Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 343–347

TETRAHEDRON: *ASYMMETRY*

A short and efficient stereoselective synthesis of all four diastereomers of sphingosine

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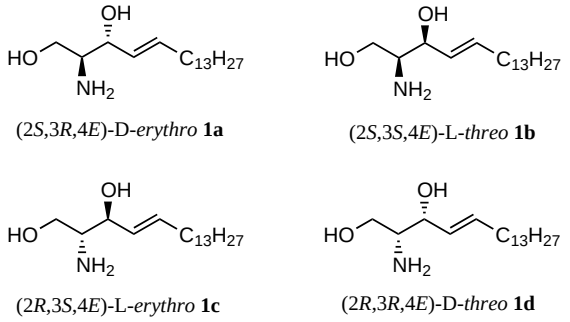
Received 27 December 2001; accepted 7 March 2002

Abstract—Practical syntheses of all four stereomers of sphingosine from serine have been achieved through highly diastereoselective reduction of the *N*-trityl protected α′-amino enone derivative **5** with $NaBH_4$ and reduction of the free α′-amino enone derivative **7** with $Zn(BH_4)_2$.

1. Introduction

Sphingolipids are distributed ubiquitously in the membranes of eukaryotic cells and in all plasma membranes.[1] Their metabolites such as ceramide, sphingosine, sphingosine-1-phosphate and glycosphingolipids are involved in diverse cellular processes including cell growth, survival, differentiation and adhesion, etc.[2] D-*erythro*-Sphingosine **1a**, which is the backbone of various sphingolipids, has itself been found to be a potent and specific inhibitor of protein kinase C and plays crucial roles in cellular signal transduction.[3] And the other diastereomers **1b–d** also show a variety of bioactivities[3a,4] (Fig. 1). Because of its biological importance the development of asymmetric synthetic methods for sphingosine has been a long standing target, and a great deal of effort has been expended to this end.[5] Recently we reported a stereodivergent synthesis of all four stereoisomers of sphingosine via *syn*/*anti* diastereoselective reduction of Boc-*N*-PMB and *N*-PMB protected α′-amino enones that were derived from serine.[6] However, this approach has some drawbacks due to the relatively lengthy procedure and problematic deprotection of the PMB group in the last step. For these reasons, we have now devised a more convenient, stereoselective synthesis of all four diastereomers of sphingosine using the *N*-trityl amine-protecting group to induce a strong directing effect through its bulk. Based on our previous reasoning and experience,[6] employment of the *N*-trityl protecting group was found to provide a more convenient access to the diastereomers: generation of the *syn* and *anti* products via non-chelation controlled reduction (open Felkin–Anh model) of tritylated amino enone **5** and chelation controlled reduction (cyclic Felkin–Anh model) of free amino enone **7**, respectively (Scheme 1).[7]



(2*S*,3*R*,4*E*)-D-*erythro* **1a**

(2*S*,3*S*,4*E*)-L-*threo* **1b**

(2*R*,3*S*,4*E*)-L-*erythro* **1c**

(2*R*,3*R*,4*E*)-D-*threo* **1d**

Figure 1. Structure of diastereomers of sphingosine.

2. Results and discussion

As shown in Scheme 2, our synthesis started with the fully protected serine methyl ester **3**, which was readily obtained from the commercially available serine derivative **2**. The protected serine ester **3** was quantitatively converted to the β-ketophosphonate **4** by treatment with excess lithium dimethyl methylphosphonate in THF at −78°C. The Horner–Wadsworth–Emmons olefination of the phosphonate **4** with tetradecyl alde-

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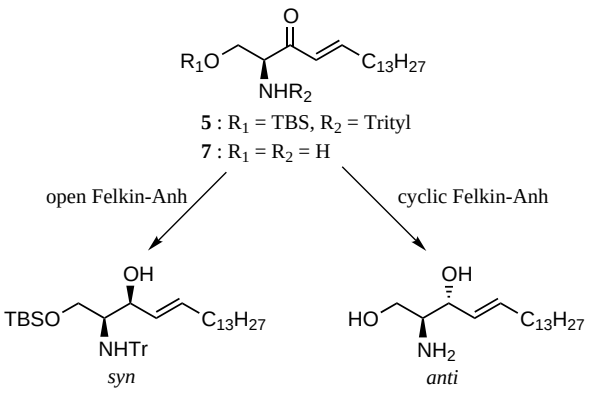
0957-4166/02/$ - see front matter
PII: S0957-4166(02)00118-0



