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Regio- and Stereocontrolled Synthesis of D-*erythro*-Sphingosine and Phytosphingosine from D-Glucosamine

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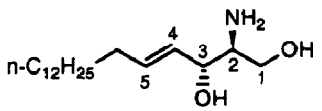
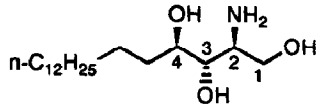
Abstract: D-*erythro*-Sphingosine (1) and phytosphingosine (2) have been efficiently synthesized from D-glucosamine by utilizing its whole carbon skeleton and functional groups. In this synthetic route, regioselective alkylation of the epoxy-tosylate **9** was achieved with a copper(I)-catalyzed Grignard reagent to give the key intermediate **10**, which was converted to both **1** and **2** *via* regioselective formation of the iodohydrin **11**.

D-*erythro*-Sphingosine [(2*S*, 3*R*, 4*E*)-2-aminooctadec-4-ene-1,3-diol] (1) and phytosphingosine [(2*S*, 3*S*, 4*R*)-2-aminooctadecane-1,3,4-triol] (2) are major backbone components of glycosphingolipids, which play important roles in biological processes on cell surfaces.[1] Sphingosines have attracted considerable interest as potent inhibitors of protein kinase C, an essential enzyme in cell regulation and signal transduction.[2] Various synthetic approaches to optically active **1**[3] and **2**[4] have been reported in the past decade in view of their biological importance.



