Improved Synthesis of Phytosphingosine and Dihydrosphingosine from 3,4,6-Tri-*O*-benzyl-D-galactal

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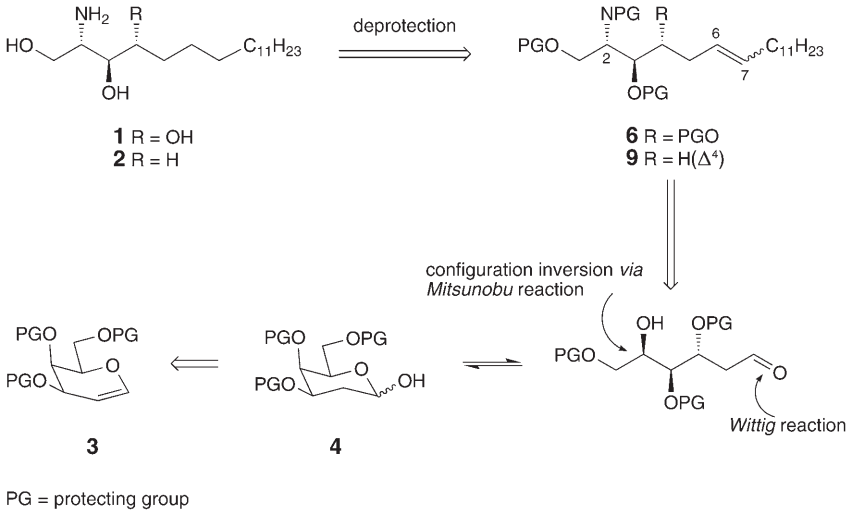
An efficient and facile synthesis of phytosphingosine and dihydrosphingosine derivatives is described with less steps and in improved overall yield (66–72%) starting from commercially available tri-*O*-benzyl-D-galactal. The key steps include *Wittig* reaction, *Mitsunobu* transformation, reduction, and deprotection.

Introduction. – Glycosphingolipids and sphingolipids are widely distributed in plasma membranes [1] and possess various biological activities [2]. As a representative example, KRN7000 [3], a glycosphingolipid analogue of agealphins [4], has shown significant immunostimulating property [5], which is related to antitumor activities in a variety of experimental and spontaneous tumor metastasis [6]. It was also reported that sphingolipids and their unnatural analogues accelerated apoptosis of U937 leukemic cell [7]. The major long-chain backbone components of glycosphingolipids and sphingolipids, such as phytosphingosine, dihydrosphingosine, and their derivatives also exhibited interesting physiological activities. For instance, D-*ribo*-(2*S*,3*S*,4*R*)-phytosphingosine (=(2*S*,3*S*,4*R*)-2-aminooctadecane-1,3,4-triol; **1**) plays an important role in cell heat-stress signaling, endocytosis, and organization of the actin cytoskeleton [8]. In addition, L-*erythro*-(2*S*,3*R*)-dihydrosphingosine (=(2*S*,3*R*)-2-aminooctadecane-1,3-diol; **2**) is known as an inhibitor of protein kinase C (PKC) [9] and acts synergistically with anticancer drugs [10]. Owing to the recognized biological importance of sphingosines and their derivatives, since they are only available in a limited amount from natural sources, efficient methods developed for their synthesis have attracted much attention from synthetic chemists.

Currently, there are many methods for synthesizing phytosphingosines and dihydrosphingosines reported in the literature [11]. Most synthetic methods employ various carbohydrate or L-serine derivatives as starting materials, and very few are based on asymmetric synthesis. However, most methods have the drawback of a lengthy synthetic route with a poor overall yield [11]. There is still a demand to develop more efficient and improved methodologies for the preparation of this type of compounds. Herein, we report a short approach to the synthesis of (2*S*,3*S*,4*R*)-C_{18}-phytosphingosine and (2*S*,3*R*)-C_{18}-dihydrosphingosine in high overall yields.

Results and Discussion. – The retrosynthetic analysis of target compounds **1** and **2** is shown in *Scheme 1*. Our goal was to rely on reduction in combination with global deprotection of intermediates **6** and **9**, which could be obtained from the key hemiacetal **4** *via Wittig* olefination [12] or *Mitsunobu* reaction [13] with inversion of the configuration. With this in mind, galactal derivative **3** served as our starting material.

