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Stereoselective total synthesis of sphingolipids

PARAMESH JANGILI, PERLA RAMESH and BISWANATH DAS*
Natural Products Chemistry Division, Indian Institute of Chemical Technology, Tarnaka, Hyderabad, Telangana 500 007, India
e-mail: biswanathdas@yahoo.com

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Abstract. A novel sphingosine, 1,2-diacetyl D-*erythro*-sphinganine having a characteristic almond flavour was isolated from the edible mushroom *Grifola gargal*. We have synthesized this sphinganine along with the three other sphingolipids, such as 1,2-diacetyl L-*threo*-sphinganine, D-*erythro*-sphinganine triacetate and L-*threo*-sphinganine triacetate using Garner aldehyde as the starting material involving the Grignard reaction and Mitsunobu inversion. The sphingolipids 1,2-diacetyl D-*erythro*-sphinganine and 1,2-diacetyl L-*threo*-sphinganine have been synthesized for the first time.

Keywords. 1,2-Diacetyl D-*erythro*-sphinganine; 1,2-diacetyl L-*threo*-sphinganine; D-*erythro*-sphinganine triacetate; sphingolipids; total synthesis; Garner aldehyde.

1. Introduction

Sphingolipids are important structural and functional components of essentially all eukaryotic cells and are abundantly located in all plasma membranes as well as in some intracellular organelles.[1,2] They exist as structural components of cell membranes in animals, plants and some microbial systems.[3] Sphingosine **1** and sphinganine (dihydrosphingosine) **2** (Figure 1) are naturally occurring bioactive compounds (long-chain, aliphatic, 2-amino-1,3 diols). Dihydrosphingosines are biosynthetic precursors of sphingolipids (e.g., ceramides, sphingomyelin, cerebrosides and gangliosides), which play important roles in biological pathways such as cell regulation and signal transduction. Sphingoid bases contain two chiral centres, *viz.,* at carbon atoms 2 and 3. Natural sphingoid bases occur in the D-*erythro* (2*S*, 3*R*) configuration, but other additional unnatural isomers have also been reported. Among the unnatural sphingoid bases L-*threo*-(2*S*, 3*S*) dihydrosphingosine (safingol) **3** (Figure 1) is of particular interest due to its medicinal importance. Safingol is an antineoplastic, antipsoriatic drug[4] and a competitive inhibitor of protein kinase C.[5]

Recently, Choi *et al.,* isolated[6] a novel sphingosine, 1,2-diacetyl D-*erythro*-sphinganine (**4**) (Figure 2), from the edible mushroom *Grifola gargal*, having a characteristic almond flavour. This mushroom is collected and eaten by native people of southern Argentina and Chile. The compound **4** suppresses the formation of osteoclasts.

In continuation of our work carried out on the synthesis of natural bioactive compounds,[7] herein we describe an efficient stereoselective total synthesis of naturally occurring sphingolipid 1,2-diacetyl D-*erythro*-sphinganine (**4**) along with three other sphingolipids, such as 1,2-diacetyl L-*threo*-sphinganine (**5**) (C-3 epimer of **4**), D-*erythro*-sphinganine triacetate (**6**) (triacetyl derivative of compound **2**) and L-*threo*-sphinganine triacetate (**7**) (triacetyl derivative of compound **3**, safingol) (Figure 2). Our planned approach to the synthesis of the target molecules was initiated from Garner aldehyde (**9**) involving the Grignard reaction and Mitsunobu inversion. To our knowledge, there are a few reports towards the total synthesis of sphingolipids **6** and **7**.[8] However, synthesis of the sphingolipids **4** and **5** are reported here for the first time.

