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Convergent Synthesis of a β-(1→3)-Mannohexaose

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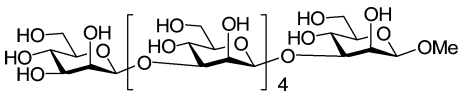

An as yet unknown β-(1→3)-mannohexaose has been synthesized by a block route involving the coupling of two trisaccharides. Comparison of three closely related attempted mannohexaose syntheses reinforces the influence of subtle matching and/or mismatching interactions on the outcome of convergent oligosaccharide synthesis.

Introduction

Insofar as the β-mannopyranosides have traditionally been considered to be one of the more challenging classes of glycosidic bond to synthesize in a stereocontrolled manner,[1−6] the β-mannans are the ultimate proving ground for methodology development in this area. Over the course of the past decade, we have developed in our laboratory a direct stereocontrolled route to the synthesis of the β-mannopyranosides,[7] based on the in situ generation and coupling of 4,6-*O*-alkylidene-protected α-mannosyl triflates,[8−11] and have applied it successfully to the synthesis of the β-(1→2)-mannan from *Candida albicans*,[12] to the β-(1→4)-mannan from hard and soft woods, and guar gum,[12] and to the alternating β-(1→3)-β-(1→4)-mannan from *Rhodotorula glutinis* and *mucilaginosa* and *Leptospira biflexa*.[13,14] An analogous synthesis of the β-(1→2)-mannan was also reported by Mallet and co-workers,[15−20] and the general approach to β-mannosides has been applied widely to the synthesis of other complex oligosaccharides.[21−30]

In this paper, we turn our attention to the β-(1→3)-mannan which, to our knowledge, and in contrast to the closely related β-(1→3)-D-rhamnan,[30,31] has yet to be found in Nature. We do so because the synthesis and provision of samples to glycomics databases should assist in the future identification of such substances in Nature, and because of the challenge this particular mannan presents to our chemistry, especially when considered

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(1) Barresi, F.; Hindsgaul, O. In *Modern Methods in Carbohydrate Synthesis*; Khan, S. H., O'Neill, R. A., Eds.; Harwood Academic Publishers: Amsterdam, 1996; pp 251−276.
(2) Ito, Y.; Ohnishi, Y. In *Glycoscience: Chemistry and Chemical Biology*; Fraser-Reid, B., Kuniaki, T., Thiem, J., Eds.; Springer-Verlag: Berlin, 2001; Vol. 2, pp 1589−1619.
(3) Pozsgay, V. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weinheim, 2000; Vol. 1, pp 319−343.
(4) Gridley, J. J.; Osborn, H. M. I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1471−1491.
(5) Demchenko, A. V. *Curr, Org, Chem.* **2003**, *7*, 35−79.
(6) Demchenko, A. V. *Synlett* **2003**, 1225−1240.
(7) Crich, D. In *ACS Symposium Series*; American Chemical Society: Washington, 2007; Vol. 960, pp 60−72.
(8) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198−1199.
(9) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321−8348.
(10) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217−11223.
(11) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015−9020.
(12) Crich, D.; Banerjee, A.; Yao, Q. *J. Am. Chem. Soc.* **2004**, *126*, 14930−14934.
(13) Crich, D.; Li, H.; Yao, Q.; Wink, D. J.; Sommer, R. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2001**, *121*, 5826−5828.
(14) Crich, D.; Li, W.; Li, H. *J. Am. Chem. Soc.* **2004**, *126*, 15081−15086.
(15) Dromer, F.; Chevalier, R.; Sendid, B.; Improvisi, L.; Jouault, T.; Robert, R.; Mallet, J. M.; Poulain, D. *Antimicrob. Agents Chemother.* **2002**, *46*, 3869−3876.
(16) For the synthesis of β-mannans by less direct routes, see refs 17−20.
(17) Nitz, M.; Bundle, D. R. *J. Org. Chem.* **2001**, *66*, 8411−8423.
(18) Mathew, F.; Mach, M.; Hazen, K. C.; Fraser-Reid, B. *Synlett* **2003**, 1319−1322.
(19) Wu, X.; Bundle, D. R. *J. Org. Chem.* **2005**, *70*, 7381−7388.
(20) Twaddle, G. W. J.; Yashunsky, D. V.; Nikolaev, A. V. *Org. Biomol. Chem.* **2003**, *1*, 623−628.
(21) Shao, N.; Guo, Z. W. *Pol. J. Chem.* **2005**, *79*, 297−307.
(22) Dudkin, V. Y.; Miller, J. S.; Danishefsky, S. J. *Tetrahedron Lett.* **2003**, *44*, 1791−1793.
(23) Dudkin, V. K.; Miller, J. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 736−738.
(24) Nicolaou, K. C.; Mitchell, H. J.; Rodriguez, R. M.; Fylaktakidou, K. C.; Suzuki, H.; Conley, S. R. *Chem. Eur. J.* **2000**, *6*, 3149−3165.
(25) Wu, X.; Schmidt, R. R. *J. Org. Chem.* **2004**, *69*, 1853−1857.
(26) Kim, K. S.; Kang, S. S.; Seo, Y. S.; Kim, H. J.; Jeong, K.-S. *Synlett* **2003**, 1311−1314.
(27) Crich, D.; Banerjee, A. *J. Am. Chem. Soc.* **2006**, *128*, 8078−8086.
(28) Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2002**, *124*, 2263−2266.
(29) Dudkin, V. Y.; Crich, D. *Tetrahedron Lett.* **2003**, *44*, 1787−1789.
(30) Crich, D.; Bowers, A. A. *Org. Lett.* **2006**, *8*, 4327−4330.
(31) Perry, M. B.; Richards, J. C. *Carbohydr. Res.* **1990**, *205*, 371−376.

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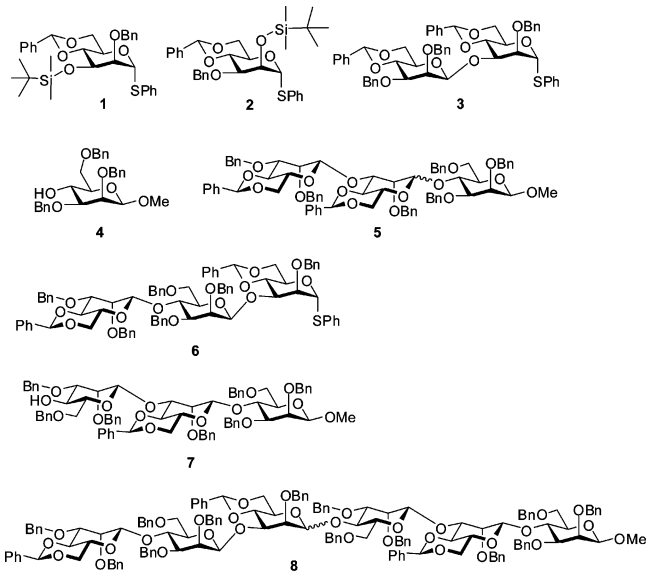
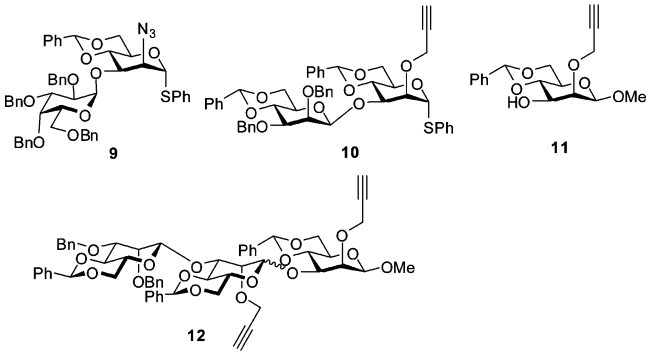
from a convergent or block synthesis standpoint. In effect, the size and nature of the O-3 substituent in 4,6-*O*-benzylidene-protected mannosyl donors has been found to influence critically the stereochemical outcome of these reactions, with the benzyl ether being ideal and both smaller and larger groups detrimental.[14,32−38]

Results and Discussion

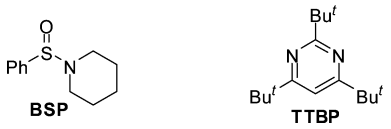
Background. The negative influence of sterically bulky protecting groups on O-3 of the mannosyl donors was first noticed with the 3-*O*-*tert*-butyldimethylsilyl protected system **1**, which was less selective than the corresponding regioisomer **2**.[36,38] Subsequently, the phenomenon reared its head in the convergent synthesis of the alternating β-(1→3)-β-(1→4)-mannan when coupling of **3** with **4** resulted in the formation of the trisaccharide **5**, but with only a 1:1 β/α ratio,[14] and that of trisaccharides **6** and **7** to give hexasaccharide **8** with a disappointing 0.67:1 β:α ratio.[14] We rationalized the influence of the size of the O-3 protecting group in terms of a steric buttressing effect between the O-2 and O-3 protecting groups, which causes undue hindrance of the β-face of the glycosyl donor and leads to the observed reduction in selectivity.[36,37,39]



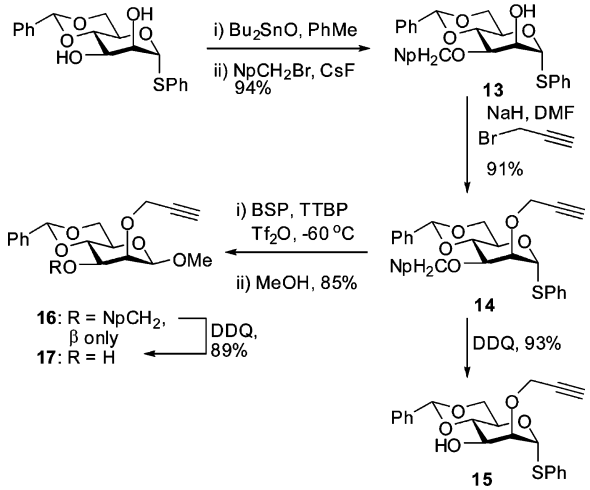
Taking a hint from the highly β-selective coupling observed by the van Boom group with the 2-azido-2-deoxy donor **9** we developed the propargyl ethers as sterically minimal protecting groups for O-2 capable of overcoming the influence of the bulky group on O-3.[40,41] On this basis, we were able to demonstrate the coupling of the disaccharide donor **10** to acceptor **11** when trisaccharide **12** was obtained in 80% yield with 5.2:1 β/α ratio.[39]



First Approach to the β-(1→3)-Mannohexaose. With this in mind, we embarked on a convergent synthesis of the β-(1→3)-mannohexaose featuring extensive use of the 2-*O*-propagryl ether protecting system. Accordingly, phenyl 4,6-*O*-benzylidene-α-D-thiomannopyranoside was converted first to the 3-*O*-naphthylmethyl ether **13**, by means of the stannylene acetal formed in situ with dibutyltin oxide, and then to the corresponding 2-*O*-propargyl ether **14**. Removal of the naphthylmethyl ether from **14** with DDQ afforded the key building block **15** in 93% yield.[42−44] Activation of **14** with BSP[11,45] and triflic anhydride in the presence of TTBP[46] at −60 °C in dichloromethane followed by quenching with methanol afforded the β-mannoside **16** in 85% yield (Scheme 1). Removal of the naphthylmethyl ether with DDQ then provided the acceptor **17** in 89% yield (Scheme 1).

