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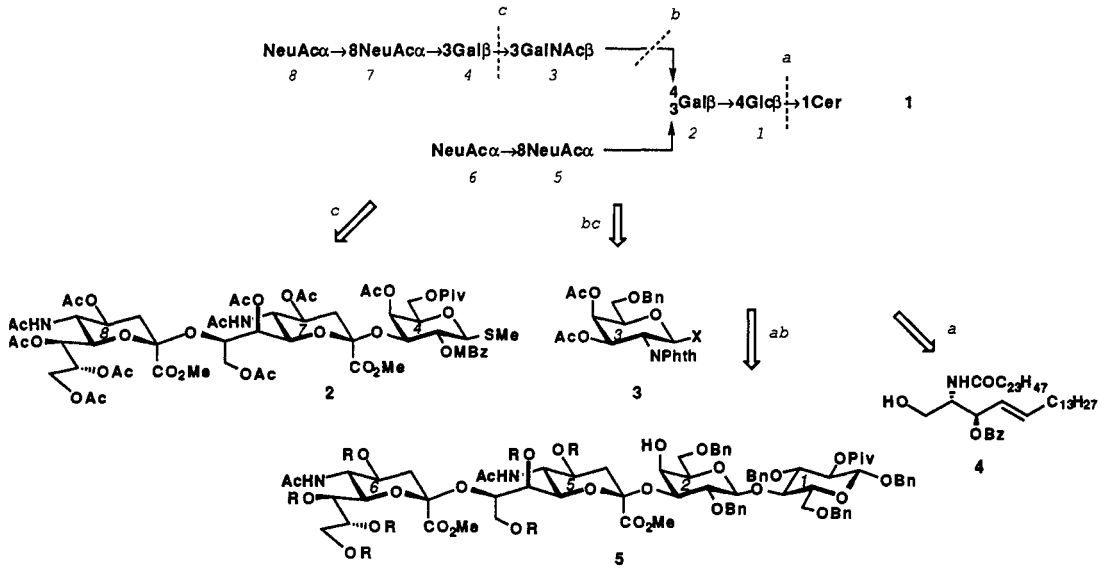
Experiments directed towards synthesis of complex glycosphingolipids: Ganglio-ganglioside GQ1b[1]

Shigeki Nunomura[a)], Yuji Matsuzaki[a)], Yukishige Ito[a)], and Tomoya Ogawa[a,b)]

a) The Institute of Physical and Chemical Research (RIKEN), Wako-shi, Saitama, 351-01 Japan; b) Faculty of Agriculture, University of Tokyo, Yayoi, Bunkyo-ku, Tokyo, 113 Japan

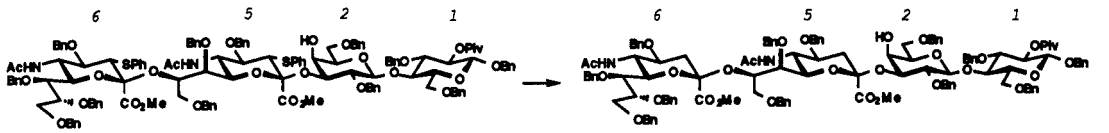
Abstract: Synthesis of a properly protected octasaccharide **18** which could be regarded as a reasonable precursor for the synthesis of GQ1b **1** was carried out in a stereo- and regio-controlled manner.

Tetrasialo ganglio-ganglioside GQ1b **1** was first isolated in 1967 from human brain[2] and then in 1972 from fish brain[3]. The structure of **1** was characterized around 1980 through chemical and enzymic degradation[4] as well as by Mass spectral data[5]. The trophic effect of GQ1b on the nervous system has been shown by employing human neuroblastoma cell line[6]. Since structurally most simple ganglioside GM_3 was synthesized for the first time in 1985[7], more efficient strategies for the synthesis of ganglio-gangliosides have been developed[8]. A total synthesis of GQ1b, however, still remains to be accomplished. In this paper, we highlight successful synthesis of a properly protected octasaccharide derivative **18** which may be regarded as a key intermediate for further conversion into GQ1b.



