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A short and efficient stereoselective synthesis of dihydrosphingosine triacetate

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Abstract

A highly enantiocontrolled synthesis of D-(+)-*erythro*-dihydrosphingosine (sphinganine) triacetate is described using the Sharpless asymmetric dihydroxylation and the regiospecific nucleophilic opening of a cyclic sulfite as key steps.

1. Introduction

Sphingosine **1** and its biosynthetic precursor, dihydrosphingosine (sphinganine, **2**) are most abundant long chain aminoalcohols possessing generally 18 or 20 carbon atoms. Sphinganine is an intermediate in the biosynthesis of sphingolipids such as ceramides, sphingomyelin, cerebrosides and gangliosides which play important roles in cell regulation and signal transduction,[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 documented in the literature. One of them is based on the ring opening of chiral epoxide with azide as the key step.[3] The second major synthetic strategy utilises carbohydrate precursors as chiral pool materials to establish the stereochemistry at C-2 and C-3.[4] The most explored methods reported so far are the stereoselective addition of an organometallic reagents to chiral aldehydes derived particularly from L-serine.[5] This approach leads to the carbon–carbon bond formation (C-3 and C-4) and simultaneously sets the stereochemistry of the C-3 hydroxyl 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 processes.[6] Although several syntheses of the target compound have already been published, each suffers either from low-yielding steps or from low stereo- or regioselectivity.[7] This is especially apparent in approaches based on the ammonolysis of epoxy alcohol intermediates.[7b,c,f] Therefore a practical, expeditious and high-yielding synthesis of the target molecule is still desirable. In connection with our studies on the synthesis of some naturally occurring lactones[8]

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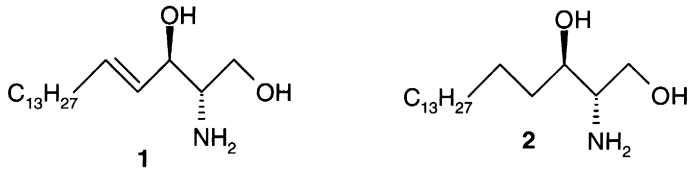
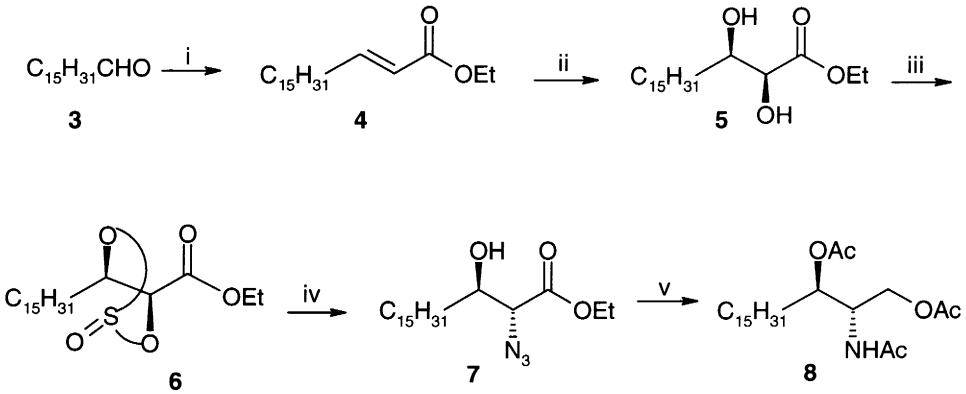
mainly by stereoselective transformation of diols via cyclic sulfates, we became interested in developing a simple and concise route to dihydrosphingosine. Herein we report a new and highly enantiocontrolled five step strategy for the synthesis of dihydrosphingosine as its triacetate derivative. The Sharpless asymmetric dihydroxylation of an appropriate olefin **4** and the regiospecific nucleophilic opening of a cyclic sulfite **6** were employed as key steps in the synthesis.