D-*erythro*-sphingosine **1**

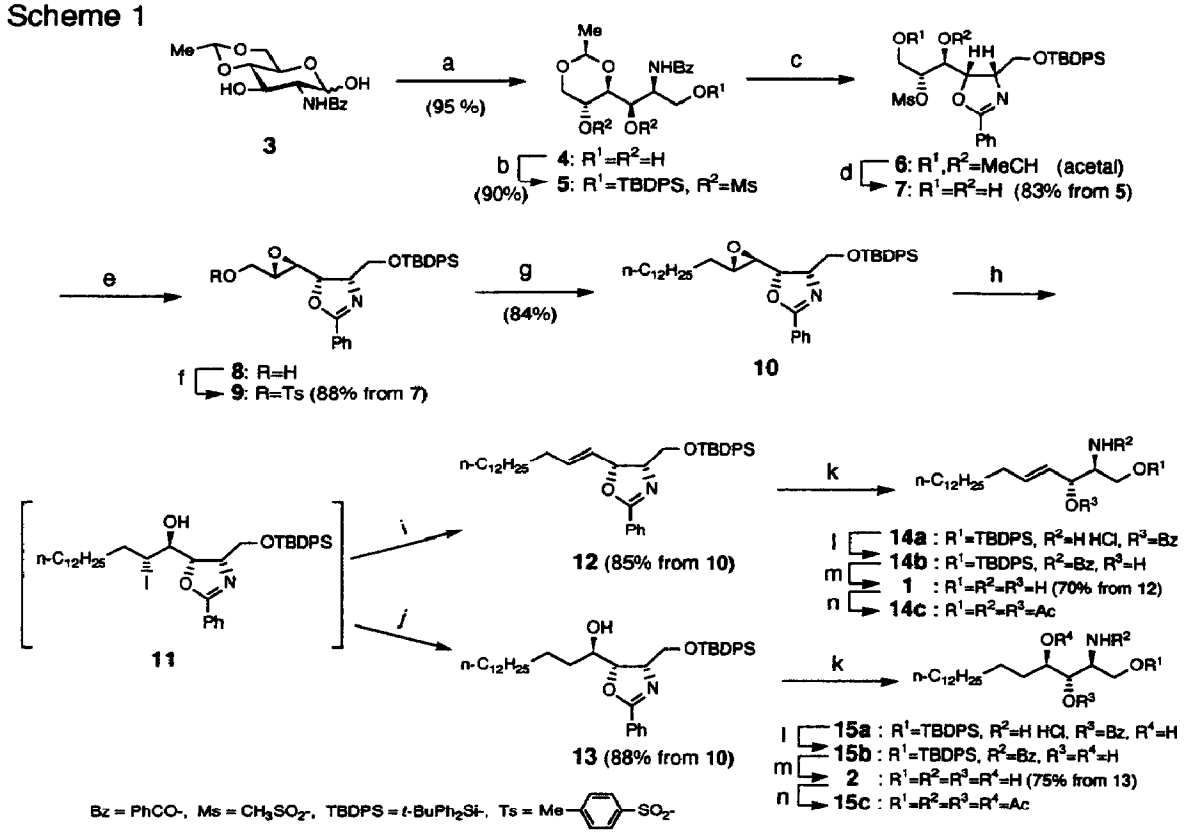


phytosphingosine **2**

We have recently reported a convenient synthesis of galactocerebroside (1-*O*-β-D-galactopyranosyl-2-*N*-palmitoyl-D-*erythro*-sphingosine) using D-glucosamine as a chiral starting material *via* 12 reaction steps.[5] Although this enantiospecific synthesis provides one of the shortest routes to glycosphingolipids,[6] it contains a low-yielding step and affords unnatural (4*Z*)-sphingosine in preference to natural (4*E*)-**1**.

In this paper, we wish to report a regio- and stereocontrolled synthesis of the two major sphingosines **1** and **2** from D-glucosamine by utilizing its contiguous chiral centers, functional groups, and whole carbon skeleton[7] as shown in Scheme 1. Thus, 4,6-*O*-ethylidene-*N*-benzoyl-D-glucosamine **3**, readily available from D-glucosamine hydrochloride in 2 steps,[5] was reduced with $NaBH_4$ in aqueous *i*-PrOH to give the 1,3,5-triol **4**,[8] m.p. 165-167 °C; $[\alpha]_D^{23}$ -13.3° (*c* 1.0, $CHCl_3$/MeOH=1) in 95% yield. Selective protection of the primary hydroxyl group of **4** with *t*-butyldiphenylsilyl (TBDPS) group, followed by methanesulfonation of the

Scheme 1



Reagents and Conditions: a) $NaBH_4$ (1.4 equiv.), *i*-PrOH-H_2O (5 : 1), 0 °C, 1 h; b) *t*-$BuPh_2SiCl$ (1.2 equiv.), pyridine, CH_2Cl_2, r.t., 24 h, then CH_3SO_2Cl (3.0 equiv.), Et_3N, CH_2Cl_2, 0 °C, 2 h; c) pyridine, Et_3N, toluene, 110 °C, 24 h; d) $TiCl_4$ (3.0 equiv.), PhSH (8 equiv.), CH_2Cl_2, 0 °C, 2 h; e) K_2CO_3 (1.2 equiv.), MeOH, 0 °C, 2 h; f) p-toluenesulfonyl chloride (1.2 equiv.), 4-dimethylaminopyridine (10 mol%), Et_3N (2.5 equiv.), CH_2Cl_2, 0 °C, 2 h; g) n-$C_{12}H_{25}MgBr$ (2 equiv.), CuBr (20 mol%), THF, -30 to 0 °C, 4 h; h) NaI (4 equiv.), Me_3SiCl (4 equiv.), H_2O (0.5 equiv.), CH_3CN, 0 to 10°C, 2 h; i) $POCl_3$ (10 equiv.), pyridine, CH_3CN, 0 to 15 °C, 4 h; j) n-Bu_3SnH (2 equiv.), AIBN, toluene, 60 °C, 30 min; k) 4N-HCl, THF (1 : 8) r.t., 24 h; l) aq. NaOH, r.t.; m) NaOH, aq. EtOH, 95 °C, 12 h; n) Ac_2O, Et_3N, DMAP, CH_2Cl_2.

secondary alcohols gave the 1-*O*-TBDPS-3,5-*O*-dimesylate **5**, $[\alpha]_D^{23}$ -5.0° (*c* 0.92)[9], in 90% yield. The dimesylate **5** was heated in pyridine and triethylamine[10] at 110 °C for 24 hr to effect complete conversion into the phenyloxazoline derivative **6**, which was partially decomposed during silica gel chromatography. Thus the crude **6** was treated with $TiCl_4$ and PhSH in CH_2Cl_2[5,11] to give the 4,6-diol **7**, $[\alpha]_D^{23}$ -62.4° (*c* 1.14)[9], in 83% overall yield from **5**. Treatment of **7** with K_2CO_3 in methanol afforded the 4,5-*trans*-epoxide **8**,[12] $[\alpha]_D^{24}$ -89.4° (*c* 0.98)[9], as a single product.[13] The C-6 hydroxyl group of **8** was tosylated for the introduction of long-chain alkyl group.