Scheme 1 (MBz = 4-Me-C_6H_4CO, Piv ≡ tBuCO, Bn ≡ $CH_2C_6H_5$)

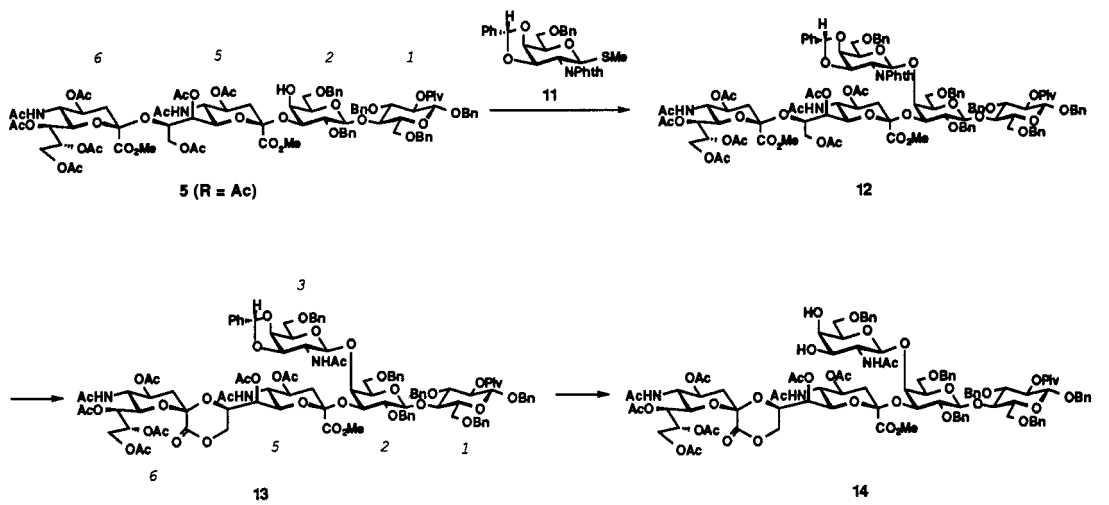
Aiming at a convergent-type synthesis of GQ1b **1**, strategic bond disconnection was planned as shown in scheme 1 which led to design completely protected building blocks **2**, **3**, **4**, and **5**. It is to be noted that 4-methylbenzoyl and pivaloyl groups at O-2 of monosaccharide residue *4* and *1* in compounds **2** and **5**, respectively, are required to serve as a stereocontrolling auxiliary[9].



6 **5 (R=Bn)**

Scheme 2

In order to study the reactivity of O-4 at residue **2** of the building block **5**, first we prepared **5** [R=Bn, R_F 0.37 in 4:1 PhMe-Me_2CO; δ_H 5.107 (dd, 8.0 and 9.5 Hz, H-2*1*), 3.748 and 3.510 (2s, 2 x OMe), 2.816 and 2.398 (2dd, 4.4 and 12.8 Hz, H-3eq[5,6]), 1.863 and 1.708 (2s, 2 x Ac), 1.104 (s, tBu)] from known compound **6**[10] in 3 steps (i Ph_3SnH, AIBN in PhH, ii NaOMe, MeOH-PhMe, iii CH_2N_2 in 39% overall yield). All of the attempted glycosylations of **5** (R=Bn) as well as **6** with **3** (X=SMe, Br, F, and $OCNHCCl_3$) in our hands occurred at NHAc groups linked to either residue *5* or *6* but not at OH group of residue *2* of **5** and **6**, resulting in the formation of only acid labile imidates.