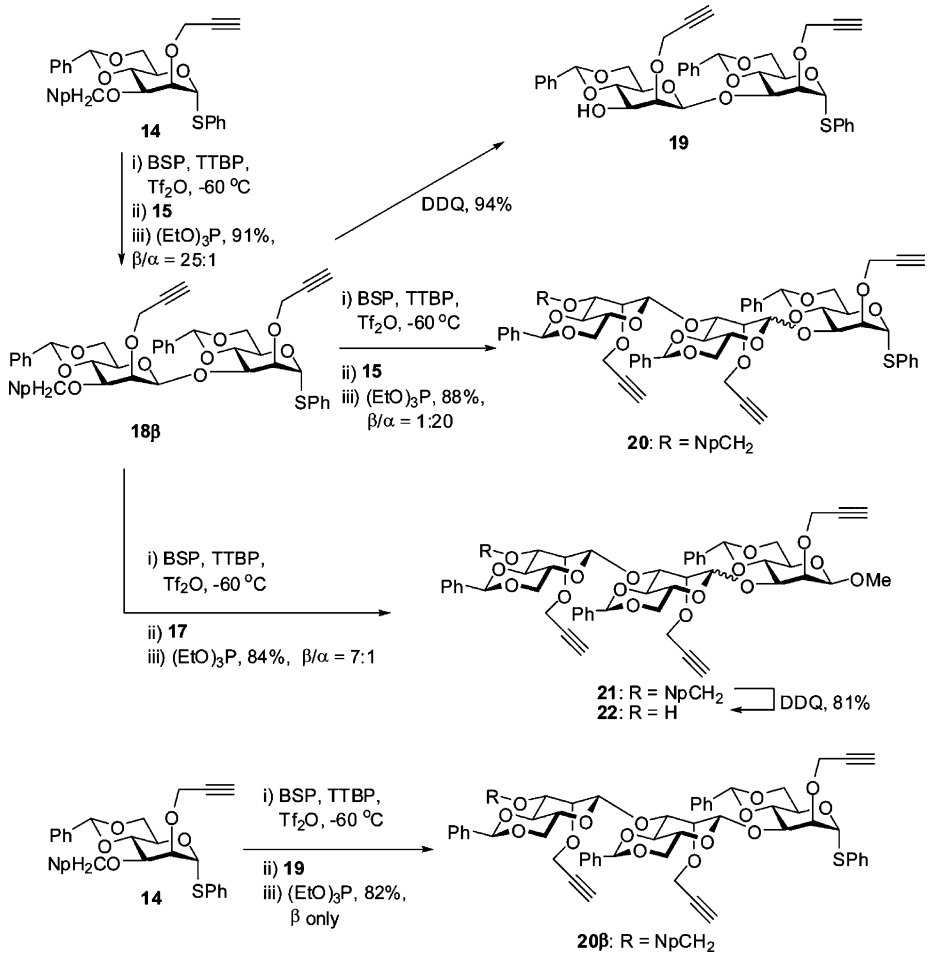


SCHEME 1. Synthesis of 15 and 17



(32) Crich, D.; Vinogradova, O. *J. Org. Chem.* **2006**, *71*, 8473−8480.
(33) Crich, D.; Li, L. *J. Org. Chem.* **2007**, *72*, 1681−1690.
(34) Crich, D.; Cai, W.; Dai, Z. *J. Org. Chem.* **2000**, *65*, 1291−1297.
(35) Crich, D.; Yao, Q. *J. Am. Chem. Soc.* **2004**, *126*, 8232−8236.
(36) Crich, D.; Dudkin, V. *Tetrahedron Lett.* **2000**, *41*, 5643−5646.
(37) Crich, D.; Jayalath, P.; Hutton, T. K. *J. Org. Chem.* **2006**, *71*, 3064−3070.
(38) Codée, J. D. C.; Hossain, L. H.; Seeberger, P. H. *Org. Lett.* **2005**, *7*, 3251−3254.
(39) Crich, D.; Jayalath, P. *Org. Lett.* **2005**, *7*, 2277−2280.
(40) Codée, J. D. C.; Litjens, R. E. J. N.; den Heeten, R.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1519−1522.
(41) Codée, J. D. C.; van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; van Boeckel, C. A. A.; van Boom, J. H.; van der Marel, G. A. *Tetrahedron* **2004**, *60*, 1057−1064.
(42) Xia, J.; Abbas, S. A.; Locke, R. D.; Piskorz, C. F.; L., A. J.; Matta, K. L. *Tetrahedron Lett.* **2000**, *41*, 169−173.
(43) Liptak, A.; Borbas, A.; Janossy, L.; Szilagyi, L. *Tetrahedron Lett.* **2000**, *41*, 4949−4953.
(44) Csávás, M.; Szabó, Z. B.; Borbás, A.; Lipták, A. In *Handbook of Reagents for Organic Synthesis: Reagents for Glycoside, Nucleotide, and Peptide Synthesis*; Crich, D., Ed.; Wiley: Chichester, 2005; pp 459−460.
(45) Crich, D.; Banerjee, A.; Li, W.; Yao, Q. *J. Carbohydr. Chem.* **2005**, *24*, 415−424.

SCHEME 2. Synthesis of Trisaccharide Donor 20 and Acceptor 22



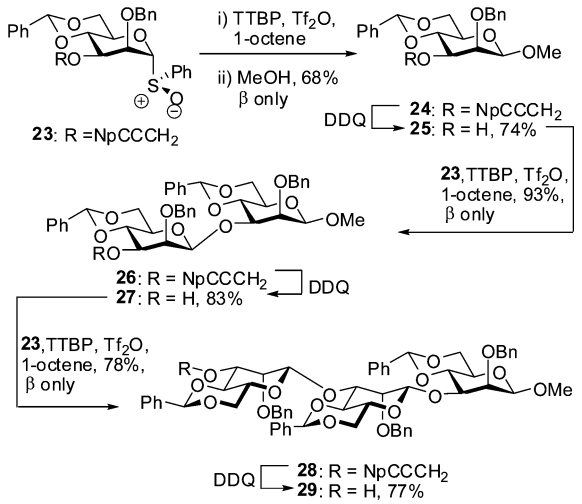
Activation of donor **14** with the BSP/triflic anhydride/TTBP combination followed by addition of acceptor **15** at −78 °C and then, before warming to room temperature, triethyl phosphite to quench any extraneous thiophiles and prevent premature activation of the new thioglycoside[41,47] afforded disaccharide **18** in 91% yield and 25:1 β/α selectivity (Scheme 2). Treatment with DDQ then provided the alcohol **19** (Scheme 2). In the same manner, coupling of donor **14** to acceptor **19** provided trisaccharide **20** in 82% yield as a single β-anomer (Scheme 2). Under the same conditions coupling of donor **18** with acceptor **17** gave the trisaccharide **21** in 84% yield with 7:1 β:α ratio (Scheme 2), from which removal of the naphthylmethyl group afforded acceptor **22** (Scheme 2). In contrast, activation of donor **18** followed by reaction with acceptor **15** gave trisaccharide **20** in 88% yield but with the unexpected β:α ratio of 1:20 (Scheme 2). The complete reversal of selectivity in going from acceptor **15** to acceptor **17** in coupling to donor **18** is remarkable and draws attention to the still poorly understood influence of acceptor structure on the outcome of glycosylation reactions.[48−50]

Unfortunately, despite repeated attempts, we were unable to realize the coupling of trisaccharide **20** with trisaccharide acceptor **22** and, thus, were forced to reconsider our approach.

Synthesis of the β-(1→3)-Mannohexaose. In redesigning our approach to the target mannan we elected to incorporate the use of the naphthylpropargyl ethers, developed in the interim,[51] as sterically minimal protecting groups cleavable in a single step with DDQ. On the basis of the developmental work, it was known that these ethers afford excellent selectivity when used as O-3 protecting groups for donors in conjunction with 2-*O*-benzyl ethers. Additionally, because the more electron-rich naphthylpropargyl system is susceptible to electrophilic attack by the activated Ph_2SO/triflic anhydride combination,[51] the use of glycosyl sulfoxides[52−55] as donors was recommended.[51] Thus, the previously described sulfoxide **23**[51] was activated with triflic anhydride in the presence of TTBP and 1-octene at −78 °C in dichloromethane before addition of methanol, resulting in the formation of the β-mannoside **24** as a single anomer (Scheme 3). In this and subsequent coupling reactions 1-octene serves as a sacrificial alkene for the trapping of electrophilic species that otherwise diminish the overall yields by reaction with one or other of the naphthylpropargyl ethers or the thioglycoside

(46) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323−326.
(47) Sliedregt, L. A. J. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1994**, *35*, 4015−4018.
(48) Paulsen, H. In *Selectivity a Goal for Synthetic Efficiency*; Bartmann, W., Trost, B. M., Eds.; Verlag Chemie: Weinheim, 1984; pp 169−190.
(49) Spijker, N. M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed.* **1991**, *30*, 180−183.
(50) Fraser-Reid, B.; López, J. C.; Gómez, A. M.; Uriel, C. *Eur. J. Org. Chem.* **2004**, 1387−1395.
(51) Crich, D.; Wu, B. *Org. Lett.* **2006**, *8*, 4879−4882.
(52) For a previous use of sacrificial alkenes in sulfoxide glycosylations, see: Kahne, D.; Walker, S.; Cheng, Y.; Engen, D. V. *J. Am. Chem. Soc.* **1989**, *111*, 6881−6882.
(53) Zhang, Y.; Fechter, E. J.; Wang, T.-S. A.; Barrett, D.; Walker, S.; Kahne, D. E. *J. Am. Chem. Soc.* **2007**, *129*, 3080−3081.
(54) Taylor, J. G.; Li, X.; Oberthür, M.; Zhu, W.; Kahne, D. E. *J. Am. Chem. Soc.* **2006**, *128*, 15084−15085.
(55) Crich, D.; Lim, L. B. L. *Org. React.* **2004**, *64*, 115−251.

SCHEME 3. Synthesis of Trisaccharide Acceptor 29

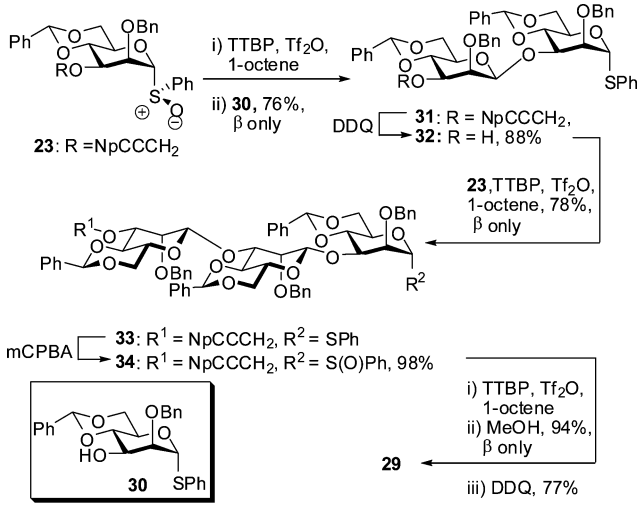


containing acceptors.[56] Removal of the naphthylpropargyl group from **24** with DDQ gave **25** (Scheme 3) which, on coupling to **23** gave disaccharide **26** as a single anomer (Scheme 3). A sequence of treatment with DDQ, coupling to **23**, and further treatment with DDQ gave the trisaccharide mono-ol **29** (Scheme 3).

The second trisaccharide required for the convergent synthesis was assembled by activation of donor **23** in the presence of 1-octene, and introduction of the known acceptor **30**,[14] when disaccharide **31** was obtained as a single anomer in 76% yield (Scheme 4). Removal of the naphthylpropargyl group from **31** gave **32**, and coupling to a second aliquot of **23** then afforded the trisaccharide **33** as a β only isomer in 78% yield (Scheme 4). Oxidation of **33** with mCPBA gave sulfoxide **34** as a single diastereomer at sulfur, which is assigned the (*R*)-configuration on the basis of previous crystallographic work.[57,58] Coupling of **34** with methanol and subsequent removal of the naphthylpropargyl protecting group provided a second more convenient entry into the acceptor trisaccharide **29** (Scheme 4). The ability to prepare the trisaccharide acceptor **29** from the donor **34** in this manner considerably enhances the efficiency of the overall protocol.