2. Experimental

2.1 *General*

Infrared spectra were recorded on Perkin-Elmer RX1 FT-IR spectrophotometer. NMR spectra were recorded on Inova 500 MHz and Bruker 300 MHz spectrometers using $CDCl_3$ and CD_3OD as solvents and Me_4Si as internal standard. The chemical shifts are expressed as δ values in parts per million (ppm) and the coupling constants (J) are given in hertz (Hz). ESIMS were recorded with VG-Autospec micromass. Optical rotations were

*For correspondence
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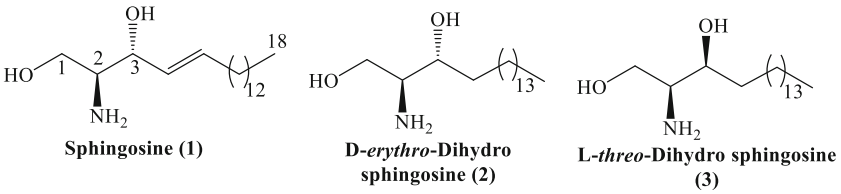


Figure 1. Structures of sphingosine (**1**) and sphinganines (dihydro sphingosines) (**2** and **3**).

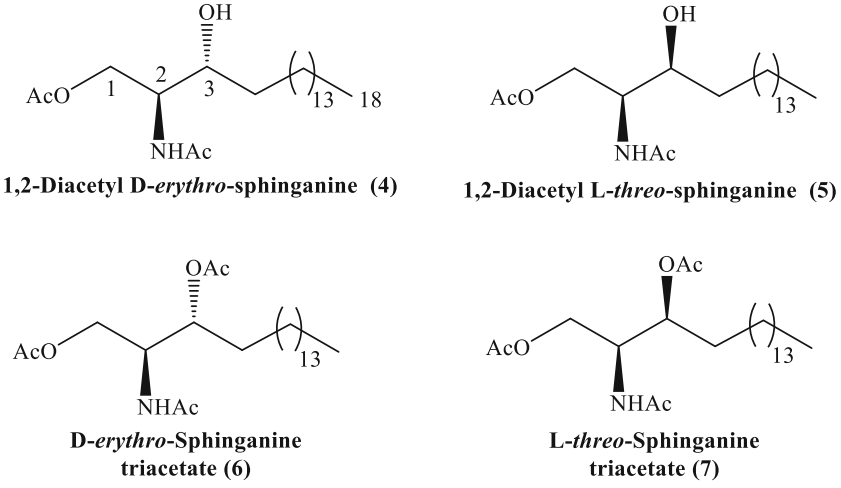


Figure 2. Structures of synthesized sphinganines (**4**–**7**).

measured with *JASCO DIP 360* digit polarimeter. All reactions were monitored by thin-layer chromatography (TLC) using silica gel F_{254} pre-coated plates.

2.2 *tert-Butyl (S)-4-((S)-1-hydroxyhexadecyl)-2, 2-dimethyloxa zolidine-3-carboxylate **(10)***

To the solution of Garner aldehyde (**9**) (2.0 g, 8.72 mmol) in THF (10 mL), was added at −78 °C pentadecyl magnesium bromide in THF (10 mL) which was prepared from 1-bromopentadecane (7.58 mL, 26.16 mmol) and Mg (0.847 g, 34.88 mmol) in the usual manner. The mixture was stirred at the same temperature (−78 °C) for 1 hour and then gradually brought to r.t. The mixture was then stirred overnight at r.t. to produce the mixture of diastereomers **10** and **10a**. The reaction was quenched by the addition of aqueous saturated NH_4Cl (10 mL) and extracted with AcOEt. The organic layer was washed with 5% aqueous HCl (10 mL), water, brine and then dried over Na_2SO_4. The two diastereomers **10** and **10a** were separated by careful CC (silica gel, 100–200 mesh, 0–5% increasing amount of AcOEt in hexane) to produce two diastereomeric alcohols **10** and **10a** in the ratio 9:1 (*syn*:*anti*, 9:1) with 86% yield. The pure alcohol **10** (2.98 g) was obtained as a colorless oil. $[\alpha]_D^{25} = -32.2$ (c =2.0, $CHCl_3$). IR $\tilde{o}_{max}$ (KBr)/cm^{-1}: 3440, 2925, 2855, 1701, 1366, 1258, 1175, 1061. ^{1}H NMR (500 MHz, $CDCl_3$): 4.10–3.49 (*m*, 4H); 1.62–1.55 (*m*, 2H); 1.49 (*s*, 12H); 1.45 (*s*, 3H); 1.25 (br. *s*, 26H); 0.88 (*t*, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 154.1; 94.2; 81.0; 72.9; 64.7; 62.3; 34.4; 32.7; 31.8; 29.6; 29.6; 29.5; 28.3; 26.4; 26.0; 24.2; 22.6; 14.0. ESIMS: m/z 442 $[M+H]^+$. Anal Calcd. for $C_{26}H_{51}NO_4$: C, 70.70; H, 11.64%. Found: C, 70.60; H, 11.68%.