Scheme 1. *Retrosynthetic Analysis of Phytosphingosine and Dihydrosphingosine*



The synthetic pathway is outlined in *Scheme 2*. Commercially available 3,4,6-tri-*O*-benzyl-D-galactal (=2,6-anhydro-1,3,4-tri-*O*-benzyl-5-deoxy-D-*arabino*-hex-5-enitol; **3**) was treated with 48% HBr and PPh_3 in CH_2Cl_2, leading to the corresponding 2-deoxysugar **4**[1]) in 87% yield. The reaction of **4** with the *Wittig* reagent derived from $C_{12}H_{25}P^+Ph_3Br^-$ in the presence of BuLi (2.5M solution in hexane) was subsequently investigated. When the reaction was carried out at $-12°$, alcohol **5**, as a mixture of two isomers, was furnished in 95% yield, whereas the diene **8** (*Scheme 3*) was exclusively generated when the reaction was performed at ambient temperature. The use of *t*-BuOK as the base instead of BuLi at either room temperature or $-12°$ further improved the yield of **8** (94%), as displayed in *Table 1*. The formation of diene **8** is presumably due to the base-promoted β-elimination in the non-cyclic isomer of **4** furnishing an α,β-unsaturated aldehyde intermediate [14].

Having introduced the chain extension, the OH group was converted into the azido group by a *Mitsunobu* reaction with inversion of the configuration. Thus, alcohols **5** and **8** were treated with diethyl azodicarboxylate (DEAD), triphenylphosphine (Ph_3P), and diphenylphosphoryl azide (DPPA) in dry THF at $-20°$ to successfully afford azides **6** and **9** in 92% and 87% yield, respectively (*cf.* [15]). It is noteworthy that the addition sequence of reagents is important for a high-yield conversion.

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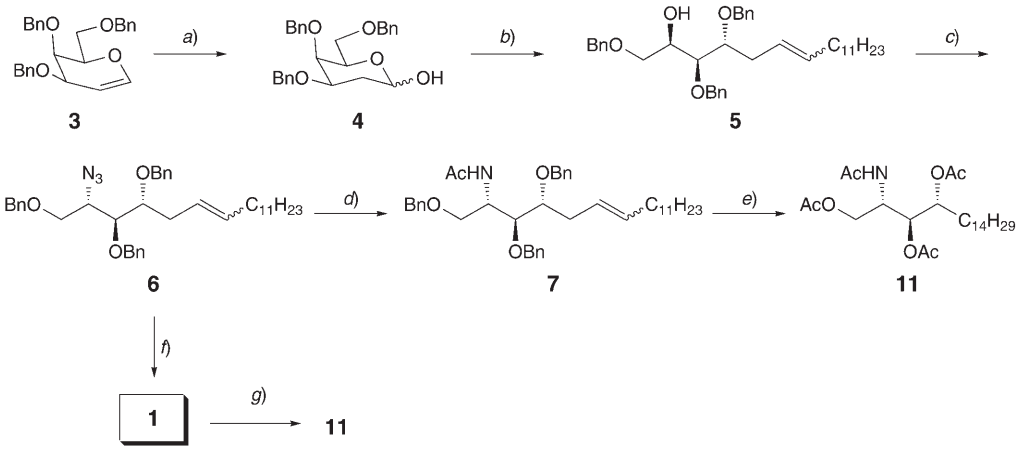
[1]) For compounds **4**–**12**, the systematic names are given in the *Exper. Part.*

Scheme 2

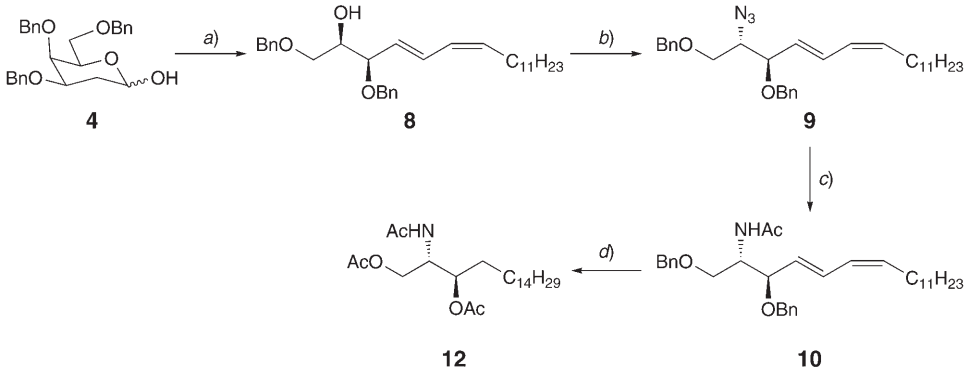


a) 48% HBr, H_2O, PPh_3/CH_2Cl_2; 87%. *b*) $C_{12}H_{25}PPh_3 \cdot Br$, BuLi, $-12°$; 95%. *c*) DPPA, Ph_3P, DEAD/THF; 92%. *d*) Ph_3P, THF/MeOH; Ac_2O, DMAP/Py; 99%. *e*) 10% Pd/C, AcOEt/MeOH; Ac_2O, DMAP/Py; 98%. *f*) 10% Pd/C, MeOH/AcOEt/AcOH. *g*) Ac_2O/Py; 92%.

