JOC Article

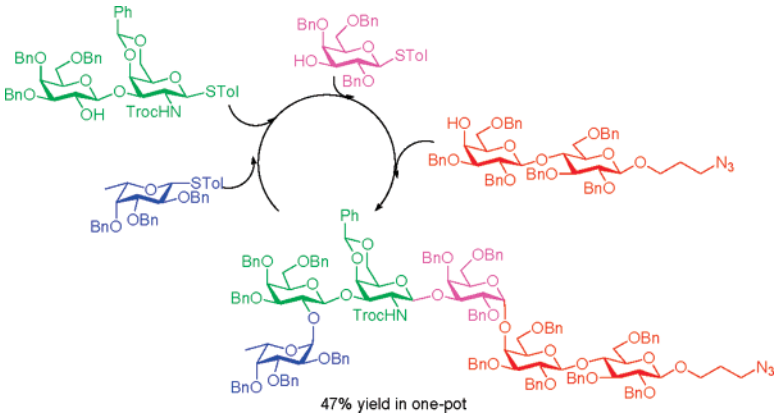
Multi-Component One-Pot Synthesis of the Tumor-Associated Carbohydrate Antigen Globo-H Based on Preactivation of Thioglycosyl Donors

Zhen Wang,[†] Luyuan Zhou,[†] Kheireddine El-Boubbou,[†] Xin-shan Ye,[‡] and Xuefei Huang*[,†]

Department of Chemistry, The University of Toledo, 2801 West Bancroft Street, MS 602, Toledo, Ohio 43606, and The State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Xue Yuan Road 38, Beijing 100083, China

Xuefei.huang@utoledo.edu

Received March 21, 2007



Two efficient routes for the rapid assembly of the tumor-associated carbohydrate antigen Globo-H hexasaccharide **2** by a preactivation based iterative one-pot strategy are reported. The first method involves the sequential coupling of four glycosyl building blocks, leading to the desired hexasaccharide in 47% overall yield in one-pot synthesis. Although model studies on constructing the challenging Gal-α-(1−4)-Gal linkage in Gb3 trisaccharide yielded the desired α linkage almost exclusively, a similar approach to assemble the hexasaccharide led to the formation of a significant amount of *β* anomer. As an alternative, the second synthesis utilized three components in one pot with the Gal-α-(1−4)-Gal linkage preformed, producing the desired hexasaccharide in a similar overall yield as the four component approach. Both methods demonstrate that oligosaccharides containing α and *β* linkages within the same molecule can be constructed in one pot via a preactivation based approach with higher glyco-assembly efficiencies than the automated solid-phase synthesis strategy. Furthermore, because glycosylations can be carried out independent of anomeric reactivities of donors, it is not necessary to differentiate anomeric reactivities of building blocks through extensive protective group adjustment for chemoselective glycosylation. This confers great flexibilities in the building block design, allowing matching of the donor with the acceptor, leading to improved overall yield.

Introduction

Globo-H **1**, a member of the globo series of glycolipids, is found overexpressed in many types of human cancer cells including breast cancer, prostate cancer, ovarian cancer, and lung carcinomas.[1−5] As a distinct tumor-associated antigenic marker, Globo-H has been conjugated to an immunogenic protein carrier,

* Corresponding author. Tel.: (419) 530-1507; fax: (419) 530-4033.
[†] The University of Toledo.
[‡] Peking University.

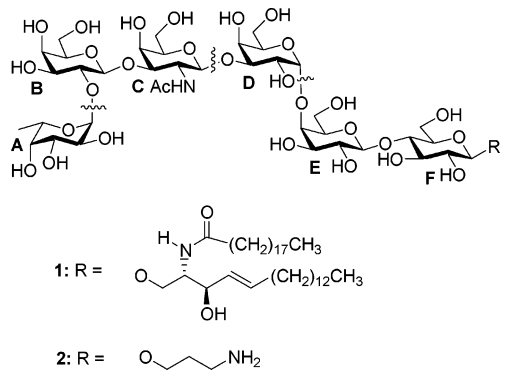
(1) Zhang, S.; Zhang, H. S.; Reuter, V. E.; Slovin, S. F.; Scher, H. I.; Livingston, P. O. *Clin. Cancer Res.* **1998**, *4*, 295.
(2) Hakomori, S.; Zhang, Y. *Chem. Biol.* **1997**, *4*, 97.
(3) Zhang, S.; Cordon-Cardo, C.; Zhang, H. S.; Reuter, V. E.; Adluri, S.; Hamilton, W. B.; Lloyd, K. O.; Livingston, P. O. *Int. J. Cancer* **1997**, *73*, 42.

10.1021/jo070585g CCC: $37.00 © 2007 American Chemical Society
Published on Web 07/21/2007

which is effective in generating protective antibodies against cancer cells. Such a construct has shown promising results in clinical trials as an anti-breast cancer vaccine.[6−9]

Because of its biological significance, Globo-H has attracted considerable attention from the synthetic community. It was first assembled by Danishefsky and co-workers using the glycal strategy,[10,11] which was subsequently refined.[12] Other elegant syntheses include Schmidt and Lassaletta's trichloroacetimidate method,[13] Boon and Zhu's two-directional glycosylation,[14] a reactivity based one-pot method by Wong and co-workers,[15−17] linear synthesis[18] and automated solid-phase synthesis[19] by the Seeberger group, as well as syntheses of the non-reducing end fragments.[20,21] However, many of the reported methods required various synthetic transformations of the oligosaccharide intermediates. Furthermore, with both α and β linkages in Globo-H, stereochemical control often became a formidable challenge.[10,14,18] Therefore, a highly efficient assembly of the Globo-H hexasaccharide is still in great demand.

We have previously developed a preactivation based iterative one-pot strategy[22−24] for construction of complex oligosaccharides. One-pot synthesis refers to the glycosylation processes where multiple step glycosylation reactions can be performed in a single reaction flask without synthetic manipulation and purification of intermediate oligosaccharides, thus overcoming a major hurdle in the conventional stepwise chemical synthesis.[25] For a high-yielding one-pot reaction, glycosyl donors and acceptors must be well-differentiated, allowing selective donor activation and subsequent glycosylation of the acceptor. This is traditionally accomplished by using building blocks containing different types of activatable aglycons (selective activation),[26,27] or carrying out glycosylations in the order of decreasing anomeric reactivities of glycosyl donors (reactivity based armed−disarmed approach),[28,29] or a combination of both strategies.[30,31] Besides the integration of several glycosylation processes into a single synthetic operation to furnish the target oligosaccharide in a few hours, the advantages of our preactivation based one-pot approach are (1) only one type of glycosyl donor (i.e., *p*-tolyl thioglycosides) is used, thus simplifying the synthetic design and (2) the preactivation approach allows us to perform glycosylations without the need to follow decreasing anomeric reactivities of donors, thus granting us much freedom in choosing protective groups to match donors and acceptors.[23,32,33] As part of the program toward establishing the scope of our method, we explored the synthesis of Globo-H **2** containing both α and β linkages by a preactivation based multicomponent one-pot strategy.

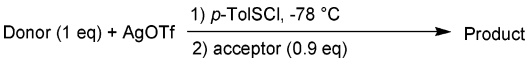


Results and Discussion

Retrosynthetically, we divided Globo-H into four fragments, **A**, **BC**, **D**, and **EF**. Although the exclusive α linkage between **A** and **B** units can be produced according to our previous studies,[24] an α/β mixture will be formed between the newly formed **AB** disaccharide and **C** due to the lack of neighboring group participation.[14] To circumvent this difficulty, **BC** disaccharide will be prepared in advance with the desired β linkage. An aminopropyl spacer will be introduced to the reducing end

(4) Kannagi, R.; Levery, S. B.; Ishijamik, F.; Hakomori, S.; Schevinsky, L. H.; Knowles, B. B.; Solter, D. *J. Biol. Chem.* **1983**, *258*, 8934.
(5) Bremer, E. G.; Levery, S. B.; Sonnino, S.; Ghidoni, R.; Canevari, S.; Kannagi, R.; Hakomori, S. *J. Biol. Chem.* **1984**, *259*, 14773.
(6) Gilewske, T.; Ragupathi, G.; Bhuta, S.; Williams, L. J.; Musselli, C.; Zhang, X.-F.; Bencsath, K. P.; Panageas, K. S.; Chin, J.; Hudis, C. A.; Norton, L.; Houghton, A. N.; Livingston, P. O.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 3270.
(7) Wang, Z. G.; Williams, L. J.; Zhang, X. F.; Zatorski, A.; Kudryashov, V.; Ragupathi, G.; Spassova, M.; Bornmann, W.; Slovin, S. F.; Scher, H. I.; Livingston, P. O.; Lloyd, K. O.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 2719.
(8) Danishefsky, S. J.; Allen, J. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 836.
(9) Slovin, S. F.; Ragupathi, G.; Adluri, S.; Ungers, G.; Terry, K.; Kim, S.; Spassova, M.; Bornmann, W. G.; Fazzari, M.; Dantis, L.; Olkiewicz, K.; Lloyd, K. O.; Livingston, P. O.; Danishefsky, S. J.; Scher, H. I. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 5710.
(10) Park, T. Y.; Kim, I. J.; Hu, S.; Bilodeau, M. T.; Randolph, J. T.; Kwon, O.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 11488.
(11) Bilodeau, M. T.; Park, T. K.; Hu, S.; Randolph, J. T.; Danishefsky, S. J.; Livingston, P. O.; Zhang, S. *J. Am. Chem. Soc.* **1995**, *117*, 7840.
(12) Allen, J. R.; Allen, J. G.; Zhang, X.-F.; Williams, L. J.; Zatorski, A.; Ragupathi, G.; Livingston, P. O.; Danishefsky, S. J. *Chem.—Eur. J.* **2000**, *6*, 1366.
(13) Lassaletta, J. M.; Schmidt, R. R. *Liebigs Ann.Chem.* **1996**, 1417.
(14) Zhu, T.; Boons, G. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3495.
(15) Huang, C.-Y.; Thayer, D. A.; Chang, A. Y.; Best, M.; Hoffmann, L.; Head, S.; Wong, C.-H. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *100*, 15.
(16) Wacowich-Sgarbi, S.; Rabuka, D.; Sgarbi, P. W. M.; Ichikawa, Y. In *Synthesis of Carbohydrates through Biotechnology*; Wang, P. G., Ichikawa, Y., Eds.; ACS Symposium Series 873; American Chemical Society: Washington, DC, 2004; pp 23−38.
(17) Burkhart, F.; Zhang, Z.; Wacowich-Sgarbi, S.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1274.
(18) Bosse, F.; Marcauelle, L. A.; Seeberger, P. H. *J. Org. Chem.* **2002**, *67*, 6659.
(19) Werz, D. D.; Castagner, B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2007**, *129*, 2770.
(20) For an example, see: Adinolfi, M.; Iadonisi, A.; Ravidá, A.; Schiattarella, M. *J. Org. Chem.* **2005**, *70*, 5316.
(21) Tanaka, H.; Matoba, N.; Takanishi, T. *Chem. Lett.* **2005**, *34*, 400.
(22) Huang, L.; Huang, X. *Chem.—Eur. J.* **2007**, *13*, 529.
(23) Huang, L.; Wang, Z.; Li, X.; Ye, X.-S.; Huang, X. *Carbohydr. Res.* **2006**, *341*, 1669.
(24) Huang, X.; Huang, L.; Wang, H.; Ye, X.-S. *Angew. Chem., Int. Ed.* **2004**, *42*, 5221.
(25) Yu, B.; Yang, Z.; Cao, H. *Curr. Org. Chem.* **2005**, *9*, 179 and references cited therein.
(26) Pornsuriyasak, P.; Demchenko, A. V. *Tetrahedron: Asymmetry* **2005**, *6*, 433 and references cited therein.
(27) Kanie, O. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 1, pp 407−426.
(28) Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H. *J. Org. Chem.* **1990**, *55*, 6068.
(29) Koeller, K. M.; Wong, C.-H. *Chem. Rev.* **2000**, *100*, 4465 and references cited therein.
(30) Tanaka, H.; Adachi, M.; Takahashi, T. *Chem.—Eur. J.* **2005**, *11*, 849 and references cited therein.
(31) Tanaka, H.; Adachi, M.; Tsukamoto, H.; Ikeda, T.; Yamada, H.; Takahashi, T. *Org. Lett.* **2002**, *4*, 4213.
(32) Fraser-Reid, B.; López, J. C.; Gómez, A. M.; Uriel, C. *Eur. J. Org. Chem.* **2004**, *2004*, 1387.
(33) Fraser-Reid, B.; López, J. C.; Radhakrishnan, K. V.; Mach, M.; Schlueter, U.; Gomez, A. M.; Uriel, C. *J. Am. Chem. Soc.* **2002**, *124*, 3198.

