JOC*Note*

Application of the 4-Trifluoromethylbenzenepropargyl Ether Group as an Unhindered, Electron Deficient Protecting Group for Stereoselective Glycosylation

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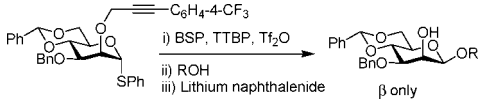
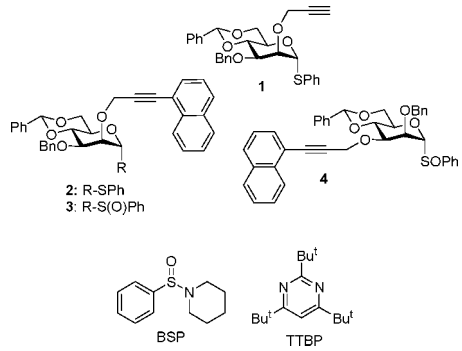


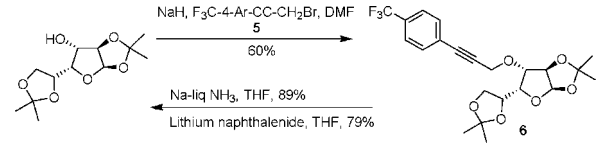
4-Trifluoromethylbenzenepropargyl ethers are stable and sterically minimal alcohol protecting groups that are readily cleaved in a single step by exposure to lithium naphthalenide. In conjunction with the 4,6-*O*-benzylidene protecting group, glycosylation reactions of 2-*O*-(4-trifluoromethylbenzenepropargyl)-protected mannosyl donors are extremely β-selective.

Protecting groups continue to play a central role in modern organic synthesis,[1] and the ability/inability to achieve selective deprotection of one protecting group in the presence of another is often key to the success/failure of a synthetic route. In response to a problem arising from the influence of protecting group size on the stereoselectivity of a glycosylation reaction, we described the application of a propargyl ether as a sterically minimal donor protecting group for β-mannosylation with donor **1**.[2]



Although the propargyl ethers were readily introduced (in 90% isolated yields) and had the anticipated effect on stereoselectivity (>95:5 β/α), they required a two-step deprotection protocol, namely an initial treatment with the base followed by catalytic osmylation of the resulting allenyl ether.[2] Subsequently, to facilitate deprotection, the propargyl ether system was modified in such a way as to be cleavable in a single step, orthogonal to the ubiquitous benzyl ethers. This was achieved through the use of the naphthyl propargyl system, which is removed in a single step with DDQ.[3] Donors **2** and **3**, however, had two limitations: incompatibility with glycosylation reactions owing to cyclization onto the oxacarbenium ion and direct reaction of the electron rich triple bond with glycosidation promoters. Nevertheless, the naphthylpropargyl system was ideal for use at the 3-*O*-position of donors, as in **4**, provided that it was used in conjunction with the sulfoxide glycosylation method and a sacrificial alkene.[3] Extending this series we now describe an electron-poor arylpropargyl system compatible with the 2-*O*-position and removable under dissolving metal conditions.

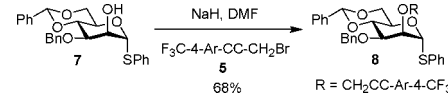
SCHEME 1. Model Protection and Deprotection of D-Glucofuranose



Alkylation of 1,2:5,6-di-*O*-acetone-D-glucofuranose with sodium hydride and 4-trifluoromethylphenyl propargyl bromide **5**[4] gave the model ether **6**, with which different reductive conditions were explored (Scheme 1). Exposure of **6** to samarium iodide, generated under standard conditions,[5] resulted in no reaction. When **6** was exposed to samarium iodide generated by mixing samarium and iodine,[6] partial loss of an isopropylidene group was observed with no formation of the desired product. Presumably unreacted iodine acted as a Lewis acid resulting in the loss of an isopropylidene group.[7]However, sodium in liquid ammonia[8] and lithium naphthalenide[9] proved effective in removing the electron-deficient propargyl ether and in affording the required deprotected sugar in good yield.

To examine the effect of the new electron-poor protecting group on the stereoselectivity of glycosylation reactions when located at O2, donor **8** was prepared by reaction of glycoside **7** with propargyl bromide **5** (Scheme 2).

