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An efficient approach for total synthesis of aminopropyl functionalized ganglioside GM1b

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ABSTRACT

A highly efficient protocol for the synthesis of aminopropyl functionalized ganglioside GM1b has been described. The full protected ganglioside GM1b was obtained in 71% yield within 5 h. The key feature of the synthetic approach was the use of sialic acid donor that was with a C-5 trichloroacetamide moiety and with a dibenzyl phosphite residue as leaving group at the anomeric carbon. The sialyl donor gave high yields and excellent α-anomeric selectivities with a wide variety of glycosyl acceptors ranging from C-3 or C-6 hydroxyls of galactoside to C-6 hydroxyl of glucosaminoside by using TMSOTf as catalyst in a mixture solution of acetonitrile and methylene chloride.

Gangliosides, sialic acids containing glycosphingolipids, are a class of structurally diverse molecules commonly present in the outer membrane of living cells and are particularly rich in tissues of central nervous system. They are involved in various biological processes such as cell differentiation, and cell growth.[1] They are also tumor-associated antigens,[2] and important cell-surface receptors, where they inter alia mediate the recruitment of leukocytes to sites of inflammation.[3] Furthermore, gangliosides are efficient receptors for the adhesion of bacteria and viruses to cells, a prerequisite for infection.[4] Ganglioside GM1b (Fig. 1, **1a**) was first isolated by Yip's group from rat brain,[5] which was described to be associated with GM1 in extremely minor quantities and was also associated with some mankind diseases.[6] However, the biological functions of GM1b have not been elucidated because of insufficient availability of material. Thus, chemical synthesis provides an attractive opportunity to evaluate its biological functions. Ganglioside GM1b had been synthesized previously by several research groups,[7] however, developing a convenient and more efficient approach for the synthesis of this ganglioside is still significant. Pre-activation based iterative one-pot oligosaccharides synthesis method was developed by Huang and his co-workers and they successfully assembled numerous complex oligosaccharides.[8] Huang's strategy granted much more freedom in protective group selection, enabling it to achieve high-yielding stereospecific glycosylations. However, this method was seldom used in the synthesis of gangliosides.[9] Herein, we describe the total synthesis of aminopropyl functionalized ganglioside GM1b (Fig. 1, **1b**) by pre-activation based iterative one-pot method.

As shown in Figure 2, the target compound can be assembled from the sialylated disaccharide **3**, the 2-*N*-Troc galactoside **4**, and lactose **5**. Due to the poor and narrow range of anomeric reactivity values,[10] sialic acid thioglycosides cannot be directly used as donor in one-pot strategy, usually sialylated disaccharides were used as building blocks in the one-pot synthesis.[8c,11] So our first attention was focused on the synthesis of the sialylated disaccharide. It is well known that owing to the low reactivity and low stereoselectivity, highly efficient α-sialylation is still one of the most difficult and challenging processes in the chemical synthesis of oligosaccharides.

In order to achieve highly efficient α-sialylation, recently, significant efforts have been made, including the use of anomeric leaving groups,[12] the introduction of an auxiliary group at C-1 and C-3,[13] the modification of the acetamide group at the C-5 posi-

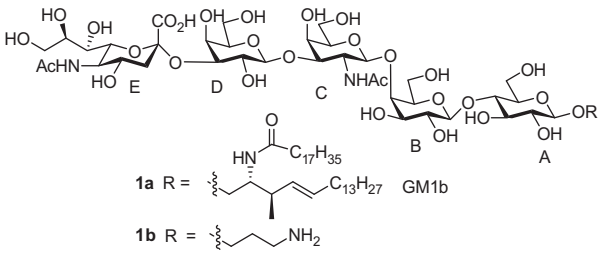

Figure 1. Structure of ganglioside GM1b.