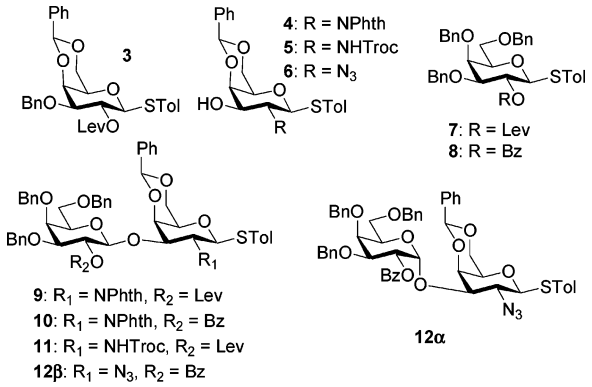
TABLE 1. Evaluation of Buiding Blocks for BC Disaccharide Synthesis



entry	donor	acceptor	product (yield)
1	**3**	**4**	
2	**7**	**4**	**9** (10%)[a]
3	**8**	**4**	**10** (30%)[a]
4	**7**	**5**	**11** (30%)[a]
5	**8**	**6**	**12*β*** (50−70%)[a]
			12α (10−20%)[a]
6	**8**	**6**	**12*β*** (72%)[b]

[a] AgOTf was added as a solution in diethyl ether to the donor dissolved in dichloromethane. Ratio of diethyl ether to dichloromethane was 1:2. [b] AgOTf was added as a solution in acetonitrile to the donor dissolved in dichloromethane. Ratio of acetonitrile to dichloromethane was 1:20.

of Globo-H **2**, which can be used for future conjugation to an immunogenic carrier protein.[8,34]



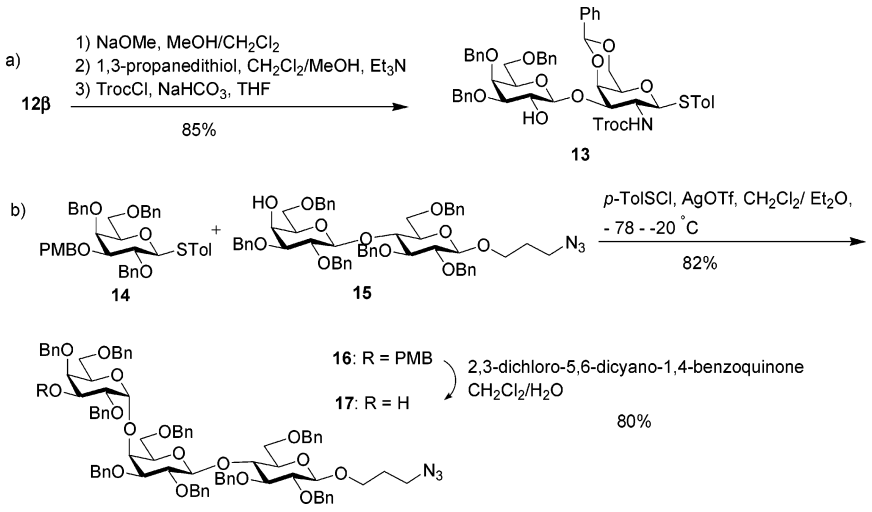
The assembly of the **BC** disaccharide was examined first using several easily prepared glycosyl donor−acceptor pairs, and the results are summarized in Table 1. Each glycosylation was carried out by preactivating the glycosyl donor[35] in mixed solvents of dichloromethane and diethyl ether using the promoter *p*-TolSOTf, formed in situ by reaction of *p*-TolSCl with AgOTf at −78 °C,[36] followed by addition of the acceptor.[24] Reaction of **3**[37] and **4**[37] was attempted without success with the recovery of acceptor **4** (Table 1, entry 1). Removal of benzylidene in donor **3** and replacing the levulinoyl with the benzoyl group led to small improvements with the recovery of most acceptors (entries 2 and 3). We next investigated the effect of substituting the bulky phthalimide (Phth) on the acceptor with more sterically accessible trichloroethoxy carbonyl (Troc) and azido moieties. While the Troc group did not have a significant effect (entry 4), glycosylation of the azido containing acceptor **6** by donor **8** produced disaccharide **12*β*** (^{1}H NMR: $\delta_{H1'} = 4.79$ ppm, $^3J_{H1',H2'} = 7.8$ Hz) in 50−70% yield along with 10−20% **12α** (^{1}H NMR: $\delta_{H1'} = 5.57$ ppm, $^3J_{H1',H2'} = 4.2$ Hz) (entry 5). The structure of **12α** was confirmed by the presence of the Bz carbonyl in the ^{13}C NMR spectrum with a chemical shift of $\delta_{Bz} = 166.5$ ppm, $^1J_{C1'-H1'} = 174$ Hz, indicating an α linakge,[38] and a HMBC correlation between $C_{1'}$ and H_3. The erosion of stereochemical control despite the presence of a participating benzoyl group on C_2 of the donor is presumably due to the competing α directing effect of ethereal solvents.[22,39−44] We found that by substituting diethyl ether with a small amount of acetonitrile to dissolve AgOTf, the formation of disaccharide **12α** can be suppressed to negligible amounts with 72% yield of the desired *β* disaccharide **12*β*** (entry 6). The enhancement of stereoselectivity is most likely due to the exclusion of diethyl ether from the reaction and/or the *β* directing effect of acetonitrile.[45] The disaccharide **12*β*** was then converted to **13** through standard transformations with an 85% overall yield (Scheme 1a). The Troc group was introduced to direct the 1,2-trans linkage in future glycosylation.

The introduction of the α-(1−4) linkage at the **DE** junction of Globo-H is challenging due to the low reactivity of the axial 4-hydroxyl group of the **E** ring and the difficulty in stereochemical control. As a model, we explored first the formation of **DEF** trisaccharide, known as Gb3 or Pk trisaccharide, which is also highly enriched on the surface of a variety of cancer cells and involved in many carbohydrate−receptor recognition events.[46] Many types of glycosyl donors, including fluoride,[11,12] chloride,[46] trichloroacetimidate,[18,19,47] phosphite,[48] phosphate,[18,19] thioglycoside,[49−51] sulfoxide,[52] and thioimidates[53] have been examined in this reaction. The yield for the formation of the Gal-α-(1−4)-Gal linkage is often not high with an anomeric mixture of products.[11,18,19,48,50] To test whether our glycosylation condition is suitable to construct this key linkage, we examined the glycosylation of lactoside **15** by thiogalactosyl donor **14** (Scheme 1b). Without any optimization, the desired trisaccharide **16** was obtained in 82% yield with only trace amounts of the *β* anomer isolated. The α stereochemistry of the newly formed glycosidic linkage in **16** was confirmed by NMR ($^1J_{C1''-H1''} =$ 174 Hz).[38] Encouraged by this result, we decided to test the possibility of assembling Globo-H using four component one-pot reactions with building blocks **18**, **13**, **19**, and **15**.

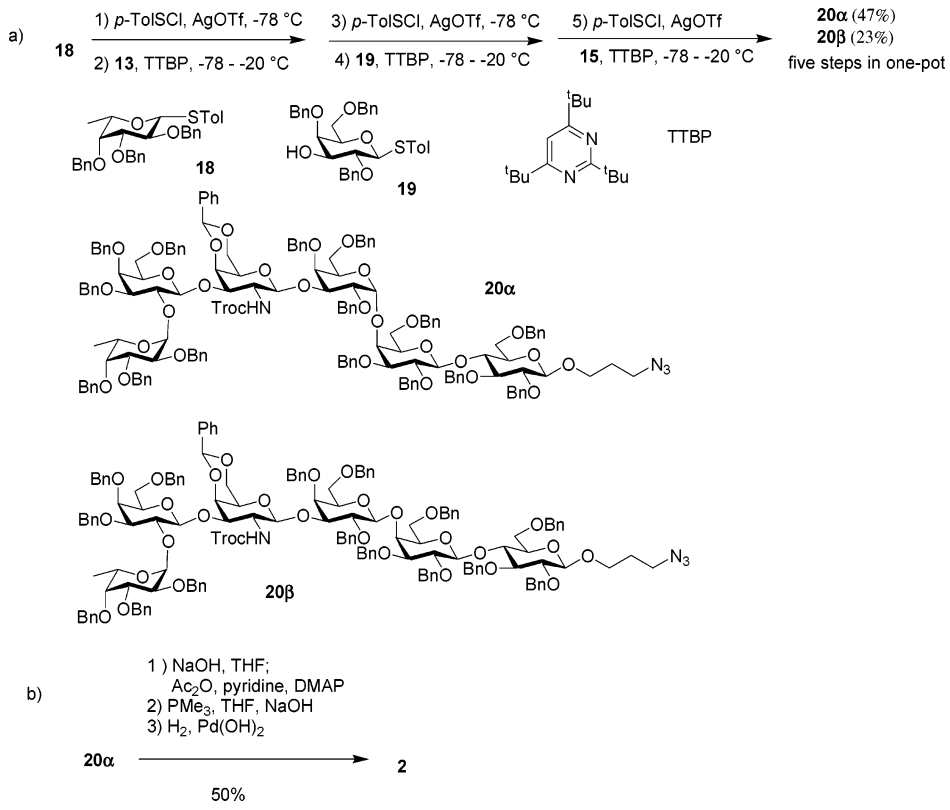
Preactivation of the fucosyl donor **18** at −78 °C with *p*-TolSCl/AgOTf was followed by the addition of the first acceptor **13** (Scheme 2a). A sterically hindered base, 2,4,6-tri-*tert*-butyl-pyrimidine (TTBP)[54] was added with the acceptor to

(34) Jennings, H. J.; Snood, R. K. In *Neoglycoconjugates: Preparation and Application*; Lee, Y. C., Lee, R. T., Eds.; Academic Press: San Diego, 1994; p 325.
(35) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321.
(36) Martichonok, V.; Whitesides, G. M. *J. Org. Chem.* **1996**, *61*, 1702.
(37) Zhang, Z.; Ollman, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734.
(38) Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293.
(39) Demchenko, A. V. *Synlett* **2003**, 1225 and references cited therein.
(40) Tokimoto, H.; Fujimoto, Y.; Fukase, K.; Kusumoto, S. *Tetrahedron: Asymmetry* **2005**, *16*, 441.
(41) Chiba, H.; Funasaka, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1629.
(42) Adinolfi, M.; Barone, G.; Iadonisi, A.; Schiattarella, M. *Tetrahedron Lett.* **2002**, *43*, 5573.
(43) Jona, H.; Mandai, H.; Chavasiri, W.; Takeuchi, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 291.
(44) Demchenko, A. V.; Stauch, T.; Boons, G.-J. *Synlett* **1997**, 818.
(45) Schmidt, R. R.; Behrendt, M.; Toepfer, A. *Synlett* **1990**, 694.
(46) Kamath, V. P.; Yeske, R. E.; Gregson, J. M.; Ratcliffe, R. M.; Fang, Y. R.; Palcic, M. M. *Carbohydr. Res.* **2004**, *339*, 1141 and references cited therein.
(47) Chen, L.; Zhao, X.-E.; Lai, D.; Song, Z.; Kong, F. *Carbohydr. Res.* **2006**, *341*, 1174 and references cited therein.
(48) Hsieh, S.-Y.; Jan, M.-D.; Patkar, L. N.; Chen, C.-T.; Lin, C.-C. *Carbohydr. Res.* **2005**, *340*, 49.
(49) Wang, C.; Li, Q.; Wang, H.; Zhang, L.; Ye, X.-S. *Tetrahedron* **2006**, *62*, 11657.
(50) Dohi, H.; Nishida, Y.; Takeda, T.; Kobayashi, K. *Carbohydr. Res.* **2002**, *337*, 983.
(51) Bhattacharyya, S.; Magnusson, B. G.; Wellmar, U.; Nilsson, U. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 886.
(52) Sarkar, A. K.; Matta, K. L. *Carbohydr. Res.* **1992**, *233*, 245.
(53) Pornsuriyasak, P.; Demchenko, A. V. *Carbohydr. Res.* **2006**, *341*, 1458.
(54) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323.

SCHEME 1



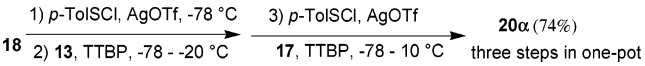
SCHEME 2



neutralize trifluomethane sulfonic acid generated from glycosylation. The reaction temperature was raised to −20 °C, and the acceptor **13** was completely consumed as judged by TLC analysis. The reaction temperature was cooled back down to −78 °C, followed by sequential addition of AgOTf, *p*-TolSCl, the second acceptor galactoside **19**, TTBP, and warming up to −20 °C. After **19** completely disappeared, the reaction temperature was lowered to −78 °C again, and the last acceptor lactoside **15**, TTBP, AgOTf, and *p*-TolSCl were added to the reaction medium. The fully protected Globo-H hexasaccharide **20**α was obtained in 47% yield from the four component one-pot reactions within 7 h, which were fully characterized by ^{1}H NMR, ^{13}C NMR, gCOSY, gHMQC, gHMBC, and HRMS. In addition, the anomer **20***β* was also produced in 23% yield.[55] Both Globo-H anomers will be useful for immunological studies as demonstrated by Danishefsky and co-workers.[10] It is noteworthy that thiogalactoside **19** has a higher anomeric reactivity than disaccharide **13**. This reversal of anomeric reactivity (i.e., a more reactive thioglycosyl acceptor is glycosylated by a less reactive thioglycosyl donor) is not possible with the reactivity based chemoselective glycosylation method.[28,29,37] The preactivation method allowed us to use the readily available building

(55) To determine the configuration of newly formed glycosyl bonds, we once isolated the intermediate oligosaccharides during one-pot synthesis and confirmed the linkages via NMR analysis.

SCHEME 3

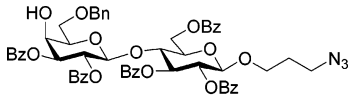


block **19** instead of going through elaborate protective group manipulations to achieve the precise anomeric reactivity.[15−17]

Recently, Seeberger and co-workers have reported an elegant synthesis of Globo-H hexasaccharide[19] with an overall yield of 30% for glyco-assembly using the automated solid-phase synthesis pioneered by their group.[56] As compared to the automated method, our synthesis of the desired Globo-H hexasaccharide achieved a higher glyco-assembly yield in a shorter amount of time without consuming a large excess of precious glycosyl building blocks. This underscores the advantage of the preactivation based iterative one-pot oligosaccharide synthesis method.

Deprotection of the hexasaccharide **20**α was performed by first removing the Troc protecting group with 1 M NaOH in THF followed by acetylation. Staudinger reduction of the azide group and subsequent catalytic hydrogenation over Pearlman's catalyst[57] gave the fully deprotected Globo-H **2** in 50% overall yield for all deprotection steps (Scheme 2b). Attempts to reduce the azide and remove benzyl groups simultaneously by hydrogenation failed even in the presence of additives such as di-^{t}butyl carbonate[58] and hydrochloric acid.

The formation of **20**β in the 4 + 2 glycosylation is surprising in view of our model studies on Gb3. Moreover, previous syntheses of Globo-H hexasaccharides through the 4 + 2 coupling of tetrasaccharide donors with lactoside acceptors by the Wong group[17] and Schmidt and Lassaletta[13] did not form any stereoisomers. This unpredicted discrepancy highlights the challenge of complex oligosaccharide assembly. The generation of **20**β may be due to the increased size of the tetrasaccharide donor in our 4 + 2 coupling as compared to donor **14**. We tested next the lactoside acceptor **21** containing multiple electron withdrawing benzoyl groups in the 4 + 2 glycosylation reaction, as the less reactive acceptor is expected to be more selective. However, the glycosylation yield was low with a large amount of acceptor recovered.



21

Since trisaccharide **16** was synthesized highly stereoselectively, as an alternative to the four component one-pot strategy, we examined a three component approach with the challenging Gal-α-(1−4)-Gal linkage preformed. The *p*-methoxybenzyl moiety in trisaccharide **16** was selectively removed to generate acceptor **17** in 80% yield (Scheme 1b). One-pot sequential glycosylation of fucoside **18** with disaccharide **13** and trisaccharide **17** produced hexasaccharide **20**α with a 74% overall yield (Scheme 3), which was identical in all aspects to **20**α prepared via the four component approach, thus further confirming our stereochemical assignments. Starting from monosaccharide and disaccharide building blocks, the overall yield for **20**α through the three component approach is similar to that of the four component route.