SCHEME 2. Preparation of Donor 8



(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley and Sons: New York, 2007. (b) Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, 1994.

(2) Crich, D.; Jayalath, P. *Org. Lett.* **2005**, *7*, 2277. For use of electron-withdrawing groups in mannopyranoside synthesis, see: (b) Srivastava, V. K.; Schuerch, C. *J. Org. Chem.* **1981**, *46*, 1121. (c) Crich, D.; Hutton, T. K.; Banerjee, A.; Jayalath, P.; Picione, J. *Tetrahedron: Asymmetry* **2005**, *16*, 105.

(3) Crich, D.; Wu, B. *Org. Lett.* **2006**, *8*, 4879. (b) Crich, D.; Wu, B.; Jayalth, P. *J. Org. Chem.* **2007**, *72*, 6806.

(4) This compound was prepared using a two-step literature procedure starting from commercially available 1-bromo-4-trifluoromethylbenzene, see: Wrobel, J.; Li, Z.; Dietrich, A.; McCabel, M.; Mihan, B.; Sredy, J.; Sullivan, D. *J. Med. Chem.* **1998**, *41*, 1084.

(5) (a) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693. (b) Molander, G. A.; Mckie, J. A. *J. Org. Chem.* **1992**, *57*, 3132.

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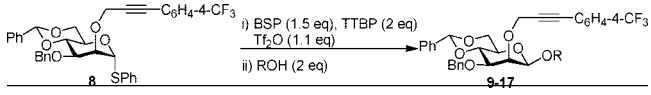
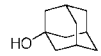
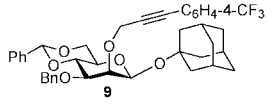
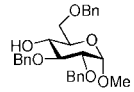
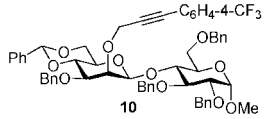
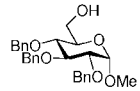
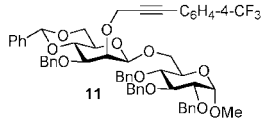
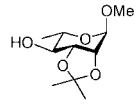
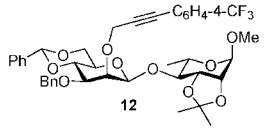
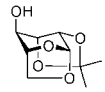
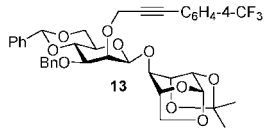
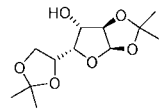
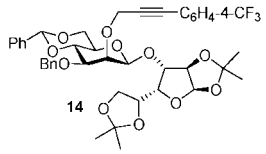
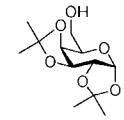
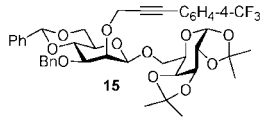
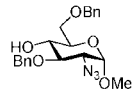
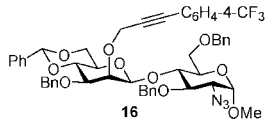
Treatment of **8** with triflic anhydride in the presence of BSP[10] and TTBP[11] at −70 °C in CH_2Cl_2, to give an intermediate glycosyl triflate,[11] followed by addition of 1-adamantanol resulted in the formation of the β-mannoside **9** with impeccable selectivity (Table 1, entry 1). A number of further couplings were then conducted with more standard glycosyl acceptors, leading to the yields collected in Table 1.

TABLE 1. Coupling Reactions of Donor 8

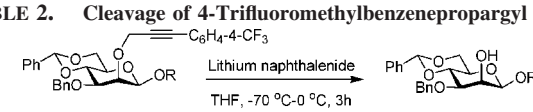


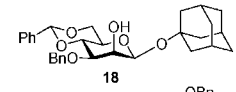
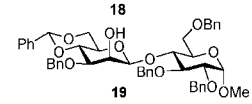
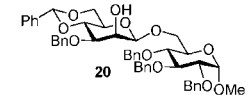
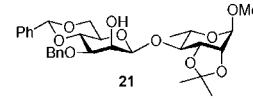
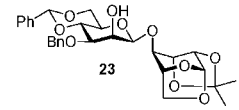
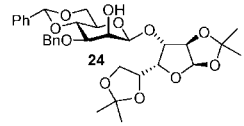
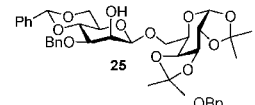
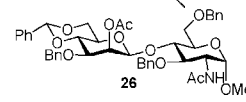
Entry	Acceptor	Coupled Product	Yield[a, b, c]
1		 **9**	72%
2		 **10**	61%
3		 **11**	62%
4		 **12**	61%
5		 **13**	59%
6		 **14**	63%
7		 **15**	50%
8		 **16**	48%[d]

