 3H), 3.89–3.85 (dd, $J = 8.5, 10.0$ Hz, 1H), 3.78 (s, 3H), 3.70–3.56 (m, 4H), 3.52–3.48 (m, 1H), 3.49 (s, 3H), 3.41 (t, $J = 10.0$ Hz, 1H), 3.29–3.26 (dd, $J = 3.0, 10.0$ Hz, 1H), 3.07–3.02 (dt, $J = 5.0, 10.0$ Hz, 1H), 1.16 (s, 9H); ^{13}C NMR (125.6 MHz, CDCl_3) δ 159.5, 153.9 (d, $J = 245.5$ Hz), 143.0 (d, $J = 11.7$ Hz), 138.9, 137.8, 137.7, 135.7, 132.8, 132.5 (d, $J = 5.7$ Hz), 130.7, 130.4, 130.3, 129.1, 128.9, 128.5, 128.4, 128.32, 128.30, 128.1, 127.7, 126.3, 122.9 (d, $J = 2.8$ Hz), 121.2, 115.6 (d, $J = 19.6$ Hz), 113.8, 101.6, 101.5 (d, $J = 161.9$ Hz), 98.9 (d, $J = 173.1$ Hz), 78.9, 78.8, 78.5, 76.4, 75.3, 75.0, 73.9, 71.9, 70.5, 68.6, 68.4, 67.5, 63.2, 55.7, 55.5, 26.8, 19.9. HRESIMS calcd for $\text{C}_{65}\text{H}_{70}\text{N}_3\text{O}_{12}\text{FSiNa}$ $[\text{M} + \text{Na}]^+$, 1154.4611; found, 1154.4583.

1-Adamantanyl 4,6-O-Benzylidene-3-O-[4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl]- β -D-mannopyranoside (18)

Prepared by the general procedure for the removal of *para*-methoxybenzyl group from **14** with a yield of 97.3 mg (80%). Colorless oil; $[\alpha]_{\text{D}}^{22}$: -5.3 (c 1.5, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.73–7.71 (m, 4H), 7.48–7.34 (m, 11H), 7.10–7.07 (dd, $J = 2.0, 11.0$ Hz, 1H), 6.73 (d, $J = 8.5$ Hz, 1H), 6.57 (t, $J = 8.5$ Hz, 1H), 5.58 (s, 1H), 4.82 (s, 1H), 4.69 (d, $J = 12.0$ Hz, 1H), 4.64 (d, $J = 12.5$ Hz, 1H), 4.30–4.27 (dd, $J = 5.0, 10.5$ Hz, 1H), 4.11 (t, $J = 9.5$ Hz, 1H), 3.92 (d, $J = 3.0$ Hz, 1H), 3.87 (t, $J = 10.5$ Hz, 1H), 3.60–3.57 (dd, $J = 4.0, 9.5$

Hz, 1H), 3.34–3.29 (dt, $J = 5.0, 10.0$ Hz, 1H), 2.59 (s, 1H), 2.18 (s, 3H), 1.86 (d, $J = 11.0$ Hz, 3H), 1.78 (d, $J = 11.5$ Hz, 3H), 1.66 (d, $J = 12.5$ Hz, 3H), 1.61 (d, $J = 12.5$ Hz, 3H), 1.12 (s, 9H); ^{13}C NMR (125.6 MHz, CDCl_3) δ 153.9 (d, $J = 245.6$ Hz), 143.1 (d, $J = 12.2$ Hz), 137.7, 135.7, 132.8, 132.0 (d, $J = 5.6$ Hz), 130.3, 129.2, 128.5, 128.0, 126.3, 123.6 (d, $J = 2.8$ Hz), 121.3, 116.2 (d, $J = 19.6$ Hz), 101.7, 93.5, 78.4, 77.2, 76.1, 71.78, 71.75, 69.0, 66.9, 42.6, 36.4, 30.9, 26.8, 19.9. HRESIMS calcd for $\text{C}_{46}\text{H}_{53}\text{O}_7\text{FSiNa}$ $[\text{M} + \text{Na}]^+$, 787.3442; found, 787.3457.