Conclusion

We have developed two routes for rapid assembly of the tumor-associated carbohydrate antigen Globo-H hexasaccharide **2** by a preactivation based one-pot strategy, demonstrating that oligosaccharides containing α and β linkages within the same molecule can be constructed in one pot. Higher glyco-assembly efficiencies have been achieved with only a near stoichiometric amount of building blocks via the preactivation based one-pot method as compared to the automated solid-phase synthesis method. However, reliable stereochemical control in glycosylation still remains a challenge, which will require further developments and studies.

Experimental Section

Characterization of Anomeric Stereochemistry. The stereochemistries of the newly formed glycosidic linkages in Globo-H hexasaccharides and intermediates were determined by $^3J_{H1,H2}$ through ^{1}H NMR and/or $^1J_{C1,H1}$ through gHMQC 2-D NMR (without ^{1}H decoupling). Smaller coupling constants of $^3J_{H1,H2}$ (around 3 Hz) indicate α linkages, and larger coupling constants $^3J_{H1,H2}$ (7.2 Hz or larger) indicate β linkages. This can be further confirmed by $^1J_{C1,H1}$ (∼170 Hz) for α linkages and $^1J_{C1,H1}$ (∼160 Hz) for β linkages.[38]

***p*-Tolyl 2-Azido-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-galactopyranoside (6).** Trichloroethoxycarbonyl chloride (7.7 mL, 57.2 mmol) was added dropwise over a period of 30 min at room temperature to a vigorously stirred solution of D-galactosamine hydrochloride (10 g, 46.3 mmol) and NaHCO3 (11.8 g, 139.9 mmol) in water (90 mL). The mixture was stirred for another 2 h and then filtered to give a yellowish solid, which was dried under vacuum. The obtained crude solid (15 g) was dissolved in pyridine (50 mL), and then acetic anhydride (30 mL) was added at 0 °C over a period of 30 min. The mixture was stirred at room temperature under N_2 overnight and then quenched with ethanol (20 mL) at 0 °C. The mixture was concentrated, and the resulting residue was diluted with ethyl acetate and washed with a saturated aqueous solution of $NaHCO_3$, 10% HCl, water, and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated. Without separation, the obtained crude solid (21 g) and p-toluenethiol (5.76 g, 46.3 mmol) were dissolved in CH_2Cl_2 (60 mL), and the solution was cooled to 0 °C. Boron trifluoride etherate (17.8 mL, 160 mmol) was added dropwise at 0 °C, and the mixture was stirred under N_2 at room temperature for 6 h. The mixture was diluted with CH_2Cl_2 (400 mL) and washed with a saturated aqueous solution of $NaHCO_3$ until the pH was 7 and then dried over Na_2SO_4, filtered, and concentrated. The obtained crude product was recrystallized from EtOAc/hexanes to afford *p*-tolyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-trichloroethoxycarbonylamino-1-thio-β-D-galactopyranoside[59] (**S1**) as a white solid (20.67 g, 76% for three steps). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.98, 2.04, 2.13 (3s, 9H, 3 × $COCH_3$), 2.34 (s, 3H, $SPhCH_3$), 3.91−3.95 (m, 2H, H-2, H-5), 4.10−4.20 (m, 2H, H-6a, H-6b), 4.73−4.80 (m, 2H, CH_2CCl_3), 4.84 (d, 1H, $J_{1,2}$ = 10.2 Hz, H-1), 5.19 (dd, 1H, $J_{2,3}$ = 10.8 Hz, $J_{3,4}$ = 2.4 Hz, H-3), 5.30 (d, 1H, $J_{NH,2}$ = 9.6 Hz, NH), 5.39 (d, 1H, $J_{3,4}$ = 2.4 Hz, H-4), 7.10−7.16 (m, 2H), 7.40−7.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 20.9, 21.4, 51.4, 62.0, 67.1, 71.2, 74.6, 74.7, 87.8, 95.7, 128.9, 129.9, 133.3, 138.7, 154.3, 170.5, 170.7, 170.8. ESI-MS $[M + Na]^+$ $C_{22}H_{26}NaCl_3NO_9S$ calcd 608.0, obsd 608.3. *p*-Tolyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-trichloroethoxy-

(56) Plante, O. J.; Palmacci, E. R.; Seeberger, P. H. *Science* **2001**, *291*, 1523.

(57) Li, J.; Wang, J.; Czyryca, P. G.; Chang, H.; Orsak, T. W.; Evanson, R.; Chang, C.-W. T. *Org. Lett.* **2004**, *6*, 1381.

(58) Cheshev, P. E.; Khatuntseva, E. A.; Gerbst, A. G.; Tsvetkov, Y. E.; Shashkov, A. S.; Nifantiev, N. E. *Russ. J. Bioorg. Chem.* **2003**, *29*, 372.

(59) Mong, T. K.-K.; Lee, H.-K.; Duron, S. G.; Wong, C.-H. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 797.

carbonylamino-1-thio-β-D-galactopyranoside **S1** (3 g, 5.1 mmol) was dissolved in MeOH (12 mL), AcOH (6 mL), and CH_2Cl_2 (6 mL). Zn powder (6 g, 92 mmol) was added slowly at 0 °C, and the mixture was stirred under N_2 at room temperature for 1 h. The mixture was filtered and concentrated to dryness. The resulting residue was diluted with CH_2Cl_2 (200 mL) and washed with a saturated aqueous solution of $NaHCO_3$ until the pH was 7 and then was dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (EtOAc) afforded *p*-tolyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-1-thio-β-D-galactopyranoside as a white solid (**S2**) (1.8 g, 85.7%). ^{1}H NMR (400 MHz, CDCl^3): d 2.02, 2.05, 2.09 (3s, 9H, 3 × $COCH_3$), 2.35 (s, 3H, $SPhCH_3$), 3.18 (t, 1H, J = 10.0 Hz, H-2), 3.91 (t, 1H, J = 6.2 Hz, H-5), 4.11 (dd, 1H, J = 6.2, 10.8 Hz, H-6a), 4.18 (dd, 1H, J = 6.2, 10.8 Hz, H-6b), 4.49 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 4.78 (dd, 1H, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 3.2 Hz, H-3), 5.36 (d, 1H, $J_{3,4}$ = 3.2 Hz, H-4), 7.10−7.18 (m, 2H), 7.44−7.50 (m, 2H); ^{13}C NMR (100 MHz, CDCl3): δ 20.8, 20.9, 20.9, 21.4, 49.9, 62.0, 66.8, 74.4, 75.2, 90.4, 128.4, 129.9, 133.3, 138.6, 170.4, 170.5, 170.7. ESI-MS $[M + H]^+$ $C_{19}H_{26}NO_7S$ calcd 412.1, obsd 412.1. *p*-Tolyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-1-thio-β-D-galactopyranoside (**S2**) (1.8 g, 4.37 mmol, 1 equiv) was dissolved in MeOH (7.5 mL) and CH_2Cl_2 (7.5 mL). 1 M NaOMe (2.2 mL, 2.2 mmol) was added, and the mixture was stirred at room temperature for 2 h. The mixture was neutralized by concd HCl until the pH was around 7 and then was concentrated and dried under vacuum. The resulting residue, K_2CO_3 (1.5 g, 10.87 mmol), and a catalytic amount of $ZnCl_2$ (40 mg, 0.3 mmol) were dissolved in MeOH (12 mL) and H_2O (3 mL). Freshly prepared TfN360 (13 mL in CH_2Cl_2, 13.1 mmol) was added, and the mixture was stirred at room temperature overnight. The solvent was evaporated, and the resulting residue was diluted with EtOAc (100 mL). The mixture was neutralized by concd HCl until the pH value was 6−7 and then was concentrated to dryness. Silica gel column chromatography (9:1 CH_2Cl_2−/MeOH) afforded *p*-tolyl 2-azido-2-deoxy-1-thio-β-D-galactopyranoside[61] (**S3**) as a white solid (1.2 g, 88%). ^{1}H NMR (600 MHz, CD_3OD): δ 2.22 (s, 3H, $SPhCH_3$), 3.37 (t, 1H, J = 9.6 Hz, H-2), 3.39−3.40 (m, 2H, H-3, H-5), 3.58−3.68 (m, 2H, H-6a, H-6b), 3.74 (d, 1H, $J_{3,4}$ = 2.4 Hz, H-4), 4.34 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 7.01−7.06 (m, 2H), 7.33−7.40 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 21.3, 62.7, 64.6, 69.8, 75.4, 80.8, 88.5, 130.7, 130.8, 130.9, 133.9, 134.0, 139.3. ESI-MS $[M + Na]^+$ $C_{13}H_{17}NaN_3O_4S$ calcd 334.1, obsd 334.3. The mixture of compound *p*-tolyl 2-azido-2-deoxy-1-thio-β-D-galactopyranoside (S3) (1.2 g, 3.85 mmol), camphorsulfonic acid (0.27 g, 1.16 mmol), and benzaldehyde dimethylacetal (0.7 mL, 4.62 mmol) in toluene (20 mL) was stirred at room temperature for 1 h and then diluted with EtOAc (200 mL). The mixture was washed with a saturated aqueous solution of $NaHCO_3$ and water and then dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (2:1 hexanes−/EtOAc) afforded **6** as a white solid (1.15 g, 75%). $[\alpha]_D$ −31.9 (c = 1, CH_2Cl_2); 1H NMR (600 MHz, $CDCl_3$): δ 2.36 (s, 3H, $SPhCH_3$), 2.62 (d, 1H, $J_{3,3-OH}$ = 10.2 Hz, OH), 3.45 (s, 1H, H-5), 3.47 (t, 1H, J = 10.2 Hz, H-2), 3.59 (dt, 1H, $J_{3,4}$ = 3.0 Hz. $J_{2,3}$ = 10.2, $J_{3,3}$-OH = 10.2 Hz, H-3), 3.99 (dd, 1H, J = 1.8, 12.6 Hz, H-6a), 4.12 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-4), 4.35 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 4.37 (dd, 1H, J = 1.8, 12.6 Hz, H-6b), 5.49 (s, 1H, CHPh), 7.11−7.12 (d, 2H, J = 7.8 Hz, aromatic), 7.35−7.41 (m, 5H, aromatic), 7.59−7.66 (m, 2H), ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.6, 62.2, 69.5, 69.96, 70.00, 73.4, 74.6, 74.7, 85.2, 101.6, 101.7, 126.5, 126.8, 128.5, 129.7, 130.1, 135.0, 137.6, 139.0. ESI-MS $[M + Na]^+$ $C_{20}H_{21}NaO_4S$ calcd 422.1, obsd 422.2; Comparison of the NMR data with those reported in the literature[37] confirmed the identity of **6**.

***p*-Tolyl 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-galactopyranoside (8).** β-D-Galactopyranosyl pentaacetate (10 g, 25.6 mmol) was dissolved in HBr in acetic acid (30 mL, 33% w/w, 173.6 mmol). After 6 h, the mixture was diluted with CH_2Cl_2 (240 mL) and poured onto crushed ice in saturated $NaHCO_3$ (600 mL). The organic phase was separated and washed again with saturated $NaHCO_3$ until the pH was about 7 and then dried over Na_2SO_4, filtered, and concentrated. The resulting residue, 2,6-lutidine (11.93 mL, 102.4 mmol), and Bu_4NBr (3.3 g, 10.24 mmol) were dissolved in CH_2Cl_2 (45 mL) and dry EtOH (8.5 mL, 6 equiv). The mixture was stirred at room temperature under N2 overnight and then concentrated and vacuum-dried to afford a colorless oil (10 g). The obtained oil was dissolved in a mixture of CH_2Cl_2/MeOH (50 mL each), and a 1 M solution of NaOMe (25.6 mL, 25.6 mmol) was added at room temperature. The mixture was stirred for 2 h at room temperature under N_2 and then concentrated and vacuum-dried. The obtained residue was dissolved in DMF (100 mL), and the solution was cooled to 0 °C. NaH (4 g, 60% NaH in mineral oil, 100 mmol) was added in portions, followed by the addition of BnBr (15 mL, 125 mmol). The mixture was stirred at room temperature under N_2 for 4 h and then diluted with EtOAc (300 mL). The mixture was washed with saturated $NaHCO_3$ and water and then dried over Na_2SO_4, filtered, and concentrated. The resulting residue (8.5 g), p-toluenethiol (6.7 g, 53.9 mmol), and $HgBr_2$ (0.46 g, 1.28 mmol) were put into CH_3CN (20 mL), and the mixture was heated at 60 °C under N_2 overnight. The solvent was evaporated, and then the residue was diluted with CH_2Cl_2 (300 mL). The mixture was washed with saturated $NaHCO_3$, water, and 10% HCl and then dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (2:1 hexanes−/EtOAc) afforded *p*-tolyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-galactopyranoside[62] (**S4**) as a white solid (6.4 g, 42% for five steps). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.04 (s, 3H, $COCH_3$), 2.29 (s, 3H, $SPhCH_3$), 3.54 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 3.0 Hz, H-3), 3.59−3.67 (m, 3H, H-5, H-6a, H-6b), 3.97 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-4), 4.41, 4.45, 4.52, 4.56 (4d, 4H, J = 12.0 Hz, CH_2Ph), 4.55 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 4.66 (d, 1H, J = 12.0 Hz, CH_2Ph), 4.93 (d, 1H, J = 12.0 Hz, CH_2Ph), 5.39 (t, 1H, J = 9.6 Hz, H-2), 6.98−7.06 (m, 2H), 7.25−7.34 (m, 15H, aromatic), 7.37−7.38 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.3, 21.4, 69.0, 70.0, 72.2, 73.0, 73.8, 74.6, 77.8, 81.7, 87.3, 127.67, 127.70, 127.99, 128.03, 128.1, 128.2, 128.4, 128.6, 129.7, 130.0, 132.7, 137.8, 138.09, 138.12, 138.7, 169.7. ESI-MS $[M + Na]^+$ $C_{36}H_{38}NaO_6S$ calcd 621.2, obsd 621.5. *p*-Tolyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-galactopyranoside (**S4**) (3 g, 5 mmol) was dissolved in a mixture of CH_2Cl_2/MeOH (50 mL each), and 1 M NaOMe (10 mL, 10 mmol) was added at room temperature. The mixture was stirred for 2 h at room temperature under N_2 and then was neutralized with Amberlite IR-120 until the pH was around 6−7. The mixture was concentrated and diluted with CH_2Cl_2 (300 mL) and washed with saturated $NaHCO_3$, 10% HCl, and water and then dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (2:1 hexanes−/EtOAc) afforded p-tolyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-galactopyranoside (**S5**) as a white solid (2.56 g, 92%). 1H NMR (600 MHz, $CDCl_3$): δ 2.29 (s, 3H, $SPhCH_3$), 2.42 (d, 1H, $J_{2,2}$-OH = 2.4 Hz, OH), 3.46 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 2.4 Hz, H-3), 3.63−3.66 (m, 3H, H-5, H-6a, H-6b), 3.95−3.98 (m, 2H, H-2, H-4), 4.44 (d, 1H, J = 12.0 Hz, CH_2Ph), 4.47 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 4.49, 4.56, 4.67, 4.73, 4.89 (5d, 5H, J = 12.0 Hz, CH_2Ph), 6.98−7.05 (m, 2H), 7.25−7.35 (m, 15H, aromatic), 7.44−7.45 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.4, 68.9, 69.3, 72.6, 73.5, 73.8, 74.6, 77.8, 83.4, 89.0, 127.6, 127.9, 127.95, 128.04, 128.05, 128.2, 128.4, 128.7, 128.8, 128.9, 129.8, 133.1, 138.0, 138.1, 138.3, 138.9. ESI-MS $[M + Na]^+$ $C_{34}H_{36}NaO_5S$ calcd 579.2, obsd 579.6. *p*-Tolyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-galactopyranoside (**S5**) (3.8 g, 6.8 mmol) and *N*,*N*-dimethylamino pyridine (DMAP) (0.08 g, 0.68 mmol) were dissolved in pyridine (20 mL), and then benzoyl chloride (2.38 mL, 20.5 mmol) was added. The mixture was stirred at room temperature

(60) Nyffeler, P. T.; Liang, C.-H.; Koeller, K. M.; Wong, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 10773.