2. Results and discussion

The synthesis of the target molecule D-(+)-*erythro*-dihydrosphingosine triacetate started from palmityl aldehyde **3** as illustrated in Scheme 1. Thus, treatment of **3** with (ethoxycarbonylmethylene)triphenylphosphorane in THF under reflux gave the Wittig product **4** in 87% yield. The dihydroxylation of olefin **4** using the well established Sharpless asymmetric dihydroxylation procedure[9] gave the diol **5** in excellent yield with 99% ee[10] having $[\alpha]_D^{20}$=+8.6 (c 2, $CHCl_3$). Diol **5** was then treated with thionyl chloride to afford the cyclic sulfite **6**[11] in 96% yield. The essential feature of our synthetic strategy shown in Scheme 1 was based on the presumption that the nucleophilic opening of the cyclic sulfite **6** would occur in a regiospecific manner at the α-carbon. It may be important to mention here that the regiospecific opening of the cyclic sulfate has been applied successfully to the stereoselective synthesis of some naturally occurring lactones.[8] In this connection it was thought worthwhile to explore the possibility of ring opening of the cyclic sulfite itself by a nucleophile in a regiospecific way. Indeed, the cyclic sulfite **6** reacted with lithium azide with apparent complete selectivity for attack at C-2, the α-position, to furnish the azido alcohol **7** in 68% yield. The carbonyl group must be responsible for the increased reactivity of the α-position.[12] The azido alcohol **7** on reduction with lithium aluminium hydride followed by subsequent acetylation afforded the target molecule as triacetate **8** in 76% yield having $[\alpha]_D^{20}$=+17.2 (c 0.2, $CHCl_3$) [lit. $[\alpha]_D^{23}$=+16.8 (c=1, $CHCl_3$),[4f] $[\alpha]_D^{23}$=+17.4 (c=1, $CHCl_3$)[7e]].



Scheme 1. (i) $Ph_3P{=}CHCO_2Et$, THF, reflux, 18 h (87%); (ii) $(DHQD)_2$–PHAL, $K_3Fe(CN)_6$, K_2CO_3, OsO_4 (cat), $MeSO_2NH_2$, *t*-BuOH:H_2O (1:1), 0°C, 24 h (94%); (iii) $SOCl_2$, CCl_4, reflux, 1.5 h (96%); (iv) (a) LiN_3, DMF, 100°C, 18 h, (b) 20% H_2SO_4: Et_2O (1:1), rt, 12 h (68%); (v) (a) $LiAlH_4$, Et_2O, 0°C to rt, overnight, (b) Ac_2O, pyridine, rt, 18 h (76%)

The physical constants for D-(+)-dihydrosphingosine triacetate obtained were in excellent agreement with the literature values.[4f,7e]

3. Conclusion

In conclusion, we have demonstrated that the stereoselective synthesis of sphinganine triacetate can be accomplished by the Sharpless asymmetric dihydroxylation and the subsequent regiospecific nucleophilic opening of the corresponding cyclic sulfite. Thus, the results described herein constitute a short, high-yielding and efficient synthesis of the protected dihydrosphingosine. To the best of our knowledge, this is the first asymmetric synthesis of sphinganine using Sharpless asymmetric dihydroxylation as the source of chirality.

4. Experimental

4.1. 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 sodium D line on a JASCO-181 digital polarimeter. Infrared spectra were recorded on an ATI MATTSON RS-1 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on Bruker AC-200 and MSL-300 NMR spectrometers, respectively. Mass spectra were obtained with a Finnigan MAT-1020 B-70 eV mass spectrometer. Elemental analyses were carried on a Carlo Erba CHNS-O analyzer. Enantiomeric excess was determined by chiral HPLC.

4.2. *Ethyl* trans-*octadec-2-enoate* ***4***

To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (5.65 g, 16.22 mmol) in dry THF (35 mL) was added dropwise a solution of hexadecanal (3 g, 12.47 mmol) in THF (5 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** (3.37 g, 87%) as a white solid. Mp 25–26°C; IR ν_{max}/cm^{-1} (neat) 2926, 2854, 1724, 1655, 1466, 1367, 1310, 1178, 1128, 1045, 980, 721; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J=6.8 Hz, 3H), 1.15–1.30 (m, 24H), 1.35 (t, J=7.2 Hz, 3H), 1.45 (m, 2H), 2.18 (ddt, J=6.98, $J_{allylic}$=1.46 Hz, 2H), 4.18 (q, J=7.2 Hz, 2H), 5.8 (dt, J_{trans}=15.63, $J_{allylic}$=1.46 Hz, 1H), 6.97 (dt, J=6.98, J_{trans}=15.63 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.4, 22.8, 28.3, 29.3, 29.5–29.9, 32.1, 32.4, 60.1, 121.6, 149.3, 166.7; MS (EI), *m/z* (%) 311 [M^{+}+1] (18.58), 265 (46.15), 264 (48.71), 222 (12.82), 213 (37.6), 155 (21.36), 127 (60), 101 (64.53), 88 (47.43), 83 (56.4), 69 (60.25), 57 (86.32), 55 (100). Anal. calcd for $C_{20}H_{38}O_2$ (310.50): C, 77.36; H, 12.33. Found: C, 77.68; H, 11.99.