4,6-O-Benzylidene-3-O-[4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl]- β -D-mannopyranosyl-(1 $\rightarrow$ 3)-1,2:5,6-di-isopropylidene- α -D-glucofuranose (19)

Prepared by the general procedure for the removal of *para*-methoxybenzyl group from **15** with a yield of 17.7 mg (80%). Colorless oil; $[\alpha]_{\text{D}}^{23} : -15.2$ (c 0.5, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.75–7.73 (m, 4H), 7.50–7.24 (m, 18H), 7.06–7.03 (dd, $J = 2.0, 11.5$ Hz, 1H), 6.85 (s, 1H), 6.83 (s, 1H), 6.70 (d, $J = 8.0$ Hz, 1H), 6.60 (t, $J = 8.5$ Hz, 1H), 5.62 (s, 1H), 5.47 (s, 1H), 4.66–4.58 (m, 3H), 4.46 (d, $J = 12.0$ Hz, 1H), 4.27–4.20 (m, 3H), 3.97–3.96 (dd, $J = 1.0, 3.0$ Hz, 1H), 3.90–3.85 (m, 2H), 3.78 (s, 3H), 2.19–1.78 (br s, 1H), 1.15 (s, 9H); ^{13}C NMR (125.6 MHz, CDCl_3) δ 153.9 (d, $J = 245.6$ Hz), 143.2 (d, $J = 11.2$ Hz), 137.5, 135.7, 132.8, 131.7 (d, $J = 5.5$ Hz), 130.3, 129.2, 128.5, 128.0, 126.2, 123.6 (d, $J = 3.8$ Hz), 121.3, 116.2 (d, $J = 18.6$ Hz), 112.3, 109.2, 105.4, 101.7, 98.3, 83.1, 80.8, 79.0, 78.6, 76.4, 73.4, 72.1, 70.0, 68.9, 67.3, 67.0, 27.0, 26.9, 26.7, 26.6, 25.7, 19.9. HRESIMS calcd for $\text{C}_{48}\text{H}_{57}\text{O}_{12}\text{FSiNa}$ $[\text{M} + \text{Na}]^+$, 895.3501; found, 895.3481.

Methyl 4,6-O-Benzylidene-3-O-[4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl]- β -D-mannopyranosyl-(1 $\rightarrow$ 6)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (20)

Prepared by the general procedure for the removal of *para*-methoxybenzyl group from **16** with a yield of 45.9 mg (84%). Colorless oil; $[\alpha]_{\text{D}}^{24} : +15.5$ (c 1.0, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ 7.73–7.70 (m, 4H), 7.47–7.20 (m, 26H), 7.10–7.08 (dd, $J = 2.0, 11.0$ Hz, 1H), 6.73 (d, $J = 8.5$ Hz, 1H), 6.58 (t, $J = 8.5$ Hz, 1H), 5.55 (s, 1H), 5.02 (d, $J = 11.0$ Hz, 1H), 4.89 (d, $J = 11.0$ Hz, 1H), 4.83 (d, $J = 11.0$ Hz, 1H), 4.80 (d, $J = 12.0$ Hz, 1H), 4.68–4.57 (m, 5H), 4.29–4.26 (dd, $J = 5.0, 10.5$ Hz, 1H), 4.18 (s, 1H), 4.09–3.99 (m, 3H), 3.91 (d, $J = 3.0$ Hz, 1H), 3.84 (t, $J = 9.5$ Hz, 1H), 3.81–3.77 (ddd, $J = 2.0, 5.0, 10.0$ Hz, 1H), 3.61–3.58 (dd, $J = 5.5, 10.0$ Hz, 1H), 3.54–3.51 (dd, $J = 3.5, 10.0$ Hz, 1H), 3.49–3.46 (dd, $J = 3.0, 9.5$ Hz, 1H), 3.44 (t, $J = 10.0$ Hz, 1H), 3.36 (s, 3H), 3.24–3.19 (dt, $J = 5.0, 10.0$ Hz, 1H), 2.41 (s, 1H), 1.13 (s, 9H); ^{13}C NMR (125.6 MHz, CDCl_3) δ 153.9 (d, $J = 246.6$ Hz), 143.2 (d, $J = 12.1$ Hz), 138.9, 138.6, 138.3, 137.6, 135.7, 132.8, 131.8 (d, $J = 5.7$ Hz), 130.3, 129.2, 128.74, 128.67, 128.5, 128.4, 128.22, 128.17, 128.0, 127.9, 126.2, 123.6 (d, $J = 2.8$ Hz), 121.2, 116.2 (d, $J = 18.6$ Hz), 101.8, 100.7, 98.1, 82.4, 80.1, 78.5, 77.7, 76.6, 76.0, 75.0, 73.6, 71.8, 70.0, 69.9, 68.8, 68.6, 67.1, 55.4, 26.7, 19.9. HRESIMS calcd for $\text{C}_{64}\text{H}_{69}\text{O}_{12}\text{FSiNa}$ $[\text{M} + \text{Na}]^+$, 1099.4440; found, 1099.4418.