(61) Luening, B.; Norberg, T.; Tejbrant, J. *Glycoconjugate J.* **1989**, *6*, 5.

(62) Lee, J.-C.; Wu, C.-Y.; Apon, J. V.; Siuzdak, G.; Wong, C. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 2753.

under N_2 for 4 h and then diluted with of CH_2Cl_2 (200 mL). The mixture was washed with saturated $NaHCO_3$, water, and 10% HCl and then dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (2:1 hexanes−/EtOAc) afforded 8 as a white solid (4.2 g, 93%). $[\alpha]_D$ +38.2 (c = 1, CH_2Cl_2); 1H NMR (600 MHz, $CDCl_3$): δ 2.25 (s, 3H, $SPhCH_3$), 3.65−3.69 (m, 4H, H-3, H-5, H-6a, H-6b), 4.03 (d, 1H, $J_{3,4}$ = 2.4 Hz, H-4), 4.41, 4.45, 4.47, 4.59, 4.61 (5d, 5H, J = 12.0 Hz, CH_2Ph), 4.71 (d, 1H, $J_{1,2}$ = 10.2 Hz, H-1), 4.97 (d, 1H, J = 12.0 Hz, CH_2Ph), 5.68 (t, 1H, J = 10.2 Hz, H-2), 6.96−6.97 (d, 2H, J = 7.8 Hz, aromatic), 7.10−7.15 (m, 5H, aromatic), 7.25−7.36 (m, 12H, aromatic), 7.41−7.42 (m, 2H, aromatic), 7.53−7.55 (m, 1H, aromatic), 8.00−8.07 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.5, 69.2, 70.8, 72.1, 73.1, 73.9, 74.7, 78.0, 81.5, 87.5, 127.8, 127.99, 128.00, 128.1, 128.2, 128.4, 128.5, 128.6, 128.7, 128.8, 129.8, 130.0, 130.2, 130.5, 133.0, 133.4, 137.9, 138.0, 138.2, 138.8, 165.6. HRMS: $[M + Na]^+$ $C_{41}H_{40}NaO_6S$ calcd 683.2443, obsd 683.2421.

General Procedure for Single Step Preactivation Based Glycosylation. A solution of donor (0.060 mmol) and freshly activated molecular sieve MS 4 Å (200 mg) in CH_2Cl_2 (2 mL) was stirred at room temperature for 30 min, and cooled to −78 °C, which was followed by the addition of AgOTf (47 mg, 0.18 mmol) dissolved in Et_2O (1 mL) without touching the wall of the flask. After 5 min, orange *p*-TolSCl (9.5 μL, 0.060 mmol) was added through a microsyringe. Since the reaction temperature was lower than the freezing point of *p*-TolSCl, *p*-TolSCl was added directly into the reaction mixture to prevent it from freezing on the flask wall. The characteristic yellow color of *p*-TolSCl in the reaction solution dissipated rapidly within a few seconds, indicating depletion of *p*-TolSCl. After the donor was completely consumed according to TLC analysis (about 5 min at −78 °C), a solution of acceptor (0.060 mmol) in CH_2Cl_2 (0.2 mL) was slowly added dropwise via a syringe. The reaction mixture was warmed to −10 °C under stirring in 2 h. Then, the mixture was diluted with CH_2Cl_2 (20 mL) and filtered over Celite. The Celite was further washed with CH_2Cl_2 until no organic compounds were observed in the filtrate by TLC. All CH_2Cl_2 solutions were combined and washed twice with a saturated aqueous solution of $NaHCO_3$ (20 mL) and twice with water (10 mL). The organic layer was collected and dried over Na_2SO_4. After removal of the solvent, the desired disaccharide was purified from the reaction mixture via silica gel flash chromatography.

***p*-Tolyl 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1 → 3)-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-galactopyranoside (12β) and *p*-Tolyl 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-α-D-galactopyranosyl-(1 → 3)-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-galactopyranoside (12α).** Compounds **12**β and **12**α were synthesized from donor **8** and acceptor **6** in 50−70 and 10−20% yields, respectively, following the general procedure of single step glycosylation. When CH_3CN (100 μL) was used instead of diethyl ether to dissolve the AgOTf, the formation of disaccharide **12**α can be suppressed to a negligible amount with 72% yield of the desired β disaccharide **12**β. For **12**β: $[\alpha]_D$ −28.5 (c = 4.3, CH_2Cl_2); 1H NMR (600 MHz, $CDCl_3$): δ 2.24 (s, 3H, $SPhCH_3$), 3.31 (s, 1H, H-5), 3.55−3.65 (m, 6H, H-2, H-3, H-3′, H-5′, H-6a′, H-6b′), 3.84 (d, 1H, J = 10.8 Hz, H-6a), 3.96 (d, 1H, $J_{3',4'}$ = 2.4 Hz, H-4′), 4.24−4.27 (m, 2H, H-4, H-6b), 4.30 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 4.44−4.47 (m, 3H, CH_2Ph), 4.59−4.62 (m, 2H, J = 12.0 Hz, CH_2Ph), 4.79 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1′), 4.98 (d, 1H, J = 12.0 Hz, CH_2Ph), 5.37 (s, 1H, CHPh), 5.62 (t, 1H, $J_{1',2'}$ = 7.8 Hz, H-2′), 6.83−6.92 (m, 2H), 7.10−7.18 (m, 5H, aromatic), 7.23−7.41 (m, 17H, aromatic), 7.43−7.52 (m, 2H), 7.49−7.59 (m, 1H), 7.94−8.04 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.4, 59.7, 69.2, 69.3, 70.1, 71.7, 72.0, 72.6, 73.7, 74.2, 74.6, 74.9, 79.3, 80.3, 85.8, 100.8, 102.3, 126.2, 126.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.4, 128.5, 128.6, 128.7, 128.9, 129.9, 130.0, 130.2, 133.1, 134.5, 137.6, 137.9, 138.0, 138.5, 138.6, 165.5; HRMS: $[M + Na]^+$ $C_{54}H_{53}N_3NaO_{10}S$ calcd 958.3349, obsd 958.3365. gHMQC (without 1H decoupling): $^1J_{C1',H1'}$ = 160.9 Hz, $^1J_{C1,H1}$ = 159.9 Hz; For **12**α: $[\alpha]_D$ +70.8 (c = 4.5, CH_2Cl_2); 1H NMR (600 MHz, $CDCl_3$): δ 2.27 (s, 3H, $SPhCH_3$), 3.26 (s, 1H, H-5), 3.57−3.65 (m, 3H, H-3, H-6a′, H-6b′), 3.79 (t, 1H, J = 9.6 Hz, H-2), 3.86 (d, 1H, J = 12.0 Hz, H-6a), 4.06 (s, 1H, H-4), 4.09 (d, 1H, $J_{3',4'}$ = 2.4 Hz, H-4′), 4.17 (dd, 1H, $J_{2',3'}$ = 10.8 Hz, $J_{3',4'}$ = 2.4 Hz, H-3′), 4.22−4.24 (m, 2H, H-5′, H-6b), 4.32 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 4.47, 4.51, 4.59, 4.66, 4.68, 4.93 (6d, 6H, J = 12.0 Hz, CH_2Ph), 5.16 (s, 1H, CHPh), 5.42 (dd, 1H, $J_{1',2'}$ = 3.6 Hz, $J_{2',3'}$ = 10.8 Hz, H-2′), 5.57 (d, 1H, $J_{1',2'}$ = 3.6 Hz, H-1′), 6.90−6.99 (m, 2H), 6.98−7.02 (m, 4H, aromatic), 7.12−7.44 (m, 19H, aromatic), 7.50−7.59 (m, 2H), 7.72−7.82 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.4, 59.6, 68.9, 69.2, 69.7, 70.0, 70.7, 71.9, 73.2, 73.4, 74.7, 75.0, 76.0, 76.9, 85.7, 93.1, 100.2, 126.1, 126.9, 127.78, 127.80, 127.82, 127.86, 127.87, 128.3, 128.45, 128.49, 128.51, 128.55, 129.68, 129.70, 129.9, 133.0, 134.3, 137.5, 138.2, 138.3, 138.4, 138.5, 166.5. ESI-MS $[M + Na]^+$ $C_{54}H_{53}N_3NaO_{10}S$ calcd 958.3, obsd 958.4. gHMQC (without 1H decoupling): $^1J_{C1',H1'}$ = 172.4 Hz, $^1J_{C1,H1}$ = 160.1 Hz.

***p*-Tolyl 3,4,6-Tri-*O*-benzyl-β-D-galactopyranosyl-(1 → 3)-4,6-benzylidene-2-(2,2,2-tri-chloroethoxycarbonylamino)-2-deoxy-1-thio-β-D-galactopyranoside (13).** Compound **12**β (1.7 g, 1.81 mmol) was dissolved in a mixture of CH_2Cl_2/MeOH (25 mL each), and 1 M NaOMe (5.4 mL, 5.4 mmol) was added at room temperature. The mixture was heated at reflux for 4 h under N_2 and then was neutralized with concd HCl until the pH was around 7. The mixture was concentrated and then diluted with CH_2Cl_2 (200 mL). The organic phase was washed with saturated aqueous solution of $NaHCO_3$, 10% HCl, and water and then dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (3:1:1 hexanes−/EtOAc−/CH_2Cl_2) afforded *p*-tolyl 3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1 → 3)-4,6-benzylidene-2-azido-2-deoxy-1-thio-β-D-galactopyranoside (S6) as a white solid (1.5 g, quantitative). 1H NMR (600 MHz, $CDCl_3$): d 2.32 (s, 3H, $SPhCH_3$), 2.52 (s, 1H, OH), 3.35 (s, br, 1H, H-5), 3.46 (dd, 1H, $J_{2',3'}$ = 9.6 Hz, $J_{3',4'}$ = 3.0 Hz, H-3′), 3.51−3.61 (m, 4H, H-3, H-5′, H-6a′, H-6b′), 3.78 (dd, 1H, $J_{1,2}$ = 10.2 Hz, H-2), 3.85 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-4′), 3.86−3.89 (dd, 1H, J = 1.8, 12.0 Hz, H-6a), 3.96 (t, 1H, J = 9.6 Hz, H-2′), 4.22 (d, 1H, $J_{3',4'}$ = 3.0 Hz, H-4), 4.31 (dd, 1H, J = 1.8, 12.0 Hz, H-6b), 4.35 (d, 1H, $J_{1,2}$ = 10.2 Hz, H-1), 4.42, 4.46 (2d, 2H, J = 12.0 Hz, CH_2Ph), 4.48 (d, 1H, $J_{1',2'}$ = 9.6 Hz, H-1′), 4.59, 4.72, 4.77, 4.90 (4d, 4H, CH_2Ph), 5.45 (s, 1H, CHPh), 6.98−7.08 (m, 2H), 7.25−7.43 (m, 20H, aromatic), 7.58−7.68 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): d 21.5, 60.2, 69.3, 69.4, 70.3, 71.4, 73.3, 73.6, 73.7, 74.3, 74.9, 75.4, 80.4, 82.1, 85.7, 101.3, 105.4, 126.2, 127.0, 127.9, 128.98, 127.99, 128.2, 128.3, 128.5, 128.6, 128.7, 128.8, 129.3, 130.1, 135.0, 138.0, 138.1, 138.5, 138.6, 138.9; HRMS: $[M + Na]^+$ $C_{47}H_{49}N_3NaO_9S$ calcd 854.3087, obsd 854.3085. *p*-Tolyl 3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1 → 3)-4,6-benzylidene-2-azido-2-deoxy-1-thio-β-D-galactopyranoside (**S6**) (1.3 g, 1.56 mmol), 1,3-propanedithiol (1.57 mL, 15.6 mmol), and Et_3N (1.10 mL, 15.6 mmol) were dissolved in a mixture of CH_2Cl_2/MeOH (10 mL each). The mixture was heated at reflux overnight under N_2 and then concentrated. The resulting residue was diluted with CH_2Cl_2 (200 mL) and then washed with a saturated aqueous solution of $NaHCO_3$ and water, dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (20:1 CH_2Cl_2/MeOH) afforded *p*-tolyl 3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1 → 3)-4,6-benzylidene-2-amino-2-deoxy-1-thio-β-D-galactopyranoside (**S7**) as a white solid (1.07 g, 85%). 1H NMR (600 MHz, $CDCl_3$): δ 2.32 (s, 4H, SPhCH3, OH), 3.25 (t, 1H, J = 9.6 Hz, H-2), 3.37 (s, 1H, H-5), 3.37−3.39 (dd, 1H, $J_{2',3'}$ = 9.6 Hz, $J_{3',4'}$ = 3.0 Hz, H-3′), 3.53 (dd, 1H, $J_{2,3}$ = 10.2 Hz, $J_{3,4}$ = 3.0 Hz, H-3), 3.55−3.59 (m, 3H, H-5′, H-6a′, H-6b′), 3.86 (d, 1H, $J_{3',4'}$ = 3.0 Hz, H-4′), 3.86 (d, 1H, J = 12.0 Hz, H-6a), 3.95 (t, 1H, J = 9.6 Hz, H-2′), 4.16 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-4), 4.29 (d, 1H, J = 12.0 Hz, H-6b), 4.35 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 4.43−4.44 (m, 3H, $J_{1',2'}$ = 10.2 Hz, H-1′, CH_2Ph), 4.57, 4.65, 4.68, 4.86 (4d, 4H, J = 12.0 Hz, CH_2Ph), 5.43 (s, 1H, CHPh), 6.95−7.08 (m, 2H), 7.23−7.42 (m, 20H, aromatic), 7.50−7.58 (m, 2H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 21.4, 49.7, 69.0, 69.6, 70.3, 71.5, 72.7, 73.0, 73.7, 74.2, 74.7, 75.4, 82.4, 83.8, 88.4, 101.1, 106.1, 126.6, 126.9, 127.79, 127.83, 127.9, 128.0, 128.2, 128.4, 128.5, 128.66, 128.68, 129.1, 129.9, 134.3, 138.08, 138.14, 138.3, 138.5, 138.6. HRMS: $[M + Na]^+$ $C_{47}H_{51}NNaO_9S$ calcd 828.3182, obsd 828.3182. *p*-Tolyl 3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1 → 3)-4,6-benzylidene-2-amino-2-deoxy-1-thio-β-D-galactopyranoside (**S7**) (1.06 g, 1.31 mmol) and solid $NaHCO_3$ (0.22 g, 2.62 mmol) were put into THF (16 mL), and then TrocCl (0.214 mL, 1.57 mmol) was added. The mixture was stirred at room temperature under N_2 for 4 h and filtrated. The filtrate was concentrated and then diluted with CH_2Cl_2 (100 mL). The mixture was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (2:1 hexanes−/EtOAc) afforded **13** as a white solid (1.2 g, 93%); [α]D −13.6 (c = 1, CH_2Cl_2); 1H NMR (600 MHz, $CDCl_3$): δ 2.32 (s, 3H, $SPhCH_3$), 3.34 (d, 1H, $J_{2',3'}$ = 7.8 Hz, $J_{3',4'}$ = 3.0 Hz, H-3′), 3.40 (s, 1H, H-5), 3.48−3.61 (m, 3H, H-5′, H-6a′, H-6b′), 3.65 (dd, 1H, $J_{1,2}$ = 10.2 Hz, JNH,2 = 7.2 Hz, H-2), 3.82 (d, 1H, $J_{3',4'}$ = 3.0 Hz, H-4′), 3.87 (d, 1H, J = 12.0 Hz, H-6a), 3.92 (t, 1H, J = 7.8 Hz, H-2′), 4.24−4.29 (m, 3H, H-3. H-4, H-6a), 4.35 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1′), 4.46 (s, 2H, CH_2CCl_3), 4.58 (d, 1H, J = 12.0 Hz, CH_2Ph), 4.66−4.71 (m, 3H, J = 12.0 Hz, CH_2-Ph), 4.78, 4.88 (2d, 2H, J = 12.0 Hz, CH_2Ph), 5.07 (d, 1H, $J_{1,2}$ = 10.2 Hz, H-1), 5.46 (s, 1H, CHPh), 5.52 (d, 1H, $J_{NH,2}$ = 7.2 Hz, NH), 7.00−7.09 (m, 2H), 7.21−7.44 (m, 20H, aromatic), 7.50−7.59 (m, 2H); 13C NMR (150 MHz, $CDCl_3$): d 21.5, 51.8, 69.2, 69.5, 70.3, 71.3, 73.0, 73.4, 73.8, 74.2, 74.7, 74.8, 76.1, 77.3, 81.9, 84.3, 95.9, 101.1, 105.0, 127.0, 127.4, 127.9, 128.0, 128.0, 128.1, 128.2, 128.3, 128.5, 128.7, 128.76, 128.77, 129.2, 130.0, 134.5, 138.10, 138.12, 138.4, 138.6, 154.3; HRMS: $[M + Na]^+$ $C_{50}H_{52}Cl_3NNaO_{11}S$ calcd 1002.2224, obsd 1002.2208.