Table. *The* Wittig *Reaction of Deoxysugar* **4** *with* $C_{12}H_{25}PPh_3 \cdot Br$ *under Different Conditions*

Base	Temperature	Yield [%]	Product
BuLi	$-12°$	95	**5**
BuLi	r.t.	90	**8**
t-BuOK	r.t. or $-12°$	94	**8**

Scheme 3



a) $C_{12}H_{25}PPh_3 \cdot Br$, *t*-BuOK; 94%. *b*) DPPA, Ph_3P, DEAD/THF; 87%. *c*) Ph_3P, THF/MeOH; Ac_2O, DMAP/Py; 98%. *d*) 10% Pd/C, AcOEt; Ac_2O, DMAP/Py; 95%.

With compounds **6** and **9** in hand, reduction of the azido group with Ph_3P and subsequent acetylation provided **7** and **10** in almost quantitative yield. Compounds **7**

and **10** were further reduced and deprotected under H_2 atmosphere followed by acetylation, affording the corresponding acetylated derivatives **11** and **12** of target molecules **1** and **2** in 98% and 95% yield, respectively. On the other hand, azide **6** can be also transformed to the phytosphingosine derivative **11** directly. After much experimentation examining the effects of various solvents, we found that a solution of **6** in MeOH/AcOEt/AcOH [16] with a catalytic amount of 10% Pd/C under an atmosphere of H_2 for 4 d at room temperature yielded the expected target molecule **1**, which was subjected to peracetylation to afford compound **11** in 92% yield.

In conclusion, although many efforts including *Schmidt*'s outstanding contribution [14] for the preparation of sphingosines and their derivatives were reported, phytosphingosine **1** and dihydrosphingosine derivative **12** were synthesized from the galactal derivative **3** *via* four or five steps in 68% (or 72%) and 66% yield, respectively. Compared with *Schmidt*'s protocol, the yield of the key step *Wittig* reaction in our approach is higher (94–95% *vs.* 84–89%), the other key transformation, the *Mitsunobu* reaction used by us, is also more efficient (with less steps and in higher yield) than *Schmidt*'s method. Applying our method, a variety of phytosphingosine and dihydrosphingosine derivatives may be prepared in an efficient way by the use of various *Wittig* reagents.

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Experimental Part

General. Tetrahydrofuran (THF) was distilled over Na/benzophenone. Reagents of commercial quality were purchased and used without further purification. All reactions were carried out under an Ar atmosphere in dry, freshly distilled solvents under anh. conditions, unless otherwise noted. Thin-layer chromatography (TLC) was performed using silica *60 F_{254}* aluminium plates, compound spots were visualized by UV (254 nm) and by staining with a yellow soln. containing $Ce(NH_4)_2(NO_3)_6$ (0.5 g) and $(NH_4)_6Mo_7O_{24}\cdot H_2O$ (24 g) in 6% H_2SO_4 (500 ml). Column chromatography (CC) was performed on silica gel (35–75 μm). ^{1}H- and ^{13}C-NMR spectra were recorded on a *Varian VXR-300M* or *Varian INOVA-500M* spectrometer at 20°; chemical shifts δ in ppm, relative to TMS (0 ppm), J in Hz. Mass spectra were recorded using a *PE SCLEX QSTAR* spectrometer.

