Pergamon

Tetrahedron Letters 43 (2002) 4889–4892

TETRAHEDRON LETTERS

Synthesis of D-*ribo*-C_{18}-phytosphingosine from D-glucosamine via the D-allosamine derivatives as key intermediates

Shun-Yuan Luo,[a] Shankar R. Thopate,[a] Ching-Yun Hsu[b] and Shang-Cheng Hung[a,*]

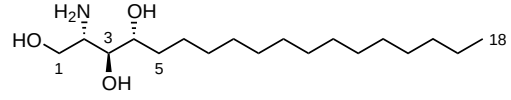
[a]*Institute of Chemistry, Academia Sinica, Taipei 115, Taiwan*

[b]*Department of Chemical Engineering, Cheng-Shiu Institute of Technology, 840 Cheng-Ching Road, Kaohsiung County 833, Taiwan*

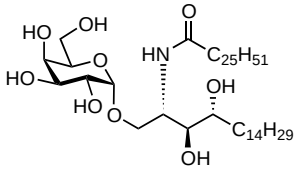
Received 22 March 2002; accepted 3 April 2002

Abstract—A straightforward synthesis of D-*ribo*-C_{18}-phytosphingosine from D-glucosamine hydrochloride in ten steps in 18.4% overall yield via the D-allosamine derivatives as key intermediates is described here.

D-*ribo*-C_{18}-Phytosphingosine **1**, (2*S*,3*S*,4*R*)-2-aminooctadecane-1,3,4-triol, is a key backbone component of sphingolipids ubiquitously distributed in many mammalian tissues,[1] plants,[2] fungi,[3] as well as marine organisms.[4] It is a bioactive lipid that has potential heat stress signal in yeast cell.[5] Its derived α-galactosylceramide **2**, exhibiting significant immunostimulatory and antitumor properties,[6] can be used as a ligand for mouse and human natural killer T cells to enhance their activities.[7] Due to the difficulty in obtaining homogeneous material from natural sources, the synthetic methods have acquired immense importance. As a result, the literature documents many asymmetric synthetic strategies to prepare phytosphingosine. Most approaches, that utilize L-serine and various carbohydrates as the starting materials, often have diastereoisomers in their syntheses which need to be separated or require lengthy routes to reach the target molecule.[8] There is an ongoing demand to develop more efficient and improved methodologies for the preparation of phytosphingosine.

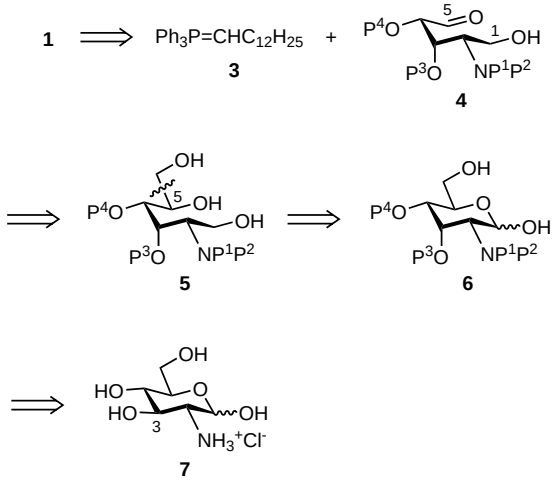


1 : D-*ribo*-C_{18}-phytosphingosine



2 : α-galactosyl ceramide

Due to the striking similarity between phytosphingosine **1** and the D-allosamine derivative **6**, with respect to the configuration at three asymmetric centers, the C2, C3, and C4, it was obvious for us to involve **6** as a key intermediate. Our retro-synthetic plan, as illustrated in Scheme 1, is to carry out the hydride reduction at the anomeric center of **6** to generate a triol **5**, which may undergo oxidative cleavage of the C5–C6 bond with sodium periodate to provide the aldehyde **4** and further



Scheme 1.