[a] Reactions were performed at 0.03 M concentration, using 2 equiv of acceptor. Isolated yields after column chromatography. [b] ^{1}H NMR spectroscopy of crude reaction mixtures revealed only β isomer formation in all cases. [c] In all cases, the hydrolysis product **17** (R = H) was the main side product. [d] Reaction was performed at 0.05 M concentration, using 4 equiv of acceptor.

Selective deprotection was achieved using lithium naphthalenide in THF by warming a −70 °C reaction mixture to 0 °C over a period of 2−3 h when **18** was obtained in 85% yield. This strategy was extended to glycosides **10** to **16** (Table 2). In almost all cases, minor amounts of debenzylated products were obtained as the side products.

TABLE 2. Cleavage of 4-Trifluoromethylbenzenepropargyl Ethers

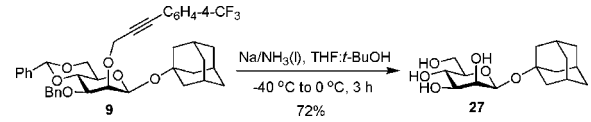


Entry	Deprotected Product	Yield[a]
1	 **18**	85%
2	 **19**	67%
3	 **20**	63%
4	 **21**	61%
5	 **23**	60%
6	 **24**	59%
7	 **25**	55%
8	 **26**	53%

[a] Isolated yields after column chromatography.

Exposure of mannoside **9** to Na in liquid ammonia cleanly gave fully deprotected 1-adamantanyl β-D-mannopyranoside **27** (Scheme 3).

SCHEME 3. Complete Deprotection



To conclude, we report the development of the electron-poor 4-trifluoromethylbenzenepropargyl ether system as an alcohol protecting group. In conjunction with the BSP glycosylation method, when introduced at the 2-position of 4,6-*O*-benzylidene-protected mannosyl donors, this system affords extremely β-selective coupling reactions and the possibility of orthogonal cleavage in a single step with lithium naphthalenide.

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(7) Szarek, W. A.; Zamojski, A.; Tiwari, K.; Ison, E. *Tetrahedron Lett.* **1986**, *27*, 3827.
(8) Iserloh, U.; Dudkin, V.; Wang, Z.-G.; Danishefsky, S. J. *Tetrahedron Lett.* **2002**, *43*, 7027.
(9) Liu, H-J.; Yip, J.; Shia, K.-S. *Tetrahedron Lett.* **1997**, *38*, 2253.

Experimental Section

General Procedure for Coupling of Mannosyl Donor 8 with Acceptors. To a stirred solution of donor **8** (0.10 g, 0.16 mmol, 1 equiv), BSP (1.5 equiv), TTBP (2 equiv), and 4 Å molecular sieves in 3.2 mL (0.05 M) of dichloromethane at −70 °C under an Ar atmosphere was added Tf_2O (1.1 equiv) slowly. The resulting yellow mixture was stirred at this temperature for 30 min, and then a solution of acceptor (2.0 equiv) in dichloromethane 2 mL was added. The stirring was continued for another 30 min, and the reaction mixture was poured into saturated aqueous $NaHCO_3$ solution. The crude product was extracted with dichloromethane (3 × 4 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (hexane/ethyl acetate) on silica gel to give the coupled products.