4.3. *Ethyl-(2*S*,3*R*)-2,3-dihydroxyoctadecanoate* ***5***

To a mixture of $K_3Fe(CN)_6$ (4.14 g, 12.6 mmol), K_2CO_3 (1.74 g, 12.6 mmol) and $(DHQD)_2$–PHAL (33 mg, 42.4 μmol, 1 mol%) in *t*-BuOH:H_2O (1:1, 50 ml) cooled at 0°C was added osmium tetroxide (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 **4** (1.3 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 (3×20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (3:2) as eluent gave **5** (1.355 g, 94%) as a white solid. Mp 65–66°C; $[\alpha]_D^{20}$=+8.6 (c 2, $CHCl_3$); IR ν_{max}/cm^{-1} ($CHCl_3$) 3400–3300, 3133, 3018, 2926, 2854, 1732, 1460, 1401, 1215, 760, 667; ^1H NMR ($CDCl_3$) δ 0.89 (t, *J*=7.5 Hz, 3H), 1.15–1.30 (m, 26H), 1.33 (t, *J*=7.5 Hz, 3H), 1.60 (m, 2H), 1.95 (d, *J*=8 Hz, 1H), 3.08 (d, *J*=4 Hz, 1H), 3.88 (m, 1H), 4.08 (dd, *J*=4, 2 Hz, 1H), 4.3 (q, *J*=7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.0, 22.5, 25.8, 29.2, 29.5, 31.8, 33.6, 61.9, 72.5, 73.2, 173.5; MS (EI), *m/z* (%) 299 [$M^+-OCH_2CH_3$] (0.5), 271 (0.9), 253 (1.3), 123 (3.6), 109 (7.6), 104 (100), 95 (15.20), 82 (17.85), 76 (32.14), 69 (14.3), 57 (14.20). Anal. calcd for $C_{20}H_{40}O_4$ (344.52): C, 69.72; H, 11.70. Found: C, 69.36; H, 12.08.

*4.4. (4*S,5R*)-4-Ethoxycarbonyl-5-pentadecyl-1,3,2-dioxathiolane-2-oxide* ***6***

A two necked round-bottomed flask equipped with a reflux condenser topped with a $CaCl_2$ guard tube and a rubber septum was charged with diol **5** (2.00 g, 5.8 mmol) and dry CCl_4 (15 mL). Thionyl chloride (1.043 g, 0.64 mL, 8.77 mmol) was added through a syringe and the reaction mixture was refluxed for 1.5 h. After completion of reaction, the reaction mixture was cooled; water (5 mL) and CH_2Cl_2 (20 mL) were added. The organic layer was separated and aqueous layer extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL) and brine (30 mL), dried (Na_2SO_4) and passed through a pad of silica gel. The filtrate was concentrated and the crude product was purified on a silica gel column using petroleum ether:EtOAc (9:1) as eluent to give **6** (2.176 g, 96%) as a colorless oil. $[\alpha]_D^{20}$=+79.21 (c 2, $CHCl_3$); IR ν_{max}/cm^{-1} (neat) 3131, 3024, 2925, 2854, 1741, 1461, 1397, 1278, 1215, 1032, 758; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J*=7 Hz, 3H), 1.15–1.30 (m, 26H), 1.34 (t, *J*=7 Hz, 3H), 1.8–1.95 (m, 2H), 4.30–4.34 (dq, *J*=7, 2 Hz, 2H), 4.50 (d, *J*=7.5 Hz, 0.5H), 4.6–4.68 (m, 0.5H), 5.05 (d, *J*=7 Hz, 0.5H), 5.09–5.17 (m, 0.5H); ^{13}C NMR ($CDCl_3$) δ 13.73, 13.8, 22.43, 24.99, 25.39, 28.81, 29.11–29.15, 31.71, 32.29, 34.73, 62.13, 62.84 (diastereomeric), 80.08, 81.36 (diastereomeric), 82.41, 86.58 (diastereomeric), 167.00; MS (EI), *m/z* (%) 390 [M^+] (0.5), 345 [$M^+-OCH_2CH_3$] (1.28), 326 [M^+-SO_2] (3.85), 325 [M^+-HSO_2] (3.8), 317 (3.85), 2.53 (15.4), 233 (14.10), 157 (6.41), 130 (19.23), 109 (52.56), 95 (96), 83 (96), 69 (97.43), 57 (100), 55 (96). Anal. calcd for $C_{20}H_{38}O_5S$ (390.57): C, 61.50; H, 9.80; S, 8.20. Found: C, 61.42; H, 9.74; S, 8.12.