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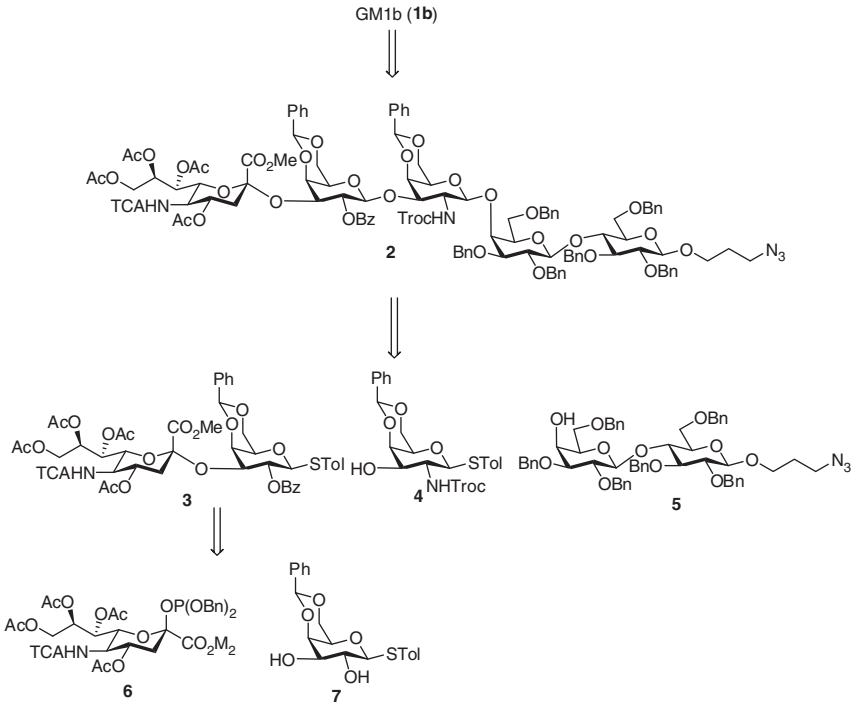
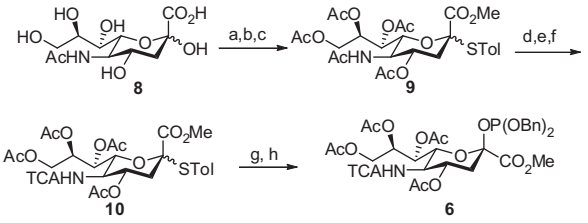


Figure 2. Retrosynthetic analysis for synthesis of GM1b (**1b**).



Scheme 1. Reagents and conditions: (a) MeOH, IR(H^+) resin, rt, overnight, almost 100%; (b) Ac_2O, Py, DMAP, 0 °C to rt, over night, 81%; (c) TolSH, $BF_3{\cdot}Et_2O$, 0 °C to rt, 4–5 h, 78%; (d) MsOH, MeOH, 60 °C, 24 h; (e) CCl_3CO_2Me, Et_3N, MeOH, rt, 1 h; (f) Ac_2O, Py, DMAP, 72% for three steps; (g) NBS, acetone, rt, 1.5 h; (h) $(BnO)_2PN^iPr_2$, *1H*-tetrazole, CH_2Cl_2, 82% for two steps.

tion of the sialyl donor into powerful electron-withdrawing groups, such as *N*,*N*-diacetyl,[14] azido,[15] *N*-TFA,[16] *N*-Troc,[17] *N*-Fmoc,[18] *N*-trichloroacetyl,[19] *N*-phthalimide,[20] 5-*N*,4-*O*-carbonyl[21] and *N*-acetyl 5-*N*,4-*O*-carbonyl,[22] or the optimized combinations of the leaving group with positional modification.[23] Here we designed sialyl donor **6** bearing the 5-*N*-trichloroacetyl (TCA) moiety, as NH-TCA can be converted into acetamide under a variety of reaction conditions including hydrogenolysis, radical reduction, and basic cleavage followed by acetylation.[24] The phosphite aglycon leaving group was chosen due to the possibility for its selective activation over a thioglycoside, on the other hand, the phosphite donor can be activated by a catalytic amount of TMSOTf and usually lead to predominant formation of the α-product during glycosylation.

