Pergamon

Tetrahedron Letters 41 (2000) 9065–9068

TETRAHEDRON LETTERS

Synthetic studies on novel fucosylated glycosphingolipids from the millipede, *Parafontaria laminata armigera*

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Received 3 August 2000; revised 13 September 2000; accepted 14 September 2000

Abstract

A novel glycosphingolipid, β-D-Man*p*-(1→4)-[(α-L-Fuc*p*-(1→3)]-β-D-Glc*p*-(1→1)-Cer, from the millipede, *Parafontaria laminata armigera*, was synthesized. A key reaction of this synthetic procedure is the formation of a spiro-orthoester and its reduction for β-selective mannosylation.

Keywords: glycosphingolipids; *Parafontaria laminata armigera*; chemical synthesis.

We have been interested in the relationship between the structure and the biological functions of glycolipids from invertebrate animal species and have so far synthesized oligosaccharides from various protostomia phyla.[1] In 1994, Sugita et al. found a novel glycolipid with β-D-Man*p*-(1→4)-[(α-L-Fuc*p*-(1→3)]-β-D-Glc*p* linkage from the periodical millipede, *Parafontaria laminata armigera*, which belongs to the class Diplopoda[2] (Fig. 1). This compound has a novel fucosylated structure and also 1,2-*cis*-β-D-mannopyranosidic linkage and it is one of the most difficult glycosidic linkages to synthesize.[3] There are two main reasons why the β-mannosidic linkage is so difficult to synthesize: (1) The anomeric effect stereoelectronically favors the α-mannosidic linkage both thermodynamically and kinetically. (2) Neighboring group participa-

Manβ(1→4)Glcβ(1-1)Cer
3
↑
Fucα1

1

Figure 1.

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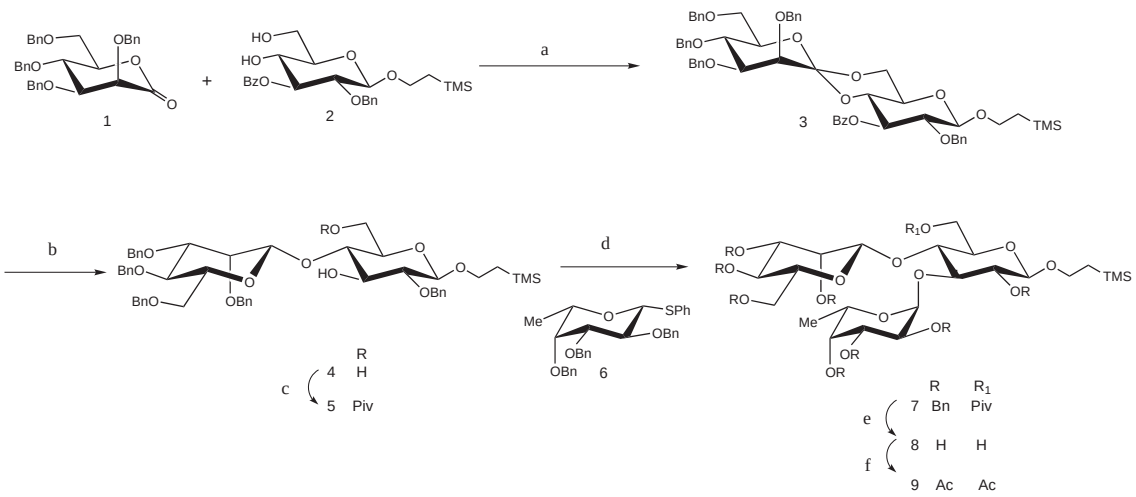
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01603-8