***p*-Tolyl 2,4,6-tri-*O*-Benzyl-1-thio-β-D-galactopyranoside (19).** β-D-Galactose pentaacetate (20 g, 51.2 mmol) and p-toluenethiol (7.3 g, 58.8 mmol) were dissolved in CH_2Cl_2. (400 mL). Boron trifluoride etherate (20.15 mL, 153.6 mmol) was added dropwise at 0 °C, and the mixture was stirred under N_2 at room temperature for 20 h. The mixture was diluted with CH_2Cl_2 (450 mL) and washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (2:1 hexanes/EtOAc) afforded *p*-tolyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (**S8**) as a white solid (21.2 g, 91%). 1H NMR (600 MHz, $CDCl_3$): δ 1.98, 2.05, 2.10, 2.12 (s, 12H, 4 × $COCH_3$), 2.35 (s, 3H, SPhCH3), 3.92 (t, 1H, J = 6.6 Hz, H-5), 4.10−4.20 (m, 2H, H-6a, H-6b), 4.66 (d, 1H, $J_{1,2}$ = 10.2 Hz, H-1), 5.04 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 3.0 Hz, H-3), 5.22 (t, 1H, J = 10.2 Hz, H-2), 5.41 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-4), 7.08−7.16 (m, 2H), 7.40−7.46 (m, 2H); 13C NMR (150 MHz, $CDCl_3$): δ 20.82, 20.86, 20.90, 21.1, 21.4, 61.8, 67.4, 67.4, 67.5, 72.2, 74.5, 87.1, 128.8, 129.9, 133.3, 138.7, 160.74 169.7, 170.3, 170.4, 170.6. ESI-MS $[M + Na]^+$ $C_{21}H_{26}NaO_9S$ calcd 477.1, obsd 477.3. Comparison of the NMR data with those reported in the literature[63] confirmed its identity. *p*-Tolyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (**S8**) (11.5 g, 25.3 mmol) was dissolved in a mixture of CH_2Cl_2/MeOH (100 mL/70 mL), and 5.14 M NaOMe (2.4 mL, 12.7 mmol) was added. The mixture was stirred at room temperature for 6 h under N_2 and then was neutralized with Amberlite IR-120 and concentrated to dryness. Silica gel column chromatography (10:1 CH_2Cl_2/MeOH) afforded *p*-tolyl 1-thio-β-D-galactopyranoside (**S9**) as a white solid (7.2 g, quantitative). 1H NMR (600 MHz, CD_3OD): δ 2.28 (s, 3H, $SPhCH_3$), 3.47 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3.4}$ = 3.0 Hz, H-3), 3.51 (t, 1H, J = 6.6 Hz, H-5), 3.55 (t, 1H, J = 9.6 Hz, H-2), 3.67−3.75 (m, 2H, H-6a, H-6b), 3.87 (d, 1H, $J_{3.4}$ = 3.0 Hz, H-4), 4.49 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 7.05−7.12 (m, 2H), 7.40−7.47 (m, 2H); 13C NMR (150 MHz, CD_3OD): d 19.9, 61.4, 69.2, 69.8, 75.1, 79.4, 89.5, 129.4, 130.9, 131.7, 137.2. ESI-MS $[M + Na]^+$ $C_{13}H_{18}NaO_5S$ calcd 309.1, obsd 309.1. *p*-Tolyl 1-thio-β-D-galactopyranoside (**S9**) (3 g, 10.4 mmol) and dibutyltin oxide (2.6 g, 10.4 mmol) were put into MeOH (45 mL). The mixture was heated at reflux for 2 h and then concentrated to dryness. DMF (30 mL) was added to the resulting residue, *p*-methoxy benzyl chloride (PMBCl, 1.5 mL, 10.4 mmol), and CsF (1.67 g, 10.4 mmol), which were then stirred under N_2 at 50 °C for 2 days and concentrated to dryness. Silica gel column chromatography (1:2 hexanes/EtOAc) afforded *p*-tolyl 3-*O*-*p*-methoxylbenzyl-1-thio-β-D-galactopyranoside (**S10**) as a white solid (2.34 g, 55% for two steps). 1H NMR (600 MHz, CD_3OD): δ 2.20 (s, 3H, $SPhCH_3$), 3.27 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 3.0 Hz, H-3), 3.35−3.38 (m, 1H, H-5), 3.58−3.65 (m, 3H, $J_{1,2}$ = 10.2 Hz, H-2, H-6a, H-6b), 3.67 (s, 3H, OCH_3), 3.94 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-4), 4.41 (d, 1H, $J_{1,2}$ = 10.2 Hz, H-1), 4.51, 4.58 (2d, 2H, J = 11.4 Hz, CH_2PhOCH_3), 6.72−6.82 (m, 2H), 6.96−7.05 (m, 2H), 7.20−7.28 (m, 2H), 7.30−7.38 (m, 2H); 13C NMR (100 MHz, CD3OD): δ 21.3, 55.76, 55.81, 62.7, 67.6, 70.3, 72.5, 80.5, 83.5, 90.8, 114.8, 130.64, 130.68, 130.8, 130.9, 131.9, 132.1, 133.1, 133.2, 138.6, 160.9. ESI-MS $[M + Na]^+$ $C_{21}H_{26}NaO_6S$ calcd 429.2, obsd 429.3. *p*-Tolyl 3-*O*-*p*-methoxylbenzyl-1-thio-β-D-galactopyranoside (**S10**) (3.4 g, 8.36 mmol) was dissolved in DMF (50 mL), and the solution was cooled to 0 °C. NaH (1.34 g, 60% NaH in mineral oil, 33.44 mmol) was added in portions, followed by the addition of BnBr (4 mL, 33.44 mmol). The mixture was stirred at room temperature under N_2 overnight and then diluted with EtOAc (250 mL). The mixture was washed with saturated $NaHCO_3$ and water and then dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (8:1 hexanes/EtOAc) afforded *p*-tolyl 2,4,6-tri-*O*-benzyl-3-*O*-*p*-methoxylbenzyl-1-thio-β-D-galactopyranoside (**14**) as a white solid (4.5 g, 80%); $[\alpha]_D$ +3.2 (c = 1, CH_2Cl_2); 1H NMR (600 MHz, $CDCl_3$): δ 2.27 (s, 3H, $SPhCH_3$), 3.56−3.65 (m, 4H, H-3, H-5, H-6a, H-6b), 3.77 (s, 3H, OCH_3), 3.87 (t, 1H, J = 9.6 Hz, H-2), 3.93 (d, 1H, $J_{3.4}$ = 2.4 Hz, H-4), 4.40, 4.45, 4.58, 4.62, 4.65, 4.72, 4.78, 4.95 (8d, 8H, J = 12.0 Hz, CH_2PhOCH_3, CH_2Ph), 4.58 (d, 1H, $J_{1,2}$ = 10.2 Hz, H-1), 6.78−6.88 (m, 2H), 6.94−7.02 (m, 2H), 7.24−7.34 (m, 15H, aromatic), 7.35−7.45 (m, 2H), 7.40−7.49 (m, 2H); 13C NMR (150 MHz, $CDCl_3$): δ 21.4, 55.5, 69.1, 72.7, 73.8, 73.9, 74.7, 75.9, 77.5, 84.2, 88.3, 114.1, 127.7, 127.96, 128.04, 128.1, 128.2, 128.4, 128.57, 128.59, 128.68, 129.5, 129.8, 130.5, 130.7, 132.5, 137.4, 138.2, 138.7, 139.1, 159.5. ESI-MS $[M + Na]^+$ $C_{42}H_{44}NaO_6S$ calcd 699.3, obsd 699.5.

Compound **14** (0.3 g, 0.44 mmol) was dissolved in a mixture of CH_2Cl_2/H_2O (2.9 mL/0.15 mL), and the solution was cooled to 0 °C. 2,3-Dichloro 5,6-dicyano-1,4-benzoquinone (DDQ, 0.12 g, 0.53 mmol) was added, and the mixture was stirred at room temperature for 3 h. The mixture was filtered and diluted with CH_2Cl_2 (30 mL), and the organic phase was washed with H_2O until the solution became colorless. Silica gel column chromatography (4:1 hexanes−/EtOAc) afforded **19** as a white solid (0.21 g, 85%); $[\alpha]_D$ −3.9 (c = 3.3, CH_2Cl_2); 1H NMR (600 MHz, $CDCl_3$): δ 2.21 (d, 1H, J = 5.4 Hz, OH), 2.30 (s, 3H, $SPhCH_3$), 3.63−3.68 (m, 5H, H-2, H-3, H-5, H-6a, H-6b), 3.89 (d, 1H, $J_{3.4}$ = 2.4 Hz, H-4), 4.44, 4.50 (2d, 2H, J = 12.0 Hz, CH_2Ph), 4.56 (d, 1H, $J_{1,2}$ = 9.0 Hz, H-1), 4.64 (d, 2H, J = 12.0 Hz, CH_2Ph), 4.73, 4.90 (2d, 2H, J = 12.0 Hz, CH_2Ph), 6.98−7.08 (m, 2H), 7.28−7.37 (m, 15H), 7.42−7.52 (m, 2H); 13C NMR (150 MHz, $CDCl_3$): δ 21.3, 68.8, 73.7, 75.1, 75.4, 75.9, 76.2, 77.5, 78.5, 87.9, 127.9, 127.98, 128.03, 128.05, 128.2, 128.53, 128.56, 128.60, 128.7, 129.8, 130.4, 132.2, 137.5, 138.0, 138.3, 138.7; HRMS: $[M + Na]^+$ $C_{34}H_{36}NaO_5S$ calcd 579.2181, obsd 579.2167.

