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Stereoselective synthesis of safingol and its natural stereoisomer from D-glycals

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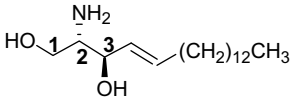
ABSTRACT

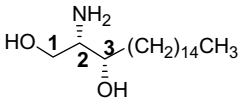
Efficient and convenient syntheses of (2*S*,3*S*)-safingol and its natural (2*S*,3*R*)-isomer have been developed from 3,4,6-tri-*O*-benzyl glycals. The key step is the one-pot reduction of an azide, saturation of the double bonds and debenzylation under catalytic hydrogenation.

Sphingosine **1** and sphiganine (dihydrosphingosines) **3** are naturally occurring (long-chain, aliphatic, 2-amino-1,3 diol) bioactive compounds. 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.[1] 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 three additional unnatural isomers have also been reported.[2] Among the unnatural sphingoid bases L-*threo*-(2*S*,3*S*) dihydrosphingosine (safingol) **2** is of particular interest due to its medicinal importance. Safingol is an antineoplastic, antipsoriatic drug[3] and a competitive inhibitor of protein kinase C.[4] It is reported that safingol inhibits enzymatic activity and ^{3}H-phorbal dibutarate binding of purified rat brain PKC (IC_{50} = 37.5 μM, 31 μM, respectively). It also inhibits human PKCα, the major overexpressed isoenzyme in MCF-7 DOXR cells (IC_{50} = 40 μM). Further, safingol enhances the cytotoxic effect of the chemotherapeutic agent mytomycin (MMC: Cat. No. 47589) in gastric cancer cells promoting drug induced apoptosis.[5–7]

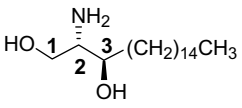
Due to its promising biological activity, a number of syntheses of safingol **2** and its stereoisomers have been reported in the literature including methods based on an enantioselective Henry reaction[8] and ketone reduction,[9] multistep synthesis from (*Z*)-2-butene-1,4-diol,[10] a chiral oxazolidinyl ester[11] and resolution based methods.[12a–c] One of the most recent syntheses of safingol was reported by Lee et al.,[13] which was based on palladium-catalyzed oxazoline formation followed by cross metathesis. Another recent report by Chattopadhyay et al.[14] begins from a D-mannitol derived aldehyde and involves a diastereoselective step in which the unrequired diastereomer is also obtained in a reasonable amount. The above-mentioned stereoselective syntheses of safingol, except that from D-mannitol,[14] either employ a chiral ligand or a chiral auxiliary, which itself may require a few steps for its



1
Sphingosine



2
Safingol



3
D-*erythro*-dihydro-sphingosine

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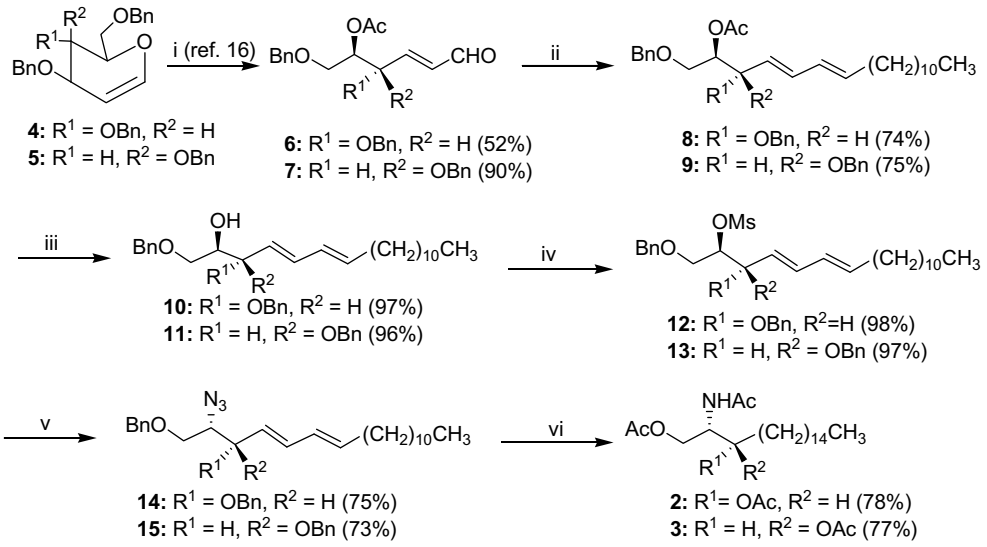