Methyl 4,6-O-Benzylidene-3-O-[4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl]- β -D-mannopyranosyl-(1 $\rightarrow$ 4)-2-azido-3,6-di-O-benzyl-2-deoxy- α -D-glucopyranoside (21)

Prepared by the general procedure for the removal of *para*-methoxybenzyl group from **17** with a yield of 24.8 mg (82%). Colorless oil; $[\alpha]_{\text{D}}^{23} : +24.8$ (c 1.0, CHCl_3); 7.73–7.71 (m, 4H), 7.47–7.18 (m, 19H), 7.07–7.05 (dd, $J = 2.0, 11.0$ Hz, 1H), 6.70 (d, $J = 8.0$ Hz, 1H), 6.58 (t, $J = 8.5$ Hz, 1H), 5.47 (s, 1H), 5.04 (d, $J = 11.0$ Hz, 1H), 4.81–4.72 (m, 3H), 4.59 (d, $J = 12.0$ Hz, 1H), 4.51 (d, $J = 12.0$ Hz, 1H), 4.46 (s, 1H), 4.40 (d, $J = 12.0$ Hz, 1H), 4.06–3.64 (m, 8H), 3.48–3.43 (m, 2H), 3.43 (s, 3H), 3.41 (t, $J = 10.0$ Hz, 1H), 3.29–3.26 (dd, $J = 3.0, 10.0$ Hz, 1H), 3.07–3.02 (dt, $J = 5.0, 10.0$ Hz, 1H), 2.46 (s, 1H), 1.14 (s, 9H); ^{13}C NMR (125.6 MHz, CDCl_3) δ 153.9 (d, $J = 245.6$ Hz), 143.2 (d, $J = 11.2$ Hz), 138.5, 137.7, 137.6, 135.7, 132.7, 131.8 (d, $J = 5.5$ Hz), 130.3, 129.2, 128.8, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 126.2, 123.3 (d, $J = 2.8$ Hz), 121.3, 116.0 (d, $J = 19.5$ Hz), 101.7, 100.5, 98.9, 78.9,

78.3, 78.5, 75.3, 75.0, 73.9, 71.8, 70.3, 69.8, 68.6, 68.3, 67.0, 63.4, 55.6, 26.7, 19.9.
HRESIMS calcd for C₅₇H₆₂N₃O₁₁FSiNa [M + Na]⁺, 1034.4035; found, 1034.4011.