1-Adamantanyl 4,6-*O*-benzylidene-2-*O*-[3-(4-trifluoromethylphenyl)-prop-2-ynyl]-3-*O*-benzyl-β-D-mannopyranoside (9). Viscous oil. $[\alpha]^{25}_D$ −37.5 (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.58−1.67 (m, 6H), 1.78−1.87 (m, 6H), 2.26 (s, 3H), 3.32−3.37 (m, 1H), 3.68 (dd, *J* = 10 Hz, *J* = 3.2 Hz, 1H), 3.93 (t, *J* = 8.1 Hz, 1H), 4.07 (d, *J* = 2.5 Hz, 1H), 4.16 (t, *J* = 9.7 Hz, 1H), 4.28 (dd, *J* = 10 Hz, *J* = 4.7 Hz, 1H), 4.80−4.92 (m, 5H), 5.61 (s, 1H), 7.23 (m, 4H), 7.38 (m, 5H), 7.53 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.6, 36.2, 42.4, 60.8, 67.2, 68.8, 72.5, 75.5, 76.9, 78.5, 84.8, 88.7, 94.7, 101.4 (J_{C-H} = 161.3 Hz), 125.2, 126.1, 126.8, 127.5, 128.3, 128.4, 128.9, 132.1, 137.7, 138.4. ^{19}F-NMR (471 MHz, $CDCl_3$): δ −64.33. ESI-HRMS calcd for $C_{40}H_{41}F_3O_6Na$ [M + Na]$^+$ 697.2753, found 697.2749.

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-[4,6-*O*-benzylidene-2-*O*-[3-(4-trifluoromethylphenyl)-prop-2-ynyl]-3-*O*-benzyl-β-D-mannopyranosyl]-α-D-glucopyranoside (10). Viscous oil. $[\alpha]^{14}_D$ −13.4 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.02−3.07 (m, 1H), 3.35 (s, 3H), 3.38−3.40 (m, 1H), 3.50−3.56 (m, 2H), 3.60 (d, *J* = 9 Hz, 1H), 3.67−3.77 (m, 2H), 3.86−3.89 (m, 2H), 3.92−3.96 (m, 1H), 4.03−4.07 (m, 2H), 4.35 (d, *J* = 12 Hz,1H), 4.45 (s, 1H), 4.63−4.68 (m, 3H), 4.72 (d, *J* = 7 Hz, 2H), 4.79−4.83 (m, 3H), 5.05 (d, *J* = 10.5 Hz, 1H), 5.52 (s, 1H), 7.24−7.27 (m, 6H), 7.30−7.37 (m, 8H), 7.40−7.41 (m, 4H), 7.43−7.44 (m, 5H), 7.48 (dd, *J* = 8 Hz, *J* = 1.5 Hz, 3H), 7.52 (d, *J* = 8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.4, 60.6, 67.2, 68.5, 68.6, 69.6, 72.7, 73.6, 75.3, 76.4, 77.7, 78.6, 79.1, 80.2, 88.4, 98.4, 101.3, 101.4 (J_{C-H} = 158.8 Hz), 125.2, 126.1, 127.3, 127.4, 127.6, 127.8, 127.9, 128.1, 128.2, 128.24, 128.3, 128.6, 128.9, 132.0, 137.5, 137.6, 138.3, 138.5, 139.3. ^{19}F-NMR (471 MHz, $CDCl_3$): δ −64.40. ESI-HRMS calcd for $C_{58}H_{57}F_3O_{11}Na$ [M + Na]$^+$ 1009.3751, found 1009.3744.

Methyl 2,3,6-Tri-*O*-benzyl-6-*O*-[4,6-*O*-benzylidene-2-*O*-[3-(4-trifluoromethylphenyl)-prop-2-ynyl]-3-*O*-benzyl-β-D-mannopyranosyl]-α-D-glucopyranoside (11). Viscous oil. $[\alpha]^{14}_D$ −6.0 (*c* 0.7, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.20−3.25 (m, 1H), 3.34 (s, 3H), 3.47−3.50 (m, 3H), 3.54 (dd, *J* = 9.7 Hz, *J* = 3.5 Hz, 1H), 3.78 (m, 1H), 3.90 (t, *J* = 10.5 Hz, 1H), 4.01 (t, *J* = 9 Hz, 1H), 4.05−4.14 (m, 4H), 4.27 (dd, *J* = 9.7 Hz, *J* = 4.5 Hz, 1H), 4.55 (d, *J* = 3.5 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.65 (d, *J* = 11.7 Hz, 1H), 4.77−4.78 (m, 2H), 4.79−4.83 (m, 4H), 4.84 (d, *J* = 8.5 Hz, 1H), 4.88 (d, *J* = 11.5 Hz, 1H), 5.00 (d, *J* = 11 Hz, 1H), 5.58 (s, 1H), 7.21−7.23 (m, 8H), 7.39−7.33 (m, 15H), 7.43−7.45 (m, 2H), 7.49−7.52 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.1, 60.4, 67.4, 68.3, 68.5, 69.6, 72.5, 73.4, 74.8, 75.0, 76.1, 76.6, 77.4, 78.5, 79.9, 82.2, 85.4, 88.1, 97.9, 101.4, 102.0 (J_{C-H} = 157.5 Hz), 125.3, 126.0, 127.6, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 128.5, 128.9, 132.1, 137.5, 138.0, 138.3, 138.4, 138.6. ^{19}F-NMR (471 MHz, $CDCl_3$): δ −64.34. ESI-HRMS calcd for $C_{58}H_{57}F_3O_{11}Na$ [M + Na]$^+$ 1009.3751, found 1009.3744.