Scheme 1. Reagents and conditions: (i) $HgSO_4$ (cat.), 0.02 N H_2SO_4,1,4-dioxane, 6 h (for compound **4**); 8 h (for compound **5**), then Ac_2O, Et_3N, 0 °C; (ii) $C_{12}H_{25}PPh_3^+Br^-$, *n*-BuLi, dry THF, −78 °C; (iii) NaOMe (cat.), MeOH, rt, 1 h; (iv) MsCl, Et_3N, 0 °C; (v) NaN_3, DMF, 100 °C, 8 h; (vi) H_2/Pd–C, MeOH (1% TFA); Ac_2O, Et_3N.

synthesis. Herein, we report a stereoselective synthesis, which takes advantage of a chiral pool (carbohydrate based) starting material to construct both the stereocenters of safingol and its diastereomer in a good overall yield of 21% and 36%, respectively. Our synthetic route uses simple reactions and involves the reduction of an azide, double bonds and debenzylation in a single pot as the key step.

In continuation of our work on the functionalization of glycals[15] towards biologically important molecules, we report a short and efficient synthesis of safingol and its isomer from tri-*O*-benzyl glycals.

The synthetic approach is outlined in Scheme 1. 3,4,6-Tri-*O*-benzylated glycals **4** and **5** were subjected to Perlin hydrolysis[16] followed by acetylation to afford *trans*-enals **6** and **7**, respectively. Wittig reaction of **6** and **7** with dodecyltriphenylphosphonium bromide gave *trans* dienes **8**[17] and **9**,[18] exclusively, in 74 and 75% yields, respectively. Methanolysis of the acetates **8** and **9** with a catalytic amount of sodium methoxide gave hydrolyzed products **10**[17] and **11**[18] in excellent yields. Conversion of the free hydroxyl group to mesylates **12**[17] and **13**[18] followed by an S_N2 displacement with sodium azide gave the products **14**[17] and **15**[18] with complete inversion of the configuration at C-2 and provided the desired *threo* and *erythro* configurations, respectively. One-pot reduction of the azide, saturation of the double bonds and deprotection of the benzyl ether was carried out using catalytic hydrogenation with 10% Pd–C on **14** and **15** followed by acetylation to give the acetylated derivatives of safingol **2** and its diastereomer **3** in 78% and 77% yields. The spectral data of these compounds were in good agreement with the reported data of the respective natural materials.[19a,b]

In conclusion, relatively short syntheses of safingol and its natural stereoisomer have been reported from D-glucal and D-galactal as chiral pools, respectively.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.112.

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17. Experimental data of selected compounds: *(2R,3S,4E,6E)*-**1,3**-*bis(benzyloxy)*-*octadeca*-**4,6**-*dien*-*2*-*yl* acetate (**8**): To a solution of dodecyltriphenylphosphonium bromide (207 mg, 0.27 mmol) in THF (5 mL) was added dropwise a 1.6 M solution of *n*-BuLi (0.26 mL, 0.42 mmol) in hexane at −78 °C, and the mixture was stirred at this temperature for 20 min. A solution of aldehyde **6** (100 mg, 0.27 mmol) in THF (5 mL) was added dropwise. The reaction mixture was allowed to stir for an additional 30 min and warmed to room temperature. It was then quenched with a saturated aqueous solution of NH_4Cl (5 mL) and extracted with EtOAc (3 × 15 mL). Usual workup followed by purification by column chromatography (1:9 EtOAc–hexane) gave **8** (163 mg,