3,4,6-Tri-O-*benzyl-2-deoxy*-D-*galactopyranose* (**4**). To a soln. of 3,4,6-tri-*O*-benzyl-D-galactal (**3**) (1.0 g, 2.31 mmol) in CH_2Cl_2 (15 ml), a mixture of 48% HBr (4 ml) and PPh_3 (8.6 g) in CH_2Cl_2 (40 ml) was added slowly, and the soln. was vigorously stirred for 24 h. The mixture was then extracted with CH_2Cl_2 (3 × 20 ml), the combined org. phase was washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. CC (petroleum ether/AcOEt 4:1) of the residue yielded 0.91 g (87%) of **4** (white solid) as a mixture of anomeric isomers (α/β 3:1). ^{1}H-NMR of major isomer ($CDCl_3$, 300 MHz): 7.36–7.25 (*m*, 20 H); 5.45 (*d*, J = 3.5, 1 H); 4.93 (*d*, J = 11.5, 1 H); 4.63–4.49 (*m*, 3 H); 4.50 (*d*, J = 12.0, 1 H); 4.30 (*d*, J = 12.0, 1 H); 4.13 (*t*, J = 6.0, 1 H); 4.00–3.97 (*m*, 1 H); 3.87 (br. *s*, 1 H); 3.61–3.57 (*m*, 2 H); 3.47 (*dd*, J = 6.0, 9.5, 1 H); 2.72 (br. *s*, 1 H); 2.24–2.18 (*m*, 1 H); 2.03–1.99 (*m*, 1 H). The spectroscopic data coincide with those reported previously [14].

*(2*R*,3*S*,4*R*,6*E/Z*)-1,3,4-Tris(benzyloxy)octadec-6-en-2-ol* (**5**). Dodecyl triphenylphosphonium bromide (1.76 g, 3.45 mmol) was dissolved in anh. THF (20 ml), the mixture was cooled to −12° with dry ice/EtOH. BuLi (1.1 ml, 2.76 mmol, 2.5M in hexane) was slowly added to the mixture dropwise. The mixture was stirred for 1 h. Then, the soln. was cooled to −12° again. Compound **4** (300 mg, 0.69 mmol) in THF (2 ml) was added slowly, and the mixture was maintained at this temp. for 2 h. The reaction was quenched with sat. aq. NH_4Cl, and the mixture was extracted with CH_2Cl_2 (3 × 30 ml). The combined org. phases were washed with brine, dried (Na_2SO_4), and evaporated. CC (petroleum ether/AcOEt

20:1) of the residue yielded 383 mg (95%) of **5** as a colorless oil. ^{1}H-NMR of major isomer ($CDCl_3$, 300 MHz): 7.35–7.25 (*m*, 15 H); 5.49–5.44 (*m*, 2 H); 4.67–4.44 (*m*, 6 H); 4.10–4.06 (*m*, 1 H); 3.74 (*dd*, *J* = 5.7, 8.4, 1 H); 3.61–3.58 (*m*, 1 H); 3.54–3.53 (*m*, 2 H); 3.11 (*d*, *J* = 3.0, 1 H); 2.46–2.40 (*m*, 2 H); 2.03–1.97 (*m*, 2 H); 1.25 (br. *s*, 18 H); 0.85 (*t*, *J* = 6.9, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 138.1; 138.08; 138.0; 136.1; 132.5; 130.5; 129.1; 128.4; 128.1; 127.8; 127.83; 127.6; 124.8; 79.6; 78.8; 73.5; 73.3; 72.6; 71.1; 69.7; 31.9; 29.64; 29.6; 29.4; 29.3; 28.8; 27.6; 22.7; 14.1. ESI-MS: 587.4 ($[M+H]^+$), 609.4 ($[M+Na]^+$). The spectroscopic data coincide with those reported previously [14].

*(2*S*,3*S*,4*R*,6*E/Z*)-2-Azido-1,3,4-tris(benzyloxy)octadec-6-ene* (=*1,1′,1″-{[(2*S*,3*S*,4*R*,6*E/Z*)-2-Azidooctadec-6-ene-1,3,4-triyl]tris(oxymethanediyl)}tribenzene*; **6**). To a soln. of compound **5** (200 mg, 0.34 mmol) in anh. THF (30 ml) were added Ph_3P (356 mg, 1.36 mmol), DEAD (237 mg, 205 µl, 1.36 mmol), and DPPA (374 mg, 293 µl, 1.36 mmol) at −20°. The mixture was stirred for 6 h at this temp., and then allowed to warm to r.t. and stirred overnight. The solvent was evaporated under reduced pressure, and the residue was directly subjected to flash CC (petroleum ether/AcOEt 220:1) to give **6** (192 mg, 92%) as a syrup. IR (KBr): 3088, 3064, 3030, 2924, 2854, 2097, 1496, 1454, 1098, 1028, 735, 697. ^{1}H-NMR of major isomer ($CDCl_3$, 500 MHz): 7.39–7.26 (*m*, 15 H); 5.53–5.48 (*m*, 2 H); 4.68–4.65 (*m*, 2 H); 4.61 (*d*, *J* = 11.5, 1 H); 4.55–4.49 (*m*, 3 H); 3.90–3.88 (*m*, 1 H); 3.78 (*dd*, *J* = 3.0, 10.0, 1 H); 3.71–3.65 (*m*, 3 H); 2.66–2.45 (*m*, 2 H); 2.06–2.02 (*m*, 2 H); 1.37–1.26 (*m*, 18 H); 0.90 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 138.2; 138.0; 137.9; 133.8; 132.5; 128.4; 128.3; 127.9; 127.8; 127.71; 127.70; 127.67; 127.60; 124.9; 79.5; 78.9; 73.8; 73.3; 71.9; 70.2; 62.2; 32.7; 31.9; 29.6; 29.6; 29.4; 29.3; 27.9; 27.6; 22.7; 14.1.