Methyl 4-*O*-[4,6-*O*-Benzylidene-2-*O*-[3-(4-trifluoromethylphenyl)-prop-2-ynyl]-3-*O*-benzyl-β-D-mannopyranosyl]-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (12). Viscous oil. $[\alpha]^{16}_D$ −49.3 (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.36 (s, 3H), 1.54 (s, 3H), 3.34 (s, 3H), 3.31−3.40 (m, 4H), 3.60−3.62 (m, 1H), 3.66−3.71 (m, 2H), 3.96 (t, *J* = 10.2 Hz, 1H), 4.08 (d, *J* = 5.5 Hz, 1H), 4.15−4.18 (m, 2H), 4.22 (d, *J* = 3.5 Hz, 1H), 4.28 (dd, *J* = 10.5 Hz, *J* = 5 Hz, 1H), 4.76−4.79 (m, 2H), 4.81 (s, 1H), 4.85−4.87 (m, 2H), 5.05 (s, 1H), 5.61 (s, 1H), 7.22−7.26 (m, 3H), 7.34−7.41 (m, 5H), 7.49−7.52 (m, 4H), 7.56 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.7, 26.4, 27.8, 54.9, 60.6, 64.0, 67.6, 68.6, 72.5, 76.0, 76.1, 77.4, 77.9, 78.3, 78.7, 84.9, 88.4, 97.8, 99.9 (J_{C-H} = 158.7 Hz), 101.4, 109.5, 125.2, 125.3, 126.0, 126.7, 127.5, 128.2, 128.3, 128.9, 132.1, 137.5, 138.3. ^{19}F-NMR (471 MHz, $CDCl_3$): δ −64.38. ESI-HRMS calcd for $C_{40}H_{43}F_3O_{10}Na$ [M + Na]$^+$ 763.2706, found 763.2672.

1,6-Anhydro-4-*O*-{4,6-*O*-benzylidene-2-*O*-[3-(4-trifluoromethylphenyl)-prop-2-ynyl]-3-*O*-benzyl-β-D-mannopyranosyl}−2,3-*O*-isopropylidene-β-D-mannopyranose (13). Viscous oil. $[\alpha]^{15}_D$ −68.5 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.53 (s, 3H), 3.34−3.39 (m, 1H), 3.68 (dd, *J* = 10 Hz, *J* = 3 Hz, 1H), 3.77 (t, *J* = 7 Hz, 1H), 3.94 (t, *J* = 10 Hz, 1H), 3.98 (d, *J* = 7 Hz, 1H), 4.02 (dd, *J* = 6 Hz, *J* = 3 Hz, 1H), 4.09 (s, 1H), 4.20 (t, *J* = 9.5 Hz, 1H), 4.25 (d, *J* = 3 Hz, 1H), 4.32 (d, *J* = 10.5 Hz, *J* = 5 Hz, 1H), 4.37 (d, *J* = 6 Hz, 1H), 4.59 (d, *J* = 6 Hz, 1H), 4.77−4.89 (m, 5H), 5.33 (d, *J* = 2.5 Hz, 1H), 5.62 (s, 1H), 7.23−7.26 (m, 4H), 7.33 −7.41 (m, 5H), 7.49−7.57 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.9, 26.0, 61.0, 64.3, 67.7, 68.4, 72.1, 72.4, 72.8, 74.9, 75.3, 76.1, 78.4, 85.1, 88.0, 99.5, 99.9 (J_{C-H} = 157.3 Hz), 110.0, 125.2, 125.3, 126.0, 126.6, 127.6, 128.3, 128.4, 129.0, 132.1, 137.3, 138.0; ^{19}F-NMR (471 MHz, $CDCl_3$): δ −64.39; ESI-HRMS calcd for $C_{39}H_{39}F_3O_{10}Na$ [M + Na]$^+$ 747.2393, found 747.2373.