* Corresponding author. Fax: 886-2-2783-1237; e-mail: schung@chem.sinica.edu.tw

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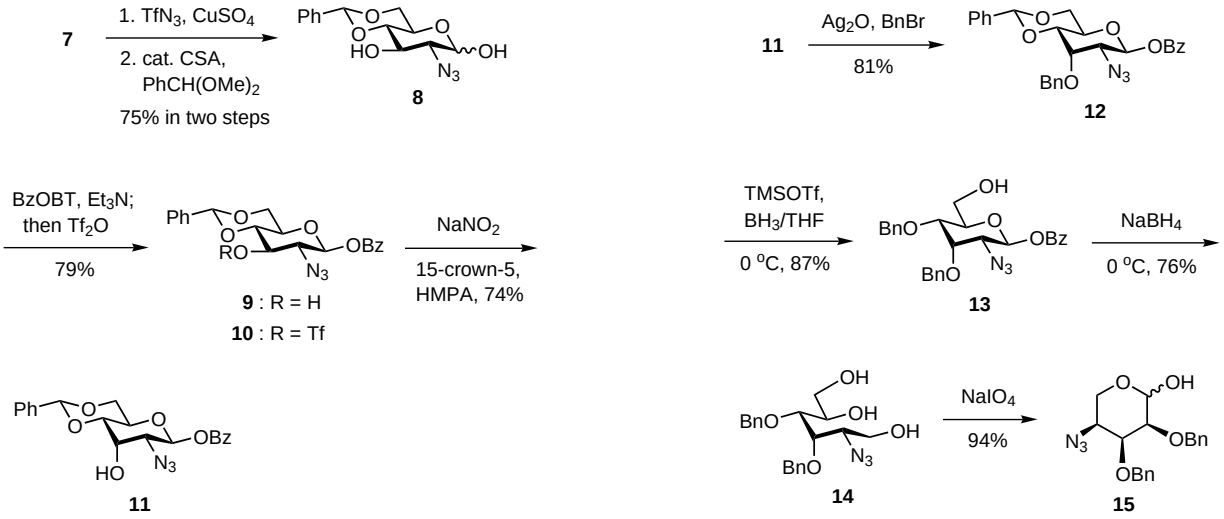

Scheme 2.

coupling with the Wittig reagent **3** to form the skeleton of phytosphingosine. The D-allosamine derivative **6** can in turn be obtained from commercially available and cheap D-glucosamine hydrochloride **7** via regioselective epimerization of hydroxyl group at the C3 position.

Our efficient synthesis of the D-allosamine derivatives is outlined in Scheme 2. Transformation of **7** into the diol **8** was executed in two steps in 75% overall yield through a combination of amino–azido conversion[9] and 4,6-*O*-benzylidenation.[10] A highly regioselective benzoylation of **8** with 1-(benzoyloxy)benzotriazole (BzOBT)[11] affording the β-anomeric ester **9** in excellent yield was recently developed by us.[12] We proceeded to study the one-pot benzoylation–triflation of **8** and the product **10** was successfully isolated in 79% yield. Nucleophilic substitution of **10** with sodium nitrite led to the alcohol **11** (74%). The absolute configuration of the D-allosamine derivative **11** was determined by its X-ray single-crystal analysis.[13] Its ORTEP drawing is presented in Fig. 1, indicating that the hydroxyl and benzoyloxy groups at the C3 and C1 positions orient toward the axial and equatorial directions, respectively.

With the key synthon **11** in hand, the total synthesis of phytosphingosine was carried out in a straightforward manner (Scheme 3). Benzylation of **11** under neutral conditions (Ag_2O, BnBr) provided the ether **12** in 81% yield. Regioselective ring opening of the benzylidene acetal at O6 with borane/tetrahydrofuran complex in the presence of trimethylsilyl trifluoromethanesulfonate[14] furnished the primary alcohol **13**[15] (87%), which was subjected to hydride reduction to produce the triol **14** in 76% yield. Oxidative cleavage of C–C single bond between the vicinal dihydroxyl groups of **14** with sodium periodate gave the cyclic hemi-acetal **15** in 94% yield. Wittig reaction of **15**

Scheme 3.