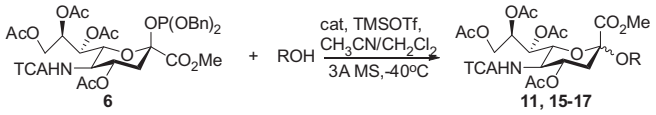
The synthesis of sialic acid donor **6** was described in Scheme 1. Treatment of **8** with acidified MeOH gave sialic acid methyl ester, which followed by acetylation of acetyl anhydride in pyridine and then treatment with *p*-toluenethiol by the promotion of boron trifluoride diethyl etherate gave thiosialoside **9**. The thiosialoside **10** was synthesized by removal of all acetyl groups from *N*-acetyl thiosialoside **9** under acidic condition, followed by selective acetylation of amino group with methyl trichloroacetate and acetylation of remaining hydroxy groups.[19] The compound **10** was treated with *N*-bromosuccinimide in aqueous acetone to convert thiocresol into hydroxyl, and the resulting intermediate was reacted with dibenzyl *N*,*N*-diisopropyl phosphoramidite in the presence of 1*H*-tetrazole to produce phosphite sialyl donor **6**.[25]

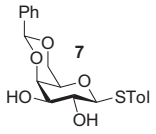
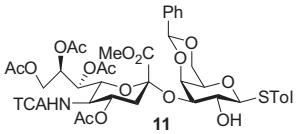
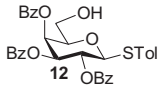
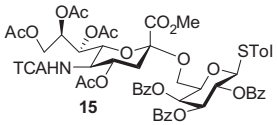
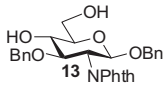
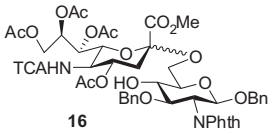
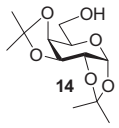
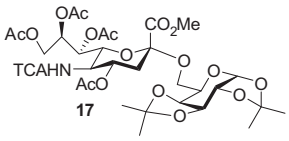
The sialylation was realized by treating a mixture of donor **6** and thioglycoside accepter **7** with a catalytic amount of TMSOTf in a mixture solvent of CH_3CN and CH_2Cl_2 (1:1) leading to disaccharide **11** in 79% yield (Table 1, entry 1), benzoylation of the free hydroxyl group of **11** gave disaccharide **3**. The α configuration was assigned by the three bond coupling constant between C1 and H_{3ax} ($^3J_{C1\text{-}H3ax}$ = 5.8 Hz) of the sialic acid.[10] This sialylation reaction for other acceptors was also examined next. A variety of acceptors including carbohydrate hydroxyl groups of galactose and glucosamine were sialylated in excellent α-selectivity and good sialylation yields (Table 1). Acid labile benzylidene and isopropylidene groups were stable under the reaction condition. This selective activation protocol is attractive as the resulting sialylated thioglycoside product can be used as a donor for further glycosylation without additional aglycon leaving group adjustment.

After achieving the sialylated disaccharide, we assessed the formation of the second building block **4**. To prepare compound **4**, the amino group of galactosamine hydrochloride **18** was protected by the trichloroethoxocarbonyl (Troc) group followed by peracetylation to give **19** (Scheme 2). The anomeric acetate in **19** was replaced with *p*-toluenethiol as promoted by boron trifluoride diethyl etherate to yield thioglycoside **20**. Zemplen reaction using sodium methoxide to remove all acetyl groups in **20** followed by benzylidenation of the newly liberated 4,6-hydroxyl groups led to the compound **4**.[9]

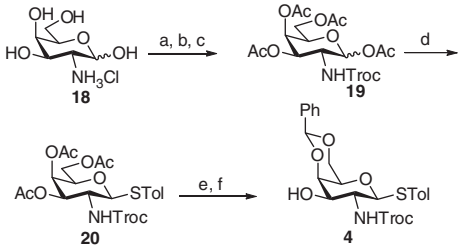
Next, our attention was focused on the preparation of lactose acceptor **5**. It is well known that the 4′-OH lactose derivatives showed a very low reactivity as glycosyl accepters.[26] As benzyl ethers are able to enhance the reactivity of neighboring hydroxyl groups in glycosylation reactions, we selected benzyl group as protection group for lactose unit **5**. The synthetic route of lactose acceptor was depicted in Scheme 3. Heating a mixture of lactose