2.3 *tert-Butyl ((2S,3S)-1,3-dihydroxyoctadecan-2-yl) carbamate **(11)***

Compound **10** (2.8 g, 6.34 mmol) and pyridinium *p*-toluene sulfonate (0.159 g, 0.634 mmol) were dissolved in MeOH (10 mL) and stirred at r.t. for 2 h. The solvent was removed under reduced pressure. The residue was purified by flash CC (silica gel, hexane/AcOEt, 7:3) to give pure compound **11** (2.34 g, 92%) as a white solid. $[\alpha]_D^{25} = +16.2$ (c = 2.5, $CHCl_3$). IR $\tilde{o}_{max}$ (KBr)/cm^{-1}: 3430, 2975, 2855, 1690, 1360, 1255, 1175, 1060. ^{1}H NMR (500 MHz, $CDCl_3$): 5.22 (*d*, J = 7.9 Hz, 1H); 4.01 (*dd*, J = 3.4, 11.4 Hz, 1H); 3.82 (*d*, J = 3.8 Hz, 1H); 3.76 (*m*, 1H); 3.53 (*m*, 1H); 2.54 (br. *s*, 2H); 1.56–1.48 (*m*, 2H); 1.46 (*s*, 9H); 1.25 (br. *s*, 26H); 0.88 (*t*, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 156.1; 79.6; 73.7; 62.3; 54.9; 34.2; 31.8; 29.6; 29.5; 29.3; 28.3; 25.9; 22.6; 14.0. ESIMS: m/z 402 $[M+H]^+$. Anal Calcd. for $C_{23}H_{47}NO_4$: C, 68.78; H, 11.80%. Found: C, 68.90; H, 11.75%.

2.4 *(2S,3S)-2-((tert-Butoxycarbonyl)amino)-3-hydroxy octadecyl acetate **(8)***

To a solution of 1,3-diol **11** (2.2 g, 5.47 mmol) in dry CH_2Cl_2 (10 mL), Et_3N (0.76 mL, 5.47 mmol) was added, followed by Ac_2O (0.51 mL, 5.47 mmol) was added at 0°C and the reaction mixture was allowed to r.t. After completion of reaction (2 h), the reaction mixture was washed with brine (10 mL) and water (10 mL), dried over Na_2SO_4 and evaporated. The crude product was purified by silica gel CC (hexane/AcOEt, 9:1) to give pure monoacetyl ester **8** (1.87 g, 77%) as a white solid. $[\alpha]_D^{25} = +3.4$ (c =0.6, $CHCl_3$). IR $\tilde{o}_{max}$ (KBr)/cm^{-1}: 3350, 2917, 2850, 1743, 1685, 1531, 1367, 1232, 1173, 1049. ^{1}H NMR (300 MHz, $CDCl_3$): 4.91 (*d*, J = 8.0 Hz, 1H); 4.28–4.17 (*m*, 1H); 4.06 (*dd*, J = 6.1, 11.0 Hz, 1H); 3.79 (*m*, 1H); 3.69–3.58 (*m*, 1H); 2.32 (br. *s*, 1H); 2.08 (*s*, 3H); 1.55–1.48 (*m*, 2H); 1.45 (*s*, 9H); 1.25 (*s*, 26H); 0.88 (*t*, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 171.2; 156.0; 79.6; 70.1; 63.4; 52.7; 33.7; 31.9; 29.7; 29.6; 29.5; 29.3; 28.3; 25.6; 22.7; 20.9; 14.1. ESI MS: m/z 466 $[M+Na]^+$. Anal Calcd. for $C_{25}H_{49}NO_5$: C, 67.68; H, 11.13%. Found: C, 67.83; H, 11.09%.