Scheme 1.

hyde under Masamune conditions provided the corresponding enone **5** in good yield.[8] Reduction of enone **5** with $NaBH_4$ in the presence of $CeCl_3{\cdot}7H_2O$ afforded the *N*,*O*-diprotected L-*threo*-sphingosine **6** in 92% d.e., presumably via an open Felkin–Anh transition state (non-chelation control) in accordance with the literature precedents.[9] Removal of the two protecting groups (*N*-trityl and *O*-TBDMS) of **6** with hot aqueous HCl in MeOH–THF yielded L-*threo*-sphingosine **1b** and in 85% yield. On the other hand, in order to obtain D-*erythro*-sphingosine **1a**, enone **5** were first deprotected with 2N HCl in MeOH–THF under reflux to give 3-ketosphingosine **7**. Reduction of 3-ketosphingosine **7** with $Zn(BH_4)_2$ in THF at −78°C produced D-*erythro*-sphingosine **1a** in 90% d.e., presumably via a cyclic Felkin–Anh transition state, probably due to the high chelating ability of the zinc ion. The *anti* stereochemistry of the reduction is in accord with our previous observations.[6] Acetylation of D-*erythro*- and L-*threo*-sphingosine with acetic anhydride afforded the triacetates **8a**,**b**, which were easier to purify and characterize. Their spectroscopic and physical properties were identical to the literature data.[10] By employing the same procedures on D-serine esters, L-*erythro*- and D-*threo*-sphingosines were also synthesized in comparable yields and stereoselectivities.

3. Conclusion

In conclusion, we have developed short (six steps from commercially available serine derivatives) and practical (51–69% overall yields) synthetic routes to the four stereoisomers of sphingosine using highly efficient *syn*/*anti* diastereoselective reduction of 3-ketosphingosine derivatives **5** and **7**, which are complementary to our previous report.[6]

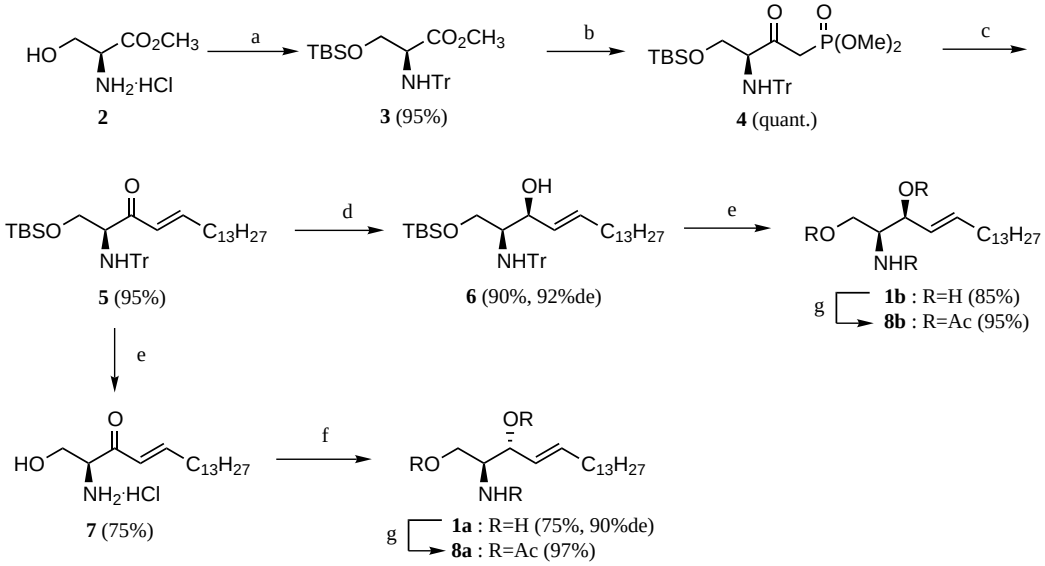
4. Experimental

4.1. General procedure

Melting points were determined on a Thomas–Hoover apparatus and were uncorrected. IR spectra were obtained on a BOMEM DA8 FT-IR Spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 300 (300 MHz) Spectrometer. Mass spectra (EI or FAB) were determined on a Micro Mass Platform II 8410E Spectrometer. Optical rotations were measured with a JASCO-DIP-360 digital polarimeter.