74%). $[\alpha]_D^{28}$ +24.00 (*c* 1.00, CH_2Cl_2); IR (neat film) 3062, 2924, 1744, 1651, 1605, 1495, 1455, 1371, 1235, 1071, 988, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.3 Hz, 3H), 1.25–1.37 (br s, 18H), 2.02 (s, 3H), 2.14–2.17 (m, 2H), 3.64 (dd, *J* = 3.4, 10.7 Hz, 1H), 3.70 (dd, *J* = 5.6, 10.7 Hz, 1H), 4.06 (t, *J* = 6.1 Hz, 1H), 4.35 (d, *J* = 11.7 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.52 (d, *J* = 12.2 Hz, 1H), 4.56 (d, *J* = 11.9 Hz, 1H), 5.09 (dd, *J* = 2.6, 6.5 Hz, 1H), 5.50–5.57 (m, 2H), 5.97 (t, *J* = 11 Hz, 1H), 6.5–6.4 (dd, *J* = 11.2, 15.1 Hz, 1H), 7.25–7.33 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 21.1, 22.6, 27.8, 29.1, 29.2, 29.3, 29.5, 29.6, 29.6, 31.8, 32.6, 68.3, 70.3, 70.4, 73.1, 73.6, 78.4, 126.6, 127.3, 127.5, 127.6, 127.6, 128.2, 128.3, 128.9, 129.1, 130.4, 133.8, 135.2, 138.0, 138.1, 173.5; HRMS calcd for $C_{34}H_{48}O_4$ $[M+Na]^+$ 543.3450, found: 543.3455.

(2R,3S,4E,6E)-**1**,**3**-*Bis(benzyloxy)octadeca*-**4**,**6**-*dien*-**2**-*ol* (**10**): Compound **8** (350 mg, 0.67 mmol) was dissolved in dry MeOH (15 mL) and a catalytic amount of NaOMe was added and the reaction mixture was allowed to stir for 1 h at room temperature. The reaction mixture was concentrated in vacuo and passed through Amberlite-120 (H^+). The crude product was purified by silica gel column chromatography (hexane–EtOAc = 9:1) to give **10** in quantitative yield. $[\alpha]_D^{28}$ +0.40 (*c* 2.25, CH_2Cl_2); IR (neat film) 3458, 3087, 2923, 1654, 1606, 1495, 1454, 1363, 1257, 1092, 1027, 989 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, *J* = 6.6 Hz, 3H), 1.27–1.25 (br s, 18H), 2.15–2.20 (m, 2H), 2.36 (br s, 1H) 3.56 (dd,*J* = 5.8, 9.7 Hz, 1H), 3.61 (dd, *J* = 3.6, 9.7 Hz, 1H), 3.92–3.95 (m, 2H), 4.38 (d, *J* = 11.7 Hz, 1H), 4.50–4.53 (br s, 2H), 4.59 (d, *J* = 11.7 Hz, 1H), 5.3–5.4 (dd, *J* = 7.8, 10.7 Hz, 1H), 5.61 (dd, *J* = 7.8, 15.6 Hz, 1H), 6.04 (dd, *J* = 10.7, 11.2 Hz, 1H), 6.56 (dd, *J* = 11.2, 15.6 Hz, 1H), 7.2–7.3 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.6, 27.8, 29.1, 29.2, 29.5, 29.6, 29.6, 31.8, 32.6, 70.2, 70.4, 70.5, 70.6, 73.2, 80.4, 126.7, 127.4, 127.5, 127.6, 127.6, 127.7, 127.9, 128.3, 128.9, 130.3, 133.8, 135.5, 136.5, 138.0, 138.1; HRMS calcd for $C_{32}H_{46}O_3$ $[M+Na]^+$ 501.3345, found: 501.3343.

(2R,3S,4E,6E)-1,3-Bis(benzyloxy)octadeca-**4**,**6**-*dien*-**2**-*yl* methanesulfonate (**12**): A solution of alcohol **10** (280 mg, 0.58 mmol) in dry CH_2Cl_2 (10 mL), and Et_3N (70 mg, 0.69 mmol) was cooled to 0 °C. Subsequently, mesyl chloride (79 mg, 0.69 mmol) was added and the reaction mixture was allowed to warm to room temperature. After 30 min, the reaction mixture was washed with brine (10 mL) and water (10 mL), dried over $MgSO_4$ and evaporated. The crude product was purified by silica gel column chromatography using (hexane:EtOAc = 8:2) to give **12** (317 mg, 98%): $[\alpha]_D^{28}$ +14.70 (*c* 1.15, CH_2Cl_2); IR (neat film) 3063, 2924, 1656, 1606, 1496, 1454, 1360, 1206, 1099, 1027, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.5 Hz, 3H), 1.25–1.38 (br s, 18H), 2.14–2.18 (m, 2H), 2.90 (s, 3H) 3.66 (dd, *J* = 4.4, 10.5 Hz, 1H), 3.74 (dd, *J* = 7.0, 10.7 Hz, 1H), 4.17 (dd, *J* = 3.9, 8.0 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.52 (br s, 2H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.86–4.89 (m, 1H), 5.51–5.60 (m, 2H), 6.02 (dd, *J* = 10.7, 11.2 Hz, 1H), 6.56 (dd, *J* = 11.2, 15.2 Hz, 1H), 7.25–7.35 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 27.8, 29.2, 29.3, 29.5, 29.5, 29.6, 29.6, 31.8, 38.5, 68.5, 70.6, 73.3, 78.9, 82.7, 126.9, 127.0, 127.6, 127.7, 127.8, 128.3, 128.4, 131.4, 134.7, 137.4, 137.6. HRMS calcd for $C_{33}H_{48}O_5S$ $[M+Na]^+$ 579.3120, found: 579.3123.