Table 1
Sialylation results using sialyl donor **6**

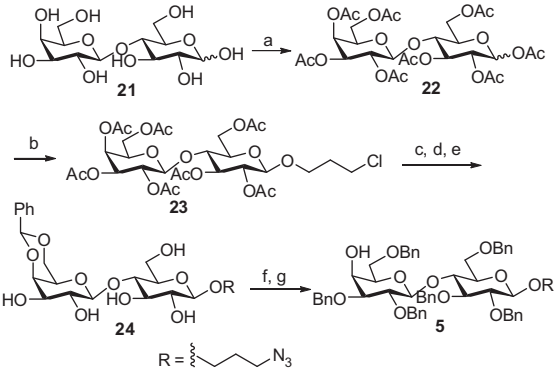


Entry	Acceptor	Product	Yield (%)	α/β	$^3J_{C1\text{-}H3ax}$(Hz)
1			79	α only	5.8
2			89	α only	4.8
3			75	20:1[a]	6.0
4			92	33:1[a]	6.2

[a] Anomeric ratios were determined by ^{1}H NMR analysis.



Scheme 2. Reagents and conditions: (a) NaOMe, MeOH; (b) trichloroethyl chloroformate, Et_3N, rt, 2 h; (c) Ac_2O, Py, DMAP, 0 °C to rt, overnight, 92% for three steps; (d) toluenethiol, $BF{\cdot}Et_2O$, CH_2Cl_2, 0 °C to rt, 4–5 h, 75%; (e) NaOMe, MeOH, −20 °C; (f) $PhCH(OMe)_2$, CSA, THF, 73% for two steps.

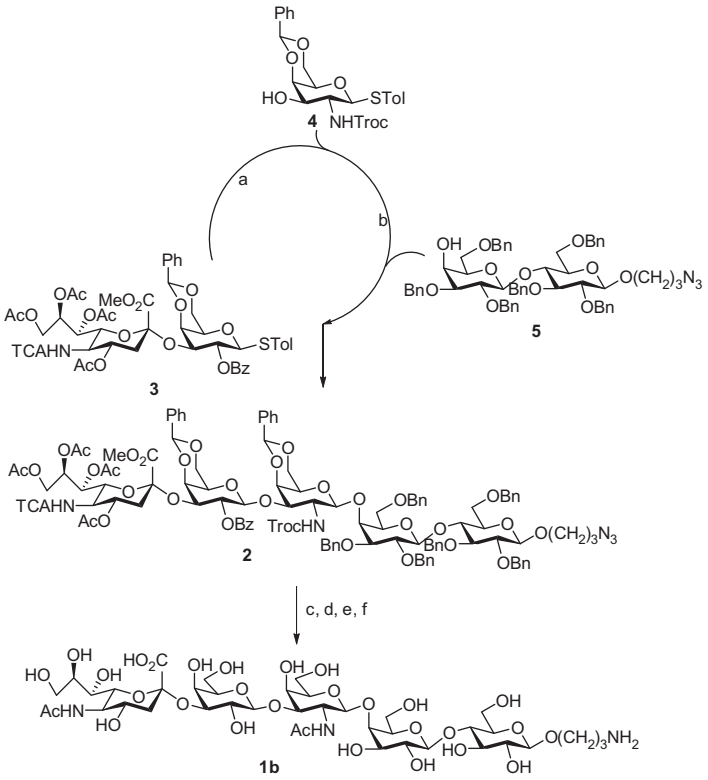


Scheme 3. Reagents and conditions: (a) NaOAc, Ac_2O, 120 °C, 3 h, 62%; (b) 3-chloropropan-1-ol, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C to rt, 5 h, 75%; (c) NaN_3, DMF, 90 °C, overnight; (d) NaOMe, MeOH; (e) $PhCH(OMe)_2$, CSA, THF, ref. 3 h, 75% for 2 steps; (f) NaH, BnBr, anhydrous DMF, rt, overnight, 85%; (g) 2 M $NaCNBH_3$-HCl, THF, rt, 75%.