Finally, activation of **34** (1.2 equiv) with triflic anhydride in the presence of 1-octene and TTBP at −78 °C in dichloromethane, followed by the addition of **29** (1.0 equiv) smoothly afforded the hexasaccharide **35** as an approximately 1:1 mixture of anomers in 61% yield, Although the two anomers of **35** could be separated with difficulty by reversed-phase HPLC, it was found to be more convenient to process the mixture with DDQ, giving the mono-ols **36**, which were much more amenable to separation. Hydrogenolysis of each anomer over Pearlman's catalysis gave the mannans **37** and **38**, respectively (Scheme 5). In this manner the synthesis of the β-(1→3)-mannohexaose **37** was completed in 8% overall yield in a highly convergent manner from two monosaccharide building blocks **23** and **30**, with only four glycosidic bond forming steps required, which, with the exception of the joining of **29** and **34** were all completely β-selective.

SCHEME 4. Convergent Synthesis of Trisaccharide Donor 34 and Acceptor 29



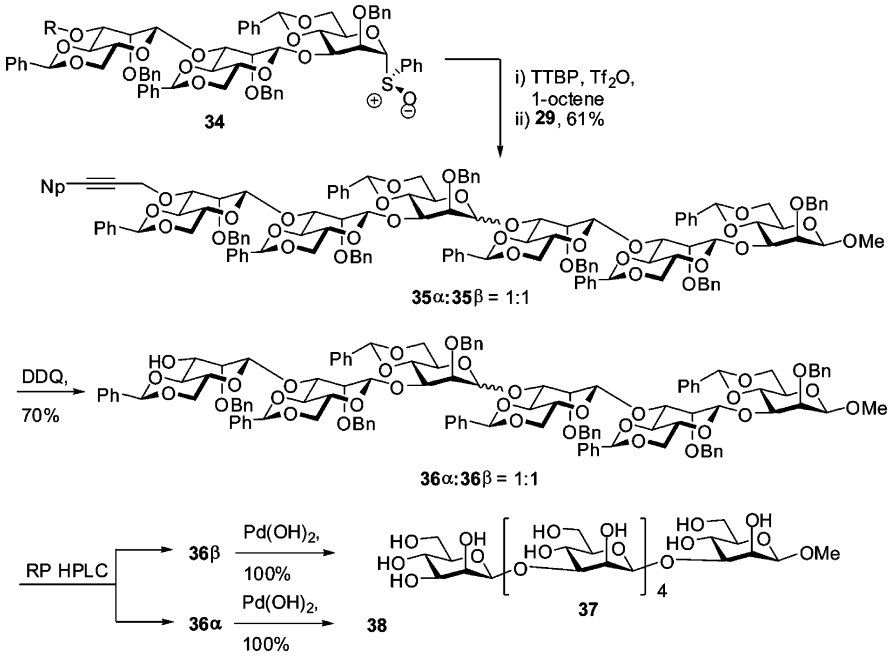
Structure of the β-(1→3)-Mannohexaose. Inspection of the ^{13}C NMR spectrum of **37** at 125 MHz revealed the presence of only three anomeric carbon signals at δ 100.8 ($^1J_{CH}$ = 157.9), δ 96.6 ($^1J_{CH}$ = 158.6), and δ 96.4 ($^1J_{CH}$ = 159.4) indicative of a highly regular open polymer. In this, **37** resembles the β-(1→4)-mannohexaose synthesized previously,[12] but is distinct from the β-(1→2)-mannooctaose in which all eight anomeric carbons were discernible owing to its disordered, collapsed helical structure.[12,59] The ^{13}C NMR of spectrum of **38** exhibited two well resolved anomeric carbon signals at δ 102.1 ($^1J_{CH}$ = 165.0) and 100.8 ($^1J_{CH}$ = 155.0), indicative of α and β configured anomeric positions respectively; the remaining four anomeric signals resonated between δ 96.5 and 96.9 but were insufficiently resolved to permit determination of the one bond C−H coupling constants.

Influence of the 3-*O*-Naphthylpropargyl Protecting on β-Mannosylation. In addition to the preliminary results described previously,[51] the coupling reactions summarized in Schemes 3 and 4 highlight the excellent β-selectivities obtained with the mannosyl donor **23**, which are comparable to those provided by corresponding 3-*O*-benzyl and naphthylmethyl ethers.[55] More noteworthy, however, is the contrast between the highly β-selective **23** and the somewhat unselective 3-*O*-propargyl system **39**,[37] which again highlights the sensitivity of these coupling reactions to substitution at the 3-position.

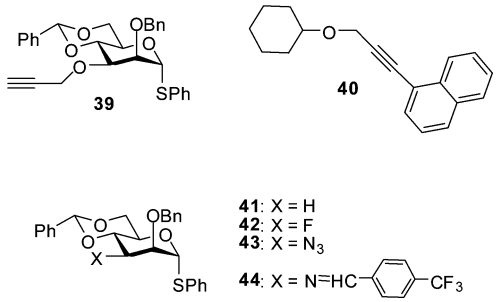
By means of the standard low-temperature NMR methods,[60] we determined the steric *A* value of the 1-naphthylpropargyloxy group in the cyclohexyl ether **40** to be 1.21, which is somewhat larger than of the simple propargyloxy group (1.10),[37] comparable to the allyloxy group (1.25),[37] a little smaller than the benzyloxy group (1.39),[37] and substantially smaller than the *tert*-butyldimethylsilylether group (1.50).[37] Taking into account the lack of selectivity seen with each of the 3-deoxy system **41**,[32] the 3-deoxy-3-fluoro system **42**[33] (*A* value for fluoride = 0.27),[60−65] and the 3-azido-3-deoxy system **43**[66] (*A* value for azide = 0.75),[61,67] but the excellent selectivity for the 3-benzylideneimino-3-deoxy system **44**,[66] we are led to the conclusion that there is a relatively narrow window for the steric bulk of the group at the 3-position, centered around the benzyloxy group, in which excellent β-selectivity is observed. As we have previously discussed,[32,33] groups that are significantly smaller than the benzyloxy ether function result in a loss of selectivity due to minimization of the developing torsional interaction

(56) Gildersleeve, J.; Smith, A.; Sakurai, D.; Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1999**, *121*, 6176−6182.
(57) Crich, D.; Mataka, J.; Sun, S.; Lam, K.-C.; Rheingold, A. R.; Wink, D. J. *J. Chem. Soc., Chem. Commun.* **1998**, 2763−2764.
(58) Crich, D.; Mataka, J.; Zakharov, L. N.; Rheingold, A. L.; Wink, D. J. *J. Am. Chem. Soc.* **2002**, *124*, 6028−6036.

SCHEME 5. Synthesis of the Mannans 37 and 38 and Completion of the Synthesis



between the O2 and O3 groups as the covalent triflate[10] flattens to the oxacarbenium ion,[68] thereby facilitating oxacarbenium ion formation and ultimately leading to a loss of selectivity. Larger groups than the benzyloxy ether result in the buttressing interaction discussed above, which also results in a loss of selectivity.



Conclusion

Trisaccharide donor **34** was successfully coupled to trisaccharide acceptor **29** to give hexasaccharide **35** in 61% yield as a 1:1 β:α mixture of anomers, whereas the closely related pair of **20** and **22** failed to give any appreciable amount of hexasaccharide under comparable conditions. As previously reported,[14] trisaccharide donor **6** was coupled to trisaccharide acceptor **7** to give hexasaccharide **8** in 88% yield but only 0.67:1 β:α ratio. These three reactions, which all involved the attempted coupling of closely related 3-*O*-glycosyl-4,6-*O*-benzylidene protected mannopyranosyl donors to the non-reducing 3-OH of mannotrioses, serve to highlight the continuing difficulty in predicting the outcome of block approaches to oligosaccharide synthesis. As the molecular weight of the donors and acceptors increase with chain length (e.g., the MW of **29** and **34** are 1053.15 and 1310.47 Da, respectively), and the concentration of the reaction mixture inevitably decreases, subtle steric and matching/mismatching effects play increasingly important roles and influence the outcome considerably.

Experimental Section

Phenyl 4,6-*O*-Benzylidene-3-*O*-(2-naphthylmethyl)-1-thio-α-D-mannopyranoside (13). A stirred solution of phenyl 4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside[69] (5.25 g, 14.6 mmol) in toluene (500 mL) was treated with Bu_2SnO (5.43 g, 21.8 mmol). The reaction mixture was refluxed for 4 h followed by removal of the solvent, affording a residue which was dissolved in DMF (50 mL). CsF (4.43 g, 29.1 mmol) and 2-bromomethylnaphthalene (4.83 g, 21.8) were then successively added into the reaction mixture, which then was stirred at 95 °C for 6 h. DMF was then removed by rotary evaporation under reduced pressure. The residue was redissolved in CH_2Cl_2 (200 mL), washed with saturated aq Na_2CO_3 and brine, dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by flash chromatography on silica gel (hexane:ethyl acetate; 4:1) to give **13** (6.76 g, 94%): $[\alpha]^{22}$ +176.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.80 (br. s, 1H), 3.89 (t, J = 10.0 Hz, 1H), 4.04 (dd, J = 3.5, 9.5 Hz, 1H), 4.23−4.27 (m, 2H), 4.33 (dd, J = 1.0, 3.5 Hz, 1H), 4.37 (dt, J = 4.5, 9.5 Hz, 1H), 4.93 (d, J = 12.0 Hz, 1H), 5.04 (d, J = 12.5 Hz, 1H), 5.62 (d, J = 1.5 Hz, 1H), 5.66 (s, 1H), 7.26−7.37 (m, 13H), 7.76−7.86 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 64.7, 68.6, 71.4, 73.2, 75.8, 79.0, 87.8, 101.8, 125.7, 126.1, 126.2, 126.3, 126.4, 127.7, 128.0, 128.3, 128.4, 128.5, 129.1, 129.2, 129.3, 131.7, 133.1, 133.3, 135.2, 137.5; ESIHRMS calcd for $C_{30}H_{28}O_5SNa$ $[M + Na]^+$ 523.1555, found 523.1545.

(59) Nitz, M.; Ling, C.-C.; Otter, A.; Cutler, J. E.; Bundle, D. R. *J. Biol. Chem.* **2002**, *277*, 3440−3446.
(60) Jensen, F. R.; Bushweller, C. H.; Beck, B. H. *J. Am. Chem. Soc.* **1969**, *91*, 344−351.
(61) Schneider, H.-J.; Hoppen, V. *J. Org. Chem.* **1978**, *43*, 3866−3873.
(62) Bugay, D. E.; Bushweller, C. H.; Danehy, C. T.; Hoogasian, S.; Blersch, J. A.; Leenstra, W. R. *J. Phys. Chem.* **1989**, *93*, 3908−3911.
(63) Subbotin, O. A.; Sergeyev, N. M. *J. Am. Chem. Soc.* **1975**, *97*, 1080−1084.
(64) Chu, P.-S.; True, N. S. *J. Phys. Chem.* **1985**, *89*, 5613−5616.
(65) Jensen, F. R.; Bushweller, C. H. *Adv. Alicycl. Chem.* **1971**, *3*, 139.
(66) Crich, D.; Xu, H. *J. Org. Chem.* **2007**, *72*, in press.
(67) Sülze, D.; Gatial, A.; Karlsson, A.; Klaeboe, P.; Nielsen, C. J. *J. Mol. Struct.* **1988**, *174*, 207−214.
(68) Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5386−5389.
(69) Oshitari, T.; Shibasaki, M.; Yoshizawa, T.; Tomita, M.; Takao, K.; Kobayashi, S. *Tetrahedron* **1997**, *53*, 10993−11006.

