Communication

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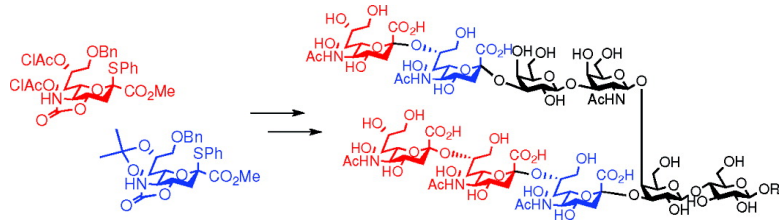

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An Efficient Convergent Synthesis of GP1c Ganglioside Epitope

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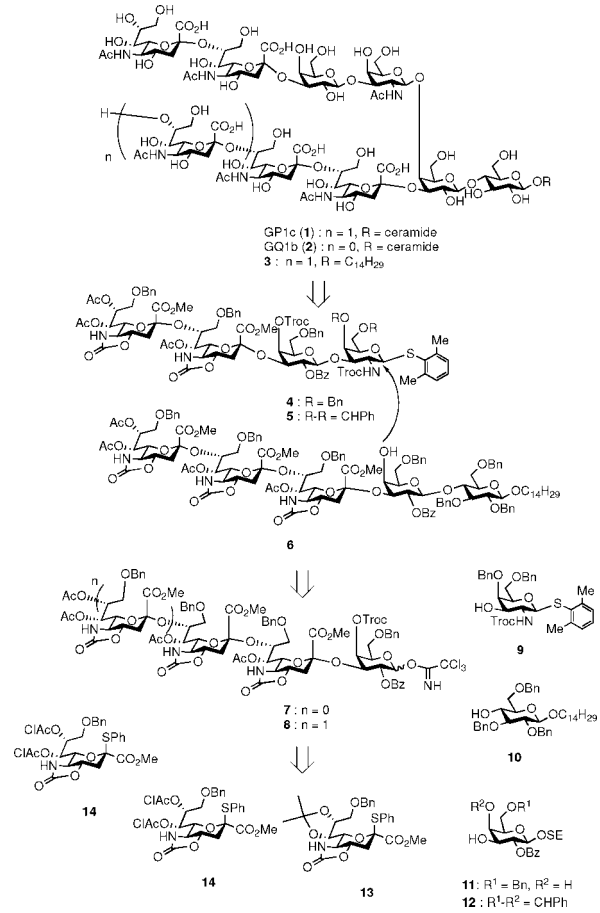
Gangliosides are a family of glycolipids, which possess sialic acids that play important roles in biological events on cell surfaces.[1] GP1c glycolipid (**1**) is one of the most complex c-series gangliosides; it is composed of a tetrasaccharide (Galβ(1,3)GalNAcβ(1,4)Galβ (1,4)Glc) that bears α(2,8) di- and trisialic acid units.[2] Glycolipids that vary in the number of sialic acids are known as the a-, b-, and c-series of gangliosides.[3] Chemical synthesis of these di/oligo-sialo-containing glycolipids and their derivatives would facilitate identification of their biological roles. However, synthesis of both the α (2,8) oligosialic acid unit and the compact and rigid 3,4 dibranched galactoside unit is challenging. Therefore, considerable efforts have been directed toward the synthesis of these complex oligosaccharides.[4] Kiso and co-workers reported an efficient synthesis of the GQ1b ganglioside (**2**) that has two α(2,8) disialic acid units. In this method, the disialic acid units were prepared by hydrolysis of colominic acid.[4e] Herein, we report an efficient convergent synthesis of the GP1c ganglioside epitope **3**.

We planned the synthesis of the GP1c epitope **3** bearing a C14 alkyl chain instead of ceramide for establishing the methodology for the synthesis of sugar parts of a-, b-, and c-series of gangliosides. Scheme 1 shows the convergent strategy for the synthesis of the GP1c epitope **3**. The nonasaccharide **3** was prepared by coupling the pentasaccharide **6** and the tetrasaccharide donor **4** at the C4 axial hydroxyl group of the latter. The pentasaccharide **6** was prepared from the α(2,8) trisialylgalactosyl imidate[5] **8** and the glucoside **10**. The tetrasaccharide donor **4** was prepared by chemoselective glycosylation of the 2,6-dimethyphenylthiogalactoside **9** with the disialyl galactosyl imidate **7**. The 2,6-dimethyphenylthio leaving group is effective in chemoselective glycosylation without aglycon transfer of thioglycoside **9**.[6] The tri- and disialylgalactosides **8** and **7** were prepared from galactoside **11** and the sialyl donors **13** and **14**, which possess a 5*N*,4*O*-carbonyl protecting group, using a simple glycosylation and deprotection procedure.[7] The sialyl donor **13** protected with an isopropylidene at the C7 and C8 hydroxyl groups was used for α(2,3) sialylation. The C7 and C8 di-*O*-chloroacetyl sialyl donor **14** was used for α(2,8) sialylation to prepare disialylgalactosides **7**. Further α(2,8) sialylation of the resulting disialylgalactosides provided the trisialylgalactosides **8**.