3-Azidopropyl 2,3,6-Tri-*O*-benzyl-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (15). D-Lactose (5 g, 13.87 mmol) was dissolved in pyridine (30 mL), and then BzCl (20 mL, 172 mmol) was added at 0 °C. The mixture was stirred at room temperature under N_2 overnight and then diluted with CH_2Cl_2 (400 mL). The mixture was washed with saturated $NaHCO_3$ and water and then dried over Na_2SO_4, filtered, and concentrated. The resulting residue was dissolved in CH_2Cl_2 (30 mL), and the solution was cooled to −10 °C. HBr in acetic acid (60 mL, 33%

(63) Tai, C.-A.; Kulkarni, S. S.; Hung, S.-C. *J. Org. Chem.* **2003**, *68*, 8719.

w/w, 104 mmol) was added, and the mixture was stirred at room temperature under N_2 for 5 h. The mixture was diluted with CH_2Cl_2 (200 mL) and poured onto crushed ice in saturated $NaHCO_3$ (400 mL). The organic phase was separated and washed again with saturated $NaHCO_3$ until the pH was about 7 and then dried over Na_2SO_4, filtered, and concentrated. The resulting residue (2 g, 1.76 mmol), 1-bromo propanol (2.3 mL, 26.4 mmol), and freshly activated molecular sieve MS 4 Å (300 mg) were put into a 100 mL round-bottomed flask containing CH2Cl2 (20 mL), and the mixture was stirred at room temperature for 30 min. AgOTf (0.54 g, 2.11 mmol) was added, and the mixture was stirred at room temperature for 1 h. The mixture was diluted with CH_2Cl_2 (100 mL) and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ and H_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (3:1 hexanes/EtOAc) afforded 3-bromopropyl 2,3,4,6-tetra-*O*-benzoyl-*β*-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzoyl-*β*-D-glucopyranoside (**S11**) as a white solid (1.6 g, 65% for 3 steps). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.96 (m, 2H, $OCH_2CH_2CH_2N_3$), 3.27 (m, 2H, $OCH_2CH_2CH_2N_3$), 3.64 (m, 1H, CH_2N_3), 3.73−3.81 (m, 2H, H-5′, H-6a′), 3.88−3.98 (m, 3H, H-5, H-6b′, CH_2N_3), 4.32 (t, 1H, J = 9.6 Hz, H-4), 4.56 (dd, 1H, J = 4.2, 12.0 Hz, H-6a), 4.67 (d, 1H, J = 12.0 Hz, H-6b), 4.75 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.96 (d, 1H, $J_{1′,2′}$ = 7.8 Hz, H-1′), 5.45 (dd, 1H, $J_{2′,3′}$ = 10.2 Hz, $J_{3′,4′}$ = 3.0 Hz, H-3′), 5.51 (t, 1H, J = 9.6 Hz, H-2), 5.78−5.80 (m, 2H, H-2′, H-4′), 5.87 (t, 1H, J = 9.6 Hz, H-3), 7.14−8.04 (m, 35H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.1, 32.3, 61.1, 62.4, 67.5, 69.9, 71.4, 71.78, 71.82, 72.83, 73.0, 76.0, 101.1, 101.4, 128.3, 128.4, 128.56, 128.63, 128.8, 129.2, 129.4, 129.5, 129.57, 129.62, 129.68, 129.74, 130.0, 133.2, 133.3, 133.4, 133.6, 164.8, 165.2, 165.3, 165.4, 165.5, 165.8. ESI-MS [M + Na]$^+$ $C_{64}H_{55}NaBrO_{18}$ calcd 1213.3, obsd 1213.6. 3-Bromopropyl 2,3,4,6-tetra-*O*-benzoyl-*β*-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzoyl-*β*-D-glucopyranoside (**S11**) (1.2 g, 1 mmol) and NaN_3 (0.66 g, 10 mmol) were dissolved in DMF (10 mL). The mixture was stirred at 60 °C for 30 h and then concentrated. The resulting residue was diluted with EtOAc (200 mL), washed with H_2O, and then dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (3:1 hexanes/EtOAc) afforded compound 3-azidopropyl 2,3,4,6-tetra-*O*-benzoyl-*β*-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzoyl-*β*-D-glucopyranoside (**S12**) as a white solid (1.04 g, 90%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.72 (m, 2H, $CH_2CH_2CH_2N_3$), 3.18 (m, 2H, $OCH_2CH_2CH_2N_3$), 3.54 (m, 1H, CH_2N_3), 3.71−3.78 (m, 2H, H-5′, H-6a′), 3.86−3.95 (m, 3H, H-5, H-6b′, CH2N3), 4.29 (t, 1H, J = 9.0 Hz, H-4), 4.53 (dd, 1H, J = 4.2, 12.0 Hz, H-6a), 4.64 (d, 1H, J = 12.0 Hz, H-6b), 4.71 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.93 (d, 1H, $J_{1′,2′}$ = 7.8 Hz, H-1′), 5.43 (dd, 1H, $J_{2′,3′}$ = 10.2 Hz, $J_{3′,4′}$ = 3.0 Hz, H-3′), 5.49 (t, 1H, J = 7.8 Hz, H-2), 5.75−5.78 (m, 2H, H-2′, H-4′), 5.85 (t, 1H, J = 9.6 Hz, H-3), 7.14−8.12 (m, 35H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.1, 48.0, 61.2, 62.5, 66.8, 67.7, 70.0, 71.5, 71.9, 72.0, 73.0, 73.2, 76.2, 101.2, 101.4, 128.4, 128.67, 128.71, 128.76, 128.82, 128.99, 129.4, 129.6, 129.66, 129.74, 129.77, 129.84, 129.86, 129.93, 130.18, 130.37, 133.40, 133.5, 133.6, 133.8, 133.9, 165.0, 165.4, 165.58, 165.60, 165.8, 166.0. ESI-MS [M + Na]$^+$ $C_{64}H_{55}NaN_3O_{18}$ calcd 1176.4, obsd 1176.8. 3-Azidopropyl 2,3,4,6-tetra-*O*-benzoyl-*β*-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzoyl-*β*-D-glucopyranoside (**S12**) (1 g, 0.86 mmol) was dissolved in MeOH (16 mL), and 5.14 M NaOMe (1.67 mL, 8.6 mmol) was added. The mixture was heated at reflux for 6 h under N_2 and then was neutralized with Amberlite IR-120 until the pH was around 7. It was filtered and concentrated to dryness. Silica gel column chromatography (4:1 CH_2Cl_2/MeOH) afforded 3-azidopropyl *β*-D-galactopyranosyl-(1 → 4)-*β*-D-glucopyranoside (**S13**) as a white solid (0.36 g, 97%). ^{1}H NMR (600 MHz, CD_3OD): δ 1.85 (m, 2H, $CH_2CH_2CH_2N_3$), 3.23 (t, 1H, J = 7.8 Hz, H-2′), 3.38−3.40 (m, 1H, H-5), 3.40−3.58 (m, 7H, H-2, H-3, H-6a, H-3′, H-5′, $OCH_2CH_2CH_2N_3$), 3.60−3.64 (m, 1H, CH_2N_3), 3.68 (dd, 1H, J = 4.8, 12.0 Hz, H-6a′), 3.76 (dd, 1H, J = 7.8, 11.4 Hz, H-4), 3.80 (d, 1H, $J_{3′,4′}$ = 3.0 Hz, H-4′), 3.83 (dd, 1H, J = 3.6, 12.0 Hz, H-6b′), 3.88 (dd, 1H, J = 4.8, 12.0 Hz, H-6b), 3.92−3.96 (m, 1H, CH_2N_3), 4.27 (d, 1H, $J_{1′,2′}$ = 7.8 Hz, H-1′), 4.34 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1); ^{13}C NMR (150 MHz, CD_3OD): δ 29.0, 48.2, 60.7, 61.3, 66.4, 69.1, 71.4, 73.5, 73.6, 75.2, 75.3, 75.9, 79.4, 103.1, 103.9. ESI-MS [M + Na]$^+$ $C_{15}H_{27}NaN_3O_{11}$ calcd 448.2, obsd 448.2. The mixture of 3-azidopropyl *β*-D-galactopyranosyl-(1 → 4)-*β*-D-glucopyranoside (**S13**) (0.5 g, 1.17 mmol), camphorsulfonic acid (0.14 g, 0.59 mmol), benzaldehyde dimethylacetal (0.2 mL, 1.35 mmol), and DMF (3 mL) were stirred at room temperature under N_2 overnight. The mixture was neutralized with solid $NaHCO_3$ (0.98 g, 1.17 mmol) and then concentrated to dryness. Silica gel column chromatography (8:1 CH_2Cl_2/MeOH) afforded 3-azidopropyl 4,6-*O*-benzylidene-*β*-D-galactopyranosyl-(1 → 4)-*β*-D-glucopyranoside[64] (**S14**) as a white solid (0.49 g, 81%). ^{1}H NMR (600 MHz, CD_3OD): δ 1.80 (m, 2H, $CH_2CH_2CH_2N_3$), 3.21 (t, 1H, J = 7.8 Hz, H-2′), 3.34−3.39 (m, 3H, H-5, $OCH_2CH_2CH_2N_3$), 3.49−3.62 (m, 6H, H-2, H-3, H-6a, H-3′, H-5′, CH_2N_3), 3.84−3.89 (m, 3H, H-4, H-6b, CH_2N_3), 4.05 (d, 1H, J = 11.4 Hz, H-6a′), 4.11−4.13 (m, 2H, H-4′, H-6b′), 4.21 (d, 1H, $J_{1′,2′}$ = 7.8 Hz, H-1′), 4.40 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 5.52 (s, 1H, CHPh), 7.27−7.48 (m, 5H, aromatic); ^{13}C NMR (100 MHz, CD_3OD): δ 30.3, 49.4, 61.8, 67.7, 68.29, 68.33, 70.3, 71.8, 73.5, 74.8, 76.3, 76.5, 77.3, 80.1, 102.2, 104.4, 104.9, 127.6, 129.2, 130.0, 139.6. ESI-MS [M + Na]$^+$ $C_{22}H_{31}NaN_3O_{11}$ calcd 536.2, obsd 536.3. 3-Azidopropyl 4,6-*O*-benzylidene-*β*-D-galactopyranosyl-(1 → 4)-*β*-D-glucopyranoside (**S14**) (2 g, 3.89 mmol) was dissolved in DMF (25 mL), and the solution was cooled to 0 °C. NaH (0.93 g, 60% NaH in mineral oil, 23.34 mmol) was added in portions, followed by the addition of BnBr (2.8 mL, 33.44 mmol). The mixture was stirred at room temperature under N_2 for 6 h and then diluted with EtOAc (250 mL). The mixture was washed with saturated aqueous $NaHCO_3$ and water and then dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (6:1 hexanes/EtOAc) afforded 3-azidopropyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-*β*-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-*β*-D-glucopyranoside[53] (**S15**) as a white solid (3 g, 80%); $[\alpha]_D$ +176.4 (*c*, 0.56, CH_2Cl_2); $[\alpha]_D$ +16.1 (*c* = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.88 (m, 2H, $CH_2CH_2CH_2N_3$), 2.93 (s, 1H, H-5′), 3.33−3.39 (m, 4H, H-3, H-5, $OCH_2CH_2CH_2N_3$), 3.42 (t, 1H, J = 7.8 Hz, H-2′), 3.60−3.64 (m, 2H, H-3′, CH_2N_3), 3.68−3.70 (d, 1H, J = 10.8 Hz, H-6a), 3.74−3.77 (t, 1H, J = 7.8 Hz, H-2), 3.84 (d, 1H, $J_{3,4}$ = 12.0 Hz, H-4), 3.86−3.89 (dd, 1H, $J_{5′,6a′}$ = 4.2 Hz, $J_{6a′,6b′}$ = 10.8 Hz, H-6a′), 3.96−3.98 (m, 2H, H-6b, CH_2N_3), 4.02 (d, 1H, $J_{3′,4′}$ = 3.0 Hz, H-4′), 4.20 (d, 1H, J = 12.0 Hz, H-6b′), 4.32, (d, 1H, J = 12.0 Hz, CH_2Ph), 4.36 (d, 1H, $J_{1′,2′}$ = 7.8 Hz, H-1′), 4.44 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.54 (d, 1H, J = 12.0 Hz, CH_2Ph), 4.72−4.85 (m, 7H, CH_2Ph), 5.19, 5.46 (2d, 2H, J = 12.0 Hz, CH_2-Ph), 7.17−7.52 (m, 30H, aromatic); ^{13}C NMR (150 MHz, $CDCl_3$): δ 29.47, 48.56, 66.57, 66.59, 66.78, 68.44, 69.19, 71.85, 73.22, 73.88, 75.33, 75.35, 75.34, 76.07, 77.80, 79.05, 79.86, 82.06, 83.30, 101.61, 103.09, 103.80, 126.81, 127.55, 127.66, 127.70, 127.87, 127.95, 127.99, 128.15, 128.33, 128.38, 128.45, 128.48, 128.59, 128.61, 128.87, 129.10, 138.32, 138.65, 138.72, 138.84, 139.09, 139.13. ESI-MS [M + Na]$^+$ $C_{57}H_{61}NaN_3O11$ calcd 986.4, obsd 986.7. 3-Azidopropyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-*β*-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-*β*-D-glucopyranoside (**S15**) (0.6 g, 0.62 mmol) and $NaBH_3CN$ (0.35 g, 5.58 mmol) were dissolved in THF (15 mL) and cooled to 0 °C. A solution of HCl in ether (2 M, 3 mL) was added, and the mixture was stirred at room temperature for 3 h and then concentrated to dryness. The obtained residue was diluted with CH_2Cl_2 and washed with 10% HCl and water and then dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (3:1 hexanes/EtOAc) afforded **15** as a white solid (0.53 g, 89%); $[\alpha]_D$ +16.1 (*c* = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.86 (m, 2H, $CH_2CH_2CH_2N_3$), 2.48 (s, 1H, OH), 3.30−3.41 (m, 6H, H-2′, H-3, H-5, H-5′, $OCH_2CH_2CH_2N_3$), 3.46−3.49 (dd, 1H, $J_{5,6a}$ = 5.4 Hz, $J_{6a,6b}$ = 9.6

(64) Yang, Z.-Q.; Puffer, E. B.; Pontrello, J. K.; Kiessling, L. L. *Carbohydr. Res.* **2002**, *337*, 1605.

Hz, H-6a), 3.55−3.70 (m, 5H, H-2, H-3′, H-6a′, H-6b, CH_2N_3), 3.79−3.81 (dd, 1H, $J_{5',6a'}$ = 4.2 Hz, $J_{6a',6b'}$ = 10.8 Hz, H-6b′), 3.94−4.01 (m, 3H, H-4, H-4′, CH_2N_3), 4.34−4.45 (m, 5H, $J_{1,2}$ = 7.8 Hz, $J_{1',2'}$ = 8.4 Hz, H-1, H-1′, CH_2Ph), 4.54, 4.64, 4.69 (3d, 3H, J = 12.0 Hz, CH_2Ph), 4.73−4.79 (m, 4H, CH_2Ph), 4.83, 4.99 (2d, 2H, J = 12.0 Hz, CH_2Ph), 7.19−7.39 (m, 30H, aromatic); ^{13}C NMR (150 MHz, $CDCl_3$): δ 29.6, 48.6, 66.4, 66.8, 68.5, 68.8, 72.3, 73.1, 73.4, 73.8, 75.36, 75.39, 75.6, 75.7, 76.8, 79.7, 81.4, 82.1, 83.2, 89.5, 102.9, 103.9, 127.6, 127.85, 127.88, 127.95, 127.99, 128.09, 128.12, 128.19, 128.26, 128.40, 128.45, 128.61, 128.67, 128.70, 128.80, 138.2, 138.5, 138.6, 138.88, 138.94, 139.4. ESI-MS $[M + Na]^+$ $C_{57}H_{63}NaN_3O_{11}$ calcd 988.5, obsd 988.8.