Phenyl 4,6-*O*-Benzylidene-3-*O*-(2-naphthylmethyl)-2-*O*-(prop-2-ynyl)-1-thio-α-D-mannopyranoside (14). To a stirred solution of compound **13** (4.66 g, 9.3 mmol) in dry DMF (25 mL) at 0 °C was added NaH (60% in oil, 0.93 g, 18.6 mmol). The reaction mixture was stirred for 15 min before propargyl bromide (1.97 mL, 18.6 mmol) was added dropwise to the mixture, and the stirring was continued for 3 h. The reaction mixture was then quenched by addition of methanol, diluted with CH_2Cl_2 (75 mL), and washed with satd $NaHCO_3$. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate; 5:1) to give **14** (5.01 g, 91%): $[\alpha]^{24}_D$ +124.8 (*c* 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (t, J = 2.3 Hz, 1H), 3.89 (t, J = 10.0 Hz, 1H), 4.07 (dd, J = 3.1, 9.5 Hz, 1H), 4.22−4.32 (m, 3H), 4.35 (dd, J = 1.4, 3.2 Hz, 1H), 4.4 (dd, J = 2.3, 16.1 Hz, 1H), 4.49 (dd, J = 2.3, 16.1 Hz, 1H), 4.93 (dd, J = 12.4 Hz, 1H), 5.03 (d, J = 12.4 Hz, 1H), 5.63 (d, J = 1.4 Hz, 1H), 5.67 (s, 1H), 7.26−7.45 (m, 3H), 7.42−7.58 (m, 10H), 7.84−7.89 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 58.8, 65.4, 68.5, 73.2, 75.4, 76.2, 77.5, 79.1, 79.4, 87.3, 101.6, 125.7, 125.0, 126.1, 126.2, 126.4, 127.7, 128.0, 128.2, 128.9, 129.2, 131.6, 133.0, 133.3, 133.6, 135.6, 137.6; ESIHRMS calcd for $C_{33}H_{30}O_5SNa$ $[M + Na]^+$ 561.1712, found 561.1722.

Phenyl 4,6-*O*-Benzylidene-2-*O*-(prop-2-ynyl)-1-thio-α-D-mannopyranoside (15). To a stirred solution of compound **14** (1.25 g, 2.3 mmol) in CH_2Cl_2 (40 mL) and water (2 mL) was added DDQ (1.05 g, 4.6 mmol) at rt. After the reaction mixture was stirred for 3 h, satd $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2. The extracts were washed several times with satd $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave an oil, which was chromatographed on silica gel (hexane/ethyl acetate 4:1) to give **15** (852 mg, 93%) as a white solid: mp 128 °C; $[\alpha]^{27}_D$ +119 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49 (t, J = 2.4 Hz, 1H), 2.5 (bs, 1H), 3.84 (t, J = 10.2 Hz, 1H), 3.9 (t, J = 9.6 Hz, 1H), 4.16 (dd, J = 3.6, 10.0 Hz, 1H), 4.21−4.24 (m, 2H), 4.27−4.32 (m, 1H), 4.34 (dd, J = 2.4, 16.1 Hz, 1H), 4.42 (dd, J = 2.4, 16.1 Hz, 1H), 5.59 (s, 1H), 5.68 (s, 1H), 7.32−7.53 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 58.6, 64.7, 68.4, 68.9, 75.7, 78.9, 79.3, 79.4, 86.4, 102.2, 126.3, 127.7, 128.3, 129.2, 131.7, 133.8, 137.2; ESIHRMS calcd for $C_{22}H_{22}O_5SNa$ $[M + Na]^+$ 421.1086, found 421.1095.

Methyl 4,6-*O*-Benzylidene-3-*O*-(2-naphthylmethyl)-2-*O*-(prop-2-ynyl)-β-D-mannopyranoside (16). To a stirred solution of donor **14** (122 mg, 0.23 mmol), BSP (57 mg, 0.27 mmol), TTBP (84.6 mg, 0.34 mmol), and 4 Å molecular sieves in CH_2Cl_2 (6 mL), at −60 °C under an Ar atmosphere, was added Tf_2O (50 μL, 0.29 mmol). After 30 min of stirring at −60 °C, dry methanol (28 μL, 0.68 mmol) was added. The reaction mixture was stirred for further 2 h at −60 °C, and then allowed to warm to room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL), the molecular sieves were filtered off and washed with saturated $NaHCO_3$. The organic layer was separated, dried, and concentrated. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate; 5:1) to give **16** (89 mg, 85%) as a colorless oil: $[\alpha]^{27}_D$ −29.8 (*c* 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.53 (t, J = 2.4 Hz, 1H), 3.30−3.35 (m, 1H), 3.52 (s, 3H), 3.67 (dd, J = 3.1, 9.9 Hz, 1H), 3.93 (t, J = 10.3 Hz, 1H), 4.17 (t, J = 9.6 Hz, 1H), 4.21 (d, J = 3.0 Hz, 1H), 4.34 (dd, J = 4.9, 10.4 Hz, 1H), 4.39 (s, 1H), 4.61 (dd, J = 2.4, 16.1 Hz, 1H), 4.65 (dd, J = 2.4, 16.1 Hz, 1H), 4.98 (d, J = 12.9 Hz, 1H), 5.0 (d, J = 12.9 Hz, 1H), 5.64 (s, 1H), 7.40−7.54 (m, 8H), 7.71−7.87 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.5, 60.0, 67.5, 68.6, 72.5, 74.9, 75.0, 78.4, 80.0, 101.5, 102.9, 125.7, 125.9, 126.0, 126.4, 127.7, 127.9, 128.1, 128.2, 128.9, 132.9, 133.2, 135.7, 137.6; ESIHRMS calcd for $C_{28}H_{28}O_6Na$ $[M + Na]^+$ 483.1784, found 483.1805.

Methyl 4,6-*O*-Benzylidene-2-*O*-(prop-2-ynyl)-β-D-mannopyranoside (17). To stirred solution of **16** (82 mg, 0.18mmol) in CH_2Cl_2 (5 mL) and water (0.1 mL) was added DDQ (81 mg, 0.36 mmol) at rt. After the reaction mixture was stirred for 3 h, satd $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2. The extract was washed several times with satd $NaHCO_3$, dried over Na_2SO_4, and concentrated on a rotary evaporator. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate; 7:3) to give **17** (51 mg, 89%) as a white solid: mp 126 °C; $[\alpha]^{27}_D$ −119.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.5 (t, J = 2.4 Hz, 1H), 3.31−3.36 (m, 1H), 3.5 (s, 3H), 3.76−3.83 (m, 2H), 3.87 (t, J = 10.3 Hz, 1H), 4.0 (dd, J = 0.5, 3.2 Hz, 1H), 4.3 (dd, J = 4.9, 10.5 Hz, 1H), 4.46 (dd, J = 2.4, 16.1 Hz, 1H), 4.48 (s, 1H), 4.6 (dd, J = 2.4, 16.1 Hz, 1H), 5.5 (s, 1H), 7.26−7.38 (m, 3H), 7.48−7.5 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 57.5, 60.6, 67.0, 68.4, 70.3, 75.5, 77.2, 79.1, 79.7, 102.0, 103.0, 126.3, 128.2, 129.1, 137.2; ESIHRMS calcd for $C_{17}H_{21}O_6$ $[M + H]^+$ 321.1338, found 321.1347.

Phenyl 4,6-*O*-Benzylidene-2-*O*-(prop-2-ynyl)-3-*O*-(2-naphthylmethyl)-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-(prop-2-ynyl)-1-thio-α-D-mannopyranoside (18). To a stirred solution of donor **14** (270 mg, 0.50 mmol), BSP (126 mg, 0.6 mmol), TTBP (187 mg, 0.8 mmol), and 4 Å molecular sieves in CH_2Cl_2 (5 mL), at −60 °C under an Ar atmosphere, was added Tf_2O (110 μL, 0.65 mmol). After 30 min, the temperature was brought down to −78 °C, and then acceptor **15** (240 mg, 0.60 mmol) in CH_2Cl_2 (3 mL) was slowly added. The reaction mixture was stirred for 2 h at −78 °C and then quenched by the addition of triethyl phosphite (255 μL, 1.5 mmol) and stirred for 1 h at −78 °C before it was allowed to reach room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL), and the molecular sieves were filtered off and washed with saturated $NaHCO_3$. The organic layer was separated, dried, and concentrated. The crude product was purified by column chromatography on neutral alumina (hexane/ethyl acetate; 7:3) to give **18** (380 mg, α:β; 1:25, 91%). For β-anomer: $[\alpha]^{27}_D$ +51.1 (*c* 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.28 (t, J = 2.4 Hz, 1H), 2.56 (t, J = 2.3 Hz, 1H), 3.24−3.29 (m, 1H), 3.67 (dd, J = 3.1, 9.8 Hz, 1H), 3.85−3.90 (m, 2H), 4.16−4.21 (m, 3H), 4.23 (t, J = 4.8, 10.2 Hz, 1H), 4.27−4.31 (m, 3H), 4.34 (dd, J = 1.5, 3.0 Hz, 1H), 4.37 (dd, J = 2.4, 16.3 Hz, 1H), 4.47 (dd, J = 2.4, 16.3 Hz, 1H), 4.65 (dd, J = 2.4, 16.0 Hz, 1H), 4.69 (dd, J = 2.4, 16.0 Hz, 1H), 4.80 (s, 1H), 4.95 (d, J = 12.8 Hz, 1H), 4.98 (d, J = 13.7 Hz, 1H), 5.57 (s, 2H), 5.63 (s, 1H), 7.26−7.53 (m, 18H), 7.80−7.86 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 58.3, 59.8, 65.2, 67.7, 68.4, 68.6, 72.5, 75.0, 75.2, 75.5, 77.9, 78.4, 79.3, 80.5, 86.6, 100.0, 101.3, 101.7, 125.7, 125.9, 126.1, 126.2, 126.4, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.9, 129.1, 129.3, 131.7, 132.9, 133.5, 137.3, 137.6; ESIHRMS calcd for $C_{49}H_{46}O_{10}SNa$ $[M + Na]^+$ 849.2710, found 849.2729

Phenyl 4,6-*O*-Benzylidene-2-*O*-(prop-2-ynyl)-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-(prop-2-ynyl)-1-thio-α-D-mannopyranoside (19). To a stirred solution of **18**β (72 mg, 0.09 mmol) in CH_2Cl_2 (10 mL) and water (0.5 mL) was added DDQ (49.4 mg, 0.22 mmol) at room temperature. After 3 h, satd $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2. The extracts were washed several times with satd $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave an oil, which was chromatographed on silica gel (hexane/ethyl acetate; 3:2) to give **19** (55 mg, 94%): $[\alpha]^{22}_D$ +27.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.5 (t, J = 2.4 Hz, 1H), 3.31−3.34 (m, 1H), 3.78 (t, J = 10.0 Hz, 1H), 3.82−3.89 (m, 3H), 4.19−4.26 (m, 2H), 4.31−4.37 (m, 3H), 4.36 (dd, J = 2.5, 16.5 Hz, 1H), 4.47 (dd, J = 2.5, 16.5 Hz, 1H), 4.55 (dd, J = 2.0, 16.0 Hz, 1H), 4.58 (dd, J = 2.0, 16.0 Hz, 1H), 4.94 (s, 1H), 5.37 (s, 1H), 5.57 (s, 1H), 5.66 (s, 1H), 7.26−7.41 (m, 9H), 7.44−7.52 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 57.8, 59.9, 65.3, 67.1, 68.5, 70.2, 74.1, 75.6, 75.8, 76.1, 76.5, 77.4, 79.0, 79.5, 79.8, 86.1, 98.9, 101.8, 126.2, 126.3, 127.9, 128.3, 129.1, 129.3, 131.7, 133.5, 137.2, 137.3; ESIHRMS calcd for $C_{38}H_{38}O_{10}SNa$ $[M + Na]^+$ 709.2084, found 709.2068.