21, acetyl anhydride, and anhydrous sodium acetate afforded peracetyllactose **22**, which underwent boron trifluoride diethyl etherate promoted glycosylation with 3-chloropropan-1-ol to provide the desired β-lactoside **23**. S_N2 displacement of the chloride with sodium azide followed by Zemplen deacetylation and regioselective benzylidenation produced lactoside **24**. The remaining hydroxyl groups were benzylated with sodium hydride and benzyl bromide in anhydrous DMF, followed by selective cleavage of benzaldehyde acetal with a solution of sodium cyanoborohydride and hydrogen chloride in dry THF to afford lactose acceptor **5.**[8b,26]

With all the building blocks in hand, we assemble the full protected GM1b using pre-activation based one-pot protocol (Scheme 4). Pre-activation of disaccharide **3** by AgOTf/*p*-TolSCl, was rapidly achieved at −78 °C. The thioglycosyl acceptor **4** was added to the reaction mixture at the same temperature. The reaction temperature was raised to −20 °C, and the acceptor **4** was completely consumed as judged by TLC analysis. The reaction temperature was cooled back down to −78 °C, followed by the addition of AgOTf, *p*-TolSCl, the lactose acceptor **5**, and warmed up to room temperature. The full protected GM1b pentasaccharide **2**[27] was obtained in 71% yield from the three component one-pot reactions within 5 h. The α-linkage between sialic acid and the galactose was conformed in the sialylation step. The β linkage for the rest of the glycosidic bonds was supported by the one bond coupling constants between the respective anomeric carbon and proton (162 Hz, 157 Hz, 160 Hz, 160 Hz).

The deprotection of pentasaccharide **2** began with the removal of Troc, trichloroacetyl, acetyl and ester protecting groups using 1 M NaOH in THF overnight (Scheme 4). The newly liberated amino group was selectively acetylated in the presence of multiple hydroxyl groups by acetic anhydride and triethylamine in methanol. Staudinger reduction of the azide group and subsequent catalytic hydrogenation over Pearlman's catalyst gave the fully deprotected GM1b analog **1b**[28] in 64% overall yield for all deprotection steps.



Scheme 4. Reagents and conditions: (a) (i) AgOTf, *p*-TolSCl, −78 °C, (ii) 4, TTBP, −78 °C to −20 °C; (b) AgOTf, *p*-TolSCl, −78 °C, (iii) 5, −78 °C to rt, 71% for two steps; (c) 1 M NaOH, THF, 50 °C, overnight; (d) Ac_2O, Et_3N, MeOH, 4–5 h; (e) PMe_3, 0.1 M NaOH, THF, 60 °C, overnight; (f) $Pd(OH)_2/C$, H_2, MeOH, H_2O, 24 h, 64%.

In conclusion, we have demonstrated the application of the sialylation reagent with trichloroacetyl (TCA) modification of the C-5 amino group and dibenzyl phosphite leaving group for an efficient and highly α-selective synthesis of natural sialosides. And also, an efficient and stereo-controlled total synthesis of aminopropyl functionalized GM1b was achieved by pre-activation one-pot protocol. The full protected GM1b was obtained in 71% yield within 5 h. With the aminopropyl side chain, this kind of GM1b analog can be readily conjugated to liposomes and proteins. This will be very useful for further investigation of its biological properties.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.077.