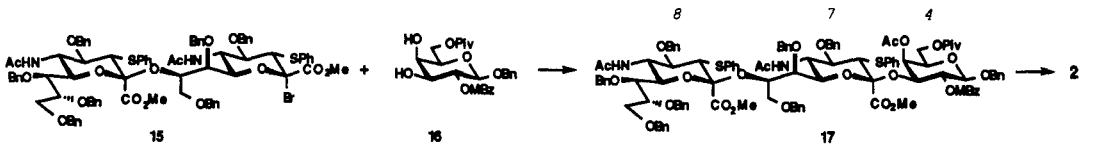


5 (R = Ac) **11** **12** **13** **14**

Scheme 3

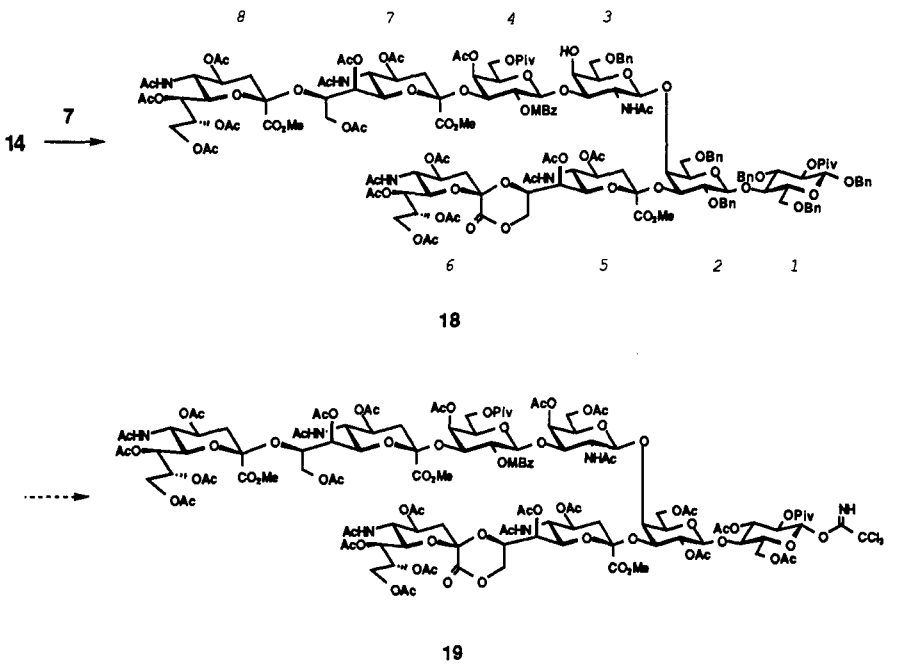
In order to lower the nucleophilicity of NHAc groups in compound **5** (R=Bn) toward glycosyl donors, we had to change the protective group of sialic acid residues from benzyl to electron withdrawing acetyl groups. According to this scenario, we studied compound **5** (R=Ac) as a glycosyl acceptor. To our delight, the glycosylation of **5** (R=Ac, ref 11) with **11** went smoothly[12] in the presence of PhSeOTf in CH_3CN to give an 89% of **12**: $[\alpha]_D$ +6.7° (c 0.6, $CHCl_3$); R_F 0.43 in 20:1 $CHCl_3$-MeOH; δ_H 6.235 (s, C*H*Ph), 5.306 (d, 8.8 Hz, H-1*3*), 2.699 and 2.671 (2dd, 4.4 and 12.8 Hz, H-3eq[5,6]), 1.744 (t, 12.8 Hz, H-3ax[5,6]), 1.197 (s, tBu). Having successfully carried out a chain elongation at O-4 of residue *2* of