Phenyl 4,6-*O*-Benzylidene-2-*O*-(prop-2-ynyl)-3-*O*-(2-naphthylmethyl)-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-(prop-2-ynyl)-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-(prop-2-ynyl)-1-thio-α-D-mannopyranoside (20α). To a stirred

solution of donor **18**β (179 mg, 0.22 mmol), BSP (54.4 mg 0.26 mmol), TTBP (80.5 mg, 0.32 mmol), and 4 Å molecular sieves in CH_2Cl_2 (3 mL), at −60 °C under an Ar atmosphere, was added Tf_2O (47 μL, 0.28 mmol). After 30 min, the temperature was brought down to −78 °C, and then acceptor **15** (103 mg, 0.26 mmol) in CH_2Cl_2 (2 mL) was slowly added. The reaction mixture was stirred for 2 h at −78 °C, quenched by the addition of triethyl phosphite (72 μL, 0.43 mmol), and stirred for 1 h at −78 °C before it was allowed to reach room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL), and the molecular sieves were filtered off and washed with saturated $NaHCO_3$. The organic layer was separated, dried, and concentrated. The crude product was purified by column chromatography on neutral alumina (hexane/ethyl acetate; 3:1) to give **20** (210 mg, α:β; 20:1, 88%). For α-anomer: $[\alpha]^{20}_D$ +37.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (t, J = 2.0 Hz, 1H), 2.53 (t, J = 2.5 Hz, 1H), 2.57 (t, J = 2.0 Hz, 1H), 3.21−3.26 (m, 1H), 3.64 (dd, J = 3.5, 10.0 Hz, 1H), 3.81−3.89 (m, 3H), 4.0−4.07 (m, 1H), 4.09−4.31 (m, 15H), 4.41 (dd, J = 2.5, 16.0 Hz, 1H), 4.63 (dd, J = 2.5, 16.0 Hz, 1H), 4.68 (dd, J = 2.5, 16.5 Hz, 1H), 4.73 (s, 1H), 4.94 (d, J = 12.5 Hz, 1H), 4.98 (d, J = 13.0 Hz, 1H), 5.31 (s, 1H), 5.50 (s, 2H), 5.65 (s, 1H), 7.26−7.53 (m, 23H), 7.80−7.89 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 57.9, 58.6, 59.8, 64.2, 64.5, 65.2, 67.7, 68.5, 68.7, 72.2, 72.4, 74.9, 75.1, 75.2, 75.3, 76.6, 77.2, 77.8, 78.4, 79.0, 79.1, 79.2, 80.5, 86.4, 99.6, 100.5, 101.5, 101.6, 102.0, 125.7, 125.9, 126.2, 126.3, 126.5, 127.7, 127.9, 128.2, 128.3, 128.4, 128.9, 129.0, 129.3, 129.4, 131.7, 133.0, 133.2, 133.4, 134.5, 134.6, 135.7, 137.3, 137.5, 137.6; ESIHRMS calcd for $C_{65}H_{62}O_{15}SNa$ $[M + Na]^+$ 1137.3702, found 1137.3699.

Phenyl 4,6-*O*-Benzylidene-2-*O*-(prop-2-ynyl)-3-*O*-(2-naphthylmethyl)-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-(prop-2-ynyl)-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-(prop-2-ynyl)-1-thio-α-D-mannopyranoside (20β). To a stirred solution of donor **14** (400 mg, 0.074 mmol), BSP (18.6 mg 0.09 mmol), TTBP (27.6 mg, 0.11 mmol), and 4 Å molecular sieves in CH_2Cl_2 (2.5 mL), at −60 °C under an Ar atmosphere, was added Tf_2O (16 μL, 0.65 mmol). After 30 min, the temperature was brought down to −78 °C, and then acceptor **19** (55 mg 0.081 mmol) in CH_2Cl_2 (2 mL) was slowly added. The reaction mixture was stirred for 2 h at −78 °C and then quenched by the addition of triethyl phosphite (24 μL, 0.15 mmol) and stirred for 1 h at −78 °C before it was allowed to reach room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and molecular sieves were filtered off and washed with saturated $NaHCO_3$. The organic layer was separated, dried, and concentrated. The crude product was purified by column chromatography on neutral alumina (hexane/ethyl acetate; 7:3) to give **20**β (69 mg, 82%): $[\alpha]^{27}_D$ −10.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.08 (t, J = 2.5 Hz, 1H), 2.47 (t, J = 2.5 Hz, 1H), 2.51 (t, J = 2.5 Hz, 1H), 3.25−3.34 (m, 2H), 3.62 (dd, J = 3.0, 10.0 Hz, 1H), 3.84 (t, J = 11.0 Hz, 1H), 3.86 (t, J = 10.0 Hz, 1H), 3.90 (t, J = 10.0 Hz, 1H), 4.03−4.04 (m, 2H), 4.14 (t, J = 10.0 Hz, 1H), 4.17 (t, J = 10.0 Hz, 1H), 4.21−4.25 (m, 5H), 4.30−4.35 (m, 2H), 4.36−4.37 (m, 2H), 4.46 (dd, J = 2.5, 16.5 Hz, 1H), 4.51 (dd, J = 2.5, 16.0 Hz, 1H), 4.62 (dd, J = 3.0, 15.0 Hz, 1H), 4.65 (dd, J = 2.5, 16.5 Hz, 1H), 4.87 (s, 1H), 4.91 (s, 1H), 4.95 (d, J = 13.5 Hz, 1H), 4.99 (d, J = 14.0 Hz, 1H), 5.43 (br. s, 1H), 5.58 (s, 1H), 5.59 (s, 1H), 5.64 (d, J = 1.5 Hz, 1H), 7.26−7.54 (m, 23H), 7.76−7.87 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 57.1, 59.5, 60.0, 65.3, 67.8, 68.5, 68.6, 72.2, 73.2, 73.9, 74.8, 74.9, 75.2, 75.3, 75.8, 75.9, 76.5, 76.9, 77.6, 78.3, 79.3, 80.3, 80.7, 86.2, 98.6, 99.1, 101.5, 101.8, 125.8, 125.9, 126.1, 126.2, 126.5, 127.7, 127.9, 128.2, 128.2, 128.3, 128.9, 129.2, 129.3, 131.7, 132.9, 133.2, 133.4, 135.7, 137.3, 137.6; ESIHRMS calcd for $C_{65}H_{62}O_{15}SNa$ $[M + Na]^+$ 1137.3702, found 1137.3698.

Methyl 4,6-*O*-Benzylidene-2-*O*-(prop-2-ynyl)-3-*O*-(2-naphthylmethyl)-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-(prop-2-ynyl)-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-(prop-2-ynyl)-β-D-mannopyranoside (21). To a stirred solution of donor **18**β (124 mg, 0.15 mmol), BSP (37.6 mg 0.18 mmol), TTBP (55.8 mg, 0.23 mmol), and 4 Å molecular sieves in CH_2Cl_2 (3 mL), at −60 °C under an Ar atmosphere, was added Tf_2O (32.8 μL 0.19 mmol). After 30 min of stirring at −60 °C, acceptor **17** (72 mg, 0.23 mmol) in CH_2Cl_2 (2 mL) was added slowly. The reaction mixture was stirred for a further 2 h at −60 °C, and then allowed to reach room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL), and the molecular sieves were filtered off and washed with saturated $NaHCO_3$. The organic layer was separated, dried, and concentrated. The crude product was purified by chromatography on silica gel (toluene/ethyl actate/CH_2Cl_2; 7:2:1) to give **21** (130 mg, α:β; 1:7, 84%). For β-anomer: $[\alpha]^{22}_D$ −82.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.94 (t, J = 2.3 Hz, 1H), 2.48−2.52 (m, 2H), 3.29−3.40 (m, 3H), 3.55 (s, 3H), 3.61 (dd, J = 3.0, 10.0 Hz, 1H), 3.84−3.93 (m, 3H), 3.97 (t, J = 10.0 Hz, 1H), 4.0−4.05 (m, 2H), 4.08 (dd, J = 3.0, 10.0 Hz, 1H), 4.17 (t, J = 10.0 Hz, 1H), 4.21 (d, J = 3.0 Hz, 1H), 4.23−4.28 (m, 3H), 4.35 (dd, J = 4.5, 10.0 Hz, 1H), 4.47 (dd, J = 2.5, 16.0 Hz, 1H), 4.49 (s, 1H), 4.55 (dd, J = 2.5, 17.0 Hz, 1H), 4.61 (dd, J = 2.5, 16.5 Hz, 1H), 4.65 (dd, J = 2.5, 16.0 Hz, 1H), 4.93 (s, 1H), 4.97 (s, 2H), 5.03 (s, 1H), 5.48 (s, 1H), 5.54 (s, 1H), 5.59 (s, 1H), 7.26−7.46 (m, 18H), 7.62−7.71 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 57.6, 59.4, 59.5, 60.0, 67.5, 67.8, 68.5, 72.0, 72.1, 72.8, 73.7, 73.8, 74.7, 74.8, 75.2, 75.3, 76.2, 76.4, 76.6, 78.2, 80.4, 80.6, 97.6, 97.8, 101.4, 101.5, 103.4, 125.8, 125.9, 125.99, 126.0, 126.1, 126.5, 127.6, 127.8, 128.1, 128.2, 128.3, 128.9, 129.9, 132.9, 133.1, 135.6, 137.2, 137.5; ESIHRMS calcd for $C_{60}H_{60}O_{16}Na$ $[M + Na]^+$ 1059.3779, found 1059.3792.

Methyl 4,6-*O*-Benzylidene-2-*O*-(prop-2-ynyl)-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-(prop-2-ynyl)-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-(prop-2-ynyl)-β-D-mannopyranoside (22). To a stirred solution of **21**β (72 mg, 0.069 mmol) in CH_2Cl_2 (10 mL) and water (0.5 mL) was added DDQ (40 mg, 0.18 mmol) at room temperature. After 3 h, satd $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2. The extracts were washed several times with satd $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave an oil, which was purified by column chromatographed on neutral alumina (hexane/ethyl acetate; 2:1) to give **22** (51 mg, 81%): $[\alpha]^{20}_D$ −116.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05 (t, J = 2.0 Hz, 1H), 2.48−2.50 (m, 2H), 2.59 (br. s, 1H), 3.35−3.45 (m, 3H), 3.56 (s, 3H), 3.76−3.86 (m, 3H), 3.91 (t, J = 10.0 Hz, 1H), 4.0 (t, J = 10.0 Hz, 1H), 4.0−4.05 (m, 2H), 4.09−4.13 (m, 2H), 4.25−4.30 (m, 4H), 4.36 (dd, J = 4.5, 10.5 Hz, 1H), 4.50 (s, 1H), 4.53 (dd, J = 2.5, 16.0 Hz, 1H), 4.55 (dd, J = 2.5, 16.0 Hz, 1H), 4.57 (dd, J = 2.5, 16.0 Hz, 1H), 4.63 (dd, J = 2.5, 16.0 Hz, 1H), 4.69 (dd, J = 2.5, 16.0 Hz, 1H), 4.70 (dd, J = 2.5, 16.0 Hz, 1H), 5.07 (s, 2H), 5.47 (s, 1H), 5.49 (s, 1H), 5.57 (s, 1H), 7.26−7.48 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 57.7, 59.4, 59.5, 60.5, 67.2, 67.7, 68.4, 68.5, 70.2, 72.1, 72.8, 73.8, 73.9, 75.1, 75.2, 76.6, 77.2, 79.3, 80.0, 80.4, 80.6, 97.6, 97.8, 101.4, 101.6, 101.9, 103.4, 126.0, 126.2, 128.1, 128.18, 128.2, 128.3, 128.9, 129.0, 129.1, 137.1, 137.2; ESIHRMS calcd for $C_{49}H_{52}O_{16}Na$ $[M + Na]^+$ 919.3148, found 919.3143.