2.5 *1,2-Diacetyl L-threo-sphinganine **(5)***

To a solution of compound **8** (0.3 g, 0.68 mmol) in CH_2Cl_2 (5 mL) excess trifluoroacetic acid (TFA) was added dropwise and stirred at r.t. for 1 h. The reaction mixture was dried on the rotary evaporator to remove the excess TFA. The resulting residue (unprotected amine) was dissolved in CH_2Cl_2 (5 mL) and basified to pH 8 with aq. $NaHCO_3$ followed by the addition of the acetyl chloride (0.053 mL, 0.75 mmol). The reaction was monitored by TLC. Upon completion (2.5 h), the reaction mixture was diluted with saturated aqueous NH_4Cl. The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4) and purified by CC to afford pure compound **5** (0.187 g, 72%) as a white solid. $[á]_D^{24} = +2.8$ (c = 0.4, $CHCl_3$). IR $\tilde{o}_{max}$ (KBr)/cm^{-1}: 3300, 2945, 2840, 1725, 1645, 1540, 1435, 1365, 1061. ^{1}H NMR (500 MHz, $CDCl_3$): 4.24 (*dd*, J = 4.0, 10.0 Hz, 1H); 4.18–4.02 (*m*, 2H); 3.68 (*m*, 1H); 2.62 (br. *s*, 1H); 2.09 (*s*, 3H); 2.02 (*s*, 3H); 1.45 (*m*, 1H); 1.25 (*s*, 27H); 0.88 (*t*, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 171.6; 170.4; 69.7; 63.4; 51.5; 33.7; 31.9; 29.6; 29.5; 29.5; 29.3; 25.7; 23.3; 22.7; 20.9; 14.1. ESI MS: m/z 386 $[M+H]^+$. Anal Calcd. for $C_{22}H_{43}NO_4$: C, 68.53; H, 11.24%. Found: C, 68.62; H, 11.21%.

2.6 *L-threo-Sphinganine triacetate **(7)***

To a solution of compound **5** (0.1 g, 0.26 mmol) in dry CH_2Cl_2 (5 mL), Et_3N (0.043 mL, 0.31 mmol) was added, followed by Ac_2O (0.029 mL, 0.31 mmol) was added at 0°C and the reaction mixture was allowed to rise to r.t. After 2 h, the reaction mixture was washed with brine (5 mL) and water (5 mL), dried over Na_2SO_4 and evaporated. The crude product was purified by silica gel CC (hexane/AcOEt, 9:1) to give L-*threo*-sphinganine triacetate **7** (0.087 g, 79%) as a white solid. $[á]_D^{24} = -12.0$ (c =0.5, $CHCl_3$). IR $\tilde{o}_{max}$ (KBr)/cm^{-1}: 2925, 2855, 1740, 1655, 1543, 1460, 1370, 1235, 1048. ^{1}H NMR (500 MHz, $CDCl_3$): 5.64 (*d*, J = 9.3 Hz, 1H); 5.06 (*m*, 1H); 4.39 (*m*, 1H); 4.07–4.01 (*m*, 2H); 2.05 (*s*, 3H); 2.02 (*s*, 3H); 1.99 (*s*, 3H); 1.62-1.54 (*m*, 2H); 1.24 (br. *s*, 26H); 0.87 (*t*, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 170.7; 170.4; 170.0; 72.4; 63.3; 50.0; 31.9; 31.2; 29.6; 29.6; 29.5; 29.3; 29.2; 25.1; 23.2; 22.6; 20.9; 20.7; 14.1. ESI MS: m/z 428 $[M+H]^+$. Anal Calcd. for $C_{24}H_{45}NO_5$: C, 67.41; H, 10.61%. Found: C, 67.25; H, 10.57%.