*(2*S*,3*S*,4*R*,6*E/Z*)-2-Acetamide-1,3,4-tris(benzyloxy)octadec-6-ene* (=N-*[(2*S*,3*S*,4*R*,6*E/Z*)-1,3,4-Tris(benzyloxy)octadec-6-en-2-yl]acetamide*; **7**). To a soln. of **6** (54 mg, 0.088 mmol) in THF (3 ml) and MeOH (6 ml) was added Ph_3P (116 mg, 0.44 mmol), and the mixture was stirred under reflux for 3 h. The mixture was evaporated to dryness, the residue was dissolved in pyridine (3.0 ml), and Ac_2O (1.5 ml) was added dropwise at 0°. The mixture was stirred for 6 h, and the solvent was removed in vacuum. CC (petroleum ether/AcOEt 3:1 to 2:1) of the residue gave the title compound **7** (55 mg, 99%) as a colorless oil. ^{1}H-NMR of major isomer ($CDCl_3$, 300 MHz): 7.33–7.26 (*m*, 15 H); 5.65 (*d*, *J* = 9.3, 1 H); 5.52–5.46 (*m*, 2 H); 4.78 (*d*, *J* = 11.4, 1 H); 4.60 (*d*, *J* = 12.0, 1 H); 4.52–4.40 (*m*, 5 H); 4.35–4.25 (*m*, 1 H); 3.78–3.73 (*m*, 2 H); 3.60–3.50 (*m*, 2 H); 2.51–2.43 (*m*, 2 H); 2.13–1.99 (*m*, 2 H); 1.78 (*s*, 3 H); 1.25–1.24 (*m*, 32 H); 0.85 (*t*, *J* = 6.6, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 169.4; 138.5; 138.0; 132.0; 128.4; 127.9; 127.8; 127.6; 125.6; 79.7; 79.3; 73.6; 73.0; 71.7; 68.9; 49.6; 31.9; 29.7; 29.4; 29.35; 27.7; 27.5; 23.4; 22.7; 14.1. HR-ESI-MS: 628.4364 ($[M+H]^+$, $C_{34}H_{50}NO_3^+$; calc. 628.4360).

*(2*R*,3*R*,4*E*,6*Z*)-1,3-Bis(benzyloxy)octadeca-4,6-dien-2-ol* (**8**). Dodecyl triphenylphosphonium bromide (587 mg, 1.15 mmol) was dissolved in anh. THF (20 ml), the soln. was cooled with an ice-salt bath, and *t*-BuOK (103 mg, 0.92 mmol) was added. The suspension was stirred for 1 h at r.t. The mixture was cooled down again, compound **4** (100 mg, 0.23 mmol) in THF (2 ml) was added slowly, and the soln. was stirred for 3 h. The reaction was quenched with sat. aq. NH_4Cl, and the mixture was extracted with CH_2Cl_2 (3 × 30 ml). The combined org. phase was washed with brine, dried (Na_2SO_4), and evaporated. CC (petroleum ether/AcOEt 20:1) of the residue gave **8** as a colorless oil (101 mg, 92%). ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.32–7.25 (*m*, 2 H); 6.57 (*dd*, *J* = 6.9, 15.3, 1 H); 6.01 (*t*, *J* = 10.5, 1 H); 5.47–5.86 (*m*, 2 H); 4.60 (*d*, *J* = 11.1, 1 H); 4.56 (*d*, *J* = 11.7, 1 H); 4.50 (*d*, *J* = 11.7, 1 H); 4.34 (*d*, *J* = 11.1, 1 H); 3.98 (*t*, *J* = 7.5, 1 H); 3.78 (br. *s*, 1 H); 3.62–3.47 (*m*, 2 H); 2.75 (br. *s*, 1 H); 2.22–2.08 (*m*, 2 H); 1.42–1.25 (*m*, 18 H); 0.88 (*t*, *J* = 6.9, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 138.0; 133.9; 130.4; 128.9; 128.3; 127.9; 127.7; 127.39; 80.4; 73.4; 70.6; 70.40; 31.9; 29.6; 27.9; 22.7; 14.6. HR-ESI-MS: 501.3332 ($[M+Na]^+$, $C_{32}H_{46}NaO_3^+$; calc. 501.3339). The spectroscopic data coincide with those reported previously [14].