Standard Procedure for Coupling Reactions of the Sulfoxide Donor 23 with the Corresponding Sugar Acceptors Using TTBP and Tf_2O. To a stirred solution of sulfoxide donor **23** (0.05 M in mixed solvent, 1.2 equiv), TTBP (1.6 equiv), and 4 Å molecular sieves in a mixed solvent of CH_2Cl_2 and 1-octene (v/v, 4/1), at −78 °C under argon atmosphere, was added Tf_2O (1.2 equiv). After the reaction mixture was stirred at −78 °C for 30 min, a solution of sugar acceptors (0.1 M, 1.0 equiv) in CH_2Cl_2 was added. Stirring was maintained for another 30 min at −78 °C before the reaction temperature was allowed to warm to −20 °C slowly. The reaction mixture was poured into aq $NaHCO_3$ solution, diluted with CH_2Cl_2, and filtered through Celite. The organic layer was separated from the filtrate, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel to give the coupled products.

Methyl 4,6-*O*-Benzylidene-2-*O*-benzyl-3-*O*-[3-(naphthalen-1-yl)prop-2-ynyl]-β-D mannopyranoside (24). To a stirred solution of sulfoxide **23** (0.15 g, 0.23 mmol), TTBP (0.094 g, 0.38 mmol), and 4 Å molecular sieves in a mixed solvent of CH_2Cl_2 and 1-octene (5 mL, v/v, 4:1), at −78 °C under argon atmosphere, was added Tf_2O (48 μL, 0.28 mmol). After the reaction mixture was stirred at −78 °C for 30 min, 1 mL of anhydrous methanol was added. The reaction mixture was stirred at −78 °C for another 30 min before being poured into aq $NaHCO_3$ solution and then diluted with CH_2Cl_2 and filtered through Celite. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate; 4:1) to give the β-coupled product **24** (0.087 g, 68%): $[\alpha]^{20}_D$ −33.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.0 Hz, 1H), 7.85 (t, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 7.0 Hz, 1H), 7.48−7.54 (m, 6H), 7.41−7.44 (dd, *J* = 7.0, 8.0 Hz, 1H), 7.33−7.36 (m, 5H), 7.28−7.29 (m, 1H), 5.65 (s, 1H), 5.03(d, *J* = 12.0 Hz 1H), 4.91 (d, *J* = 12.0 Hz, 1H), 4.60−4.68 (m, 2H), 4.48 (s, 1H), 4.36 (dd, *J* = 4.5, 10.5 Hz, 1H), 4.24 (t, *J* = 9.5 Hz, 1H), 4.09 (d, *J* = 3.0 Hz, 1H), 3.95−4.00 (m, 2H), 3.56 (s, 3H), 3.44 (dt, *J* = 5.0, 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 137.5, 133.4, 133.1, 130.7, 129.0, 128.9, 128.4, 128.32, 128.25, 128.2, 127.5, 126.9, 126.5, 126.2, 126.1, 125.2, 120.2, 103.3, 101.6, 90.2, 84.5, 78.6, 76.3, 75.1, 68.7, 67.6, 59.0, 57.5; ESIHRMS calcd for $C_{34}H_{32}O_6Na$ $[M + Na]^+$ 559.2097, found 559.2094.

Standard Procedure for Removal of the 1-Naphthylpropargyl Protecting Group with DDQ. To a stirred solution of the 1-naphthylpropargyl-protected saccharide (0.06 M) in CH_2Cl_2 and water (CH_2Cl_2/water, v/v, 20:1) was added DDQ (1.5 equiv). The resulting mixture was stirred at rt for 2−3 h. When the reaction was over as monitored by TLC, the reaction mixture was quenched by adding aq $NaHCO_3$ solution and then diluted with CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layer was washed with brine, dried and concentrated. The residue was purified by chromatography on silica gel to give the deprotected product.

Methyl 4,6-*O*-Benzylidene-2-*O*-benzyl-β-D-mannopyranoside (25). Removal of the naphthylpropargyl protecting group from **24** (0.42 g, 0.78 mmol) by the standard protocol gave compound **25** (0.21 g, 0.56 mmol) in 74% yield: $[\alpha]^{20}_D$ −122.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.50 (m, 2H), 7.30−7.42 (m, 8H), 5.55 (s, 1H), 5.08 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.49 (s, 1H), 4.34 (dd, *J* = 5.0, 10.5 Hz, 1H), 3.76−3.93 (m, 4H), 3.59 (s, 3H), 3.35 (dt, *J* = 5.0, 9.5 Hz, 1H), 2.31 (br. s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 137.3, 129.1, 128.6, 128.3, 128.24, 128.15, 128.0, 126.3, 103.5, 102.0, 79.4, 78.4, 75.7, 70.8, 68.6, 67.1, 57.6; ESIHRMS calcd for $C_{21}H_{24}O_6Na$ $[M + Na]^+$ 395.1471, found 395. 1486.

Methyl 4,6-*O*-Benzylidene-2-*O*-benzyl-3-*O*-[3-(naphthalen-1-yl)prop-2-ynyl]-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranoside (26). Coupling of sulfoxide **23** (0.16 g, 0.25 mmol) with donor **25** (0.08 g, 0.21 mmol) by the standard coupling protocol gave disaccharide **26** (0.17 g, 0.19 mmol) in 93% yield: $[\alpha]^{20}_D$ −81.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.0 Hz, 1H), 7.85 (t, *J* = 7.5 Hz, 2H), 7.65 (d, *J* = 7.0 Hz, 1H), 7.18−7.54 (m, 23H), 5.62 (s, 1H), 5.53 (s, 1H), 4.98 (d, *J* = 12.0, Hz, 1H), 4.93 (d, *J* = 12.5 Hz, 1H), 4.74 (t, *J* = 12.5 Hz, 2H), 4.58−4.66 (m, 2H), 4.48 (s, 1H), 4.36 (dd, *J* = 4.5, 10.5 Hz, 1H), 4.20 (dd, *J* = 5.0, 10.5 Hz, 1H), 4.07−4.15 (m, 4H), 3.94−3.98 (m, 2H), 3.86 (t, *J* = 10.5 Hz, 1H), 3.76 (d, *J* = 3.0 Hz, 1H), 3.60 (s, 4H), 3.41 (dt, *J* = 5.0, 10.0 Hz, 1H), 3.02 (dt, *J* = 5.0, 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.1, 137.5, 137.4, 133.4, 133.2, 130.7, 129.1, 128.9, 128.8, 128.4, 128.3, 128.2, 128.1, 127.3, 127.0, 126.5, 126.3, 126.2, 125.2, 120.3, 103.7, 101.8, 101.5, 97.4, 90.5, 84.4, 78.3, 77.0, 76.0, 74.8, 74.3, 73.5, 72.9; ESIHRMS calcd for $C_{54}H_{52}O_{11}Na$ $[M + Na]^+$ 899.3408, found 899.3444.

Methyl 4,6-*O*-Benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranoside (27). Removal of the naphthylpropargyl protecting group from **26** (0.135 g, 0.15 mmol) by the standard protocol gave deprotected compound **27** (0.091 g, 1.28 mmol) in 77% yield: $[\alpha]^{21}_D$ −113.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.46 (m, 6H), 7.21−7.7.38 (m, 10H), 7.17−7.20 (m, 4H), 5.05 (d, *J* = 11.0 Hz, 1H), 5.00 (d, *J* = 12.5 Hz, 1H), 4.53 (d, 11.0 Hz, 1H), 4.52 (s, 1H), 4.38 (dd, *J* = 4.5, 10.5 Hz, 1H), 4.18 (dd, *J* = 5.0, 10.5 Hz, 1H), 4.07−4.15 (m, 3H), 4.02 (d, *J* = 2.5 Hz, 1H), 3.96 (t, *J* = 10.5 Hz, 1H), 3.71−3.76 (m, 2H), 3.62 (s, 3H), 3.57 (d, *J* = 4.0 Hz, 1H), 3.41−3.48 (m, 2H), 2.98 (dt, *J* = 4.5, 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 137.4, 137.2, 129.1, 129.0, 128.5, 128.4, 128.2, 127.8, 126.2, 103.8, 101.84, 101.80, 97.0, 79.5, 77.6, 75.1, 74.4, 73.3, 72.6, 70.2, 68.7, 68.5, 67.8, 67.0; ESIHRMS calcd for $C_{41}H_{44}O_{11}Na$ $[M + Na]^+$ 735.2782, found 735.2761.

Methyl 4,6-*O*-Benzylidene-2-*O*-benzyl-3-*O*-[3-(naphthalen-1-yl)prop-2-ynyl]-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranoside (28). Method 1. Coupling of sulfoxide **23** (0.095 g, 0.15 mmol) with donor **27** (0.09 g, 0.13 mmol) by the standard coupling protocol gave trisaccharide **28** (0.12 g, 0.10 mmol) in 78% yield. **Method 2.** Coupling of sulfoxide donor **34** (0.07 g, 0.05 mmol) with methanol (1 mL, excess) by standard coupling protocol gave trisaccharide **28** (0.061 g, 0.05 mmol) in 94% yield: $[\alpha]^{24}_D$ −100.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.0 Hz, 1H), 7.84 (t, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 7.0 Hz, 1H), 7.28−7.53 (m, 25H), 7.17−7.20 (m, 5H), 7.11−7.12 (m, 3H), 5.60 (s, 1H), 5.57 (s, 1H), 5.51 (s, 1H), 5.04 (d, *J* = 12.5 Hz, 1H), 5.01 (d, *J* = 12.0 Hz, 1H), 4.92 (d, 12.0 Hz, 1H), 4.80 (d, *J* = 13.0 Hz, 1H), 4.77 (d, *J* = 12.0 Hz, 1H), 4.60−4.70 (m, 3H), 4.52−4.54 (m, 1H), 4.38 (dd, *J* = 4.5, 10.0 Hz, 1H), 3.72−4.25 (m, 17H), 3.62 (s, 3H), 3.44 (dt, *J* = 4.5, 9.5 Hz, 1H), 3.12 (dt, *J* = 4.5, 9.5 Hz, 1H), 3.02 (dt, *J* = 4.5, 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.3, 138.2, 137.5, 137.43, 137.38, 133.4, 133.2, 130.7, 129.0, 128.9, 128.6, 128.44, 128.39, 128.2, 128.11, 128.08, 127.8, 127.3, 126.9, 126.5, 126.23, 126.18, 126.15, 125.2, 120.3, 103.8, 101.72, 101.67, 101.5, 97.7, 97.3, 90.4, 84.4, 78.4, 76.97, 76.93, 76.2, 74.9, 74.2, 74.1, 73.8, 73.3, 73.0, 72.7, 68.7, 68.6, 67.8, 58.7, 57.7; ESIHRMS calcd for $C_{74}H_{72}O_{16}Na$ $[M + Na]^+$ 1239.4713, found 1239.4680.

Methyl 4,6-*O*-Benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(l→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranoside (29). Removal of protecting group from compound **28** (0.094 g, 0.08 mmol) by the standard deprotection protocol gave trisaccharide **29** (0.065 g, 0.06 mmol) in 77% yield: $[\alpha]^{29}_D$ −120.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.47 (m, 9H), 7.19−7.36 (m, 21H), 5.60 (s, 1H), 5.47 (s, 1H), 5.37 (s, 1H), 5.03−5.07 (m, 2H), 4.97 (d, *J* = 12.0 Hz, 1H), 4.81 (d, *J* = 12.5 Hz, 1H), 4.72 (d, *J* = 11.0 Hz, 1H), 4.55 (d, *J* = 12.5 Hz, 1H), 4.54 (s, 1H), 4.38 (dd, *J* = 5.0, 10.5 Hz, 1H), 4.30 (s, 1H), 4.10−4.23 (m, 5H), 4.00−4.04 (m, 2H), 3.96 (t, *J* = 10.0 Hz, 1H), 3.75−3.86 (m, 5H), 3.70 (d, *J* = 4.0 Hz, 1H), 3.63 (s, 3H), 3.60−3.63 (m, 1H), 3.42−3.48 (m, 1H), 3.01−3.12 (m, 2H), 2.47 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 138.2, 137.4, 137.4, 129.1, 129.0, 128.60, 128.55, 128.4, 128.2, 128.1, 127.9, 127.8, 126.3, 126.22, 126.16, 103.8, 101.80, 101.75, 101.7, 97.4, 97.2, 79.6, 77.6, 77.3, 75.1, 74.3, 73.6, 73.3, 72.9, 72.7, 70.2, 68.7, 68.6, 67.8, 67.1, 57.7; ESIHRMS calcd for $C_{61}H_{64}O_{16}Na$ $[M + Na]^+$ 1075.4087, found 1075.4090.