Chemo- and regioselective substitution of the tosyloxy group of **9** was achieved[14] by treatment with dodecylmagnesium bromide (2 equiv.) in the presence of CuBr (20 mol%)[15] at -30 to 0 °C to give the desired coupling product **10**,[16] $[\alpha]_D^{24}$ -65.8° (*c* 1.18)[9], in 84% yield. A by-product obtained was non-coupling, 5,6-unsaturated 4-ol (allylic alcohol, *ca.* 8% yield) and *ca.* 6% of **9** was recovered, but the addition product to the epoxide of **9** was not obtained.

To construct the olefin moiety of **1**, deoxygenation of the epoxide in **10** was then examined. Among several attempts,[17] the stereospecific deoxygenation was accomplished most successfully by the procedure of Cornforth *et al.*[18] with modification. Thus, treatment of **10** with NaI and chlorotrimethylsilane in wet acetonitrile[19] gave the iodohydrin(s), which without isolation was treated with $POCl_3$ and pyridine[20] to afford the *E*-olefin **12**, $[\alpha]_D^{24}$ -62.8° (*c* 0.84)[9]; ^{1}H-NMR $J_{4,5}$=15.4 Hz, exclusively in 85% yield. Although the *E*-olefin should be formed from both of the two possible regio-isomers of the iodohydrin, the 5-iodo-4-ol **11** was found to be a predominant isomer (>20 : 1) in this case based on the ^{1}H-NMR spectra of the crude iodohydrin and its *O*-acetate.[21] The regioselective formation of **11** was also observed in the reaction of **10** with other hydrogen iodide sources,[19] *e.g.*, LiI with AcOH, presumably resulting from the steric hindrance near to C-4. For confirmation of the structure, the crude **11** was treated with Bu_3SnH to give **13**, $[\alpha]_D^{24}$ -61.7° (*c* 1.42)[9], which corresponds to a protected phytosphingosine.

Finally, deprotection was accomplished in two steps as follows. Acidic hydrolysis of **12** caused the fission of the phenyloxazoline ring to give 3-*O*-benzoylsphingosine derivative **14a**, which changed to *N*-benzoyl derivatives **14b** upon treatment with aqueous NaOH. When this alkaline solution (*ca.* 1N-NaOH) was heated at 95 °C, the TBDPS group was cleaved immediately, whereas the complete hydrolysis of the benzamide required about 12 hours. The crude hydrolysate was purified by silica gel chromatography (CH_2Cl_2 : MeOH : 2N-NH_4OH = 40:10:1) to afford sphingosine **1**, m.p. 74-76 °C; $[\alpha]_D^{24}$ -1.2° (*c* 1.0)[9,22], in 70% yield from **12** (31% overall yield from **3**). In a similar manner, phytosphingosine **2**, m.p. 98-101 °C; $[\alpha]_D^{24}$ +8.7° (*c* 0.80, pyridine)[22], was obtained from **13** in 75% yield (35% overall yield from **3**). The structures of **1** and **2** were further confirmed by conversion into the known triacetate **14c**,[23] m.p. 105-106 °C; $[\alpha]_D^{24}$ -12.9° (*c* 0.95)[9], and tetraacetate **15c**,[23] m.p. 34-37 °C; $[\alpha]_D^{24}$ +28.0° (*c* 1.30)[9], whose physical data were identical with the reported values in all respects.

In summary, both D-*erythro*-sphingosine and phytosphingosine were efficiently synthesized from D-glucosamine *via* an almost common route except for reducing steps. It should be noted that the key reactions involved in this route were highly regio- and stereoselective.