2.7 *(2S,3R)-2-((tert-Butoxycarbonyl)amino) octadecane-1,3-diyl diacetate **(12)***

The monoacetyl ester **8** (1.0 g, 2.25 mmol) was dissolved in anhydrous THF (20 mL), AcOH (0.257 mL, 4.50 mmol) and PPh_3 (1.18 g, 4.50 mmol) were added at 0 °C. To the reaction mixture, a solution of diisopropyl azodicarboxylate (0.88 mL, 4.50 mmol) in anhydrous THF (10 mL) was added. The solution was stirred at r.t. and after 2 h the reaction was quenched by the addition of water (10 mL), and extracted with Et_2O (30 mL). After phase separation the organic phase was dried (Na_2SO_4), concentrated and purified by CC to give pure **12** (0.843 g, 77%) as a colorless oil. $[\alpha]_D^{25} = +12.1$ (c = 0.3, $CHCl_3$). IR $\tilde{o}_{max}$ (KBr)/cm^{-1}: 2925, 2854, 1746, 1723, 1368, 1236, 1171. ^{1}H NMR (300 MHz, $CDCl_3$): 5.02 (*m*, 1H); 4.92 (*dd*, J = 6.2, 12.5 Hz, 1H); 4.09-3.99 (*m*, 2H); 2.06 (*s*, 6H); 1.67-1.57 (*m*, 2H); 1.45 (*s*, 9H); 1.25 (br. *s*, 26H); 0.88 (*t*, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 170.8; 168.6; 151.3; 79.9; 72.3; 62.9; 51.2; 31.9; 31.2; 29.6; 29.6; 29.5; 29.4; 29.3; 28.3; 25.0; 22.6; 21.0; 20.8; 14.1. ESI MS: m/z 486 $[M+H]^+$. Anal Calcd. for $C_{27}H_{51}NO_6$: C, 66.77; H, 10.58%. Found: C, 66.85; H, 10.54%.

2.8 *D-erythro-Sphinganine triacetate **(6)***

To a solution of compound **12** (0.8 g, 1.64 mmol) in CH_2Cl_2(5 mL), excess trifluoroacetic acid was added dropwise and stirred at r.t. for 1 h. The reaction mixture

was dried on the rotary evaporator to remove the excess TFA. The resulting residue (unprotected amine) was dissolved in CH_2Cl_2 (8 mL) and basified to pH 8 with aq. $NaHCO_3$ followed by the addition of the acetyl chloride (0.128 mL, 1.80 mmol). The reaction was monitored by TLC. Upon completion (2.5 h), the reaction mixture was diluted with saturated aqueous NH_4Cl. The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4) and purified by CC to afford pure D-*erythro*-sphinganine triacetate **6** (0.507 g, 72%) as a white solid. $[á]_D^{24} = +12.7$ (c = 1.1, $CHCl_3$). IR $\tilde{o}_{max}$ (KBr)/cm^{-1}: 2935, 2840, 1729, 1646, 1540, 1462, 1360, 1239, 1061. ^{1}H NMR (500 MHz, $CDCl_3$): 5.90 (*d*, J = 9.0 Hz, 1H); 4.90 (*m*, 1H); 4.38 (*m*, 1H); 4.25 (*dd*, J = 6.1, 11.5 Hz, 1H); 4.06 (*d*, J = 4.0, 11.7 Hz, 1H); 2.07 (*s*, 3H); 2.06 (*s*, 3H,); 2.00 (*s*, 3H); 1.60 (*m*, 2H); 1.24 (br. *s*, 26H,); 0.88 (*t*, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 170.9; 170.9; 169.7; 74.0; 62.5; 50.5; 31.9; 31.4; 29.6; 29.6; 29.5; 29.4; 29.3; 25.3; 22.6; 20.9; 20.8; 14.1. ESI MS: m/z 428 $[M+H]^+$. Anal Calcd. for $C_{24}H_{45}NO_5$: C, 67.41; H, 10.61%. Found: C, 67.30; H, 10.64%.