Phenyl 4,6-*O*-Benzylidene-2-*O*-benzyl-3-*O*-[3-(naphthalen-1-yl)prop-2-ynyl]-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-1-thio-α-D-mannopyranoside(31). Coupling of sulfoxide donor **23** (0.105 g, 0.17 mmol) with thioglycoside **30** (0.050 g, 0.11 mmol) by the standard coupling protocol gave disaccharide **31** (0.081 g, 0.085 mmol) as a colorless syrup in 76% yield: $[\alpha]^{24}_D$ +37.6 (*c* 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.5 Hz, 1H), 7.85 (t, *J* = 7.5 Hz, 2H), 7.67 (d, *J* = 7.0 Hz, 1H), 7.20−7.53 (m, 28H), 5.64 (s, 1H), 5.63 (s, 1H), 5.56 (s, 1H), 5.02 (d, *J* = 11.5 Hz, 1H), 4.83 (d, *J* = 11.5 Hz, 1H), 4.65−4.72 (m,

3H), 4.48 (d, J = 12.5 Hz, 1H), 4.41(dd, J = 3.0, 10.0 Hz, 1H), 4.24−4.36 (m, 5H), 4.18 (t, J = 9.5 Hz, 1H), 4.07−4.08 (m, 1H), 3.95 (d, J = 3.0 Hz, 1H), 3.91 (t, J = 10.0 Hz, 2H), 3.77 (dd, J = 3.5, 10.0 Hz, 1H), 3.12 (dt, J = 4.5, 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 137.6, 137.5, 137.1, 133.8, 133.4, 133.2, 131.8, 130.7, 129.3, 129.1, 129.0, 128.9, 128.61, 128.55, 128.4, 128.2, 128.1, 127.9, 127.3, 127.0, 126.5, 126.3, 126.2, 126.1, 125.2, 120.3, 101.9, 101.5, 98.4, 90.5, 86.0, 84.5, 78.4, 77.4, 76.6, 75.7, 75.0, 72.7, 72.1, 68.64, 68.56, 67.7, 65.5, 58.8; ESIHRMS calcd for $C_{59}H_{54}O_{10}SNa$ $[M + Na]^+$ 977.3336, found 977.3380.

Phenyl 4,6-*O*-Benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-1-thio-α-D-mannopyranoside (32). Removal of the naphthylpropargyl group from compound **31** (1.30 g, 1.36 mmol) by the standard protocol gave product **32** (0.95 g, 1.20 mmol) in 88% yield: $[\alpha]^{25}_D$ −2.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.49 (m, 6H), 7.24−7.38 (m, 19H), 5.68 (s, 1H), 5.64 (s, 1H), 5.33 (s, 1H), 5.06 (d, J = 11.0 Hz, 1H), 4.77 (d, J = 12.0 Hz, 1H), 4.62 (d, J = 12.0 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.42 (dd, J = 3.0, 10.0 Hz, 1H), 4.35−4.40 (m, 2H), 4.22−4.30 (m, 3H), 4.12−4.13 (m, 1H), 3.92 (t, J = 10.0 Hz, 1H), 3.83 (t, J = 9.0 Hz, 1H), 3.74−3.78 (m, 2H), 3.58−3.66 (m, 1H), 3.10 (dt, J = 4.5, 9.5 Hz, 1H), 2.53 (d, J = 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 137.44, 137.36, 137.1, 133.7, 131.8, 129.3, 129.08, 129.05, 128.7, 128.6, 128.5, 128.4, 128.2, 127.9, 127.8, 126.3, 102.0, 101.8, 97.8, 86.1, 79.8, 77.5, 77.30, 77.25, 75.4, 74.9, 72.4, 72.2, 70.2, 68.7, 68.6, 67.0, 65.6; ESIHRMS calcd for $C_{46}H_{46}O_{10}SNa$ $[M + Na]^+$ 813.2704, found 813.2694.

Phenyl 4,6-*O*-Benzylidene-2-*O*-benzyl-3-*O*-[3-(naphthalen-1-yl)-prop-2-ynyl]-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-1-thio-α-D-mannopyranoside (33). Coupling of sulfoxide donor **23** (0.063 g, 0.10 mmol) with thioglycoside **32** (0.062 g, 0.08 mmol) by the standard coupling protocol gave trisaccharide **33** (0.074 g, 0.06 mmol) as a colorless syrup in 73% yield: $[\alpha]^{27}_D$ −40.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, J = 8.0 Hz, 1H), 7.84 (t, J = 7.5 Hz, 2H), 7.63 (d, J = 7.0 Hz, 1H), 7.44−7.52 (m, 10H), 7.28−7.40 (m, 20H), 7.18−7.23 (m, 5H), 7.11−7.12 (m, 3H), 5.66 (s, 1H), 5.60 (s, 1H), 5.56 (s, 1H), 5.49 (s, 1H), 4.99 (d, J = 12.0 Hz, 1H), 4.93 (d, J = 12.0 Hz, 1H), 4.77 (t, J = 12.0 Hz, 2H), 4.53−4.70 (m, 4H), 4.43 (dd, J = 3.0, 10.0 Hz, 1H), 4.06−4.35 (m, 10H), 3.85−3.94 (m, 6H), 3.71 (dd, J = 3.0, 10.0 Hz, 1H), 3.08−3.14 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.2, 137.5, 137.4, 137.0, 133.7, 133.4, 133.2, 131.9, 130.7, 129.3, 129.0, 128.9, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.3, 126.9, 126.5, 126.3, 126.2, 125.2, 120.3, 101.8, 101.7, 101.5, 98.0, 90.4, 85.8, 84.4, 78.4, 76.1, 75.4, 74.9, 74.2, 73.9, 73.4, 72.3, 71.9, 68.6, 67.8, 65.5, 58.7; ESIHRMS calcd for $C_{79}H_{74}O_{15}SNa$ $[M + Na]^+$ 1317.4641, found 1317.4630.

Phenyl 4,6-*O*-Benzylidene-2-*O*-benzyl-3-*O*-[3-(naphthalen-1-yl)-prop-2-ynyl]-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-1-thio-α-D-mannopyranoside *S*-Oxide (34). To a stirred solution of **33** (0.98 g, 0.76 mmol) in CH_2Cl_2 (40 mL) was added a solution of *m*-CPBA (77%, 0.17 g, 0.76 mmol) in CH_2Cl_2 (2 mL) dropwise at −78 °C. The resultant mixture was stirred for 1 h during which time the temperature was allowed to warm up to −20 °C slowly. The reaction mixture was then quenched by pouring into aq $NaHCO_3$ solution and was diluted with CH_2Cl_2. The organic layer was separated, washed with 1 M aq NaOH solution and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate; 1.5:1) to give the title compound **34** (0.98 g, 98%): $[\alpha]^{25}_D$ −103.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, J = 8.0 Hz, 1H), 7.84 (t, J = 8.0 Hz, 2H), 7.11−7.65 (m, 39H), 5.58 (s, 2H), 5.48 (s, 1H), 5.01 (d, J = 12.0 Hz, 1H), 4.93 (d, J = 12.0 Hz, 1H), 4.58−4.77 (m, 7H), 4.43−4.52 (m, 2H), 4.11−4.31 (m, 8H), 4.08 (t, J = 9.5 Hz, 1H), 3.94 (t, J = 10.0 Hz, 1H), 3.85−3.88 (m, 4H), 3.71−3.78 (m, 2H), 3.15 (dt, J = 5.0, 10.0 Hz, 1H), 3.08 (dt, J = 5.0, 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6, 138.8, 138.3, 137.5, 137.1, 136.6, 133.4, 133.2, 131.9, 130.7, 129.6, 129.2, 129.0, 128.9, 128.7, 128.5, 128.3, 128.23, 128.19, 128.1, 127.8, 127.4, 127.0, 126.5, 126.3, 126.2, 125.2, 124.4, 120.3, 101.9, 101.7, 101.5, 98.4, 97.9, 96.3, 90.4, 84.4, 78.4, 77.3, 77.0, 76.4, 76.1, 74.9, 74.3, 73.9, 73.7, 72.7, 72.1, 70.7, 70.2, 68.6, 68.2, 67.8, 58.6; ESIHRMS calcd for $C_{79}H_{74}O_{16}SNa$ $[M + Na]^+$ 1333.4590, found 1333.4589.

Methyl 4,6-*O*-Benzylidene-2-*O*-benzyl-3-*O*-[3-(naphthalen-1-yl)prop-2-ynyl]-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-α-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranoside (35α) and Methyl 4,6-*O*-Benzylidene-2-*O*-benzyl-3-*O*-[3-(naphthalen-1-yl)-prop-2-ynyl]-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranoside (35β). To a stirred solution of sulfoxide donor **34** (120 mg, 0.09 mmol), TTBP (40 mg, 0.16 mmol), and 4 Å molecular sieves in a mixed solvent of CH_2Cl_2 and 1-octene (7.5 mL, v/v, 4:1), at −78 °C under argon atmosphere, was added Tf_2O (15 μL, 0.09 mmol). After the reaction mixture was stirred at −78 °C for 30 min, a solution of acceptor **29** (80 mg, 0.075 mmol) in CH_2Cl_2 (1.5 mL) was added. The stirring was maintained for 30 min at −78 °C, and the reaction temperature was allowed to warm to −20 °C slowly over 30 min. The resultant mixture was stirred for another 30 min at −20 °C before it was quenched by pouring into aq $NaHCO_3$ solution. The mixture was diluted with CH_2Cl_2 and filtered through Celite. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate; 2:1→ 1.5:1) to give a mixture of hexasaccharides **35**α, **35**β (103 mg, 61%) in 1:1 ratio as estimated by ^{1}H NMR spectroscopy of the mixture. Separation of 30 mg of the mixture by RP HPLC using a gradient of 90% A to 100% A over 144 min (A: CH_3CN, B: H_2O; Varian Microsorb C_{18} 250 × 21.4 mm; flow rate: 5 mL/min; UV detection: 215 nm) gave pure samples of **35**α, **35**β.

Hexasaccharide 35α: $[\alpha]^{20}_D$ −127.7 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, J = 8.5 Hz, 1H), 7.82 (t, J = 8.0 Hz, 2H), 7.62 (d, J = 7.0 Hz, 1H), 7.05−7.50 (m, 61H), 6.97 (d, J = 7.5 Hz, 2H), 5.63 (s, 1H), 5.57 (s, 1H), 5.56 (s, 1H), 5.55 (s, 1H), 5.45 (s, 1H), 5.39 (s, 1H), 4.45−5.07 (m, 15H), 4.39 (dd, J = 3.5, 9.0 Hz, 2H), 3.68−4.25 (m, 33H), 3.63 (s, 3H), 3.60−3.65 (m, 1H), 3.45 (dt, J = 4.5, 9.0 Hz, 1H), 3.05−3.12 (m, 3H), 3.01 (dt, J = 4.5, 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.29, 138.27, 138.2, 137.9, 137.7, 137.5, 137.4, 137.3, 133.4, 133.2, 130.7, 129.5, 129.00, 128.96, 128.91, 128.85, 128.7, 128.6, 128.47, 128.45, 128.4, 128.34, 128.29, 128.24, 128.21, 128.16, 128.1, 128.0, 127.88, 127.85, 127.8, 127.3, 126.9, 126.5, 126.3, 126.2, 125.2, 120.3, 103.9, 102.2, 101.8, 101.69, 101.65, 101.5, 98.8, 98.5, 97.6, 97.3, 90.4, 84.4, 78.8, 78.3, 77.3, 76.9, 76.1, 76.0, 75.1, 74.8, 74.24, 74.16, 74.1, 73.9, 73.8, 73.7, 73.5, 73.3, 73.2, 72.6, 72.4, 72.1, 71.8, 68.7, 68.6, 67.8, 67.7, 67.5, 64.6, 58.6, 57.7; ESIHRMS calcd for $C_{134}H_{132}O_{31}Na$ $[M + Na]^+$ 2259.8645, found 2259.8513.