(2S,3S,4E,6E)-2-Azidooctadeca-4,6-diene-**1**,**3**-*diyl)bis-(oxy)bis(methylene)dibenzene* (**14**): To a solution of mesylate **12** (290 mg, 0.52 mmol) in dry DMF was added NaN_3 (203 mg, 3.1 mmol) and the mixture stirred at 100 °C for 8 h. DMF was removed under reduced pressure, and the reaction mixture washed with H_2O and the aqueous phase was extracted with EtOAc (3 × 15 mL). Usual workup and purification by column chromatography gave **14** (196 mg, 75%) $[\alpha]_D^{28}$ −12.00 (*c* 0.05, CH_2Cl_2); IR (neat film) 3028, 2924, 2853, 2096, 1652, 1606, 1495, 1454, 1364, 1262, 1101, 1027, 989 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.6 Hz, 3H), 1.25–1.38 (br s, 18H), 2.14–2.19 (m, 2H), 3.55–3.63 (m, 3H), 4.04 (dd, *J* = 11.7, 10.0 Hz, 1H), 4.37 (d, *J* = 9.5 Hz, 1H), 4.47–4.54 (m, 2H), 4.60 (d, *J* = 11.7 Hz, 1H), 5.50–5.59 (m, 2H), 6.01 (dd, *J* = 10.9, 11.0 Hz, 1H), 6.56 (dd, *J* = 11.2, 15.1, 1H), 7.25–7.38 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 27.8, 29.2, 29.3, 29.5, 29.6, 31.8, 64.8, 69.6, 70.3, 70.4, 73.4, 79.5, 127.2, 127.6, 127.7, 127.8, 128.3, 128.4, 128.5 130.4, 134.4, 137.7, 137.9; HRMS calcd for $C_{32}H_{45}N_3O_2$ $[M+Na]^+$ 526.3409, found: 526.3406. *N,O,O-Triacetyl*-L-*threo-dihydrosphingosine* (**2**): A mixture of olefin **14** (150 mg, 0.29 mmol) and Pd/C (10% content, 50 mg) in MeOH (20 mL, containing 1% of TFA) was stirred for 28 h at room temperature under a H_2 atmosphere (5 atm). The catalyst was filtered, and the filtrate was concentrated in vacuo to give crude safingol. This crude product was acetylated using Ac_2O, Et_3N to give acetylated safingol, which was purified on a short silica gel column using EtOAc–hexane (4:6) as eluent to furnish the target compound **2** (70 mg, 78%) as a white solid; $[\alpha]_D^{28}$ −10.40 (*c* 1.05, CH_2Cl_2); IR (neat film) 3299, 2924, 2853, 1744, 1658, 1543, 1462, 1371, 1233, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, *J* = 6.6 Hz, 3H), 1.22 (br s, 26H), 1.52 (m, 2H), 1.99 (s, 3H), 2.03 (s, 3H), 2.05 (s, 3H), 4.00–4.01 (m, 2H), 4.38 (m, 1 H), 5.04 (m, 1H), 5.63 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 20.7, 20.9, 22.6, 23.2, 25.1, 29.2, 29.3, 29.3, 29.5, 29.6, 29.6, 29.6, 31.2, 31.8, 50.0, 63.3, 72.4, 169.9, 170.4, 170.7; HRMS calcd for $C_{24}H_{45}NO_5$ $[M+H]^+$ 428.3298, found: 428.3370.

18. See Supplementary data for additional spectral data.
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