References and notes

1. (a) Varki, A. *Glycobiology* **1993**, *3*, 97–130; (b) Schauer, R. *Glycoconjugate J.* **2000**, *17*, 485–499; (c) Angata, T.; Varki, A. *Chem. Rev.* **2002**, *102*, 439–469.
2. (a) Higashi, H.; Hirabayashi, Y.; Fukui, Y.; Kaiki, M.; Matsumoto, M.; Ueda, S.; Kato, S. *Cancer Res.* **1985**, *45*, 3796–3802; (b) Hakomo, S. *Annu. Rev. Immunol.* **1984**, *2*, 103–126.
3. Vinson, M.; Mucklow, S.; May, A. P.; Jones, E. Y.; Kelm, S.; Crocker, P. R. *Trends Glycosci. Glycotechnol.* **1997**, *9*, 283–297.
4. (a) Bertozzi, C. R.; Kiessling, L. L. *Science* **2001**, *291*, 2357–2364; (b) Varki, A.; Cummings, R.; Esko, J.; Freeze, H.; Hart, G. W.; Marth, J. *Essentials of Glycobiology*; Cold Spring Harbor Laboratory Press: New York, 1999.
5. Yip, M. C. M. *Biochem. Biophys. Res. Commun.* **1973**, *53*, 737–744.
6. (a) Odaka, M.; Yuki, N.; Kokubun, N.; Hirata, K.; Kuwabara, S. *J. Neurol. Sci.* **2003**, *211*, 93–97; (b) Matsuo, M.; Odaka, M.; Koga, M.; Tsuchiga, K.; Hamasaki, Y.; Yuki, N. *J. Neurol. Sci.* **2004**, *217*, 225–228; (c) Ravindranath, M. H.; Muthugounder, S.; Presser, N.; Selvan, S. R.; Portoukalian, J.; Brosman, S.; Morton, D. L. *Biochem. Biophys. Res. Commun.* **2004**, *324*, 154–165; (d) Santafé, M. M.; Sabaté, M. M.; Garcia, N.; Ortiz, N.; Lanuza, M. A.; Tomas, J. *Ann. Neurol.* **2005**, *57*, 396–407; (e) Tatsumoto, M.; Koga, M.; Gilbert, M.; Odaka, M.; Hirata, K.; Kuwabara, S.; Yuki, N. *J. Neuroimmunol.* **2006**, *177*, 201–208.
7. (a) Sugimoto, M.; Fujikura, K.; Nunomura, S.; Horisaki, T.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1990**, *31*, 385–388; (b) Prabhanjan, H.; Ishida, H.; Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1991**, *211*, c1–c5.
8. (a) Huang, X.; Huang, L.; Wang, H.; Ye, X.-S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5221–5224; (b) Wang, Z.; Zhou, L.; El-Boubou, K.; Ye, X.-S.; Huang, X. *J. Org. Chem.* **2007**, *72*, 6409–6420; (c) Sun, B.; Srinivasan, B.; Huang, X. *Chem. Eur. J.* **2008**, *14*, 7072–7081; (d) Wang, Z.; Xu, Y.; Yang, B.; Tiruchinapally, G.; Sun, B.; Liu, R.; Dulaney, S.; Liu, J.; Huang, X. *Chem. Eur. J.* **2010**, *16*, 8365–8375.
9. Sun, B.; Yang, B.; Huang, X. *Sci. Chin. Chem.* **2012**, *55*, 31–35.
10. Ye, X.-S.; Huang, X.; Wong, C.-H. *Chem. Commun.* **2001**, 974–975.
11. (a) Hsu, C.-H.; Chu, K.-C.; Lin, Y.-S.; Han, J.-L.; Peng, Y.-S.; Ren, C.-T.; Wu, C.-Y.; Wong, C.-H. *Chem. Eur. J.* **2010**, *16*, 7154–7160; (b) Zhang, Z.; Niikura, K.; Huang, X.; Wong, C.-H. *Can. J. Chem.* **2002**, *80*, 1051–1054.
12. (a) Cai, S.; Yu, B. *Org. Lett.* **2003**, *5*, 3827–3830; (b) Okamoto, K.; Goto, T. *Tetrahedron* **1990**, *46*, 5835–5857; (c) Martin, T. J.; Schmidt, R. R. *Tetrahedron Lett.* **1992**, *33*, 6123–6126; (d) De Meo, C.; Parker, O. *Tetrahedron: Asymmetry* **2005**, *16*, 303–307; (e) Dziadek, S.; Brocke, C.; Kunz, H. *Chem. Eur. J.* **2004**, *10*, 4150–4162; (f) Li, Y.; Ruan, X.; Li, X.; Li, Y. *J. Org. Chem.* **2008**, *73*, 4287–4290.
13. (a) Hanashima, S.; Akai, S.; Sato, K. *Tetrahedron Lett.* **2008**, *49*, 5111–5114; (b) Haberman, J. M.; Gin, D. Y. *Org. Lett.* **2003**, *5*, 2539–2541; (c) Ito, Y.; Ogawa, T. *Tetrahedron* **1990**, *46*, 89–102; (d) Castro-Palomino, J. C.; Tsvetkov, Y. E.; Schmidt, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 5434–5440.
14. (a) Crich, D.; Li, W. *Org. Lett.* **2006**, *8*, 959–962; (b) Demochenko, A. V.; Boons, G. J. *Chem. Eur. J.* **1999**, *5*, 1278–1283.
15. Yu, C.-S.; Niikura, K.; Lin, C.-C.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2001**, *40*, 2900–2903.
16. a) Lin, C.-C.; Huang, K.-T.; Lin, C.-C. *Org. Lett.* **2005**, *7*, 4169–4172; (b) Iwayama, Y.; Ando, H.; Ishida, H.; Kiso, M. *Chem. Eur. J.* **2009**, *15*, 4637–4648.
17. (a) Hanashima, S.; Seeberger, P. H. *Chem. Asian J.* **2007**, *2*, 1447–1459; (b) Hanashima, S.; Castagner, B.; Esposito, D.; Nokami, T.; Seeberger, P. H. *Org. Lett.* **2007**, *9*, 1777–1779.
18. Adachi, M.; Tanaka, H.; Takahashi, T. *Synlett* **2004**, 609–614.