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2. (a) Hannun, Y.A.; Bell, R.M. *Science* **1989**, *243*, 500. (b) Merrill, A.H.; Nimkar, S.; Menaldino, D.; Hannun, Y.A.; Loomis, C.; Bell, R.M.; Tyagi, S.R.; Lambeth, J.D.; Stevens, V.L.; Hunter, R.; Liotta, D.C. *Biochemistry* **1989**, *28*, 3138.
3. More than 20 synthetic approaches to **1** have been reported so far; for short (7 steps) and practical routes: (a) from D-xylose or D-galactose: Kiso, M.; Nakamura, A.; Tomita, Y.; Hasegawa, A. *Carbohydr. Res.* **1986**, *158*, 101; and (b) from L-serine: Garner, P.; Park, J.M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 4395. For other methods: (c) asymmetric synthesis: Julina, R.; Herzig, T.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1986**, *69*, 368. (d) from D-glucosamine: Sugawara, T.; Narisada, M. *Carbohydr. Res.* **1989**, *194*, 125. (e) a recent report: Yadav, J.S.; Vidyanand, D.; Rajagopal, D. *Tetrahedron Lett.* **1993**, *34*, 1191; and references cited therein.
4. To our knowledge, **2** and/or its *N*-acyl derivatives have been synthesized *via* eight routes; for example: (a) Gigg, J.; Gigg, R.; Warren, C.D. *J. Chem. Soc. (C)* **1966**, 1872. (b) Mulzer, J.; Brand, C. *Tetrahedron* **1986**, *42*, 5961. (c) Schmidt, R.R.; Maier, T. *Carbohydr. Res.* **1988**, *174*, 169. (d) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1989**, *30*, 5507. (e) Dondoni, A.; Fantin, G.;

Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439.
5. Murakami, T.; Minamikawa, H.; Hato, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1875.
6. For the other short route, see: Nicolaou, K.C.; Caulfield, T.; Kataoka, H.; Kumazawa, T. *J. Am. Chem. Soc.*, **1988**, *110*, 7910. See also Ref. 3a and 3b.
7. All previous syntheses from D-glucosamine[3d,4a,5] required one or two carbon degradation.
8. All new compounds gave satisfactory spectroscopic data and solid compounds (**4**, **1**, **2**, **14c**, **15c**) gave satisfactory elemental analyses consisitent with the assigned structures.
9. Optical rotations were measured in $CHCl_3$.
10. Triethylamine is necessary to avoid the fission of the phenyloxazoline ring by methanesulfonic acid formed; Gigg, R.; Conant, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2006.
11. Homma, K.; Takenoshita, H.; Mukaiyama, T. *Bull. Chem. Soc. Japan* **1990**, *63*, 1898.
12. **8**: ^{1}H-NMR (360 MHz, $CDCl_3$); epoxide protons : δ 3.22 (1H, quint., $J_{4,5}$=$J_{5,6}$=2.0, $J_{5,6'}$=4.0 Hz, H-5), 3.77 (1H, dd, $J_{4,5}$=2.0, $J_{3,4}$=5.1 Hz, H-4).
13. For related reactions, see: (a) Corey, E.J.; Clark, D.A.; Goto, G.; Marfat, A.; Mioskowski, C.; Samuelsson, B.; Hammarström, S. *J. Am. Chem. Soc.* **1980**, *102*, 1436. (b) Rollin, P.; Pougny, J.-R. *Tetrahedron* **1986**, *42*, 3479.
14. To the best of our knowledge, chemoselective substitution of the primary tosyloxy group adjacent to secondary epoxide has been achieved only with lithium organocuprates (2.5 to 5 equiv.), see: (a) Mori, K.; Ebata, T. *Tetrahedron* **1986**, *42*, 3471. (b) Ref. 13b. (c) For a recent review on organocopper reagents, see: Lipshutz, B.H.; Sengupta, S. *Org. React.* **1992**, *41*, pp. 135-631.
15. CuI was also effective for the coupling, whereas Li_2CuCl_4 had no effect.
16. **10**: ^{1}H-NMR data: δ 0.88 (3H, t, *J*=6.5), 0.98 (9H, s, t-Bu), 1.25 (22H, s-like), 1.44 (2H, m), 2.96 (1H, dt, *J*=2.0, 5.4 Hz, H-5), 3.52 (1H, dd, *J*=2.1, 5.7 Hz, H-4), 3.94 (1H, dd, *J*=5.7, 10.9 Hz, H-1), 4.16 (1H, dd, *J*=2.9, 10.9 Hz, H-1'), 4.48 (1H, ddd, *J*=2.9, 5.6, 9.5 Hz, H-2), 4.55 (1H, dd, *J*=5.7, 9.5 Hz, H-3), 7.34-7.47 (9H, m, Ph), 7.67 (4H, m, Ph), 7.95 (2H, m, Ph).
17. For example: (a) Behan, J.M.; Johnstone, R.A.W.; Wright, M.J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1216. (b) Sonnet, P.E. *J. Org. Chem.* **1978**, *43*, 1841. (c) Capto, R.; Mangoni, L.; Neri, O.; Palumbo, G. *Tetrahedron Lett.* **1981**, *22*, 3551.
18. Cornforth, J.W.; Cornforth, R.H.; Mathew, K.K. *J. Chem. Soc.* **1959**, 112.
19. The iodohydrin was obtained by treatment with a combination of iodide (LiI, NaI, Bu_4NI) and acid (AcOH, CF_3CO_2H, BF_3·OEt_2, Me_3SiCl). However, the reaction proceeded most rapidly by using NaI and Me_3SiCl in CH_3CN; for this reagent system, see: Irifune, S.; Kibayashi, T.; Ishii, Y.; Ogawa, M. *Synthesis* **1988**, 366.
20. No reducing agent such as $SnCl_2$ was necessary; Crabbé, T.; Guzmán, A. *Tetrahedron Lett.* **1972**, 115.
21. For *O*-acetate of the iodohydrin, ^{1}H signals at δ 5.38 (1H, dd, *J*=2.6, 8.9 Hz) and 4.67 (1H, ddd, *J*=2.6, 4.3, 9.9 Hz) could be unambiguously assigned to C-4 and C-5 protons, respectively.
22. Reported melting points and optical rotations; **1**: m.p. 81.5-82.5 °C[3a], 72-75 °C[3b], 68-72 °C[3d], 78.4-80.8 °C[3e]; $[\alpha]_D$ -0.58° (c 1.67, $CHCl_3$)[3b], -2.72° (c 1.1, $CHCl_3$)[3e]. **2**: m.p. 103 °C[4b], 95 °C[4c], 98-100 °C[4e]; $[\alpha]_D$ +7.9° (c 1.0, pyridine)[4b], $[\alpha]_{578}$ +8.5° (c 1, pyridine)[4c]. **14c** : m.p. 102.5-103.5 °C[3b], 101-102 °C[3c], 103.5-104.5°C[3d]; $[\alpha]_D$ -13.0° (c 1.08, $CHCl_3$)[3b], -12.8° (c 1, $CHCl_3$)[3c], -12.6° (c 0.75, $CHCl_3$)[3d]. **15c**: m.p. 48 °C[4b], syrup[4e]; $[\alpha]_D$ +26.3° (c 2, $CHCl_3$)[4b], +24.7° (c 0.5, $CHCl_3$)[4d].
23. ^{1}H-NMR data (360 MHz, $CDCl_3$): **14c**: δ 0.88 (3H, t, *J*=6.8), 1.25 (20H, s-like), 1.33 (2H, m), 1.98, 2.06, 2.07 (each 3H, each s), 2.02 (2H, m), 4.04 (1H, dd, *J*=3.9, 11.6 Hz, H-1), 4.30 (1H, dd, *J*=6.0, 11.6 Hz, H-1'), 4.43 (1H, m, H-2), 5.28 (1H, t-like, *J*=6.7, H-3), 5.39 (1H, dd, *J*=7.4, 15.3, H-4), 5.70 (1H, d, *J*=9.1 Hz, NH), 5.79 (1H, dt, *J*=6.8, 15.3 Hz, H-5); (*Cf.* Ref. 3b, 3d). **15c**: δ 0.88 (3H, t, *J*=6.8 Hz), 1.25 (24H, s-like), 1.65 (2H, m), 2.03 (3H, s), 2.05 (6H, s), 2.08 (3H, s), 4.00 (1H, dd, *J*=3.0, 11.7 Hz, H-1), 4.29 (1H, dd, *J*=4.8, 11.7 Hz, H-1'), 4.47 (1H, m, H-2), 4.93 (1H, dt, *J*=3.3, 9.6 Hz, H-4), 5.11 (1H, dd, *J*=3.0, 8.3 Hz, H-3), 6.01 (1H, d, *J*=9.4 Hz, NH); (*Cf.* Ref. 4c, 4e).

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