3-Azidopropyl 2,3-Di-*O*-benzoyl-6-*O*-benzyl-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (21). 3-Azidopropyl 4,6-*O*-benzylidene-β-D-galactopyranosyl-(1 → 4)-β-D-glucopyranoside (0.5 g, 0.97 mmol) was dissolved in pyridine (20 mL), and then BzCl (1.1 mL, 9.7 mmol) was added at 0 °C. The mixture was stirred at room temperature under N_2 overnight and then diluted with CH_2Cl_2 (100 mL). The mixture was washed with a saturated aqueous solution of $NaHCO_3$ and water and then dried over Na_2SO_4, filtered, and concentrated. The mixture of the resulting residue and $NaBH_3CN$ (0.6 g, 9.7 mmol) in THF (20 mL) was cooled to 0 °C, and then a solution of HCl in ether (2 M) was added until the solution was acidic. The mixture was stirred at room temperature for 3 h and then concentrated to dryness. The resulting residue was diluted with CH_2Cl_2 and washed with 10% aqueous HCl and water and then dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (2:1 hexanes/EtOAc) afforded **21** as a gel-like solid (0.7 g, 70% for two steps); $[\alpha]_D$ +47.9 (c = 1, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.70 (m, 2H, $CH_2CH_2CH_2N_3$), 3.01−3.08 (m, 2H, H-6a′, H-6b′), 3.12−3.19 (m, 2H, $OCH_2CH_2CH_2N_3$), 3.45 (t, 1H, J = 6.0 Hz, H-5′), 3.48−3.52 (m, 1H, CH_2N_3), 3.81−3.87 (m, 2H, H-5, CH_2N_3), 4.17−4.26 (m, 4H, H-4, H-4′, CH_2Ph), 4.42 (dd, 1H, J = 4.8, 12.0 Hz, H-6a), 4.60 (dd, 1H, J = 1.8, 12.0 Hz, H-6b), 4.65 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.76 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1′), 5.12 (dd, 1H, $J_{2',3'}$ = 10.5 Hz, $J_{3',4'}$ = 3.0 Hz, H-3′), 5.37 (t, 1H, J = 7.8 Hz, H-2), 5.69−5.75 (m, 2H, H-3, H-2′), 7.20−8.02 (m, 30H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.0, 48.0, 62.5, 66.6, 67.2, 67.5, 70.1, 72.0, 73.1, 73.1, 73.4, 73.5, 74.4, 76.4, 101.0, 101.4, 127.7, 128.0, 128.6, 129.0, 129.2, 129.3, 129.7, 129.81, 129.84, 129.91, 129.93, 129.98, 130.01, 133.29, 133.37, 133.47, 137.8, 165.2, 165.43, 165.45, 165.88, 165.93; HRMS: $[M + Na]^+$ $C_{57}H_{53}N_3NaO_{16}$ calcd 1058.3324, obsd 1058.3315.

3-Azidopropyl 2,4,6-Tri-*O*-benzyl-3-*O*-*p*-methoxybenzyl-α-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (16). After the donor **14** (400 mg, 0.59 mmol), acceptor **15** (540 mg, 0.56 mmol), and activated molecular sieve MS-4 Å (500 mg) were stirred for 30 min at room temperature in a mixture solvent of Et_2O (8 mL) and CH_2Cl_2 (16 mL), the mixture was cooled to −78 °C, followed by the addition of AgOTf (456 mg, 1.77 mmol) in Et_2O (12 mL). The mixture was vigorously stirred for 10 min, then *p*-TolSCl (93.7 μL, 0.59 mmol) was added, and the reaction mixture was stirred for 2 h from −78 to −40 °C (see the General Procedure for Single Step Preactivation Based Glycosylation for precautions). The mixture was concentrated under vacuum to dryness. The resulting residue was diluted with CH_2Cl_2 (100 mL), followed by filtration. The organic phase was washed with saturated aqueous $NaHCO_3$ and H_2O and then dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (2:1 hexanes/EtOAc) afforded **16** as a gel-like solid (702 mg, 82%); $[\alpha]_D$ +37.3 (c = 2.6, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.86 (m, 2H, $OCH_2CH_2CH_2N_3$), 3.15 (dd, 1H, J = 4.8, 8.4 Hz, H-6a), 3.28−3.38 (m, 6H, H-2′, H-3, H-5, H-5′, $OCH_2CH_2CH_2N_3$), 3.47−3.50 (m, 2H, H-5″, H-6b), 3.55−3.70 (m, 4H, H-2, H-3′, H-6a′, CH_2N_3), 3.76 (s, 3H, OCH_3), 3.82 (m, 1H, H-6a″), 3.93−3.98 (m, 3H, H-4, H-4′, CH_2N_3), 4.02−4.07 (m, 5H, H-2″, H-3″, H-6b′, CH_2Ph), 4.17 (dd, 1H, H-4″), 4.21−4.28 (2d, 2H, J = 12.0 Hz, CH_2Ph), 4.33−4.36 (m, 4H, $J_{1',2'}$ = 7.8 Hz, H-1′, H-6b″, CH_2Ph), 4.44−4.52 (m, 5H, $J_{1,2}$ = 7.8 Hz, H-1, CH_2Ph), 4.68−4.80 (m, 7H, CH_2Ph), 4.85−4.87 (m, 2H, CH_2Ph), 5.04 (d, 1H, $J_{1'',2''}$ = 3.0 Hz, H-1″), 5.07 (d, 1H, CH_2Ph), 6.77−7.46 (m, 49H, aromatic); ^{13}C NMR (150 MHz, $CDCl_3$): δ 29.5, 48.6, 55.5, 66.7, 67.9, 68.1, 68.4, 69.7, 72.3, 72.4, 73.26, 73.30, 73.4, 73.50, 74.0, 75.0, 75.13, 75.19, 75.3, 75.50, 75.52, 76.7, 77.4, 79.5, 79.7, 81.9, 82.9, 101.1, 103.1, 103.7, 113.8, 127.62, 127.66, 127.68, 127.72, 127.74, 127.76, 127.83, 127.84, 127.86, 127.89, 127.91, 128.11, 128.21, 128.37, 128.40, 128.42, 128.48, 128.50, 128.51, 128.52, 128.54, 128.56, 128.63, 128.80, 129.08, 138.26, 138.59, 138.66, 138.83, 138.86, 138.99, 139.01, 139.20, 139.33, 159.1; HRMS: $[M + Na]^+$ $C_{92}H_{99}N_3NaO_{17}$ calcd 1540.6872, obsd 1540.6831. gHMQC (without ^{1}H decoupling): $^1J_{C1'',H1''}$ = 169.0 Hz, $^1J_{C1',H1'}$ = 160.1 Hz, $^1J_{C1,H1}$ = 160.0 Hz.

3-Azidopropyl 2,4,6-Tri-*O*-benzyl-α-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (17). Compound 16 (0.51 g, 0.34 mmol) was dissolved in a mixture of CH_2Cl_2/H_2O (4.9 mL/0.5 mL), and the solution was cooled to 0 °C. DDQ (0.84 g, 0.37 mmol) was added, and the mixture was stirred at room temperature for 4 h. The mixture was filtered and diluted with CH_2Cl_2 (100 mL), and the organic phase was washed with H_2O until the solution became colorless. Silica gel column chromatography (4:1 hexanes/EtOAc) afforded **17** as a white solid (0.37 g, 80%). $[\alpha]_D$ +34.6 (c = 1, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.87 (m, 2H, $CH_2CH_2CH_2$), 3.17 (dd, 1H, J = 4.8, 8.4 Hz, H-6a), 3.27−3.39 (m, 6H, H-2′, H-3, H-5, H-5′, OCH_2), 3.44−3.62 (m, 6H, H-2, H-3′, H-5″, H-6b, H-6a′, CH_2N_3), 3.69−3.82 (m, 3H, H-2″, H6a″, H-6b′), 3.91−4.14 (m, 9H, H-4, H-4′, H-4″, H-3″, CH_2N_3, CH_2Ph), 4.34−4.39 (m, 3H, $J_{1',2'}$ = 7.8 Hz, H-1′, H-6a″, CH_2Ph), 4.45 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.47−4.54 (m, 4H, CH_2Ph), 4.67−4.84 (m, 8H, CH_2Ph), 5.07 (d, 1H, J = 12.0 Hz, CH_2Ph), 5.10 (d, 1H, $J_{1'',2''}$ = 3.0 Hz, H-1″), 7.13−7.39 (m, 45H, aromatic); ^{13}C NMR (150 MHz, $CDCl_3$): δ 29.5, 48.6, 66.8, 67.9, 68.0, 68.5, 69.5, 70.3, 72.4, 73.27, 73.33, 73.38, 73.43, 75.1, 75.31, 75.36, 75.47, 75.51, 75.53, 77.2, 77.9, 79.6, 81.8, 81.9, 83.2, 89.5, 99.9, 103.0, 103.8, 127.5, 127.74, 127.76, 127.78, 127.79, 127.85, 127.86, 127.88, 127.92, 127.95, 128.00, 128.02, 128.10, 128.27, 128.34, 128.35, 128.42, 128.44, 128.52, 128.55, 128.56, 128.58, 128.60, 128.71, 128.79, 138.27, 138.48, 138.57, 138.62, 138.82, 138.83, 138.93, 139.02, 139.6; HRMS: $[M + Na]^+$ $C_{84}H_{91}N_3NaO_{16}$ calcd 1420.6297, obsd 1420.6276.

***p*-Tolyl 2,3,4-Tri-*O*-benzyl-1-thio-β-L-fucopyranoside (18).** L-Fucose (10 g, 60.9 mmol) and DMAP (0.72 g, 6.01 mmol) were dissolved in anhydrous pyridine (100 mL), and acetic anhydride (40 mL) was added at room temperature in a period of 30 min. The mixture was stirred at room temperature under N_2 overnight and then quenched with ethanol (20 mL) at 0 °C. The mixture was concentrated, and the resulting residue was diluted with ethyl acetate (300 mL), and washed with water, saturated $NaHCO_3$, 10% aqueous hydrochloric acid, and brine. The organic phase was dried over Na_2SO_4 and then filtered and concentrated. Silica gel column chromatography (2:1 hexanes−/EtOAc) afforded the 1,2,3,4-tetra-*O*-acetyl-L-fucopyranoside as a white solid (21 g, quantitative, α/β mixtures) with the α isomer (**S16**) as the major product. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.01 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6), 1.86, 1.87, 2.01, 2.04 (4s, 12H, 4 × $COCH_3$), 4.15 (m, 1H, H-5), 5.15 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-2), 5.16−5.20 (m, 2H, H-3, H-4), 6.18 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1); ^{13}C NMR (150 MHz, $CDCl_3$): δ 16.0, 20.6, 20.7, 20.8, 21.0, 66.6, 67.3, 67.9, 70.6, 89.9, 169.2, 170.0, 170.2, 170.6. ESI-MS $[M + Na]^+$ $C_{14}H_{20}NaO_9$ calcd 355.1, obsd 355.3. The obtained α/β mixture of 1,2,3,4-tetra-*O*-acetyl-L-fucopyranoside (21 g) and *p*-toluenethiol (8.32 g, 67 mmol) were dissolved in CH_2Cl_2 (180 mL) and cooled to 0 °C. Boron trifluoride etherate (10.5 mL, 83 mmol) was added dropwise at 0 °C, and the mixture was stirred under N_2 at room temperature overnight. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ until the pH was around 7 and then dried over Na_2SO_4, filtered, and concentrated. The obtained crude product was recrystallized

by EtOAc/hexanes to give *p*-tolyl 2,3,4-tri-*O*-acetyl-1-thio-β-L-fucopyranoside[63] (**S17**) as a white solid (11.6 g, 48%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.15 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6), 1.90, 2.01, 2.07 (3s, 9H, 3 × $COCH_3$), 2.26 (s, 3H, $SPhCH_3$), 3.74 (m, 1H, H-5), 4.58 (d, 1H, $J_{1,2}$ = 10.2 Hz, H-1), 4.98 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 3.0 Hz, H-3), 5.13 (t, 1H, J = 9.6 Hz, H-2), 5.18 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-4), 7.00−7.09 (m, 2H), 7.30−7.39 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 16.7, 20.8, 20.9, 21.1, 21.3, 67.5, 70.5, 72.6, 73.2, 86.9, 129.3, 129.8, 133.0, 138.3, 169.6, 170.3, 170.8. ESI-MS $[M + Na]^+$ $C_{19}H_{24}NaO_7S$ calcd 419.1, obsd 419.2. *p*-tolyl 2,3,4-tri-*O*-acetyl-L-thio-β-L-fucopyranoside (**S17**) (9.2 g, 23.2 mmol) was dissolved in a mixture of CH_2Cl_2/MeOH (70 mL/50 mL), and 1 M NaOMe (12 mL, 11.6 mmol) was added at room temperature. The mixture was stirred for 2 h at room temperature under N_2, neutralized with Amberlite IR-120, concentrated, and vacuum-dried. The obtained residue (6 g) was dissolved in DMF (100 mL) and cooled to 0 °C. NaH (3.6 g, 60% NaH in mineral oil, 88 mmol) was added in portions, followed by the addition of BnBr (10.5 mL, 88 mmol) 30 min later. The mixture was stirred at room temperature under N_2 for 2 h and then diluted with EtOAc (300 mL). The mixture was washed with saturated aqueous solution of $NaHCO_3$ and water and then dried over Na_2SO_4, filtered, and concentrated. The obtained crude product was recrystallized by EtOAc/hexanes to give **18**[37] as a white solid (9.4 g, 75% for two steps); $[\alpha]_D$ −9.4 (c = 1, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.25 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6), 2.29 (s, 3H, $SPhCH_3$), 3.50 (m, 1H, H-5), 3.58 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 2.4 Hz, H-3), 3.62 (d, 1H, $J_{3,4}$ = 2.4 Hz, H-4), 3.89 (t, 1H, J = 9.6 Hz, H-2), 4.55 (d, 1H, $J_{1,2}$ = 10.2 Hz, H-1), 4.66 (d, 1H, J = 12.0 Hz, CH_2Ph), 4.72−4.81 (m, 4H, J = 12.0 Hz, CH_2Ph), 5.00 (d, 1H, J = 12.0 Hz, CH_2Ph), 6.94−7.08 (m, 2H), 7.27−7.40 (m, 15H, aromatic), 7.44−7.56 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 17.6, 21.4, 73.1, 74.8, 75.8, 76.8, 77.4, 84.8, 88.1, 127.7, 127.8, 127.95, 127.97, 128.2, 128.4, 128.59, 128.62, 128.70, 129.78, 130.7, 132.4, 137.4, 138.6, 138.7, 139.0. ESI-MS $[M + Na]^+$ $C_{34}H_{36}NaO_4S$ calcd 563.2, obsd 563.5.