19. Tanaka, H.; Adachi, M.; Takahashi, T. *Chem. Eur. J.* **2005**, *11*, 849–862.
20. (a) Tanaka, K.; Fujii, Y.; Tokimoto, H.; Mori, Y.; Tanaka, S.; Bao, G.; Siwu, E. R. O.; Nakayabu, A.; Fukase, K. *Chem. Asian J.* **2009**, *4*, 574–580; (b) Tanaka, K.; Goi, T.; Fukase, K. *Synlett* **2005**, 2958–2962.
21. (a) Tanaka, H.; Tateno, Y.; Nishiura, Y.; Takahashi, T. *Org. Lett.* **2008**, *10*, 5597–5600; (b) Farris, M. D.; De Meo, C. *Tetrahedron Lett.* **2007**, *48*, 1225–1227.
22. (a) Crich, D.; Li, W. *J. Org. Chem.* **2007**, *72*, 2387–2391; b) Crich, D.; Li, W. *J. Org. Chem.* **2007**, *72*, 7794–7797; (c) Wang, Y.-J.; Jia, J.; Gu, Z.-Y.; Liang, F.-F.; Li, R.-C.; Huang, M.-H.; Xu, C.-S.; Zhang, J.-X.; Men, Y.; Xing, G.-W. *Carbohydr. Res.* **2011**, *346*, 1271–1276; (d) Sun, B.; Jiang, H. *Tetrahedron Lett.* **2011**, *52*, 6035–6038.
23. (a) Liang, F.-F.; Chen, L.; Xing, G.-W. *Synlett* **2009**, 425–428; (b) Crich, D.; Wu, B. *Org. Lett.* **2008**, *10*, 4033–4035; (c) Yu, C.-S.; Niikura, K.; Lin, C.-C.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2001**, *113*, 2984–2987; (d) Wang, Y.; Ye, X.-S. *Tetrahedron Lett.* **2009**, *50*, 3823–3826.
24. (a) Donohoe, T. J.; Logan, J. G.; Laffan, D. D. P. *Org. Lett.* **2003**, *5*, 4995–4998; (b) Sherman, A. A.; Yudina, O. N.; Mironov, Y. V.; Sukhova, E. V.; Shashkov, A. S.; Menshov, V. M.; Nifantieva, N. E. *Carbohydr. Res.* **2001**, *336*, 13–46; (c) Bélot, F.; Jacquinet, J.-C. *Carbohydr. Res.* **2000**, *325*, 93–106.
25. Bhattacharya, S. K.; Danishefsky, S. J. *J. Org. Chem.* **2000**, *65*, 144–151.
26. Sun, B.; Pukin, A. V.; Visser, G. M.; Zuilhof, H. *Tetrahedron Lett.* **2006**, *47*, 7371–7374.