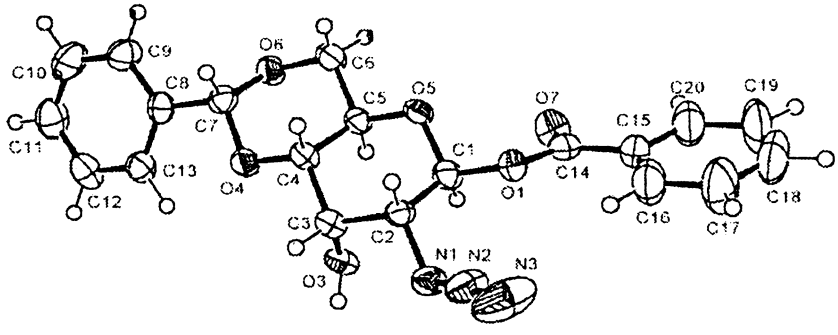

Figure 1. ORTEP drawing of compound **11**.

with $Ph_3P{=}CHC_{12}H_{25}$ **3** yielded the (*Z*)-olefin **16** (87%), which was further reduced under hydrogenation conditions to afford the expected target molecule **1** in 96% yield. Comparison of our data of its per-acetylated derivative **17** with the literature report[8e] revealed identity with respect to ^1H and ^{13}C spectra.

In conclusion, we have successfully developed a straightforward route to synthesize D-*ribo*-C_{18}-phytosphingosine **1** from D-glucosamine hydrochloride **7** in ten steps in 18.4% overall yield. Conversion of **7** into 2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranosyl benzoate **11** was efficiently achieved in four steps. A three-stepped functional group transformation of **11** led to 5-azido-5-deoxy-3,4-di-*O*-benzyl-L-allitol **14**, which underwent oxidative cleavage of C1–C2 single bond, coupling with Wittig reagent **3**, and one-pot reduction of azido group, (*Z*)-double bond as well as two benzyl groups under hydrogenation conditions to give the target compound **1**.

Acknowledgements

We dedicate this paper to Professor Chun-Chen Liao on the occasion of his 60th birthday. This work was supported by the National Science Council of Republic of China (NSC 90-2323-B-001-008).

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13. Colorless crystals from chloroform/hexane, $C_{20}H_{17}N_3O_6$, fw = 395.37, crystal dimensions: 0.38×0.31×0.13 mm^3, crystal system: orthorhombic, space group: $P2_1$, unit cell dimensions: $a = 6.1725(7)$, $b = 8.6279(17)$, $c = 18.2294(22)$ Å, $V = 965.83(25)$ Å^3, $Z = 2$, $D_{calcd} = 1.360$ g cm^{-3}, wavelength = 0.71073 Å, $F(000) = 412$, $\mu = 0.10$ mm^{-1}, $2\theta(\max) = 50.0$. The deposition number at the Cambridge Crystallographic Data Centre is CCDC 173067.
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15. The selected physical data of new compounds is listed. Compound **13**: ^1H NMR (400 MHz, $CDCl_3$) δ 8.07–8.05 (m, 2H, ArH), 7.59–7.55 (m, 1H, ArH), 7.45–7.25 (m, 12H, ArH), 6.28 (d, $J = 8.4$ Hz, 1H, H-1), 4.88 (d, $J = 11.2$ Hz, 1H, $PhCH_2$), 4.80 (d, $J = 11.2$ Hz, 1H, $PhCH_2$), 4.62 (d, $J = 11.6$ Hz, 1H, $PhCH_2$), 4.54 (d, $J = 11.6$ Hz, 1H, $PhCH_2$), 4.22 (t, $J = 2.4$ Hz, 1H, H-3), 4.18 (ddd, $J = 9.6$, 6.0, 3.0 Hz, 1H, H-5), 3.90 (ddd, $J = 12.2$, 5.1, 3.0 Hz, 1H, H-6a), 3.75 (ddd, $J = 12.2$, 8.0, 6.0 Hz, 1H, H-6b), 3.62 (dd, $J = 9.6$, 2.4 Hz, 1H, H-4), 3.49 (dd, $J = 8.4$, 2.4 Hz, 1H, H-2), 1.71 (dd, $J = 8.0$, 5.1 Hz, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.64 (C), 137.89 (C), 137.35 (C),