*4.5. Ethyl-(2*R,3R*)-2-azido-3-hydroxyoctadecanoate* ***7***

To a solution of cyclic sulfite **6** (0.5 g, 1.28 mmol) in dry DMF (10 mL) was added LiN_3 (0.125 g, 2.56 mmol) under argon. The reaction mixture was stirred at 100°C for 18 h under argon. The solvent was removed under reduced pressure, to the residue was added 20% aqueous H_2SO_4:Et_2O (1:1, 10 mL) and the mixture was stirred at room temperature for 12 h. Excess $NaHCO_3$ was added to it and the reaction mixture was stirred for 20 min and then extracted with ether (3×20 mL). The organic layer was separated and passed through a Celite and silica gel bed. Removal of solvent afforded the crude product as a dark yellow oil which was purified on a silica gel column using petroleum ether:EtOAc (3:1) as eluent to give **7** (0.321 g, 68%) as a colorless low-melting solid. $[\alpha]_D^{20}$=−4.85 (c 2, $CHCl_3$); IR ν_{max}/cm^{-1} ($CHCl_3$) 3476, 2922, 2853, 2109, 1741, 1460, 1373, 1263, 1191, 1119, 1095, 1028; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J*=7 Hz, 3H), 1.15–1.30 (m, 26H), 1.36 (t, *J*=7 Hz, 3H), 1.62 (m, 2H), 2.23 (m, 1H), 3.22 (m, 1H), 4.14 (dd, *J*=6, 8 Hz, 1H), 4.34 (q, *J*=7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.76, 13.80, 22.46, 29.18–29.51,

31.77, 61.20, 71.00, 72.5, 170.0; MS (EI), *m/z* (%) 369 [M^+] (2.6), 367 (10.52), 341 [M^+-N_2] (1.31), 268 (9.87), 253 (20), 241 (26.31), 167 (6.58), 154 (15.13), 111 (44.08), 104 (40.8), 97 (93.42), 83 (100), 71 (81.58), 55 (44.08), 57 (75.65). Anal. calcd for $C_{20}H_{39}N_3O_3$ (369.53): C, 65.00; H, 10.64; N, 11.37. Found: C, 64.89; H, 10.80; N, 11.65.

*4.6. (2*S,3R*)-2-Acetamido-1,3-diacetoxyoctadecane **8***

To a stirred suspension of $LiAlH_4$ (25 mg. 0.66 mmol) in dry Et_2O (8 mL) at 0°C was added dropwise a solution of **7** (100 mg, 0.27 mmol) in Et_2O (5 mL) through a syringe. The reaction mixture was subsequently warmed to room temperature and stirred overnight. It was next hydrolysed with water (1 mL) and filtered through Celite. The Celite bed was washed with MeOH (3×20 mL). The total filtrate was concentrated to an off white solid which was subsequently acetylated with Ac_2O (0.5 mL) and pyridine (1 mL). After stirring for 18 h, the solvent was stripped off under reduced pressure and the residue was purified on a silica gel column using petroleum ether:EtOAc (1:1) as eluent to give the triacetate **8** (88 mg, 76%) as a white solid. It was further recrystallised from petroleum ether/EtOAc. Mp 96–98°C (lit. 97–98°C,[7e] 95–97°C,[4f] 89–91°C;[7a] $[\alpha]_D^{20}$=+17.2 (c 0.2, $CHCl_3$) [lit. +16.8 (c=1, $CHCl_3$),[4f] +17.4 (c=1, $CHCl_3$)[7e]]; IR ν_{max}/cm^{-1} ($CHCl_3$) 3291, 2913, 2847, 1730, 1646, 1537, 1368, 1233, 1036; ^{1}H NMR ($CDCl_3$) δ 0.84 (t, *J*=6.5 Hz, 3 H), 1.14–1.23 (m, 26H), 1.50–1.60 (m, 2H), 1.97 (s, 3H), 2.00 (s, 3H), 2.02 (s, 3H), 3.99–4.21 (m, 2H), 4.33–4.37 (m, 1H), 4.98–5.01 (m, 1H), 5.77–5.80 (d, *J*=8 Hz, 1H); MS (EI), *m/z* (%) 427 [M^+] (1.31), 354 (3.94), 308 (2.63), 307 (5.26), 295 (6.58), 294 (35.53), 188 (6.58), 145 (7.9), 144 (56.58), 102 (27.63), 85 (81.6), 84 (100).

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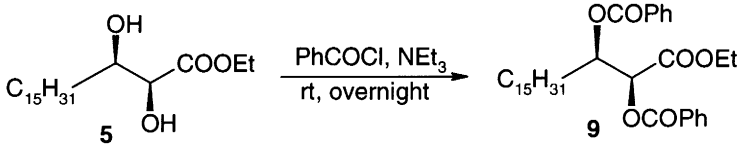
10. For the measurement of enantiomeric excess, the diol **5** was converted into its dibenzoate **9**. The enantiomeric purity of the dibenzoate **9** was estimated to be in excess of 99% by HPLC using Lichrocart 250-4 (4mm ID×25cm) HPLC-Cartridge (R.R.-Whelk-01), 10% *i*PrOH in hexane, 1 mL/min.



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