27. *Compound **2**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10–8.07 (m, 2H), 7.58–7.49 (m, 4H), 7.39–7.19 (m, 30H), 7.08–7.02 (m, 3H), 6.63 (d, 1H, J = 9.5 Hz), 6.42 (d, 1H, J = 9.5 Hz),5.54–5.42 (m, 3H), 5.39 (s, 1H), 5.26 (d, 1H, J = 9.5 Hz), 5.12 (d, 1H, J = 7.5 Hz), 4.99–4.92 (m, 3H), 4.87–4.72 (m, 5H), 4.67–4.56 (m, 3H), 4.55–4.51 (m, 2H), 4.46–4.26 (m, 9H), 4.21–4.07 (m, 7H), 4.00–3.93 (m, 2H), 3.91–3.86(m, 1H), 3.77–3.53 (m, 8H), 3.49 (t, 1H), 3.46 (s, 3H), 3.41–3.23 (m, 7H), 2.68 (dd, 1H, J = 4.5, 12.8 Hz), 2.25 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H), 1.94 (s, 3H), 1.92–1.85 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 170.5, 170.47, 170.2, 168.7, 165.3, 162.2, 154.5, 139.11, 139.10, 139.04, 139.03, 139.0, 138.97, 138.96, 138.94, 138.93, 138.6, 138.54, 138.52, 138.5, 138.47, 138.4, 138.0, 133.2, 130.5, 130.1, 129.3, 128.6, 128.57, 128.52, 128.5, 128.43, 128.4, 128.36, 128.2, 128.15, 128.14, 128.1, 127.8, 127.77, 127.7, 127.6, 127.5, 126.6, 103.8, 102.7, 100.9, 100.6, 100.5, 97.0, 96.4, 92.2, 83,1, 82.5, 81.9, 80.3, 76.8, 76.2, 75.6, 75.5, 75.45, 75.4, 74.0, 73.4, 73.3, 73.1, 73.0, 72.9, 72.3, 71.8, 70.2, 69.4, 69.1, 68.5, 68.4, 67.7, 67.6, 67.2, 66.8, 66.7, 66.5, 62.4, 54.7, 53.1, 51.8, 48.6, 38.9, 29.5, 21.7, 21.0, 20.9, 20.8. HRMS: $[M+Na]^+$ $C_{113}H_{121}Cl_6N_5NaO_{35}$ calcd for 2340.5871, obsd 2340.5837.
28. *Compound **1b**:* ^{1}H NMR (500 MHz, D_2O) δ 4.71 (d, 1H, J = 8.5 Hz), 4.50–4.43 (m, 3H), 4.12–4.05 (m, 3H), 4.01–4.39 (m, 3H), 3.85 (d, 1H, J = 3.5 Hz), 3.83–3.79 (dd, 1H, J = 13, 4 Hz), 3.79–3.65 (m, 14H), 3.65–3.50 (m, 7H), 3.46–3.41 (m, 2H), 3.32–3.23 (m, 2H), 3.10–3.04 (t, 2H), 2.63–2.57 (dd, 1H, J = 12.5, 4.0 Hz), 1.97 (s, 3H), 1.94 (s, 3H), 1.96–1.92 (t, 1H), 1.90–1.84 (m, 2H). ^{13}C NMR (125 MHz, D_2O) δ 175.1, 174.9, 174.2, 104.8, 102.7, 102.6, 102.2, 101.8, 80.5, 78.7, 77.2, 75.0, 74.9, 74.5, 74.2, 73.2, 72.8, 72.6, 72.4, 70.8, 68.8, 68.7, 68.1, 68.0, 63.0, 61.2, 61.1, 60.8, 60.2, 51.7, 51.3, 37.7, 27.1, 22.7, 22.2. HRMS: $[M+Na]^+$ $C_{40}H_{69}N_3NaO_{29}$ calcd 1078.3914, obsd 1078.3942.