A Stereoselective Synthesis of Dihydrosphingosine

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Dedicated to Prof. Dr. Richard R. Schmidt on the occasion of his 65th birthday

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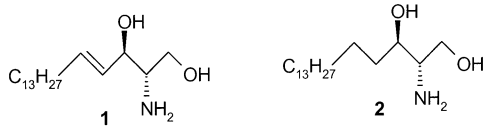
A highly enantioselective synthesis of D-(+)-*erythro*-dihydrosphingosine (sphinganine) as its triacetate derivative **10**, starting from palmityl alcohol (**3**) and employing the Sharpless asymmetric dihydroxylation as the key step, is described.

Introduction

Sphingosine (**1**) and its biosynthetic precursor, dihydrosphingosine (sphinganine, **2**) are highly abundant, long-chain amino alcohols, generally possessing 18 or 20 carbon atoms. Sphinganine is known to be an important precursor in the biosynthesis of sphingolipids such as ceramides, sphingomyelin, cerebrosides and gangliosides, which play important roles in cell regulation, cell growth modulation and signal transmission,[1] with sphinganine itself found to be an inhibitor of protein kinase C.[2]



Various methods for the synthesis of sphingosine (**1**), dihydrosphingosine (**2**) and their derivatives have been reported. One is based on the ring-opening of a chiral epoxide with azide as the key step.[3] The second major synthetic strategy uses chiral pool carbohydrate precursors to establish the stereochemistry at C-2 and C-3.[4] The most commonly employed methods are the diastereoselective addition of an organometallic reagent to chiral aldehydes, derived particularly from L-serine.[5] This approach leads to the carbon−carbon bond formation (C-3 and C-4) and simultaneous fixing of the stereochemistry of the C-3 hydroxy group in one step. The other interesting synthetic methodologies involve the use of a variety of chiral precursors to build up the structure by nucleophilic addition process.[6] However, there are sufficient drawbacks to most of these procedures to confirm the need for a practical and alternative approach to the synthesis of the target molecule. In connection with our studies on the enantioselective synthesis of some naturally occurring compounds,[7] mainly by stereoselective transformation of diols via cyclic sulfite/sulfates, we became interested in developing a simple and feasible route to dihydrosphingosine. Here we report a new and highly enantioselective synthesis of sphinganine, in which the Sharpless asymmetric dihydroxylation was employed as the key step and as the source of chirality in the synthesis.

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Results and Discussion

Scheme 1 summarizes our synthesis of sphinganine as its triacetate derivative **10**. The commercially available palmityl alcohol (**3**) was converted into the corresponding aldehyde, which on treatment with (ethoxycarbonylmethylene)triphenylphosphorane in THF under reflux gave the Wittig product **4** in 89% yield. Compound **4** was subjected to DIBAL-H reduction to furnish the corresponding allylic alcohol **5**[8] in 92% yield. The dihydroxylation of olefin **5** with osmium tetraoxide and potassium ferricyanide as co-oxidant in the presence of 1,4-bis(dihydroquinidin-9-*O*-yl)-phthalazine [$(DHQD)_2PHAL$] ligand under the Sharpless asymmetric dihydroxylation reaction conditions[9] gave the (2*R*,3*R*)-triol **6** in excellent yield, with $[\alpha]_D^{20} = +7.2$ (c = 1.0, $CHCl_3$). Sharpless asymmetric dihydroxylation (SAD) on the allylic alcohols presented in Scheme 2, with different long alkyl chains, is reported to give the two stereogenic centres, in 95−97% enantiomeric excess.[10]

Thus, by analogy, the triol **6** prepared was assumed to be enantiomerically pure.

Furthermore, in order to achieve the synthesis of azidosphinganine **9** from the triol **6**, we required the transformation of a hydroxy group into an azido one, with concomitant reversal of stereochemistry at the 2-position. To this end, protection of **6** as a benzylidene derivative was effected, using benzaldehyde dimethylacetal in the presence of a catalytic amount of *p*TSA to afford a mixture of 1,3- and 1,2-benzylidene compounds in 9:1 ratio. The desired major 1,3-benzylidene compound **7** was separated by silica gel column chromatography. Compound **7** was then converted into the 5-*O*-mesylate derivative, which on reaction with sodium azide in DMF afforded compound **8** with the desired stereochemistry at the 5-position. The benzylidene protecting group was cleaved by treating **8** with 3 N hydrochloric acid to furnish the azidosphinganine **9** in 72% yield,