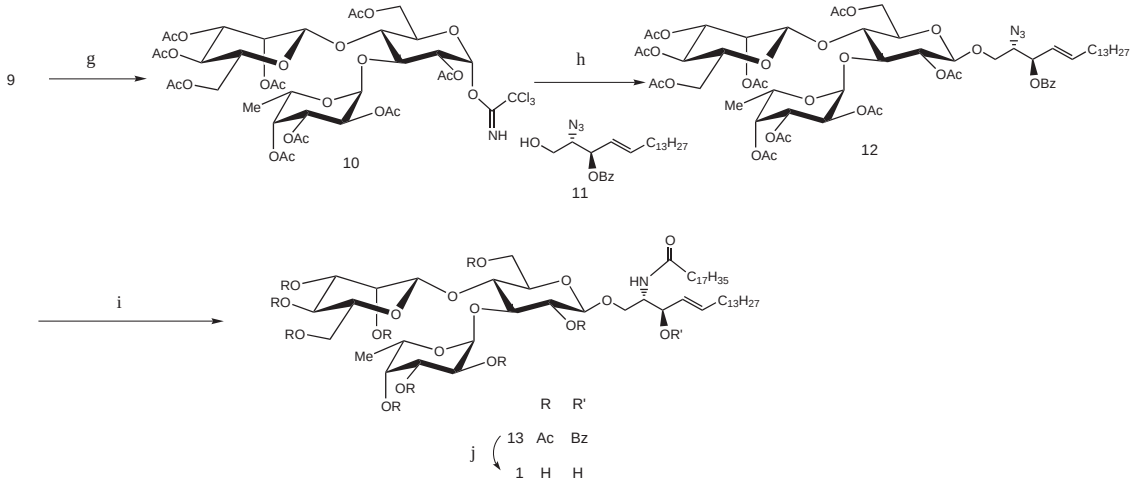
tion via an ester gives α-mannopyranosides. Construction of a β-mannosidic linkage has been developed by many carbohydrate chemists.[3,4] Further application of these methods to the synthesis of aspargine-linked oligosaccharide and the glycolipid from the fresh-water bivalve, *Hyriopsis schlegelii*, is under current investigation.[5]

On the other hand, Ikegami et al. reported a highly stereoselective β-(1→4)-glycosidic bond formation by reductive cleavage of cyclic orthoesters.[6] This method is based on a two-step glycosylation procedure; the first step is the formation of an orthoester from two sugar moieties and the second step is the reductive cleavage of one C–O orthoester bond. We applied this method to the synthesis of the glycolipid, and this is the first report on the total synthesis of the natural products. Coupling of 2,3,4,6-tetra-*O*-benzyl-D-mannopyranolactone (**1**)[6] with diol **2** in toluene in the presence of trimethylsilyl trifrate and methoxy trimethylsilane for 3 h at room temperature gave the 2-(trimethylsilyl)ethyl 4,6-*O*-(2,3,4,6-tetra-*O*-benzyl-mannopyranosylidene)-2-*O*-benzyl-3-*O*-benzoyl-β-D-glucopyranoside (**3**)[7] in 67% yield. The structure of **3** was determined by reference to Ohtake's report.[6a] Next, the reduction of the orthoester **3** and removal of the benzoyl ester of the glucose derivative with $LiAlH_4$–$AlCl_3$ smoothly occurred to produce the glycoside **4**[8] (56%) in completely regio- and stereoselective fashion. Selective 6-*O*-pivaloylation of **4** gave compound **5** (57%), which was used as an acceptor. The glycosylation of compound **5** with phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside (**6**)[9] in the presence of NIS and TfOH as the glycosyl promoter and MS 4Å in dichloromethane for 5 h at 0°C gave the desired α-glycoside **7** in 65% yield. After depivaloylation and debenzylation, compound **8** was converted to peracetylated trisaccharide **9** (Scheme 1). For the selective removal of the 2-(trimethylsilyl)ethyl group, compound **9** was treated[10] with trifluoroacetic acid in dichloromethane for 1–2 h at 0°C to give the 1-hydroxy compounds which, on further treatment[11] with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane for 2 h at 0°C, gave the corresponding donor carbohydrate **10**. Glycosylation[12] of (2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol **11**[13] with the glycosyl donor **10**, which was carried out in the presence of TMSOTf and MS 4Å for 2 h at 0°C, afforded the desired β-glycoside **12** (41%). Selective reduction[14] of the azido group in **12** with triphenylphosphine in 20:1 benzene–water



Scheme 1. Reagents: (a) TMSOTf, TMSOMe, toluene; (b) $LiAlH_4$, $AlCl_3$, CH_2Cl_2–Et_2O; (c) PivCl, Pyr, 0°C; (d) NIS, TfOH, CH_2Cl_2, 0°C; (e) (1) NaOMe, MeOH, (2) Pd–C/H_2, MeOH; (f) Ac_2O, Pyr

gave the amine, which on condensation with stearic acid using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC) in dichloromethane, gave the fully protected derivative **13** (74%). Finally, removal of the acyl groups in **13** under basic conditions and column chromatography on Sephadex LH-20 furnished the target glycolipid **1** (Scheme 2). The structure and purity of **1** were demonstrated by the ^{1}H NMR and TOFMS data.[15] In conclusion, a highly efficient synthesis of a novel fucosylated glycosphingolipid from the millipede, *Parafontaria laminata armigera*, has been achieved for the first time.