*(2*S*,3*R*,4*E*,6*Z*)-2-Azido-1,3-bis(benzyloxy)octadeca-4,6-diene* (=*1,1′-({(2*S*,3*R*,4*E*,6*Z*)-2-Azidooctadeca-4,6-diene-1,3-diyl]bis(oxymethanediyl)}dibenzene*; **9**). Compound **9** was obtained in 87% yield according to the procedure described for the synthesis of **6**. Colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.25–7.17 (*m*, 10 H); 6.47 (*dd*, *J* = 10.8, 15.3, 1 H); 5.96 (*t*, *J* = 10.8, 1 H); 5.56–5.43 (*m*, 2 H); 4.54 (*d*, *J* = 11.7, 1 H); 4.46–4.41 (*m*, 2 H); 4.28 (*d*, *J* = 11.7, 1 H); 3.93 (*dd*, *J* = 5.4, 8.4, 1 H); 3.65–3.48 (*m*, 3 H); 2.10 (*dd*, *J* = 6.9, 14.4, 2 H); 1.47–1.18 (*m*, 18 H); 0.80 (*t*, *J* = 6.9, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 137.9; 137.8; 134.3; 130.9; 128.44; 128.4; 127.7; 127.6; 127.2; 79.2; 73.4; 70.3; 69.4; 64.4; 31.9; 29.7; 29.6; 29.56; 29.5; 29.3; 29.26; 27.8; 22.7; 14.1. HR-ESI-MS: 521.3856 ($[M+NH_4]^+$, $C_{32}H_{50}NO_3^+$; calc. 521.3850).

(2S,3R,4E,6Z)-2-Acetamide-1,3-bis(benzyloxy)octadeca-4,6-diene (= N-*[(2S,3R,4E,6Z)-1,3-Bis(benzyloxy)octadeca-4,6-dien-2-yl]acetamide*; **10**). Compound **10** was obtained according to the procedure described for the synthesis of **7**. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.31–7.25 (*m*, 10 H); 6.50 (*dd*, *J* = 10.8, 14.7, 1 H); 6.00 (*t*, *J* = 10.5, 1 H); 5.73 (*d*, *J* = 9.0, 1 H); 5.63–5.44 (*m*, 2 H); 4.64 (*d*, *J* = 12.0, 1 H); 4.60 (*d*, *J* = 11.7, 1 H); 4.50 (*d*, *J* = 11.7, 1 H); 4.30 (*d*, *J* = 11.7, 1 H); 4.29–4.22 (*m*, 1 H); 4.01 (*t*, *J* = 7.5, 1 H); 3.81 (*dd*, *J* = 7.5, 9.9, 1 H); 3.55 (*dd*, *J* = 3.9, 9.6, 1 H); 2.18–2.13 (*m*, 2 H); 1.89 (*s*, 3 H); 1.25 (br. *s*, 18 H); 0.87 (*t*, *J* = 6.9, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 169.5; 138.3; 138.0; 133.5; 130.1; 129.9; 128.4; 127.8; 127.6; 127.4; 79.3; 77.3; 73.1; 70.4; 68.4; 51.9; 31.9; 29.6; 29.5; 29.33; 29.3; 27.8; 23.4; 22.7. HR-ESI-MS: 542.3605 ($[M+Na]^+$, $C_{34}H_{49}NNaO_3^+$; calc. 542.3610).