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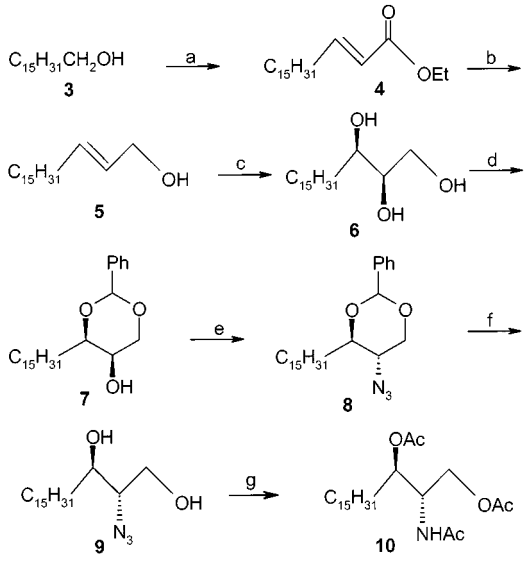
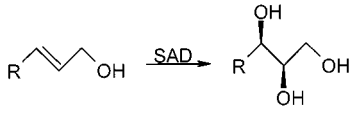


Scheme 1. Reagents: (a) (i) P_2O_5, DMSO, CH_2Cl_2, Et_3N, 0 °C, (ii) $Ph_3P{=}CHCO_2Et$, THF, reflux, 18 h (89%); (b) DIBAL-H, Et_2O, 0 °C (92%); (c) $(DHQD)_2PHAL$, OsO_4, $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*BuOH:H_2O (1:1), 24 h, 0 °C (91%); (d) $PhCH(OMe)_2$, *p*TSA, CH_2Cl_2, room temp., overnight (69%); (e) (i) $MeSO_2Cl$, Et_3N, DMAP (cat.), CH_2Cl_2, room temp., overnight, (ii) NaN_3, DMF, 80 °C, 24 h (83%); (f) 3 N HCl, MeOH, room temp., overnight (72%); (g) (i) $LiAlH_4$, Et_2O, 0 °C, room temp., overnight, (ii) Ac_2O, pyridine, room temp., 18 h (71%)



Scheme 2 $R = C_nH_{2n+1}$, n = 5,6,7,8,9,10,11,12

identical in all respects to the reported compound.[4f] Transformation of azido alcohol **9** into the target molecule **10** was readily accomplished by reduction with lithium aluminium hydride and subsequent acetylation.[4f]

Conclusion

In conclusion, an asymmetric synthesis of sphinganine has been achieved using for the first time the Sharpless asymmetric dihydroxylation as the source of chirality. The merits of this synthesis are high-yielding reaction steps, high enantioselectivity and various possibilities available for structural modification. The other enantiomer can be synthesized by α-dihydroxylation of olefin **5** and following the reaction sequence as shown above.

Experimental Section

General Information: Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 60−80°C was used. − Melting points are uncorrected. − Optical rotations were measured using the sodium D line of a JASCO-181 digital polarimeter. − Infrared spectra were recorded with an ATI MATTSON RS-1 FT-IR spectrometer. − ^1H NMR spectra were recorded with a Bruker AC-200 spectrometer. − Mass spectra were obtained with a TSQ 70, Finningen MAT mass spectrometer. − Elemental analyses were carried out with a Carlo Erba CHNS-O analyzer.

Ethyl *trans*-Octadec-2-enoate (4): A two-necked, round-bottomed flask was charged with hexadecanol (8 g, 33 mmol) and CH_2Cl_2 (150 mL) under nitrogen and then cooled in ice. DMSO (5.16 g, 4.7 mL, 66 mmol) and P_2O_5 (9.4 g, 66 mmol) were added sequentially. The reaction mixture was stirred and allowed to warm to room temperature until the TLC showed complete disappearance of the starting material (45 min). The flask was cooled to 0°C and Et_3N (16 mL, 115 mmol) was added dropwise over 1 min. Stirring was continued for 45 min in the ice bath and another 45 min at room temperature. The reaction mixture was quenched with 150 mL of 10% aq. HCl and the solution extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuum to give hexadecanal as a pale yellow, low-melting solid, which was used in the next step without further purification. − To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (11.8 g, 33.8 mmol) in dry THF (80 mL) was added dropwise a solution of hexadecanal in THF (10 mL) at room temperature. The reaction mixture was refluxed for 18 h. The solvent was removed under reduced pressure and the crude product was purified on a silica gel column, using petroleum ether/EtOAc (9:1) as eluent, to give **4** (9.165 g, 89%) as a white solid; m.p. 25−26°C. Spectroscopic properties (IR, ^1H NMR, mass) are in agreement with those described.[7d]