3-O-[4,6-*O*-Benzylidene-2-*O*-[3-(4-trifluoromethylphenyl)-prop-2-ynyl]-3-*O*-benzyl-β-D-mannopyranosyl]-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (14). Viscous oil. $[\alpha]^{23}_D$ −18.8 (*c* 1.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.37 (s, 3H), 1.44 (s, 3H), 1.49 (s, 3H), 3.33 (m, 1H), 3.68 (d, *J* = 8 Hz, 1H), 3.92 (t, *J* = 10.2 Hz, 1H), 4.09 (d, *J* = 8.5 Hz, 1H), 4.16−4.18 (m, 2H), 4.21−4.22 (m, 2H), 4.31−4.32 (m, 2H), 4.37−4.40 (m, 2H), 4.50 (s, 1H), 4.62 (s, 1H), 4.71−4.79 (m, 3H), 4.90 (d, *J* = 12.5 Hz, 1H), 5.62 (s, 1H), 5.85 (s, 1H), 7.25−7.27 (m, 3H), 7.35−7.38 (m, 5H), 7.48−7.49 (m, 2H), 7.55−7.56 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.6, 26.2, 26.5, 26.7, 60.6, 66.0, 67.7, 68.4, 73.0, 73.5, 75.8, 77.8, 78.6, 80.3, 80.6, 82.6, 85.3, 87.9, 99.5 (J_{C-H} = 155.0 Hz), 101.5, 104.9, 108.5, 111.9, 125.3, 126.0, 126.5, 127.6, 127.8, 128.3, 128.4, 129.0, 132.1, 137.4, 138.1. ^{19}F-NMR (471 MHz, $CDCl_3$): δ −64.47. ESI-HRMS calcd for $C_{42}H_{45}F_3O_{11}Na$ [M + Na]$^+$ 805.2812, found 805.2806.

6-*O*-[4,6-*O*-Benzylidene-2-*O*-[3-(4-trifluoromethylphenyl)-prop-2-ynyl]-3-*O*-benzyl-β-D-mannopyranosyl]-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (15). Viscous oil. $[\alpha]^{15}_D$ −76.2 (*c* 1.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (s, 6H), 1.4 (s, 3H), 1.50 (s, 3H), 3.33−3.35 (m, 1H), 3.63−3.69 (m, 2H), 3.92 (t, *J* = 10.2 Hz, 1H), 4.05 (dd, *J* = 8 Hz, *J* = 2 Hz, 1H), 4.13−4.17 (m, 2H), 4.2 (dd, *J* = 8 Hz, *J* = 1.5 Hz, 1H), 4.28 (d, *J* = 3 Hz, 1H), 4.30−4.34 (m, 2H), 4.60 (dd, *J* = 8 Hz, *J* = 2.5 Hz, 1H), 4.63 (s, 1H), 4.77 (d, *J* = 6 Hz, 1H), 4.8 (d, *J* = 2H, 1H), 4.83 (s, 1H), 4.86 (d, *J* = 3.5 Hz, 1H), 7.55 (d, *J* = 5 Hz, 1H), 5.6 (s, 1H), 7.18−7.22 (m, 4H), 7.30−7.33 (m, 2H), 7.36−7.40 (m, 3H), 7.48−7.51 (m, 2H), 7.53−7.56 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.4, 25.1, 26.0, 60.8, 67.4, 68.1, 68.5, 70.1, 70.7, 71.5, 72.6, 75.8, 78.5, 84.8, 88.5, 96.3, 101.5, 102.5 (J_{C-H} = 157.5 Hz), 108.8, 109.6, 125.2, 126.0, 126.8, 127.5, 127.6, 128.2, 128.3, 128.9, 132.1, 132.2, 137.5, 138.2. ^{19}F-NMR (471 MHz, $CDCl_3$): δ −64.38. ESI-HRMS calcd for $C_{42}H_{45}F_3O_{11}Na$ [M + Na]$^+$ 805.2812, found 805.2787.