(2S,3S,4R)-N,O,O,O-*Tetraacetyl*-D-ribo-*phytosphingosine* (= N-*[(1S,2S,3R)-2,3-Bis(acetyloxy)-1-[(acetyloxy)methyl]heptadecyl]acetamide*; **11**). *Method A*. Compound **6** (18 mg, 0.029 mmol) and 10% Pd/C (20.0 mg) in MeOH (6.0 ml), AcOEt (3.0 ml), and AcOH (1.0 ml) were stirred for 4 d under H_2. The catalyst was then removed by filtration through *Celite*, and the filtrate was concentrated. The residue was dissolved in pyridine (5.0 ml), Ac_2O (1.0 ml) was added, and the mixture was stirred for 4 h. The mixture was concentrated. CC (petroleum ether/AcOEt 2 : 1) of the residue provided product **11** (13 mg, 92%) as a white solid. ^{1}H-NMR ($CDCl_3$, 500 MHz): 5.92 (*d*, *J* = 9.5, 1 H); 5.10 (*dd*, *J* = 3.0, 8.5, 1 H); 4.95–4.92 (*m*, 1 H); 4.50–4.44 (*m*, 1 H); 4.29 (*dd*, *J* = 5.0, 11.5, 1 H); 4.00 (*dd*, *J* = 3.0, 11.5, 1 H); 2.06 (*s*, 3 H); 2.03 (*s*, 6 H); 2.00 (*s*, 3 H); 1.78–1.58 (*m*, 2 H); 1.24 (br. *s*, 26 H); 0.88 (*t*, *J* = 7.0, 3 H). The spectroscopic data coincide with those reported previously [17].

Method B. Compound **7** (50 mg, 0.08 mmol) and 10% Pd/C (10.0 mg) in MeOH (8.0 ml) and AcOEt (4.0 ml) were stirred for 2 d under H_2. The catalyst was then removed by filtration through *Celite*, and the filtrate was concentrated. The residue was dissolved in pyridine (2 ml) and Ac_2O (1 ml), and the mixture was stirred for 6 h. The mixture was concentrated. CC (petroleum ether/AcOEt 2 : 1) of the residue provided product **11** (42 mg, 98%).

(2S,3R)-N,O,O-*Triacetyl*-D-erythro-*dihydrosphingosine* (= N-*[(1S,2R)-2-(Acetyloxy)-1-[(acetyloxy)methyl]heptadecyl]acetamide*; **12**). Compound **12** was obtained in 95% yield according to the procedure described for the synthesis of **11**, *Method B.* ^{1}H-NMR ($CDCl_3$, 500 MHz): 5.85 (*d*, *J* = 9.5, 1 H); 4.95 (*dt*, *J* = 5.0, 10.5, 1 H); 4.42–4.36 (*m*, 1 H); 4.25 (*dd*, *J* = 5.0, 11.5, 1 H); 4.06 (*dd*, *J* = 3.5, 11.5, 1 H); 2.07 (*s*, 3 H); 2.06 (*s*, 3 H); 2.00 (*s*, 3 H); 1.65–1.52 (*m*, 2 H); 1.33–1.24 (br. *s*, 26 H); 0.88 (*t*, *J* = 7.0, 3 H). The spectroscopic data coincide with those reported previously [18].

REFERENCES

[1] J. M. Kaufer, S. Hakomori, 'Handbook of Lipids Research: Sphingolipid Biochemistry', Plenum Press, New York, 1983, p. 1; T. Kolter, K. Sandhoff, *Angew. Chem., Int. Ed.* **1999**, *38*, 1532.

[2] Y. A. Hannun, R. M. Bell, *Science* **1989**, *243*, 500; E. A. Cremeti, S. A. Fischl, *Lipids* **2000**, *35*, 937; J. M. Harouse, S. Bhat, S. L. Spitalnik, *Science* **1991**, *253*, 320.

[3] K. Morita, K. Motoki, K. Akimoto, T. Natori, T. Sakai, E. Sawa, K. Yamaji, Y. Koezuka, E. Kobayashi, H. Fukushima, *J. Med. Chem.* **1995**, *38*, 2176; Y. Hayakawa, S. Rovero, G. Forni, M. J. Smyth, *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 9464.

[4] T. Natori, M. Morita, K. Akimoto, Y. Koezuka, *Tetrahedron* **1994**, *50*, 2771.

[5] T. Kawano, J. Cui, Y. Koezuka, I. Toura, Y. Kaneko, K. Motoki, H. Ueno, R. Nakagawa, H. Sato, E. Kondo, H. Koseki, M. Taniguchi, *Science* **1997**, *278*, 1626.