***trans*-Octadec-2-en-1-ol (5):** To a solution of **4** (2.6 g, 8.37 mmol) in dry Et_2O (70 mL) at 0°C was added dropwise DIBAL-H (19 mL, 19 mmol, 1 M in toluene) through a syringe. The reaction mixture was allowed to warm to room temperature over 0.5 h, then recooled to 0°C and treated with 1 N HCl (50 mL). The resulting gel was dissolved by dropwise addition of 6 N HCl. The ethereal phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with sat. $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. Silica gel column chromatography of the crude product, using petroleum ether/EtOAc (8:2) as eluent, gave **5** (2.07 g, 92%) as a white solid; m.p. 47−48°C (ref.[8] 46−48°C). Spectroscopic data (IR, ^1H NMR, mass) are in full agreement with those described.[8]

(2*R*,3*R*)-Octadecane-1,2,3-triol (6): To a mixture of $K_3Fe(CN)_6$ (4.14 g, 12.6 mmol), K_2CO_3 (1.74 g, 12.6 mmol) and $(DHQD)_2PHAL$ (33 mg, 42.4 μmol, 1 mol-%) in *t*BuOH/H_2O (1:1, 50 mL) at 0°C was added osmium tetraoxide (170 μL, 0.1 M solution in toluene, 0.4 mol-%), followed by methanesulfonamide (0.4 g, 4.2 mmol). After stirring for 5 min at 0°C, the olefin **5** (1.13 g, 4.2 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 24 h and then quenched with solid sodium sulfite (6 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (5 × 30 mL). The combined organic phases were washed with 10% KOH and brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (4:6) as eluent gave **6** (1.16 g, 91%) as a white solid; m.p. 86−88°C. − $[\alpha]_D^{20} = +8$ (c = 1.0, $CHCl_3$/MeOH,1:1). − IR (nujol): $\tilde{\nu}$ = 3400−3200, 2919, 2851, 1458, 1375, 1074 cm^{-1}. − ^1H NMR ($CDCl_3$/[D_6]DMSO, 200 MHz): δ = 0.9 (t, J = 6 Hz, 3 H), 1.2−1.4 (m, 27 H), 1.45−1.55 (m, 3 H), 2.63 (br. s, 1 H), 3.47−3.51 (m, 1 H), 3.56−3.82 (m, 3 H). − MS; *m/z*: 302 [M^+], 279, 167, 149. − $C_{18}H_{38}O_3$ (302.5): calcd. C 71.46, H 12.66; found C 71.09, H 12.39.

(2*R*,3*R*)-1,3-*O*-Benzylideneoctadecane-1,2,3-triol (7): To a solution of **6** (1.00 g, 3.3 mmol) in dry CH_2Cl_2 (60 mL) was added *p*TSA

(60 mg) and benzaldehyde dimethylacetal (0.61 g, 3.96 mmol); the mixture was stirred at room temperature overnight. Subsequently it was neutralized with sat. aq. $NaHCO_3$ (10 mL).The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with aq. $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. Column chromatography on silica gel, using petroleum ether/acetone (9.2:0.8) as eluent, furnished **7**, the major product (0.89 g, 69%), as a white solid; m.p. 69−70°C. − $[\alpha]_D^{20}$ = +7.2 (*c* = 1.0, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3423, 2917, 2849, 1605, 1451, 1377, 1276, 1215, 1079, 1026, 751 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.9 (t, *J* = 6 Hz, 3 H), 1.15−1.45 (m, 26 H), 1.71 (m, 2 H), 2.40 (br. s, 1 H), 3.65−3.90 (m, 2 H), 4.03−4.09 (dd, *J* = 2, 12 Hz, 1 H), 4.21−4.28 (dd, *J* = 2, 12 Hz, 1 H), 5.58 (s, 1 H), 7.37−7.42 (m, 3 H), 7.51-7.55 (m, 2 H). − MS; *m*/*z*: 391 [M + 1], 390 [M^+], 389, 285, 107. − $C_{25}H_{42}O_3$ (390.6): calcd. C 76.87, H 10.84; found C 76.53, H 10.67.