The syntheses of the di- and trisialyl building blocks **4** and **6** are shown in Scheme 2. Treatment of both 3,4-dihydroxyl galactoside **11** and 1.0 equiv of the sialyl donor **13**, which is protected with an isopropylidene at the C7 and C8 hydroxyl groups, with NIS/cat. TfOH in CH_2Cl_2 at -78 °C provided the α(2,3)-sialyl galactoside **16** in 90% yield with complete α-selectivity. Use of the di-*O*-chloroacetyl donor **14** reduced both the yield and α-selectivity of the coupling product **15**. Use of the 4,6-*O*-benzylidene galactoside **12** as an acceptor for α(2,3) sialylation also reduced the yield and selectivity.[8] Protection of the resulting C4 hydroxyl group of **16** with a Troc group, followed by removal of the acetal, provided the diol **17**. Treatment of the diol **17** and

Scheme 1



the di-*O*-chloroacetyl-protected sialyl donor **14** (2.0 equiv) with NIS/cat. TfOH in CH_2Cl_2/CH_3CN = 3:2 at -78 °C provided the α(2,8) disialoside **19** in 91% yield with complete α-selectivity. The use of pure CH_2Cl_2 as solvent for α(2,8) sialylation of **17** reduced the coupling yield of **19** but did not affect the α-selectivity. The sialyl donor **13** was not effective in the α(2,8) sialylation, and use of **13** resulted in a reduction in α-selectivity (77%, α:β = 54:46). Deprotection of the chloroacetyl groups on **19** afforded the triol acceptor **20** in 87% yield. Trisialyl formation from **20** using 3.0 equiv of donor **14** under the same reaction conditions provided the trisialyl galactoside **22** in 72% yield (α:β > 90:10). Trisialoside **22** had an α-anomeric configuration, as determined based on the $^3J_{C1-H3ax}$ coupling constants ($^3J_{C\text{-}1,H\text{-}3ax}$ = 4.9, 4.9, and 6.1 Hz). The imidates **7** and **8** were prepared in a stepwise procedure, as follows: (i) removal of the chloroacetyl groups from **19** and **22**; (ii) acetylation of the remaining hydroxyl group; (iii) removal of the 2-trimethylsilylethyl group at the anomeric position; and, (iv) treatment of the hemiacetal with trichloroacetonitrile to provide the

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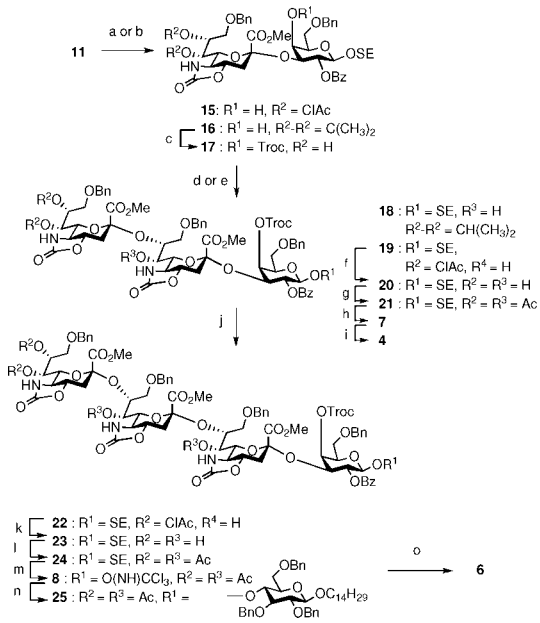
Scheme 2