1-Adamantanyl 4,6-O-Benzylidene-2-O-(4-methoxybenzyl)-β-D-mannopyranoside (22)

22 was prepared by the general procedure for the removal of 4-(*tert*-butyldiphenylsilyloxy)-3-fluorobenzyl group using microwave reactor (method A) from **14** with a yield of 49.5 mg (74%). **22** was also prepared by the general procedure for the removal of 4-(*tert*-butyldiphenylsilyloxy)-3-fluorobenzyl group with conventional heating (method B) from **14** with a yield of 45.3 mg (77%). Colorless oil; [α]_D²⁴: −65.8 (c 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.51–7.31 (m, 7H), 6.91 (s, 1H), 6.89 (s, 1H), 5.53 (s, 1H), 5.08 (d, *J* = 11.5 Hz, 1H), 4.89 (s, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.29–4.26 (dd, *J* = 5.0, 10.5 Hz, 1H), 3.87 (t, *J* = 10.5 Hz, 1H), 3.82 (s, 3H), 3.82–3.73 (m, 3H), 3.36–3.31 (dt, *J* = 5.0, 9.5 Hz, 1H), 2.39 (d, *J* = 8.5 Hz, 1H), 2.20 (s, 3H), 1.90 (d, *J* = 11.0 Hz, 3H), 1.83 (d, *J* = 11.5 Hz, 3H), 1.69 (d, *J* = 12.5 Hz, 3H), 1.64 (d, *J* = 12.0 Hz, 3H); ¹³C NMR (125.6 MHz, CDCl₃) δ 159.7, 153.9 (d, *J* = 245.6 Hz), 143.0 (d, *J* = 12.0 Hz), 137.7, 135.7, 134.1, 132.8, 132.2 (d, *J* = 6.5 Hz), 131.9, 130.3, 130.1, 129.8, 129.4, 129.1, 128.4, 128.0, 127.9, 126.3, 123.3 (d, *J* = 3.8 Hz), 121.2 (d, *J* = 1.9 Hz), 116.0 (d, *J* = 18.6 Hz), 114.1, 101.7, 87.3, 79.2, 77.5, 76.1, 72.7, 72.4, 68.7, 65.7, 55.5, 26.7, 19.9. HRESIMS calcd for C₃₁H₃₈O₇Na [M + Na]⁺, 545.2515; found, 545.2515.

4,6-O-Benzylidene-2-O-(4-methoxybenzyl)-β-D-mannopyranosyl-(1→3)-1,2:5,6-di-isopropylidene-α-D-glucofuranose (23)

Prepared by the general procedure for the removal of 4-(*tert*-butyldiphenylsilyloxy)-3-fluorobenzyl group using microwave reactor (method A) from **15** with a yield of 19.7 mg (76%). Colorless oil; [α]_D²³: −53.0 (c 0.4, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.49–7.47 (m, 2H), 7.37–7.27 (m, 5H), 6.92 (s, 1H), 6.90 (s, 1H), 5.94 (d, *J* = 3.5 Hz, 1H), 5.55 (s, 1H), 4.90 (d, *J* = 11.5 Hz, 1H), 4.71 (s, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 3.5 Hz, 1H), 4.44 (d, *J* = 11.0 Hz, 1H), 4.42 (d, *J* = 11.0 Hz, 1H), 4.36 (d, *J* = 3.5 Hz, 1H), 4.33–4.28 (m, 2H), 4.18–4.15 (dd, *J* = 6.5, 8.5 Hz, 1H), 4.10–4.10 (dd, *J* = 5.5, 8.5 Hz, 1H), 3.89–3.79 (m, 3H), 3.82 (s, 3H), 3.38–3.33 (dt, *J* = 5.0, 10.0 Hz, 1H), 2.52 (s, 1H), 1.53 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H); ¹³C NMR (125.6 MHz, CDCl₃) δ 159.6, 137.4, 130.2, 130.1, 129.4, 128.5, 126.5, 114.3, 112.3, 109.1, 105.2, 102.2, 100.3, 83.0, 81.0, 80.7, 79.5, 77.9, 75.3, 73.2, 70.9, 68.7, 67.4, 66.7, 55.5, 26.98, 26.94, 26.5, 25.8. HRESIMS calcd for C₃₃H₄₂O₁₂Na [M + Na]⁺, 653.2574; found, 653.2556.