Hexasaccharide 35β: $[\alpha]^{20}_D$ −132.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, J = 8.0 Hz, 1H), 7.83 (t, J = 7.5 Hz, 2H), 7.63 (d, J = 7.0 Hz, 1H), 7.09−7.51 (m, 63H), 5.62 (s, 1H), 5.55 (s, 1H), 5.53 (s, 1H), 5.51 (s, 1H), 5.50 (s, 1H), 5.48 (s, 1H), 4.98−5.08 (m, 5H), 4.89 (d, J = 12.0 Hz, 1H), 4.66−4.83 (m, 7H), 4.59−4.63 (m, 2H), 4.53−4.54 (m, 1H), 4.39 (dd, J = 4.5, 10.5 Hz, 2H), 3.78−4.24 (m, 30H), 3.68 (dd, J = 3.0, 9.5 Hz,

1H), 3.63 (m, 4H), 3.45 (dt, J = 5.0, 9.5 Hz, 1H), 3.13 (dt, J = 5.0, 9.5 Hz, 1H), 3.01−3.08 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.3, 138.2, 138.1, 137.5, 137.43, 137.37, 137.3, 133.4, 133.2, 130.6, 128.99, 128.95, 128.91, 128.8, 128.7, 128.5, 128.42, 128.35, 128.3, 128.21, 128.19, 128.1, 127.93, 127.87, 127.3, 126.9, 126.5, 126.24, 126.17, 126.1, 125.2, 120.3, 103.9, 101.8, 101.70, 101.63, 101.5, 97.5, 97.3, 90.4, 84.4, 78.4, 76.9, 76.1, 74.9, 74.2, 73.9, 73.8, 73.5, 73.3, 73.2, 72.5, 72.4, 72.1, 72.0, 68.7, 68.5, 67.8, 58.6, 57.7; ESIHRMS calcd for $C_{134}H_{132}O_{31}Na$ $[M + Na]^+$ 2259.8645, found 2259.8560.

Methyl 4,6-*O*-Benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-Benzylidene-2-*O*-benzyl-α-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranoside (36α) and Methyl 4,6-*O*-Benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-2-*O*-benzyl-β-D-mannopyranoside (36β). Removal of the naphthylpropargyl group from a 1:1 mixture of **35α and 35β** (85 mg, 0.038 mmol) by the standard deprotection protocol gave **36** as a mixture of anomers (55 mg, 70%). Separation by RP HPLC using a gradient of 80% A to 100% B over 144 min (A: CH_3CN, B: H_2O; Varian Microsorb C_{18} 250 × 21.4 mm; flow rate: 10 mL/min; UV detection: 215 nm) gave pure samples of **36α**, **36β** respectively. **Hexasaccharide 36α**: $[\alpha]^{21}_D$ −122.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.52 (m, 11H), 7.12−7.41 (m, 47H), 7.01 (d, J = 7.5 Hz, 2H), 5.64 (s, 1H), 5.59 (s, 1H), 5.55 (s, 2H), 5.41 (s, 1H), 5.36 (s, 1H), 4.81−5.08 (m, 7H), 4.76 (d, J = 3.5 Hz, 1H), 4.73 (d, J = 3.5 Hz, 1H), 4.48−4.55 (m, 2H), 4.41 (dt, J = 4.5, 10.0 Hz, 2H), 3.74−4.32 (m, 30H), 3.70 (d, 3.5 Hz, 1H), 3.66−3.68 (m, 1H), 3.64 (s, 3H), 3.57−3.58 (m, 1H), 3.45 (dt, J = 5.0, 10.0 Hz, 1H), 3.00−3.16 (m, 4H), 2.47 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 138.2, 138.1, 137.9, 137.7, 137.4, 137.34, 137.30, 137.2, 129.5, 129.1, 128.94, 128.90, 128.7, 128.6, 128.43, 128.38, 128.3, 128.23, 128.18, 128.15, 128.1, 128.0, 127.94, 127.90, 127.8, 126.24, 126.21, 126.1, 103.8, 102.1, 101.8, 101.7, 101.6, 98.8, 98.2, 97.5, 97.3, 79.6, 78.7, 77.6, 77.2, 76.9, 76.0, 75.0, 74.23, 74.19, 74.1, 73.9, 73.72, 73.67, 73.5, 73.1, 72.5, 72.3, 72.0, 71.8, 70.2, 68.7, 68.6, 68.5, 67.7, 67.6, 67.5, 67.0, 64.6, 64.2, 57.7; ESIHRMS calcd for $C_{121}H_{124}O_{31}Na$ $[M + Na]^+$ 2095.8019, found 2095.7938. **Hexasaccharide 36β:** $[\alpha]^{21}_D$ −152.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44−7.47 (m, 14H), 7.22−7.36 (m, 49H), 5.63 (s, 1H), 5.49−5.53 (m, 4H), 5.37 (s, 1H), 4.97−5.08 (m, 6H), 4.75−4.84 (m, 5H), 4.53−4.55 (m, 2H), 4.40 (dd, J = 4.5, 10.0 Hz, 1H), 3.70−4.26 (m, 33H), 3.64 (s, 3H), 3.55−3.58 (m, 1H), 3.45 (dt, J = 4.5, 9.0 Hz, 1H), 3.01−3.17 (m, 5H), 2.47 (br. s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 138.22, 138.16, 137.4, 137.3, 129.1, 129.0, 128.72, 128.66, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 126.3, 126.2, 126.1, 103.9, 101.81, 101.79, 101.7, 101.6, 97.5, 97.4, 97.3, 79.6, 77.7, 75.1, 74.2, 74.0, 73.9, 73.5, 73.3, 73.2, 72.5, 72.4, 72.0, 70.2, 68.7, 68.6, 67.8, 67.7, 67.1, 57.7; ESIHRMS calcd for $C_{121}H_{124}O_{31}Na$ $[M + Na]^+$ 2095.8019, found 2095.7932.

Methyl β-D-Mannopyranosyl-(1→3)-β-D-mannopyranosyl-(1→3)-β-D-mannopyranosyl-(1→3)-β-D-mannopyranosyl-(1→3)-β-D-mannopyranoside (37). A mixture of hexasaccharide **36β** (19 mg, 0.01mmol) and 10% $Pd(OH)_2$/C (30 mg) in a mixed solvent of methanol (2.0 mL) and ethyl acetate (0.5 mL) was shaken under 50 psi of H_2 for 40 h. The mixture was filtered through Celite, followed by removal of the solvent under reduced pressure to give mannohexose **37** (10 mg, 100%): $[\alpha]^{19}_D$ −68.9 (*c* 0.25, MeOH: H_2O, 1:1); ^{1}H NMR (500 MHz, D_2O) δ 4.65−4.74 (m, 6H), 4.42 (s, 1H), 4.13 (s, 3H), 4.04 (s, 1H), 3.92 (s, 1H), 3.79−3.85 (m, 11H), 3.40−3.43 (m, 1H), 3.40 (s, 3H), 3.26−3.29 (m, 6H); ^{13}C NMR (500 MHz, D_2O) δ 100.8 ($^1J_{CH}$ = 157.9), 96.6 ($^1J_{CH}$ = 158.6), 96.4 ($^1J_{CH}$ = 159.4), 81.7, 78.9, 78.8, 78.7, 76.3, 76.0, 75.8, 72.8, 70.7, 67.7, 67.6, 67.1, 66.8, 65.2, 65.1, 61.0, 56.8; ESIHRMS calcd for $C_{37}H_{64}O_{31}Na$ $[M + Na]^+$ 1027.3324, found 1027.3334.

Methyl β-D-Mannopyranosyl-(1→3)-β-D-mannopyranosyl-(1→3)-α-D-mannopyranosyl-(1→3)-β-D-mannopyranosyl-(1→3)-β-D-mannopyranosyl-(1→3)-β-D-mannopyranoside (38). A mixture of hexasaccharide **36α** (23 mg, 0.01mmol) and 10% $Pd(OH)_2$/C (30 mg) in a mixed solvent of methanol (2.0 mL) and ethyl acetate (0.5 mL) was shaken under 50 psi of H_2 for 21 h until the reaction was over as monitored by TLC. The mixture was filtered through Celite followed by removal of the solvent under reduced pressure to give mannohexose **38** (12 mg, 100%): $[\alpha]^{19}_D$ −40.0 (*c* 0.5, MeOH/H_2O, 1:1); ^{1}H NMR (500 MHz, D_2O) δ 5.03 (s, 1H), 4.43 (s, 1H), 4.05−4.12 (m, 5H), 3.93 (s, 1H), 3.80−3.81 (m, 7H), 3.53−3.68 (m, 12H), 3.39−3.44 (m, 4H), 3.20−3.30 (m, 7H); ^{13}C NMR (500 MHz, D_2O) δ 102.1 ($^1J_{CH}$ = 165.0), 100.8 ($^1J_{CH}$ = 155), 96.9, 96.7, 96.54, 96.49, 80.2, 79.0, 77.2, 76.4, 76.2, 76.1, 76.0, 75.9, 73.1, 72.9, 72.1, 70.8, 70.5, 67.83, 67.78, 67.2, 66.9, 66.3, 65.3, 65.2, 62.5, 61.1, 61.0, 57.4, 56.9, 48.9; ESIHRMS calcd for $C_{37}H_{64}O_{31}Na$ $[M + Na]^+$ 1027.3324, found 1027.3338.

1-Naphthylpropargylcyclohexyl Ether (40). A mixed solution of propargyl cyclohexyl ether[70] (0.94 g, 6.8 mmol) and 1-bromonaphthalene (1.05 mL, 7.5 mmol) in triethylamine (20 mL) was degassed by bubbling Ar gas for 30 min, and then $PdCl_2(PPh_3)_2$ (0.24 g, 0.34 mmol) and CuI (0.064 g, 0.34mmol) were successively added into the reaction mixture. The resulting mixture was stirred at 50−55 °C overnight under Ar and then was filtered through Celite. The filter cake was washed with CH_2Cl_2, and the filtrate was concentrated under vacuum and residue was purified by chromatography on silica gel (hexane/ethyl acetate; 20:1) to afford the title compound **40** (0.80 g, 44%) as a colorless oil: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 1.25−1.42 (m, 5H), 1.55−1.60 (m, 1H), 1.78−1.79 (m, 2H), 2.00−2.03 (m, 2H), 3.62−3.66 (m, 1H), 4.55 (d, J = 2.5 Hz, 2H), 7.43−7.47 (m, 1H), 7.54−7.61 (m, 2H), 7.69−7.70 (m, 1H), 7.86−7.90 (m, 2H), 8.33 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 24.1, 25.8, 32.1, 55.8, 76.7, 83.0, 91.4, 91.4, 120.5, 125.2, 126.0, 126.4, 126.8, 128.3, 128.8, 130.5, 133.2, 133.3; ESIHRMS (EI) calcd for $C_{19}H_{20}O[M]^+$ 264.1514, found 264.1521.

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Supporting Information Available: Copies of spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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