2.9 *N-((2S,3R)-1,3-Dihydroxyoctadecan-2-yl) acetamide (**13**)*

To a solution of triacetate **6** (0.4 g, 0.935 mmol) in absolute MeOH (6 mL) was added anhydrous Na_2CO_3 (0.118 g, 1.12 mmol). The mixture was stirred at r.t. for 1 h. Then, the solution was filtered, the solvent evaporated and the solid residue was purified over silica gel (eluent, CH_2Cl_2 with increasing amount of MeOH) to give 1,3-diol **13** (0.263 g, 82%) as a white solid. $[\alpha]_D^{25} = +6.6$ (c = 0.2, CH_3OH). IR $\tilde{o}_{max}$ (KBr)/cm^{-1}: 3400, 2940, 2835, 1650, 1548, 1430, 1362, 1061. ^{1}H NMR (500 MHz, CD_3OD): 3.86 (*m*, 1H); 3.72–3.64 (*m*, 2H); 3.59 (*m*, 1H); 1.97 (*s*, 3H); 1.52 (*m*, 2H); 1.28 (br. *s*, 26H); 0.89 (*t*, 3H, J = 7.0 Hz). ^{13}C NMR (125 MHz, CD_3OD): 173.4; 72.3; 62.1; 57.0; 34.8; 33.1; 30.8; 30.5; 26.8; 23.7; 22.8; 14.4. ESI MS: m/z 344 [M+H]+. Anal Calcd. for $C_{20}H_{41}NO_3$: C, 69.92; H, 12.03%. Found: C, 70.04; H, 12.00%.

2.10 *1,2-Diacetyl D-erythro-sphinganine (**4**)*

To a solution of 1,3-diol **13** (0.1 g, 0.29 mmol) in dry CH_2Cl_2 (4 mL), Et_3N (0.04 mL, 0.29 mmol) was added, followed by Ac_2O (0.027 mL, 0.29 mmol) was added at 0°C and the reaction mixture was allowed to rise to r.t. After completion of reaction (2 h), the reaction mixture was washed with brine (5 mL) and water (5 mL), dried over Na_2SO_4 and evaporated. The crude product was purified by silica gel CC using (AcOEt/hexane, 2:8) to give pure 1,2-diacetyl D-*erythro*-sphinganine **4** (0.088 g, 79%) as a white solid. $[\alpha]_D^{25} = +6.2$ (c =0.25, CH_3OH). IR $\tilde{o}_{max}$ (KBr)/cm^{-1}: 3279, 2918, 2850, 1739, 1650, 1555, 1465, 1341, 1221. ^{1}H NMR (500 MHz, $CDCl_3$): 5.98 (*d*, J = 7.9 Hz, 1H); 4.33 (*dd*, J = 11.6, 6.4 Hz, 1H); 4.18 (*dd*, J = 11.6, 3.2 Hz, 1H); 4.11 (*m*, 1H); 3.63 (*m*, 1H); 2.06 (*s*, 3H); 2.00 (*s*, 3H); 1.47 (*m*, 2H); 1.24 (br. *s*, 26H); 0.86 (*t*, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 171.3; 170.3; 72.6; 63.1; 52.9; 34.0; 31.9; 29.6; 29.6; 29.5; 29.3; 25.9; 23.3; 22.7; 20.9; 14.1. ESI MS: m/z 386 $[M+H]^+$. Anal Calcd. for $C_{22}H_{43}NO_4$: C, 68.53; H, 11.24%. Found: C, 68.70; H, 11.21%.