133.72 (CH), 130.04 (CH), 128.91 (C), 128.59 (CH), 128.49 (CH), 128.29 (CH), 128.14 (CH), 127.97 (CH), 127.92 (CH), 127.75 (CH), 92.30 (CH), 74.94 (CH_2), 74.86 (CH), 74.72 (CH), 73.94 (CH_2), 72.05 (CH), 62.35 (CH), 61.46 (CH_2); HRMS (FAB, M^+–H) calcd for $C_{27}H_{26}N_3O_6$ 488.1822, found 488.1826. Compound **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.29 (m, 10H, ArH), 4.72 (d, J=11.2 Hz, 2H, $PhCH_2$), 4.66 (d, J=11.2 Hz, 1H, $PhCH_2$), 4.60 (d, J=11.2 Hz, 1H, $PhCH_2$), 3.91–3.81 (m, 4H), 3.78–3.74 (m, 3H), 3.68–3.65 (m, 1H), 2.67 (d, J=3.9 Hz, 1H, OH), 2.07 (s, 1H, OH), 1.90 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.42 (C), 137.20 (C), 128.60 (CH), 128.56 (CH), 128.22 (CH), 128.15 (CH), 128.10 (CH), 79.07 (CH), 78.82 (CH), 73.72 (CH_2), 73.66 (CH_2), 71.52 (CH), 63.82 (CH_2), 63.52 (CH), 62.36 (CH_2); HRMS (FAB, MH^+) calcd for $C_{20}H_{26}N_3O_5$ 388.1872, found 388.1871. Compound **15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.25 (m, 10H, ArH), 5.15 (dd, J=5.5, 4.4 Hz, 1H, H-1), 4.84 (d, J=11.2 Hz, 1H, $PhCH_2$), 4.80 (d, J=12.0 Hz, 1H, $PhCH_2$), 4.72 (d, J=12.0 Hz, 1H, $PhCH_2$), 4.71 (d, J=11.2 Hz, 1H, $PhCH_2$), 4.06 (t, J=2.8 Hz, 1H, H-3), 3.86 (d, J=6.4 Hz, 2H, H-5), 3.45 (dt, J=2.8, 6.4 Hz, 1H, H-4), 3.36 (dd, J=5.5, 2.8 Hz, H-2), 2.99 (d, J=4.4 Hz 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.30 (C), 136.80 (C), 128.56 (CH), 128.47 (CH), 128.30 (CH), 128.07 (CH), 127.89 (CH), 127.81 (CH), 127.73 (CH), 91.81 (CH), 77.83 (CH), 75.76 (CH_2), 74.36 (CH), 71.02 (CH_2), 61.72 (CH_2), 56.72 (CH); HRMS (FAB, MH^+) calcd for $C_{19}H_{22}N_3O_4$ 356.1610, found 356.1619. Compound **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.25 (m, 10H, ArH), 5.78 (td, J=7.2, 11.2 Hz, 1H, H-6), 5.45 (dd, J=11.2, 9.4 Hz, 1H, H-5), 4.73 (d, J=11.2 Hz, 1H, $PhCH_2$), 4.62 (d, J=11.2 Hz, 1H, $PhCH_2$), 4.61 (d, J=11.2 Hz, 1H, $PhCH_2$), 4.41 (dd, J=9.4, 5.0 Hz, 1H, H-4), 4.33 (d, J=11.2 Hz, 1H, $PhCH_2$), 3.86 (dd, J=11.6, 5.0 Hz, 1H, H-1a), 3.79 (dd, J=11.6, 5.0 Hz, 1H, H-1b), 3.68 (t, J=5.0 Hz, 1H, H-3), 3.56 (t, J=5.0 Hz, 1H, H-2), 2.02–1.97 (m, 2H, H-7), 1.30 (bs, 20H, $10CH_2$), 0.86 (t, J=6.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.06 (C), 137.77 (C), 137.011 (CH), 128.40 (CH), 128.14 (CH), 127.77 (CH), 127.71 (CH), 125.73 (CH), 81.35 (CH), 74.40 (CH), 74.12 (CH_2), 70.21 (CH_2), 62.95 (CH), 62.69 (CH_2), 31.91 (CH_2), 29.65 (CH_2), 29.50 (CH_2), 29.37 (CH_2), 29.35 (CH_2), 28.02 (CH_2), 22.68 (CH_2), 14.10 (CH_3); HRMS (FAB, MH^+–N_2) calcd for $C_{32}H_{48}NO_3$ 494.3634, found 494.3639.