Scheme 2. Reagents: (g) (1) CF_3COOH–CH_2Cl_2, 0°C, (2) CCl_3CN, DBU, CH_2Cl_2, 0°C; (h) TMSOTf, CH_2Cl_2, 0°C; (i) (1) Ph_3P, benzene–H_2O, (2) WSC, $C_{17}H_{35}COOH$, CH_2Cl_2; (j) NaOMe, 1,4-dioxane–MeOH

Acknowledgements

This work was supported by the Uehara Memorial Foundation and also supported by a Grant-in-Aid for Encouragement of Young Scientists, No. 70296531, from the Ministry of Education, Science, Sports and Culture of Japan. The authors thank Dr. H. Ohtake (Faculty of Pharmaceutical Sciences, Teikyo University) for valuable discussions.

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7. $[\alpha]_D^{23} = +0.32°$ ($c = 1.0$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.89–7.01 (m, 55H, 11×Ph), 5.50 (t, 1H, $J_{2,3} = J_{3,4} = 9.8$ Hz, H-3), 4.86–4.47 (m, 10H, 5×benzyl methylene), 4.62 (d, 1H, $J_{1,2} = 8.0$ Hz, H-1), 4.23 (t, 1H, H-4), 4.02–3.98 (m, 1H, -OC$\underline{H}_2$CH$_2$-), 3.89–3.82 (m, 4H, H-3′, 4′, 6a, 6b), 3.75 (dd, 1H, $J_{2',3'} = 3.0$ Hz, H-2′), 3.72–3.63 (m, 3H, H-6′a, 6′b, -OC$\underline{H}_2$CH$_2$-), 3.58–3.53 (m, 2H, H-2, 5′), 3.48 (dt, 1H, H-5). ^{13}C NMR δ: 110.7 (C-1′), 104.0 (C-1), 80.5 (C-3′), 79.4 (C-2), 75.04 (C-benzyl methylene), 74.98 (C-2′), 74.32 (C-benzyl methylene), 74.25 (C-4′), 74.0 (C-5′), 73.9 (C-benzyl methylene), 73.1 (C-3), 73.0 (C-benzyl methylene), 71.5 (C-benzyl methylene), 71.0 (C-4), 68.6 (C-6′), 68.1 (C-$\underline{C}$H$_2$CH$_2$Si), 66.1 (C-5), 60.4 (C-6), 18.6 (C-CH$_2\underline{C}$H$_2$Si), −1.4 ($SiMe_3$). MALDI-TOFMS: calcd for $C_{59}H_{66}O_{12}Si$: m/z 994. Found: m/z 1017 $(M+Na)^+$.
8. $[\alpha]_D^{23} = -10.7°$ ($c = 1.0$ $CHCl_3$); NMR data of anomeric parts: ^1H NMR ($CDCl_3$) δ: 4.49 (s, 1H, H-l′), 4.41 (d, 1H, $J_{1,2} = 7.9$ Hz, H-1), ^{13}C NMR ($CDCl_3$) δ: 102.7 (C-1, $J_{C,H} = 155.2$ Hz), 101.8 (C-1′, $J_{C,H} = 151.0$ Hz). MALDI-TOFMS: calcd for $C_{52}H_{64}O_{11}Si$: m/z 892. Found: m/z 915 $(M+Na)^+$.
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15. $[\alpha]_D^{23} = -7.3°$ ($c = 0.2$, 1:1 $CHCl_3$–MeOH); NMR data of anomeric parts: ^1H NMR (1:1 $CDCl_3$–CD_3OD) δ: 5.11 (d, 1H, $J_{1,2} = 3.7$ Hz, H-1 of Fuc), 4.60 (s, 1H, H-1 of Man), 4.34 (d, 1H, $J_{1,2} = 7.9$ Hz, H-1 of Glc). MALDI-TOFMS: calcd for $C_{54}H_{101}NO_{17}$: m/z 1036. Found: m/z 1059 $(M+Na)^+$.