4.2. L-(*N*-Trityl-*O*-*tert*-butyldimethylsilyl)serine methyl ester 3

To a solution of L-serine methyl ester HCl **2** (0.5 g, 3.2 mmol) and Et_3N (1 mL, 7.3 mmol) in CH_2Cl_2 (30 mL) at −20°C under an N_2 atmosphere was added *tert*-butyldimethylsilyl chloride (0.85 g, 3.85 mmol). The resulting solution was stirred for 48 h at room tempera-



Scheme 2. *Reagents and conditions*: (a) (i) TBSCl, Et_3N, CH_2Cl_2, rt, (ii) TrCl, Et_3N, CH_2Cl_2, rt; (b) $LiCH_2PO(OMe)_2$, THF, −78°C; (c) $C_{13}H_{27}CHO$, DBU, LiCl, THF, rt; (d) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0°C; (e) 2N HCl, THF–MeOH, reflux; (f) $Zn(BH_4)_2$, THF, −78°C; (g) Ac_2O, pyridine, 0°C.

ture. To the solution were added trityl chloride (0.98 g, 3.52 mmol) and then Et_3N (0.6 mL, 4.2 mmol) and the resulting mixture was heated under reflux for 2 h. After cooling to room temperature, water (15 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3×30 mL) and the extract was washed with brine, dried ($MgSO_4$) and passed through a short pad of silica gel. After concentration, the pale yellow residue was crystallized from EtOH/H_2O (4:1) to give **3** as a white solid (1.53, 95%). Compound **3**: mp 88–89°C. $[\alpha]_D^{25}=+45.8$ (*c* 1.0, $CHCl_3$). IR (NaCl film): $\nu=3443$, 2951, 1734, 1113 cm^{-1}. ^1H NMR ($CDCl_3$) δ −0.04 (3H, s), −0.01 (3H, s), 0.82 (9H, s), 2.68 (1H, brs), 3.14 (3H, s), 3.44 (1H, brs), 3.60 (1H, dd, $J=9.6$, 7.2 Hz), 3.87 (1H, dd, $J=9.6$, 7.2 Hz), 7.10–7.48 (15H, m). ^{13}C NMR ($CDCl_3$) δ −5.5, −5.4, 18.2, 25.7, 51.4, 58.3, 66.1, 70.6, 126.4, 127.8, 128.8, 146.0, 174.4. EIMS: $m/z=973$ $(2M+Na)^+$. Anal. calcd for $C_{29}H_{37}NO_3Si$: C, 73.22; H, 7.84; N, 2.94. Found: C, 73.53; H, 7.74; N, 2.97%.

4.3. [4-(*tert*-Butyldimethylsilanyloxy)-3-tritylamino-2-oxo-butyl]phosphonic acid dimethyl ester 4

To a stirred solution of dimethyl methylphosphonate (11.8 mL, 105.1 mmol) in dry THF (300 mL) at −78°C under an N_2 atmosphere was added *n*-BuLi (1.6 M in *n*-hexane, 92 mL, 147.1 mmol) over 0.5 h. After stirring at the same temperature for 0.5 h, a solution of **3** (10 g, 21.0 mmol) in dry THF (30 mL) was added. The resulting mixture was allowed to slowly warm to −20°C and then quenched with saturated aq. NH_4Cl (200 mL). The mixture was extracted with EtOAc (3×200 mL), and the extract was washed with brine, dried ($MgSO_4$) and passed through a short pad of silica gel. After concentration, **4** was obtained quantitatively as a yellow oil (12 g) and used in the next step without further purification.

4.4. (2*S*,4*E*)-2-[*N*-(Trityl)amino]-1-*O*-*tert*-butyldimethylsilyl-3-oxo-4-octadecene 5