[6] R. Nakagawa, K. Motoki, H. Ueno, R. Lijima, H. Nakamura, E. Kobayashi, A. Shimosaka, Y. Koezuka, *Cancer Res.* **1998**, *58*, 1202; R. Nakagawa, I. Serizawa, K. Motoki, H. Ueno, R. Lijima, H. Nakamura, E. Kobayashi, Y. Koezuka, *Oncol. Res.* **2000**, *12*, 51; N. Fuji, Y. Ueda, H. Fujiwara, T. Toh, T. Yoshimura, H. Yamagishi, *Clin. Cancer Res.* **2000**, *6*, 3380; T. Kawano, J. Cui, Y. Koezuka, I. Toura, Y. Kaneko, H. Sato, E. Kondo, M. Harada, H. Koseki, T. Nakayama, *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 5690; E. Cretney, K. Takeda, H. Yagita, M. Glaccum, J. J. Peschon, M. J. Smyth, *J. Immunol.* **2002**, *168*, 1356.

[7] Y. T. Chang, J. Choi, S. Ding, E. E. Prieschl, T. Baumruker, J. M. Lee, S. K. Chung, P. G. Schultz, *J. Am. Chem. Soc.* **2002**, *124*, 1856.

[8] B. Zanolari, S. Friant, K. Funato, C. Sütterlin, B. J. Stevenson, H. Riezman, *EMBO J.* **2000**, *19*, 2824; R. Schneiter, *BioEssays* **1999**, *21*, 1004; G. B. Wells, R. C. Dickson, R. L. Lester, *J. Biol. Chem.* **1998**, *273*, 7235.
[9] R. A. Rajewski, D. G. Kosednar, T. A. Matches, O. S. Wong, K. Burchett, K. Thakker, *J. Pham. Biomed. Anal.* **1995**, *13*, 247; C. W. Sachs, A. R. Safa, S. D. Harrison, R. L. Fine, *J. Biol. Chem.* **1995**, *270*, 26639.
[10] B. J. Maurer, M. C. Cabot, C. P. Reynolds, *AACR Annu. Meet. Abstr.* **2000**, 1520; G. K. Schwartz, A. Haimovitz-Friedman, S. K. Dhupar, D. Ehleiter, P. Maslak, L. Lai Jr., F. Loganzo, D. P. Kelsen, Z. Fuks, A. P. Albino. *J. Natl. Cancer Inst.* **1995**, *87*, 1394.
[11] M. Lombardo, M. G. Capdevila, F. Pasi, C. Trombini, *Org. Lett.* **2006**, *8*, 3303; C. C. Lin, G. T. Fan, J. M. Fang, *Tetrahedron Lett.* **2003**, *44*, 5281; H. Y. Chiu, D.-L. M. Tzou, L. N. Patkar, C. C. Lin, *J. Org. Chem.* **2003**, *68*, 5788; A. J. Ndakala, M. Hashemzadeh, R. C. So, A. R. Howell, *Org. Lett.* **2002**, *4*, 1719; S. Raghavan, A. Rajender, *J. Org. Chem.* **2003**, *68*, 7094; K. Mori, K. Uenishi, *Liebigs Ann. Chem.* **1994**, 41; J. Yoshida, M. Nakagawa, H. Seki, T. Hino, *J. Chem. Soc., Perkin Trans. 1* **1992**, 343; W. R. Roush, M. A. Adam, *J. Org. Chem.* **1985**, *50*, 3752; E. J. Reist, P. H. Christie, *J. Org. Chem.* **1970**, *10*, 3521; A. Dondoni, G. Fantin, M. Fogagnolo, P. Pedrini, *J. Org. Chem.* **1990**, *55*, 1439; S. Sugiyama, M. Honda, T. Komori, *Liebigs Ann. Chem.* **1988**, 619; J. Mulzer, C. Brand, *Tetrahedron* **1986**, *42*, 5961; S. Sugiyama, M. Honda, T. Komori, *Liebigs Ann. Chem.* **1990**, 1069.
[12] G. Wittig, O. Schöllkopf, *Chem. Ber.* **1954**, *87*, 1318.
[13] O. Mitsunobu, *Synthesis* **1981**, 1.
[14] R. Wild, R. R. Schmidt, *Liebigs Ann.* **1995**, 755.
[15] B. Jiang, C. G. Yang, J. Wang, *J. Org. Chem.* **2002**, *67*, 1396.
[16] X. S. Ye, F. Sun, M. Liu, Q. Li, Y. H. Wang, G. S. Zhang, L. H. Zhang, X. L. Zhang, *J. Med. Chem.* **2005**, *48*, 3688.
[17] S. Y. Luo, S. R. Thopate, C. Y. Hsu, S. C. Hung, *Tetrahedron Lett.* **2002**, *43*, 4889.
[18] H. Azuma, S. Tamagaki, K. Ogino, *J. Org. Chem.* **2000**, *65*, 3538.

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