Methyl 2-Azido-3,6-di-*O*-benzyl-4-*O*-[4,6-*O*-benzylidene-2-*O*-[3-(4-trifluoromethylphenyl)-prop-2-ynyl]-3-*O*-benzyl-β-D-mannopyranosyl]-α-D-glucopyranoside (16).[12] To facilitate easier separation of **16** from excess acceptor and hydrolysis product **17**, the crude mixture from the workup was acetylated under standard

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(11) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, *2*, 323.

conditions and purified. Viscous oil. $[\alpha]^{22}_D$ −2.6 (*c* 1.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 3.03−3.08 (m, 1H), 3.92 (s, 3H), 3.40−3.41 (m, 3H), 3.60 (d, J = 9 Hz, 1H), 3.70−3.74 (m, 2H), 3.85−3.89 (m, 2H), 4.04−4.08 (m, 3H), 4.37 (d, J = 12.5 Hz, 1H), 4.44 (s, 1H), 4.68−4.79 (m, 6H), 4.83 (d, J = 12.5 Hz, 1H), 5.21 (d, J = 10 Hz, 1H), 5.52 (s, 1H), 7.26−7.29 (m, 6H), 7.33−7.42 (m, 12H), 7.48−7.53 (m, 6H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.7, 61.1, 63.1, 67.4, 68.4, 68.6, 70.5, 73.0, 73.9, 75.3, 76.8, 77.8, 78.8, 78.9, 85.1, 88.4, 98.9, 101.0 (J_{C-H} = 156.5 Hz), 101.6, 125.4, 125.5, 126.3, 127.6, 127.9, 128.3, 128.4, 128.5, 128.6, 128.8, 129.1, 132.2, 137.6, 137.8, 138.7, 138.7. ^{19}F-NMR (471 MHz, $CDCl_3$): δ −64.4. ESI-HRMS calcd for $C_{51}H_{50}F_3N_3O_{10}Na$ $[M + Na]^+$ 944.3346, found 944.3362.

Global Deprotection with Sodium in Liquid Ammonia: 1-Adamantyl β-D-mannopyranoside (27). Mannopyranoside **9** (0.1 g, 0.12 mmol, 1 equiv) was dissolved in a mixture of liquid ammonia (2 mL), THF (4 mL) and tertiary butanol (2 mL). To this solution at −70 °C was added sodium (0.03 g, 10 equiv) in 4 pieces, and the reaction mixture was warmed to −40 °C and the intense blue solution was stirred for 1 h. After the reaction completion (TLC 10% CH_3OH:$CHCl_3$), the reaction mixture at −20 °C was slowly quenched with saturated aqueous ammonium chloride solution (4 mL). The product was extracted with dichloromethane (3 × 4 mL). The organic layer was dried ($MgSO_4$) and concentrated to afford a crude product that was purified on a silica chromatography (2, 4, 5, 8, 10% $CHCl_3$/CH_3OH) to afford 27 mg (72%) of **27**. White solid: Mp: 218−220 °C: $[\alpha]^{11}_D$ −27.4 (*c* 0.7, CH_3OH); ^1H NMR (400 MHz, CD_3OD): δ 1.63−1.70 (m, 6H), 1.79−1.92 (m, 6H), 2.13 (m, 3H), 3.16−3.20 (m, 1H), 3.45 (dd, J = 8.8 Hz, J = 3.2 Hz, 1H), 3.65−3.69 (m, 2H), 3.82 (dd, J = 11.6 Hz, J = 2 Hz, 1H), 4.82 (d, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ 31.0, 36.2, 42.3, 61.8, 67.3, 72.9, 74.3, 74.8, 76.6, 93.4. ESI-HRMS calcd for $C_{16}H_{26}NaO_6$ $[M + Na]^+$ 337.1627, found 337.1613.