3-Azidopropyl 2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl-(1 → 2)-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1 → 3)-4,6-benzylidene-2-(2,2,2-tri-chloroethoxycarbonylamino)-2-deoxy-β-D-galactopyranosyl-(1 → 3)-2,4,6-tri-*O*-benzyl-α-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (20α) and 3-Azidopropyl 2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl-(1 → 2)-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1 → 3)-4,6-benzylidene-2-(2,2,2-tri-chloroethoxycarbonylamino)-2-deoxy-β-D-galactopyranosyl-(1 → 3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (20β). After the donor **18** (50 mg, 92.47 μmol) and freshly activated molecular sieve MS-4 Å (500 mg) were stirred for 30 min at room temperature in Et_2O (4 mL), the solution was cooled to −78 °C, followed by the addition of AgOTf (72 mg, 277.4 μmol) in Et_2O (1.5 mL). The mixture was stirred for 5 min at −78 °C, and then *p*-TolSCl (14.7 μL, 92.47 μmol) was added into the solution (see the General Procedure for Single Step Preactivation Based Glycosylation for precautions) The mixture was vigorously stirred for 5 min, followed by the addition of a solution of acceptor **13** (77.1 mg, 78.60 μmol) and TTBP (23 mg, 92.47 μmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 2 h from −78 to −20 °C, and then the mixture was cooled down to −78 °C, followed by the addition of AgOTf (24 mg, 92.47 μmol) in Et_2O (1 mL). The mixture was stirred for 10 min at −78 °C, and then *p*-TolSCl (12.5 μL, 78.60 μmol) was added into the solution. After stirring for 5 min, a solution of acceptor **19** (30.9 mg, 55.48 μmol) and TTBP (23 mg, 92.47 μmol) in CH_2Cl_2 (1 mL) was added slowly along the flask wall into the mixture, and the reaction mixture was stirred for 2 h from −78 to −20 °C. The mixture was cooled down again to −78 °C, followed by sequential additions of AgOTf (24 mg, 92.47 μmol) in Et_2O (1 mL), the last acceptor **15** (35.7 mg, 36.99 μmol), and TTBP (23 mg, 92.47 μmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 10 min at −78 °C, and then *p*-TolSCl (12.5 μL, 78.60 μmol) was added into the solution. The reaction mixture was stirred for 2 h from −78 to 10 °C and then was quenched with Et_3N (40 μL) and concentrated under vacuum to dryness. The resulting residue was diluted with CH_2Cl_2 (30 mL), followed by filtration. The organic phase was washed with a saturated aqueous solution of $NaHCO_3$ and H_2O and then dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (2:1 hexanes−/EtOAc) afforded 46.6 mg of **20**α (47%) and 22.4 mg of **20**β (23%), respectively, as colorless gel. For **20**α: $[\alpha]_D$ −18.0 (c = 2.4, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.42 (d, 3H, J = 6.6 Hz, H-6‴‴), 1.84 (m, 2H, OCH_2-$CH_2CH_2N_3$), 2.80 (s, 1H), 3.19 (m, 1H), 3.27−3.39 (m, 7H), 3.46−3.68 (m, 11H), 3.76−3.86 (m, 5H), 3.92−4.25 (m, 17H), 4.29−4.59 (m, 18H), 4.64−4.87 (m, 13H), 4.94 (d, 1H, $J_{1'',2''}$ = 3.0 Hz, H-1″), 5.06 (d, 1H, J = 11.4 Hz), 5.24 (d, 1H, J = 11.4 Hz), 5.42 (s, 1H), 5.55 (d, 1H, $J_{1'''',2''''}$ = 3.6 Hz, H-1‴‴), 7.00−7.45 (m, 80H, aromatic); ^{13}C NMR (150 MHz, $CDCl_3$): δ 16.1, 29.4, 29.9, 48.5, 54.4, 66.2, 66.6, 66.7, 67.7, 68.1, 68.4, 69.0, 69.2, 69.4, 72.0, 72.1, 72.5, 72.7, 72.9, 73.1, 73.22, 73.24, 73.28, 73.57, 73.63, 73.77, 73.9, 74.57, 74.67, 74.76, 74.78, 74.94, 75.13, 75.18, 75.27, 75.4, 76.2, 76.3, 76.8, 77.6, 78.6, 79.2, 79.7, 80.4, 81.5, 81.7, 82.0, 84.1, 95.8, 97.5, 100.8, 101.8, 102.6, 102.7, 102.8, 103.6, 126.6, 127.03, 127.06, 127.24, 127.28, 127.31, 127.41, 127.44, 127.55, 127.61, 127.67, 127.68, 127.70, 127.76, 127.79, 127.81, 127.93, 128.01, 128.02, 128.11, 128.16, 128.18, 128.20, 128.34, 128.38, 128.42, 128.45, 128.50, 128.56, 128.65, 128.68, 128.72, 128.76, 128.77, 129.1, 129.9, 137.9, 138.2, 138.3, 138.44, 138.45, 138.47, 138.67, 138.81, 138.94, 138.99, 139.1, 139.4, 139.7, 139.8, 154.0; HRMS: $[M + Na]^+$ $C_{154}H_{163}Cl_3N_4O_{31}$ calcd 2692.0265, obsd 2692.0332. gHMQC (without ^{1}H decoupling): $^1J_{C1'''',H1''''}$ = 171.9 Hz, $^1J_{C1'',H1''}$ = 169.8 Hz, other four $^1J_{C1,H1}$ = 160.1, 160.1, 162.6, 162.6 Hz.

For **20**β: $[\alpha]_D$ −4.2 (c = 1, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.60 (d, 3H, J = 6.6 Hz, H-6‴‴), 1.85 (m, 2H, OCH_2-$CH_2CH_2N_3$), 3.22−3.63 (m, 21H), 3.66−3.79 (m, 6H), 3.86−3.99 (m, 6H), 4.05−4.24 (m, 7H), 4.28−4.51 (m, 18H), 4.55−4.60 (m, 4H), 4.63−4.79 (m, 8H), 4.85−4.94 (m, 3H), 5.09−5.13 (m, 2H), 5.22 (d, 1H, J = 12.0 Hz), 5.49 (s, 1H), 5.55 (d, 1H, $J_{1'''',2''''}$ = 3.6 Hz, H-1‴‴), 6.92−7.43 (m, 80H, aromatic); ^{13}C NMR (150 MHz, $CDCl_3$): δ 16.4, 29.5, 29.9, 48.5, 54.7, 66.6, 67.1, 68.2, 68.8, 69.0, 69.2, 69.3, 70.0, 72.3, 72.68, 72.74, 73.0, 73.3, 73.67, 73.69, 73.75, 73.80, 73.96, 74.75, 74.99, 75.12, 75.2, 75.4, 75.8, 76.2, 76.3, 76.6, 78.4, 79.3, 79.9, 80.6, 81.4, 81.8, 82.6, 83.2, 83.7, 96.0, 97.4, 101.6, 101.9, 102.8, 103.1, 103.7, 126.8, 126.92, 126.96, 127.1, 127.2, 127.36, 127.40, 127.45, 127.48, 127.51, 127.53, 127.67, 127.69, 127.73, 127.76, 127.83, 127.87, 127.90, 127.93, 128.01, 128.07, 128.10, 128.16, 128.27, 128.28, 128.34, 128.35, 128.38, 128.44, 128.50, 128.52, 128.53, 128.60, 128.64, 128.67, 128.71, 129.2, 138.1, 138.2, 138.3, 138.43, 138.47, 138.51, 138.57, 138.86, 138.88, 138.97, 139.06, 139.24, 139.51, 139.8, 140.0, 154.1; HRMS: $[M + Na]^+$ $C_{154}H_{163}Cl_3N_4NaO_{31}$ calcd 2692.0265, obsd 2692.0254. $^1J_{C1'''',H1''''}$ = 170.9 Hz, other five $^1J_{C1,H1}$ = 162.0 Hz, 162.0, 162.0, 162.0, 159.4 Hz.

Three component one-pot synthesis procedure: after the donor **18** (50 mg, 92.47 μmol) and activated molecular sieve MS-4 Å (500 mg) were stirred for 30 min at room temperature in Et_2O (6 mL), the solution was cooled to −78 °C, followed by the addition of AgOTf (72 mg, 277.4 μmol) in Et_2O (1.5 mL). The mixture was stirred for 5 min at −78 °C, and then *p*-TolSCl (14.7 μL, 92.47 μmol) was added into the solution (see the General Procedure for Single Step Preactivation Based Glycosylation for precautions). The mixture was vigorously stirred for 10 min, followed by addition of a solution of acceptor **13** (81.7 mg, 83.22 μmol) and TTBP (23 mg, 92.47 μmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 2 h from −78 to −20 °C, and then the mixture was cooled down to −78 °C, followed by sequential additions of AgOTf (24 mg, 92.47 μmol) in Et_2O (1 mL), acceptor **17** (90.5 mg, 64.73 μmol), and TTBP (23 mg, 92.47 μmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 5 min at −78 °C, and then *p*-TolSCl (13.2

μL, 83.22 μmol) was added into the solution. The reaction mixture was stirred for 3 h from −78 to 10 °C and then was quenched with Et_3N (40 μL) and concentrated under vacuum to dryness. The resulting residue was diluted with CH_2Cl_2 (30 mL), followed by filtration. The organic phase was washed with saturated aqueous $NaHCO_3$ and H_2O and then dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (2:1 hexanes−/EtOAc) afforded **20**α as a colorless gel (128 mg, 74%).

3-Azidopropyl α-L-Fucopyranosyl-(1 → 2)-β-D-galactopyranosyl-(1 → 3)-2-acetamido-2-deoxy-β-D-galactopyranosyl-(1 → 3)-α-D-galactopyranosyl-(1 → 4)-β-D-galactopyranosyl-(1 → 4)-β-D-glucopyranoside (2). The mixture of **20**α (0.075 g, 0.028 mmol), 1 M NaOH (0.56 mL, 0.56 mmol), and THF (4 mL) was stirred at 50 °C overnight and then concentrated to dryness. The resulting residue was diluted with CH_2Cl_2 (50 mL), and the organic phase was washed by H_2O and then dried over Na_2SO_4, filtered, and concentrated to dryness. The resulting residue was dissolved in pyridine (2 mL), and a catalytic amount of DMAP was added. Acetic anhydride (0.5 mL, 5.3 mmol) was added dropwise, and the mixture was stirred at room temperature under N_2 for 4 h. The reaction was quenched by adding a few drops of H_2O and then diluted with EtOAc (20 mL). The organic phase was washed with a saturated aqueous solution of $NaHCO_3$ and H_2O, and then dried over Na_2SO_4, filtered, and concentrated to dryness. Silica gel column chromatography (2:1 hexanes−/EtOAc) afforded the N-acetylation product as a white solid. The mixture of the N-acetylation product, 1 M of PMe_3 in THF (56 μL, 0.056 mmol), 0.1 M NaOH (0.5 mL, 0.05 mmol), and THF (3 mL) was stirred at 60 °C under N_2 overnight. The mixture was concentrated, and the resulting residue was diluted with CH_2Cl_2 (50 mL). The organic phase was washed with H_2O and then dried over Na_2SO_4, filtered, and concentrated to dryness. The resulting residue was purified by quickly passing through a short silica gel column (10:1, CH_2Cl_2−/MeOH). The mixture of the obtained solid and $Pd(OH)_2$ in MeOH/H_2O/HOAc (3 mL/1 mL/1 mL) was stirred under H_2 at room temperature overnight and then filtered. The filtrate was concentrated to dryness under vacuum and then was coevaporated with H_2O (10 mL) 3 times to remove AcOH. The aqueous phase was further washed with CH_2Cl_2 (5 mL × 3) and EtOAc (5 mL × 3), and then the aqueous phase was dried under vacuum to afford **2** (acetate salt) as a white solid (16.2 mg, 50% for three steps). $[\alpha]_D$ +27.8 (c = 1.4, H_2O); ^{1}H NMR (600 MHz, D_2O): δ 1.00 (d, 3H, J = 6.6 Hz, H-6‴″), 1.74 (s, 3H), 1.79 (m, 2H), 1.83 (s, 3H), 2.95 (t, 2H, J = 6.6 Hz), 3.12 (t, 1H, J = 8.4 Hz), 3.36−3.89 (m, 32H), 4.02−4.03 (m, 2H), 4.18 (t, 1H, J = 6.0 Hz), 4.29 (d, 2H, J = 7.8 Hz), 4.32 (d, 1H, J = 7.8 Hz), 4.40 (d, 1H, J = 7.8 Hz), 4.69 (d, 1H, J = 3.6 Hz), 5.02 (d, 1H, J = 3.6 Hz); ^{13}C NMR (150 MHz, D_2O): δ 15.4, 22.3, 23.4, 26.8, 37.7, 51.8, 60.1, 60.5, 61.1, 66.9, 67.9, 68.1, 68.6, 69.2, 69.3, 69.6, 70.2, 71.0, 72.0, 72.2, 73.0, 73.7, 74.5, 74.7, 75.0, 75.2, 75.6, 76.2, 76.4, 77.3, 78.3, 78.8, 99.4, 100.6, 102.2 (×2), 103.5, 104.1, 174.4; HRMS: $[M + Na]^+$ $C_{41}H_{72}N_2NaO_{30}$ calcd 1095.4068, obsd 1095.4048. $^1J_{C1‴″,H1‴″}$ = 170.0 Hz, $^1J_{C1″,H1″}$ = 171.2 Hz, other four $^1J_{C1,H1}$ = 162.6, 163.9, 162.4, 162.4 Hz.

Acknowledgment. We are grateful for financial support from the University of Toledo, the National Institutes of Health (R01-GM-72667), and the Pardee foundation. We dedicate this work to Prof. Nina Berova, Columbia University, for her guidance and continual encouragement over the years.

Supporting Information Available: Selected ^{1}H, ^{13}C, and 2-D NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070585G