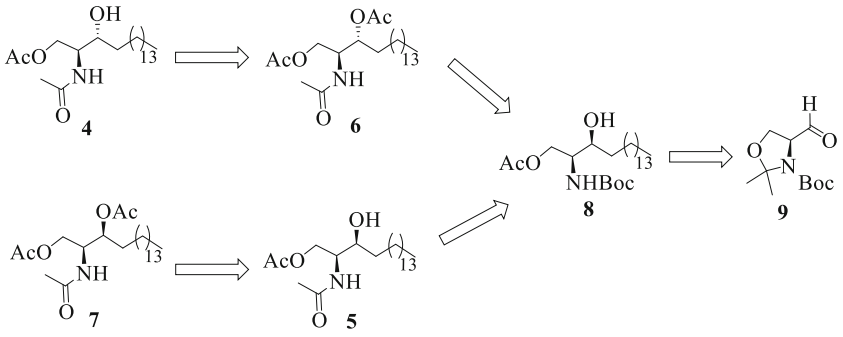
3. Results and Discussion

The retrosynthetic analysis (Scheme 1) indicates that the 1,2-diacetyl D-*erythro*-sphinganine **4** can be synthesized from the D-*erythro*-sphinganine triacetate **6**, which can be prepared from the monoacetyl ester **8**. On the other hand, L-*threo*-sphinganine triacetate **7** can be prepared from its diacetyl compound **5**, which can also be prepared from the same monoacetyl ester **8**. The monoacetyl compound **8** can in turn, be prepared from the Garner aldehyde **9**.

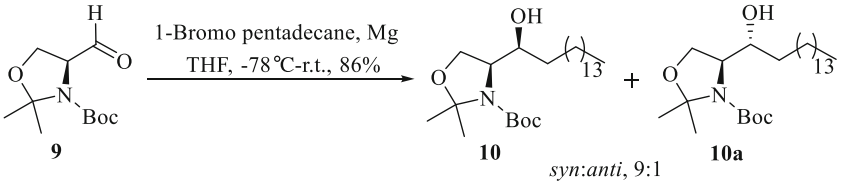
The present synthesis was initiated by treatment of the Garner aldehyde **9** with 1-bromo pentadecane and Mg in THF at −78°C and the mixture was brought to r.t. to produce the diastereomeric alcohols **10** and **10a** (Scheme 2). The stereochemistry of the two diastereomers **10** and **10a** were assigned by following *Buono's* method.[9] According to this method, *syn* alcohol is major product compared to anti-alcohol. This stereochemistry is further confirmed by subsequent conversion to the target molecules. The two diastereomers were separated by careful CC (silica gel 100–200 mesh, 0–5% increasing amount of AcOEt in hexane), which produced **10** and **10a** in the ratio 9:1 (*syn*:*anti*, 9:1) with 86% yield.

Due to less amount of minor diastereomer **10a**, we have synthesized 1,2-diacetyl D-*erythro*-sphinganine (**4**) and D-*erythro*-sphinganine triacetate (**6**) from major diastereomer **10**.

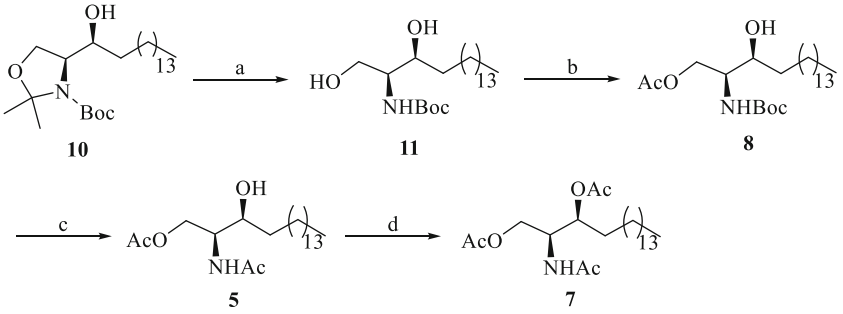
The acetonide group of alcohol **10** was deprotected by treatment with PPTS in MeOH to form diol **11** with 92% yield[10] (Scheme 3). The 1,3-diol **11** was mono protected of its primary hydroxyl group as acetyl ester **8** by treatment with Ac_2O and Et_3N in CH_2Cl_2 with 77% yield.[11] The mono acetyl ester **8** was converted to 1,2-diacetyl L-*threo*-sphinganine **5** by following two steps: i) Boc group was deprotected from **8** by using excess TFA in CH_2Cl_2; ii) unprotected amine was converted to *N*-acylated amine on treatment with acetyl chloride, aq.$NaHCO_3$ in CH_2Cl_2 with 72% yield.[12]