General Procedure for Selective Reduction. 1-Adamantyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranoside (18). Lithium naphthalenide in THF (0.25 M) was generated by dissolving Li (3−5 mg) in a solution of naphthalene (64 mg, 0.5 mmol) in THF (2 mL) at room temperature and allowing the reaction mixture to stir under Ar for 2 h. This dark-green solution of lithium naphthalide (10 equiv) was dropwise added to a solution of sugar **9** (34 mg, 0.05 mmol, 1 equiv) in THF (1 mL) kept at −78 °C. The resultant reaction mixture was allowed to warm up to 0 °C over a period of 3 h and then quenched with a saturated solution of aqueous ammonium chloride (2.5 mL). The crude product was extracted with methylene chloride (3 × 4 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica (3, 5, 10, 15, 20, 25% Ethyl acetate/Hexane) to afford **18** (21 mg, 85%). Viscous oil. $[\alpha]^{11}_D$ −8.7 (*c* 0.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.59−1.66 (m, 6H), 1.77−1.86 (m, 6H), 2.16 (m, 3H), 2.64 (s, 1H), 3.31−3.35 (m, 1H), 3.66 (dd, J = 9.8 Hz, J = 3 Hz, 1H), 3.88 (t, J = 9.8 Hz, 1H), 3.98 (d, J = 3 Hz, 1H), 4.15 (t, J = 9.8 Hz, 1H), 4.27 (dd, J = 9.8 Hz, J = 5 Hz, 1H), 4.78−4.86 (m, 3H), 7.26−7.32 (m, 4H), 7.33−7.40 (m, 4H), 7.49−7.50 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.7, 36.2, 42.4, 66.7, 68.8, 71.6, 72.3, 75.8, 78.3, 93.3, 126.1, 127.7, 127.9, 128.2, 128.9, 137.6, 138.2; ESI-HRMS calcd for $C_{30}H_{36}O_6Na$ $[M + Na]^+$ 515.2410, found 515.2413.

Methyl 2-Acetamido-3,6-di-*O*-benzyl-4-*O*-(4,6-*O*-benzylidene-2-*O*-acetyl-3-*O*-benzyl-β-D-mannopyranosyl)-α-D-glucopyranoside (26). Sugar **16** was subjected to the general reduction procedure. Work up was followed by acetylation under standard conditions to afford **26** in 53% yield after purification.

$[\alpha]^{22}_D$ +11.6 (*c* 0.3, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 1.83 (s, 3H), 2.17 (s, 3H), 3.07 (dt, J = 4.5 Hz, J = 12 Hz, 1H), 3.32 (s, 3H), 3.40 (d, J = 3.5 Hz, 1H), 3.40 (d, J = 3.5 Hz, 1H), 3.53 (dd, J = 10.5 Hz, J = 20.5 Hz, 2H), 3.65 (t, J = 10 Hz, 2H), 3.76 (dd, J = 3.5 Hz, J = 11 Hz, 1H), 3.86 (t, J = 9.5 Hz, 1H), 4.08 (t, J = 10.5 Hz, 1H), 4.10−4.14 (m, 1H), 4.16−4.21 (, 1H), 4.42 (d, J = 11.5 Hz, 1H), 4.53 (d, J = 2 Hz,1H), 5.54 (d, J = 6.5 Hz, 1H), 4.64 (d, J = 12 Hz, 1H), 4.69 (d, J = 3.5 Hz, 1H), 4.89 (d, J = 11.5 Hz, 1H), 5.22 (d, J = 9 Hz, 1H), 5.40 (d, J = 3 Hz, 1H), 5.51 (s, 1H), 7.26−7.39 (m, 17H), 7.47−7.49 (m, 2H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.3, 23.6, 52.5, 55.3, 67.1, 68.5, 68.6, 69.5, 70.3, 71.8, 73.7, 74.4, 76.0, 78.0, 78.1, 78.2, 126.3, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.8, 129.1, 137.7, 137.9, 138.1, 139.2, 169.9, 170.6 ; ESI-HRMS calcd for $C_{45}H_{51}NO_{12}Na$ $[M + Na]^+$ 820.3309, found 820.3336.

Compounds 19, 20, 21, 23, 24, and 25. The spectral data for these compounds are consistent with the literature data.[13]

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Supporting Information Available: Details of the preparation of compounds **6** and **8**, characterization data for compounds **17** and **22**, and copies of ^1H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The acceptor in this example was prepared in 5 steps according to the literature procedure, see: (a) Westman, J.; Nilsson, M.; Ornitz, D. M.; Svahn, C.-M. *J. Carbohydr. Chem.* **1995**, *14*, 95. (b) Yu, B.; Chen, J.; Lin, F.; Zhou, Y. *Carbohydr. Res.* **2006**, *341*, 1619.

(13) Crich, D.; Jayalath, P.; Hutton, T. K. *J. Org. Chem.* **2006**, *71*, 3064.