A solution of **4** (11 g, 19.4 mmol), tetradecyl aldehyde (8.24 g, 38.8 mmol), DBU (2.94 mL, 19.2 mmol) and LiCl (1.65 g, 38.8 mmol) in dry THF (170 mL) was stirred at room temperature under an N_2 atmosphere. After 5 h, 1 M citric acid (50 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3×150 mL) and the extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel (*n*-hexane/EtOAc = 30:1) to yield **5** as a pale yellow oil (12 g, 95%). Compound **5**: $[\alpha]_D^{25}=+59.6$ (*c* 1.19, $CHCl_3$). IR (NaCl film): $\nu=3445$, 2926, 2854, 1692, 1627, 1464, 1105 cm^{-1}. ^1H NMR ($CDCl_3$) δ −0.04 (3H, s), −0.01 (3H, s), 0.82 (9H, s), 0.88 (3H, t, $J=6.3$ Hz), 1.26–1.39 (22H, m), 1.98 (2H, m), 3.25 (1H, brs), 3.42 (1H, dd, $J=9.5$, 7.5 Hz), 3.68 (1H, m), 3.84 (1H, dd, $J=9.5$, 4.4 Hz), 5.80 (1H, d, $J=15.7$ Hz), 6.35 (1H, dt, $J=15.7$, 6.8 Hz), 7.11–7.49 (15H, m). ^{13}C NMR ($CDCl_3$) δ −5.5, −5.6, 14.1, 18.2, 22.7, 25.8, 28.0, 29.3, 29.4, 29.5, 29.7, 31.9, 32.2, 61.3, 66.7, 70.9, 126.3, 127.8, 128.5, 129.0, 146.0, 146.5, 203.0. FABMS: m/z 654 $(M+H)^+$. HRMS (EI, m/z): calcd for $C_{43}H_{63}NO_2Si$ 653.4628, found 653.4637.

4.5. (2*S*,3*S*,4*E*)-2-[*N*-(Trityl)amino]-1-*O*-*t*-butyldimethylsilyl-4-octadecen-1,3-diol 6

To a stirred solution of **5** (2.4 g, 3.67 mmol) in MeOH (100 mL) at 0°C were added $CeCl_3{\cdot}7H_2O$ (2.73 g, 7.34 mmol) and then $NaBH_4$ (0.56 g, 14.68 mmol). After 3 h, water was slowly added to quench the reaction. The mixture was extracted with EtOAc (3×100 mL) and the extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting oil was purified by flash chromatography using *n*-hexane/EtOAc (30:1) to give **6** as a colorless oil (2.17 g, 90%, 92% d.e. based on ^1H NMR). Compound **6**: $[\alpha]_D^{25}=-10.9$ (*c* 3.0, $CHCl_3$), IR (NaCl film): $\nu=3479$, 2926, 2854, 1673, 1464 cm^{-1}. ^1H NMR ($CDCl_3$) δ −0.13 (3H, s), −0.11 (3H, s), 0.82 (9H, s), 0.88 (3H, t, $J=6.3$ Hz), 1.26–1.35 (22H, m), 2.01 (2H, m), 2.64 (1H, dd, $J=9.8$, 6.2 Hz), 2.79 (1H, m), 3.03 (1H, dd, $J=9.8$, 2.3 Hz), 3.80 (1H, dd, $J=6.8$, 6.7 Hz), 5.39 (1H, dd, $J=15.3$, 7.5 Hz), 5.64 (1H, dt, $J=15.3$, 6.7 Hz), 7.16–7.55 (15H, m). ^{13}C NMR ($CDCl_3$) δ −5.2, −5.3, 14.5, 18.5, 23.1, 26.2, 29.7, 29.8, 29.9, 30.0, 30.1, 32.3, 32.9, 56.7, 62.3, 71.3, 74.2, 127.0, 128.3, 129.2, 130.3, 135.1, 147.1, 157.7. FABMS: $m/z=656$ $(M+H)^+$. HRMS (EI, m/z): calcd for $C_{43}H_{65}NO_2Si$ 655.4785, found 655.4785.