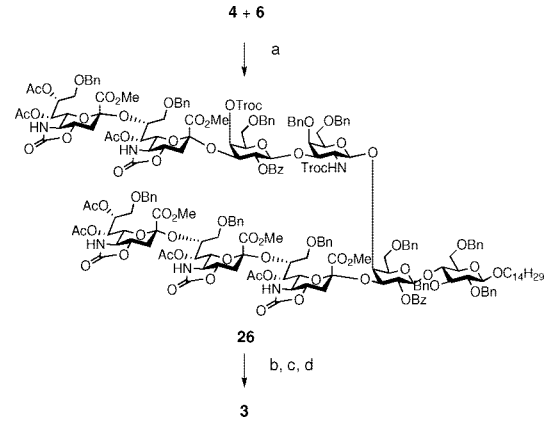


Reagents and conditions: (a) **13** (1.0 equiv), NIS, cat. TfOH, CH_2Cl_2, MS3A, −78 °C, 90%, α only; (b) **14** (1.0 equiv), NIS, cat. TfOH, CH_2Cl_2, MS3A, −78 °C, 82%, α/β = 87:13; (c) (i) TrocCl, Py, CH_2Cl_2, 96%; (ii) CSA, MeOH, rt, 92%; (d) **14** (2.0 equiv), NIS, cat. TfOH, CH_2Cl_2/CH_3CN = 3:2, MS3A, −78 °C, 91%, α/β = >95:5; (e) **13** (2.0 equiv), NIS, cat. TfOH, CH_2Cl_2/CH_3CN = 3:2, MS3A, −78 °C, 77%, α/β = 54:46; (f) thiourea, 2,6-lutidine, DMF, 60 °C, 87%; (g) Ac_2O, Py, CH_2Cl_2, cat. DMAP, −50 °C, 92%; (h) (i) TFA, CH_2Cl_2; (ii) CCl_3CN, Cs_2CO_3, CH_2Cl_2, 0 °C, 93% from **21**, α/β = 68:32; (i) **9**, TMSOTf, CH_2Cl_2, MS4A, −78 to −45 °C, 95%; (j) **14** (3.0 equiv), NIS, cat. TfOH, CH_2Cl_2/CH_3CN = 3:2, MS3A, −78 °C, 72%, α/β = >90:10; (k) thiourea, 2,6-lutidine, DMF, 60 °C, 75%; (l) A_2O, Py, cat. DMAP, CH_2Cl_2, −30 °C, 87%; (m) (i) TFA, CH_2Cl_2, (ii) CCl_3CN, Cs_2CO_3, CH_2Cl_2, 0 °C, 90% from **24**, α/β = 84:16; (n) **10**, TMSOTf, CH_2Cl_2, MS4A, −65 to −40 °C, 93%; (o) Zn dust, AcOH, THF, 0 °C, 94%.

corresponding imidates **7** and **8**. The chloroacetyl esters at the C7 and C8 positions underwent partial hydrolysis during imidate formation with trichloroacetonitrile. Treatment of the trisialyl galactosyl donor **8** and glucoside **10** with a catalytic amount of TMSOTf provided the pentasaccharide **25** in 93% yield. The miner isomer generated in the trisialylation can be removed in the purification of acetylated product **24**. Selective deprotection of the Troc group afforded acceptor **6** in 94% yield. In addition, preparation of the donor **4** was achieved by chemoselective glycosidation of **7** at the secondary alcohol with 1.2 equiv of thioglycoside **9** in the presence of a catalytic amount of TMSOTf, providing the tetrasaccharide **4** in 95% yield.

Synthesis of the GP1c epitope **3** from **4** and **6** is illustrated in Scheme 3. Treatment of both the pentasaccharide acceptor **6** and 2.0 equiv of the tetrasaccharide donor **4** with NIS and a catalytic amount of TfOH at 0 °C provided the protected nonasaccharide **26** in 64% yield. In contrast, use of the corresponding 4,6-benzyliden acetal-protected tetrasaccharide **5** resulted in a complex reaction mixture. These results indicate that 4,6 di-*O*-benzyl protection on the galactoside is important for the synthesis of the compact and rigid branched structure from the sialyl galactoside. Deprotection of the protected nonasaccharide **26** was achieved using a three-

Scheme 3



Reagents and conditions: (a) **4** (2.0 equiv), NIS, cat. TfOH, MS4A, 0 °C, 64%; (b) $LiOH \cdot H_2O$, Dioxane, H_2O, 80 °C; (c) Ac_2O, $NaHCO_3$, H_2O then LiOH, H_2O; (d) $Pd(OH)_2$, H_2, MeOH, H_2O, 53% from **26**.

step procedure: (i) hydrolysis of acyl protecting groups; (ii) acetylation of the C5 amino groups; and (iii) hydrogenolysis of the resulting benzyl ethers to provide the fully deprotected nonasaccharide **3** in 53% yield based on **26**.

In conclusion, we describe an efficient convergent synthesis of the GP1c epitope **3**. The reactivity of the saccharide structure was tuned by careful selection of a protecting group to match the requisite glycosidation and glycosylation. Various glycosyl acceptors and donors with different oligosialoglycans can be prepared by use of two 5*N*,4*O*-carbonyl-protected thiosialosides. The method described herein is amenable to the synthesis of a-, b-, and c-series ganglioside epitopes.

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

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(8) Details were described in the Supporting Information.

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