(2*R*,3*R*)-2-Azido-1,3-*O*-benzylideneoctadecane-1,3-diol (8): To a solution of **7** (0.5 g, 1.28 mmol) in dry CH_2Cl_2 (20 mL) at 0°C was added methanesulfonyl chloride (0.254 g, 2.2 mmol), Et_3N (0.5 mL) and DMAP (cat.). The reaction mixture was stirred at room temperature overnight and then poured into an Et_2O/H_2O mixture. The organic phase was separated and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with water and brine, dried (Na_2SO_4) and concentrated to a yellow waxy solid which was used directly in the next step. − To the solution of above mesylate in dry DMF (20 mL) was added sodium azide (0.42 g, 6.4 mmol) and the reaction mixture was stirred at 80°C for 24 h. It was cooled and poured into water, and extracted with petroleum ether/acetone (9.5:0.5, 4 × 20 mL). The organic extracts were washed with water and brine, dried (Na_2SO_4) and concentrated. Column chromatography on silica gel, using petroleum ether/acetone (9.5:0.5) as eluent, gave **8** (0.44 g, 83%) as a white solid; m.p. 109−110°C. − $[\alpha]_D^{20}$ = −6.6 (*c* = 1.0, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 2919, 2851, 2097, 1600, 1452, 1372, 1109, 1074, 1029, 745, 693 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.89 (t, *J* = 6 Hz, 3 H), 1.15−1.4 (m, 26 H), 1.71 (m, 2 H), 3.96−3.99 (m, 2 H), 4.11−4.17 (dd, *J* = 2, 12 Hz, 1 H), 4.52−4.62 (dd, *J* = 2, 12 Hz, 1 H), 5.60 (s, 1 H), 7.36−7.42 (m, 3 H), 7.50−7.58 (m, 2 H). − MS; *m*/*z*: 415 [M^+], 414, 310. − $C_{25}H_{41}N_3O_2$ (415.6): calcd. C 72.25, H 9.94, N 10.10; found C 72.08, H 10.03, N 9.86.

(2*S*,3*R*)-2-Azidooctadecane-1,3-diol (9): To a solution of **8** (0.1 g, 0.24 mmol) in methanol (10 mL) was added 3 N HCl (1 mL); the mixture was stirred for 24 h at room temperature. The reaction mixture was concentrated and coevaporated with toluene (2 × 10 mL). The residue thus obtained was triturated with *n*-hexane to afford the crude product, which was recrystallized from EtOAc/*n*-hexane to give **9** (0.057 g, 72%) as a white solid; m.p. 78 −80°C (ref.[4f] 77−79°C). − $[\alpha]_D^{20}$ = +4.1 (*c* = 0.5, $CHCl_3$) [ref.[4f] +4.2 (*c* = 0.5, $CHCl_3$/MeOH, 1:1)]. − IR ($CHCl_3$): $\tilde{\nu}$ = 3450−3400, 2925, 2854, 2100, 1465, 1338, 1215, 922, 699 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.89 (t, *J* = 6.5 Hz, 3 H), 1.15−1.45 (m, 26 H), 1.45−1.55 (m, 2 H), 2.50 (br. s, 1 H), 3.17−3.30 (m, 2 H), 3.82−3.98 (m, 2 H), 4.59−4.71 (m, 1 H). − MS; *m*/*z*: 327 [M^+], 285, 267.

(2*S*,3*R*)-2-Acetamido-1,3-diacetoxyoctadecane (10): To a suspension of $LiAlH_4$ (4.7 mg, 123 μmol) in Et_2O (10 mL) at 0°C was added a solution of **9** (20 mg, 61 μmol) in Et_2O (2 mL). The reaction mixture was allowed to warm to room temperature and stirred overnight. Excess $LiAlH_4$ was destroyed by slow addition of 5% aq. NaOH until effervescence ceased. EtOAc (10 mL) was added and the mixture was stirred for 15 min. The white cake was filtered and washed with EtOAc (3 × 10 mL). The organic layer was dried (K_2CO_3) and concentrated to an off white solid, which was subsequently acetylated with Ac_2O (0.15 mL) and pyridine (1 mL). After stirring for 24 h, the solvent was coevaporated with toluene, and the residue was purified on a silica gel column, using petroleum ether/EtOAc (1:1) as eluent, to give the triacetate **10** (18.5 mg, 71%) as a white solid. It was further recrystallized from hexane/EtOAc; m.p. 95−97°C (ref.[4f] 95−97°C). − $[\alpha]_D^{20}$ = +17.0 (*c* = 0.2, $CHCl_3$) [ref.[4f] +16.8 (*c* = 1, $CHCl_3$)]. Spectroscopic data are in full agreement with those reported.[4f]