compoun **5**, N-phthaloyl function of the protected pentasaccharide **12** was then converted into N-acetyl group in 4 steps (i LiI-Py, ii NH_2NH_2-H_2O, iii Ac_2O-MeOH, iv CH_2N_2, 95% overall) to give **13**: $[\alpha]_D$ -5.5° (c 0.9, $CHCl_3$); R_F 0.33 in 5:3 Me_2CO-hexane; δ_H 6.276 (s, C*H*Ph), 5.117 (dd, 8.4 and 9.2 Hz, H-2^1), 3.996 (s, O*Me*), 2.242 (dd, 4.7 and 13.5 Hz, H-3eq$^{5 \text{or } 6}$), 1.789 (t, 12.8 Hz, H-3ax^5), 1.169 (s, tBu). Treatment of **13** with 4:1 AcOH-H_2O afforded 87% of **14** which is ready for further chain elongation at O-3 of residue *3*. Compound **14** had $[\alpha]_D$ -5.5° (c 0.3, $CHCl_3$); R_F 0.33 in 19:1 $CHCl_3$-MeOH; δ_H 5.200 (ddd, 5.5, 11.3 and 16.5 Hz, H-4^6), 5.135 (dd, 8.1 and 9.2 Hz, H-2^1), 5.024 (ddd, 5.1, 12.1 and 16.8 Hz, H-4^5), 2.346 (dd, 5.5 and 14.0 Hz, H-3eq^6), 2.240 (t, 14.0 Hz, H-3ax^6), 2.196 (dd, 5.1 and 14.3 Hz, H-3eq^5), 1.716 (t, 14.3 Hz, H-3ax^5), 1.170 (s, tBu).



Scheme 4

The building block **2** was prepared[10] starting from **15** (ref.10). Glycosylation of **16** with 0.66 equivalent of **15** in the presence of $Hg(CN)_2$-$HgBr_2$-MS4A in CCl_4 and subsequent acetylation gave 33% of **17**: δ_H 5.311 (d, 3.4 Hz, H-4^4), 3.421 and 2.963 (2d, 10.3 and 10.6 Hz, H-$3^{7,8}$). Further conversion of **17** into **2** was achieved in 4 steps (i Ph_3SnH, AIBN in PhH, ii H_2, 10% Pd-C in MeOH, iii Ac_2O-Py-DMAP, iv MeSSnBu_3-$SnCl_4$, 17% overall). Compound **2** had R_F 0.38 in 20:1 $CHCl_3$-MeOH; $[\alpha]_D$ +29.3° (c 0.4



Scheme 5

in $CHCl_3$); δ_H 4.864 (d, 9.6 Hz, H-1^4), 3.828 and 3.796 (2s, 2 x OMe), 2.365 (s, C_6H_5*Me*), 2.221, 2.183, 2.166, 2.165, 2.137, 2.047, 2.046, 2.045, 1.956, 1.915 and 1.829 (11s, 10 x Ac and S*Me*), 1.202 (s, tBu). Crucial coupling of **14** with 1 equivalent of **2** in the presence of PhSeOTf in $(CH_2Cl)_2$ afforded 16% of the designed octasaccharide **18** along with 67% of recovered pentasaccharide **14**. It is to be noted that reaction of trichloroacetimidate corresponding to **2** with **14** in the presence of either TMSOTf or BF_3•OEt_2 in the same solvent failed completely. Stereochemistry of the glycosylation was confirmed by the following ^1H NMR of the compound **18**: R_F 0.28 in 1:2 $CHCl_3$-THF; δ_H 5.395 (dd, 7.7 and 9.5 Hz, H-2^4), 4.801 (d, 7.7 Hz, H-1^4), 3.800, 3.785, and 3.785 (3s, 3 x OMe), 2.368 (s, Ph*Me*), 1.177 and 1.162 (2s, 2 x tBu). The regiochemistry of the coupling was confirmed by ^1H NMR of the acetate of **18** which contained a deshielded signal for H-4^3 at δ 5.420 (d, 3.7 Hz). The Compound **18** could be regarded as a plausible precursor for the imidate **19**.

In summary, a first synthesis of properly protected octasaccharide **18** which was regarded a key intermediate for the synthesis of GQ1b was achieved by controlling the reactivity of OH-4 of residue *2* relative to NHAc of residues *5* and *6* in compound **5** by changing the protective groups of hydroxyl functions from benzyl to acetyl. Crucial coupling between pentasaccharide block **14** and trisaccharide block **2** was finally executed in the presence of thiophilic promoter.

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