Methyl 4,6-O-Benzylidene-2-O-(4-methoxybenzyl)-β-D-mannopyranosyl-(1→6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (24)

Prepared by the general procedure for the removal of 4-(*tert*-butyldiphenylsilyloxy)-3-fluorobenzyl group using microwave reactor (method A) from **16** with a yield of 13.3 mg (78%). Colorless oil; [α]_D²³: −15.0 (c 0.4, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.47–7.27 (m, 22H), 6.89 (s, 1H), 6.88 (s, 1H), 5.51 (s, 1H), 5.02 (d, *J* = 11.0 Hz, 1H), 4.96 (d, *J* = 11.0 Hz, 1H), 4.91 (d, *J* = 11.0 Hz, 1H), 4.84 (d, *J* = 11.0 Hz, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.59 (s, 1H), 4.52 (d, *J* = 11.5 Hz, 1H), 4.34 (s, 1H), 4.29–4.26 (dd, *J* = 5.0, 10.0 Hz, 1H), 4.17–4.15 (dd, *J* = 2.0, 10.0 Hz, 1H), 4.04 (t, *J* = 9.5 Hz, 1H), 3.88–3.75 (m, 7H), 3.71–3.66 (dt, *J* = 3.5, 9.5 Hz, 1H), 3.58–3.54 (dd, *J* = 5.5, 10.5 Hz, 1H), 3.51–3.49 (dd, *J* = 3.5, 10.0 Hz, 1H), 3.45 (t, *J* = 10.0 Hz, 1H), 3.37 (s, 3H), 3.28–3.23 (dt, *J* = 5.0, 10.0 Hz, 1H), 2.35 (d, *J* = 9.0 Hz, 1H); ¹³C NMR (125.6 MHz, CDCl₃) δ 159.7, 138.8, 138.5, 138.3, 137.5, 130.4, 130.2, 129.3, 128.72, 128.70, 128.5, 128.43, 128.38, 128.3, 128.2, 128.1, 128.0, 126.4, 114.2, 102.5, 102.2, 98.1, 82.4, 80.2, 79.5, 78.1, 77.9, 76.2, 75.5, 75.1, 73.7, 70.9, 70.0, 68.8, 68.7, 67.3, 55.5, 55.4. HRESIMS calcd for C₄₉H₅₄O₁₂Na [M + Na]⁺, 857.3513; found, 857.3504.

Methyl 4,6-O-Benzylidene-2-O-(4-methoxybenzyl)- β -D-mannopyranosyl-(1 $\rightarrow$ 4)-2-azido-3,6-di-O-benzyl-2-deoxy- α -D-glucopyranoside (25)

Prepared by the general procedure for the removal of 4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl group using microwave reactor (method A) from **17** with a yield of 21.2 mg (78%). Colorless oil; $[\alpha]_D^{24}$: -9.0 (c 0.5, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.49–7.27 (m, 17H), 6.88–6.86 (m, 2H), 5.43 (s, 1H), 5.19 (d, J = 11.0 Hz, 1H), 4.91 (d, J = 11.5 Hz, 1H), 4.81 (d, J = 3.5 Hz, 1H), 4.76 (d, J = 12.0 Hz, 1H), 4.70 (d, J = 11.0 Hz, 1H), 4.57 (d, J = 11.0 Hz, 1H), 4.48 (s, 1H), 4.44 (d, J = 11.5 Hz, 1H), 4.08–4.03 (m, 2H), 3.86 (t, J = 9.5 Hz, 1H), 3.80 (s, 3H), 3.73–3.62 (m, 5H), 3.50–3.47 (m, 2H), 3.47 (s, 3H), 3.38 (t, J = 10.0 Hz, 1H), 3.07–3.02 (dt, J = 5.0, 10.0 Hz, 1H); ^{13}C NMR (125.6 MHz, CDCl_3) δ 159.7, 138.7, 137.54, 137.48, 130.4, 130.1, 129.4, 129.0, 128.6, 128.5, 128.43, 128.40, 128.3, 128.2, 127.8, 126.5, 126.3, 114.1, 102.2, 101.8, 98.9, 79.3, 78.9, 78.8, 77.9, 75.9, 75.3, 74.0, 71.0, 70.5, 68.6, 68.3, 67.1, 63.2, 55.7, 55.5. HRESIMS calcd for $\text{C}_{42}\text{H}_{47}\text{N}_3\text{O}_{11}\text{Na}$ [$\text{M} + \text{Na}$] $^+$, 792.3108; found, 792.3138.