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[1] Y. A. Hannun, R. M. Bell, *Science* **1989**, *243*, 500−507.
[2] G. K. Schwartz, J. Jiang, D. Kelsen, A. P. Albino, *J. Nat. Cancer Inst.* **1993**, *85,* 402−407.
[3] A. Sibuya, K. Kawashima, M. Ikeda, I. Kitawaga, *Tetrahedron Lett.* **1989**, *30,* 7205−7208.
[4] [4a] P. Kumar, R. R. Schmidt, *Synthesis* **1998**, 33−35. − [4b] R. R. Schmidt, in *Synthesis in Lipid Chemistry* (Ed.: J. H. P. Tyman), Royal Society of Chemistry: Cambridge, UK, **1996**, pp. 93−118 and references cited therein. − [4c] T. Murakami, M. Hato, *J. Chem. Soc., Perkin Trans. 1* **1996**, 823−827. − [4d] Y-L. Li, Y-L. Wu, *Liebigs Ann*. **1996**, 2079−2082. −[4e] R. R. Schmidt, T. Bär, R. Wild, *Synthesis* **1995**, 868−876. − [4f] R. Wild, R. R. Schmidt, *Liebigs Ann. Chem*. **1995**, 755−764. − [4g] N. Hirata, Y. Yamagiwa, T. Kamikawa, *J. Chem. Soc., Perkin Trans. 1* **1991**, 2279−2280.
[5] [5a] R. Villard, F. Fotiadu, G. Buono, *Tetrahedron: Asymmetry* **1998**, *9*, 607−611. − [5b] A. Dondoni, D. Perrone, E. Turturici, *J. Chem. Soc, Perkin Trans. 1* **1997**, 2389−2393. − [5c] L. Williams, Z. Zhang, F. Shao, P. Carroll, M. M. Joullie, *Tetrahedron* **1996**, *52*, 11673−11694. −[5d] K. Soai, K. Takahashi, *J. Chem. Soc, Perkin Trans. 1* **1994**, 1257−1258. − [5e] P. Herold, *Helv. Chim. Acta* **1988**, *71*, 354−362. − [5f] S. Nimkar, D. Menaldino, A. H. Merrill, D. Liotta, *Tetrahedron Lett*. **1988**, *29*, 3037−3040. − [5g] P. Garner, J. M. Park, E. J. Malecki, *J. Org. Chem.* **1988**, *53*, 4395−4398.
[6] [6a] P. Spanu, G. Rassu, L. Pinna, L. Battistini, G. Casiraghi, *Tetrahedron: Asymmetry* **1997**, *8*, 3237−3243. − [6b] F. A. Davis, G. V. Reddy, *Tetrahedron Lett.* **1996**, *37,* 4349−4352. − [6c] S. Katsumura, N. Yamamoto, E. Fukuda, S. Iwams, *Chem. Lett.* **1995**, 393−394 and references cited therein. − [6d] C. W. Jefford, J. McNulty, Z-H. Lu, *J. Chem. Soc, Chem. Commun*. **1995**, 123−124.
[7] [7a] P. Kumar, K. Saravanan, *Tetrahedron* **1998**, *54*, 2161−2168. − [7b] G. C. G. Pais, R. A. Fernandes, P. Kumar, *Tetrahedron* **1999**, *55*, 13445−13450. − [7c] R. A. Fernandes, P. Kumar, *Tetrahedron: Asymmetry* **1999**, *10*, 4349−4356. − [7d] R. A. Fernandes. P. Kumar, *Tetrahedron: Asymmetry* **1999**, *10*, 4797−4802.
[8] W. R. Roush, M. A. Adam, *J. Org. Chem.* **1985**, *50*, 3752−3757.
[9] [9a] L. F. Tietze, J. Golitzer, *Synthesis* **1998**, 873−878. − [9b] H. Becker, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 448−451. − [9c] S. Torri, P. Liu, N. Bhuvaneswari, C. Amatore, A. Jutand, *J. Org. Chem.* **1996**, *61*, 3055−3060. − [9d] For a review on asymmetric dihydroxylation, see: H. C. Kolb, M. S. VanNiewenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483−2547.
[10] Z.-B. Zhang, Z.-M. Wing, Y.-X. Wang, H.-Q. Liu, G.-X. Lei, M. Shi, *J. Chem. Soc., Perkin Trans. 1* **2000**, 53−57.

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