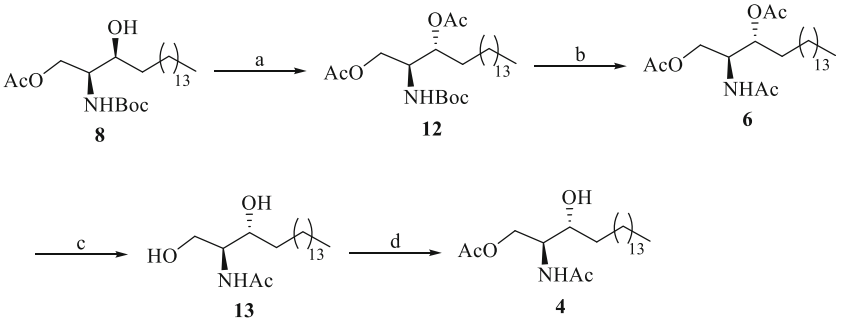
Scheme 1. Retrosynthetic analysis of sphingolipids.



Scheme 2. Grignard reaction on Garner aldehyde.



Scheme 3. (a) PPTS/MeOH, r.t., 2 h, 92%. (b) Ac_2O, Et_3N, CH_2Cl_2, 0 °C-r.t., 2 h, 77%. (c) i) TFA/CH_2Cl_2, r.t., 1 h. ii) Acetyl chloride, $NaHCO_3$, CH_2Cl_2-H_2O, r.t., 2.5 h, 72% (Over two steps). (d) Ac_2O, Et_3N, CH_2Cl_2, 0 °C-r.t., 2 h, 79%.



Scheme 4. (a) PPh_3, AcOH, DIAD, THF, 0 °C-r.t., 4 h, 77%. (b) i) TFA/CH_2Cl_2, r.t., 1 h. ii) AcCl, $NaHCO_3$, CH_2Cl_2-H_2O, r.t., 2.5 h, 73% (Over two steps). (c) Na_2CO_3/MeOH, r.t., 1 h, 82%. (d) Ac_2O, Et_3N, CH_2Cl_2, 0 °C-r.t., 2 h, 79%.

1,2-Diacetyl L-*threo*-sphinganine **5** was converted to L-*threo*-sphinganine triacetate **7** by treatment with Ac_2O and Et_3N in CH_2Cl_2 with 79% yield.

The mono acetyl ester **8** was subjected to Mitsunobu inversion by using triphenyl phosphine (PPh_3), AcOH and diisopropyl azodicarboxylate (DIAD) in dry THF

to obtain 1,3-diacetyl compound **12** with 77% yield[13] (Scheme 4). 1,3-Diacetyl compound **12** was converted to D-*erythro*-sphinganine triacetate **6** by following two steps: i) Boc group was deprotected from **12** by using excess TFA in CH_2Cl_2; ii) unprotected amine was converted to *N*-acylated amine on treatment with AcCl, aq. $NaHCO_3$ in CH_2Cl_2 with 73% yield. D-*erythro*-sphinganine triacetate **6** was converted to 1,3-diol **13** by treatment with Na_2CO_3 in MeOH[14] at r.t. with 82% yield. The 1,3-diol **13** was mono protected of its primary hydroxyl group as acetyl ester by treatment with Ac_2O and Et_3N in CH_2Cl_2 to produce 1,2-diacetyl D-*erythro*-sphinganine **4** with 79% yield. The physical (optical rotation) and the spectral (^1H and ^{13}C NMR and MS) properties of **4** were found to be identical to those reported for the naturally occurring compound.[6]

4. Conclusions

In conclusion, we have described the stereoselective total synthesis of naturally occurring sphingolipid 1,2-diacetyl D-*erythro*-sphinganine (**4**) along with three other sphingolipids, namely, 1,2-diacetyl L-*threo*-sphinganine (**5**) (C-3 epimer of **4**), D-*erythro*-sphinganine triacetate (**6**) (triacetyl derivative of compound **2**) and L-*threo*-sphinganine triacetate (**7**) (triacetyl derivative of compound **3**, Safingol). Synthesis of 1,2-Diacetyl D-*erythro*-sphinganine (**4**) and 1,2-diacetyl L-*threo*-sphinganine (**5**) are reported here for the first time.

Supplementary information (SI)

All the copies of ^1H NMR and ^{13}C NMR are given in the supporting information. Supplementary Information is available at www.ias.ac.in/chemsci.

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