1-Adamantanyl 4,6-O-Benzylidene-3-O-[4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl]-2-O-(4-methoxybenzyl)- α -D-mannopyranosyl-(1 $\rightarrow$ 3)-4,6-O-benzylidene-2-O-(4-methoxybenzyl)- β -D-mannopyranoside (26 α) and 1-Adamantanyl 4,6-O-Benzylidene-3-O-[4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl]-2-O-(4-methoxybenzyl)- β -D-mannopyranosyl-(1 $\rightarrow$ 3)-4,6-O-benzylidene-2-O-(4-methoxybenzyl)- β -D-mannopyranoside (26 β)

Prepared by the general glycosylation procedure, radical chromatographic purification (5 % ethyl acetate in toluene) on silica gel provided **26** with a yield of 48.2 mg (71%, β : α = 11.4:1). **26 α** : colorless oil; $[\alpha]_D^{24}$: -12.5 (c 0.2, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.69–7.27 (m, 22H), 7.06–7.03 (dd, J = 2.0, 11.0 Hz, 1H), 6.91 (s, 1H), 6.89 (s, 1H), 6.74 (s, 1H), 6.72 (s, 1H), 6.63–6.62 (m, 3H), 6.51 (t, J = 8.5 Hz, 1H), 5.61 (s, 1H), 5.56 (s, 1H), 5.34 (s, 1H), 4.84 (d, J = 11.5 Hz, 1H), 4.82 (s, 1H), 4.77 (d, J = 12.5 Hz, 1H), 4.49 (d, J = 12.5 Hz, 1H), 4.44 (d, J = 11.5 Hz, 1H), 4.33 (d, J = 12.0 Hz, 1H), 4.28–4.12 (m, 5H), 3.96–3.78 (m, 5H), 3.72 (s, 3H), 3.72–3.66 (m, 2H), 3.48 (s, 3H), 3.40–3.35 (dt, J = 5.0, 10.0 Hz, 1H), 2.18 (s, 3H), 1.86 (d, J = 12.0 Hz, 3H), 1.77 (d, J = 11.5 Hz, 3H), 1.68–1.59 (m, 6H), 1.10 (s, 9H); ^{13}C NMR (125.6 MHz, CDCl_3) δ 159.39, 159.38, 153.9 (d, J = 245.7 Hz), 142.9 (d, J = 12.2 Hz), 137.9, 137.8, 135.6, 132.8, 132.4 (d, J = 5.0 Hz), 130.3, 130.2, 129.9, 129.7, 129.6, 129.0, 128.6, 128.5, 128.4, 128.0, 126.4, 126.3, 123.0 (d, J = 2.8 Hz), 121.0, 115.8 (d, J = 19.6 Hz), 113.84, 113.80, 102.0, 101.6, 99.8 ($^1J_{\text{CH}}$ = 169.5 Hz), 95.0 ($^1J_{\text{CH}}$ = 155.4 Hz), 79.2, 79.1, 78.2, 75.8, 75.7, 75.0, 74.6, 72.3, 72.0, 69.1, 69.0, 67.2, 64.9, 55.4, 55.1, 42.6, 36.4, 30.8, 26.7, 19.9. HRESIMS calcd for $\text{C}_{75}\text{H}_{83}\text{O}_{14}\text{FSiNa}$ [$\text{M} + \text{Na}$] $^+$, 1277.5434; found, 1277.5403. **26 β** : colorless oil; $[\alpha]_D^{24}$: -54.2 (c 1.0, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.73–7.72 (m, 4H), 7.49–7.17 (m, 21H), 6.70–6.65 (m, 5H), 6.57 (t, J = 8.5 Hz, 1H), 5.61 (s, 1H), 5.49 (s, 1H), 4.93 (d, J = 12.5 Hz, 1H), 4.871 (s, 1H), 4.87 (d, J = 12.0 Hz, 1H), 4.82 (d, J = 12.0 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.44 (d, J = 12.5 Hz, 1H), 4.36 (d, J = 12.0 Hz, 1H), 4.32–4.29 (dd, J = 5.0, 10.5 Hz, 1H), 4.18–4.15 (dd, J = 5.0, 10.5 Hz, 1H), 4.10 (t, J = 9.5 Hz, 1H), 4.06–4.03 (dd, J = 3.0, 10.5 Hz, 1H), 4.00 (t, J = 10.0 Hz, 1H), 3.96 (t, J = 10.0 Hz, 1H), 3.88 (s, 1H), 3.83 (t, J = 10.5 Hz, 1H), 3.80 (d, J = 3.0 Hz, 1H), 3.73 (s, 3H), 3.60 (s, 3H), 3.60–3.59 (m, 1H), 3.42–3.38 (dt, J = 5.0, 9.5 Hz, 1H), 3.16–3.13 (dd, J = 3.0, 9.5 Hz, 1H), 2.85–2.80 (dt, J = 4.5, 9.5 Hz, 1H), 2.22 (s, 3H), 1.94 (d, J = 11.0 Hz, 3H), 1.86 (d, J = 11.0 Hz, 3H), 1.70 (d, J = 12.0 Hz, 3H), 1.66 (d, J = 12.5 Hz, 3H), 1.13 (s, 9H); ^{13}C NMR (125.6 MHz, CDCl_3) δ 159.6, 159.2, 153.9 (d, J = 245.7 Hz), 142.9 (d, J = 11.2 Hz), 137.8, 135.7, 132.8, 132.5 (d, J = 5.5 Hz), 131.0, 130.8, 130.4, 130.24, 130.21, 129.1, 129.0, 128.41, 128.37, 128.0, 126.5, 126.2, 122.8 (d, J = 3.7 Hz), 121.1, 115.7 (d, J = 19.6 Hz), 113.9, 113.7, 102.0, 101.5, 97.4 ($^1J_{\text{CH}}$ = 156.5 Hz), 95.8 ($^1J_{\text{CH}}$ = 154.0 Hz), 78.4, 77.8, 77.2, 75.9, 75.0, 74.3, 73.76, 73.74, 73.6, 71.2, 69.1, 68.7, 67.9, 67.7, 55.45, 55.42, 42.8, 36.4, 30.9, 26.8, 19.0. HRESIMS calcd for $\text{C}_{75}\text{H}_{83}\text{O}_{14}\text{FSiNa}$ [$\text{M} + \text{Na}$] $^+$, 1277.5434; found, 1277.5483.

1-Adamantanyl 4,6-O-Benzylidene-3-O-[4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl]-2-O-(4-methoxybenzyl)- β -D-mannopyranosyl-(1 $\rightarrow$ 2)-4,6-O-benzylidene-3-O-[4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl]- β -D-mannopyranoside (27)

Prepared by the general glycosylation procedure with a yield of 98.4 mg (62%). **27**: colorless oil; $[\alpha]_D^{23}$: -29.7 (*c* 2.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.75–7.71 (m, 8H), 7.48–7.34 (m, 22H), 7.26–7.22 (dd, *J* = 2.0, 12.0 Hz, 1H), 6.91–6.89 (dd, *J* = 1.5, 12.0 Hz, 1H), 6.84 (s, 1H), 6.82 (s, 1H), 6.63 (d, *J* = 8.5 Hz, 1H), 6.76 (t, *J* = 8.0 Hz, 1H), 6.58–6.51 (m, 3H), 5.59 (s, 1H), 5.47 (s, 1H), 4.97 (d, *J* = 12.0 Hz, 1H), 4.93 (d, *J* = 12.0 Hz, 1H), 4.87 (s, 1H), 4.80 (s, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.31–4.22 (m, 5H), 4.15 (t, *J* = 9.5 Hz, 1H), 4.04 (t, *J* = 9.5 Hz, 1H), 4.01 (d, *J* = 3.5 Hz, 1H), 3.90 (t, *J* = 10.0 Hz, 1H), 3.76 (t, *J* = 9.5 Hz, 1H), 3.74 (s, 3H), 3.60–3.58 (dd, *J* = 3.0, 10.0 Hz, 1H), 3.43–3.41 (dd, *J* = 3.0, 10.0 Hz, 1H), 3.37–3.32 (dt, *J* = 5.0, 9.5 Hz, 1H), 3.29–3.25 (dt, *J* = 5.0, 10.0 Hz, 1H), 2.18 (s, 3H), 1.76 (d, *J* = 10.0 Hz, 3H), 1.70 (d, *J* = 11.0 Hz, 3H), 1.67 (d, *J* = 11.5 Hz, 3H), 1.60 (d, *J* = 12.0 Hz, 3H), 1.14 (s, 9H); ¹³C NMR (125.6 MHz, CDCl₃) δ 159.3, 153.88 (d, *J* = 245.0 Hz), 153.85 (d, *J* = 246.1 Hz), 142.83 (d, *J* = 12.1 Hz), 142.79 (d, *J* = 12.1 Hz), 137.9, 137.7, 135.7, 132.91, 132.88, 132.87, 132.7 (d, *J* = 5.7 Hz), 132.3 (d, *J* = 6.0 Hz), 131.2, 131.0, 130.2, 129.1, 129.0, 128.5, 128.4, 128.0, 126.30, 126.26, 123.1 (d, *J* = 2.8 Hz), 121.0, 120.9, 116.0 (d, *J* = 18.5 Hz), 115.7 (d, *J* = 19.6 Hz), 113.7, 104.4 (¹*J*_{CH} = 154.0 Hz), 101.8, 101.5, 94.6 (¹*J*_{CH} = 154.0 Hz), 79.1, 78.5, 78.3, 76.6, 75.7, 74.0, 73.9, 70.7, 70.6, 69.2, 68.9, 68.0, 67.5, 55.4, 42.8, 36.4, 30.8, 26.8. HRESIMS calcd for C₉₀H₉₈O₁₄F₂Si₂Na [M + Na]⁺, 1519.6361; found, 1519.6327.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Assembly of 4-(*tert*-Butyldiphenylsiloxy)-3-fluorobenzyl bromide

Scheme 2.
Orthogonality with *p*-Methoxybenzyl Ethers

Scheme 3.
Preparation of Glycosyl Donor **13**

Scheme 4.
Disaccharide Synthesis

Table 1

Glycosylation Reactions with Donor **13**

ROH	Product	Yield	$\beta:\alpha$ ratio
	14	85%	11.7:1
	15	82%	β only
	16	79%	8.2:1
	17	62%	β only

Table 2

Selective Deprotection of Glycosides.^a

ROH	DDQ Product (% yield)	TBAF Product (% yield)
	18 (80)	22 (74) ^b
	19 (80)	22 (77) ^c
	20 (84)	23 (76)
	21 (82)	24 (78)
		25 (78)

^a) The deprotections were conducted with the anomerically pure β-anomer.^b) Heating in a microwave reactor.^c) Conventional heating in DMF solution.