4.6. L-*threo*-Sphingosine 1b

To a stirred solution of **6** (350 mg, 0.53 mmol) in THF (3 mL) and MeOH (10 mL) was added 2N aqueous HCl solution (1 mL). The resulting mixture was stirred at 40°C for 5 h and then cooled to room temperature. The mixture was washed with *n*-hexane (2×20 mL) and evaporated under reduced pressure. The resulting residue was dissolved in H_2O (20 mL) and adjusted to pH ~ 10 with 1N NaOH. The mixture was extracted with chloroform (3×20 mL) and the extract was washed with brine, dried (Na_2SO_4) and concentrated to provide **1b** as a white solid (136 mg, 85%). L-*threo*-Sphingosine **1b**: mp 87–88°C. $[\alpha]_D^{25}=+1.5$ (*c* 0.5, $CHCl_3$). {lit.[10c] mp 86–87°C. $[\alpha]_D^{24}=+2.7$ (*c* 1.0, $CHCl_3$)}. ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, $J=6.4$ Hz), 1.26–1.37 (22H, m), 2.02–2.14 (6H, m), 2.81 (1H, m), 3.55 (1H, dd, $J=10.8$, 4.2 Hz), 3.68 (1H, dd, $J=10.8$, 4.2 Hz), 4.01 (1H, dd, $J=6.0$, 5.9 Hz), 5.45 (1H, dd, $J=15.4$, 6.7 Hz), 5.75 (1H, dt, $J=15.4$, 6.7 Hz). ^{13}C NMR ($CDCl_3$) δ 14.5, 23.1, 29.6, 29.7, 29.8, 29.9, 30.0, 30.1, 32.3, 32.7, 56.9, 65.2, 74.3, 130.2, 134.7. EIMS: $m/z=300$ $(M+H)^+$.

4.7. L-*threo*-Sphingosine-*N*,*O*,*O*-triacetate 8b

To a stirred solution of **1b** (24 mg, 0.08 mmol) in pyridine (0.5 mL) at 0°C under an N_2 atmosphere were added consecutively acetic anhydride (39 mg, 0.38 mmol) and DMAP (cat.). The mixture was stirred at room temperature for 1 h, and then poured into water and extracted with EtOAc (3×10 mL). The combined extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Recrystallization from *n*-hexane afforded **8b** as a white solid (32 mg, 95%) which was identical in all spectroscopic detail to the literature data.[10c] L-*threo*-Sphingosine-*N*,*O*,*O*-triacetate **8b**: mp 42–44°C. $[\alpha]_D^{25}=+7.65$ (*c* 0.56, $CHCl_3$).

{lit.[10c] mp 42–44°C. $[\alpha]_D^{25}=+7.0$ (*c* 2.05, $CHCl_3$)}. ^1H NMR ($CDCl_3$) δ 0.87 (3H, t, $J=6.7$ Hz), 1.17–1.40 (22H, m), 1.99–2.07 (11H, m), 4.00–4.12 (2H, m), 4.39 (1H, m), 5.33–5.42 (2H, m), 5.66 (1H, d, $J=9.3$ Hz). 5.74 (2H, m). ^{13}C NMR ($CDCl_3$) δ 14.5, 21.5, 23.1, 23.7, 29.2, 29.5, 29.7, 29.8, 30.0, 30.1, 32.3, 32.7, 51.3, 63.5, 124.4, 137.8, 170.3, 170.5, 171.1.

4.8. (2*S*,4*E*)-2-Amino-3-oxo-4-octadecen-1-ol·HCl 7

To a stirred solution of **5** (0.6 g, 0.92 mmol) in MeOH (10 mL) and THF (2 mL) was added 2N HCl solution (1 mL). This reaction mixture was heated under reflux for 1 h. After cooling, the reaction mixture was washed with *n*-hexane (3×20 mL) and then evaporated under reduced pressure. The resulting residue was recrystallized from *i*-PrOH/Et_2O (1:3) to afford **7** as a white solid (0.23 g, 75%). (2*S*,4*E*)-2-Amino-3-oxo-4-octadecen-1-ol·HCl **7**: mp 148–150°C. $[\alpha]_D^{25}=+24.4$ (*c* 0.95, MeOH). IR (NaCl film): $\nu=3444$, 2921, 2851, 1673, 1635 cm^{-1}. ^1H NMR (CD_3OD) δ 0.90 (3H, t, $J=6.9$ Hz), 1.29–1.55 (22H, m), 2.31 (2H, m), 3.99 (2H, m), 4.43 (1H, dd, $J=4.7$, 3.9 Hz), 6.42 (1H, d, $J=15.8$ Hz), 7.16 (1H, dt, $J=15.8$, 6.8 Hz). ^{13}C NMR (CD_3OD) δ 13.4, 22.7, 28.0, 29.3, 29.4, 29.5, 29.6, 29.7, 32.0, 32.8, 59.7, 59.8, 75.8, 125.6, 152.3, 192.8. FABMS: $m/z=298$ $(M+H)^+$. Anal. calcd for $C_{18}H_{36}ClNO_2$: C, 64.74; H, 10.87; N, 4.19. Found: C, 64.65; H, 10.84; N, 4.30%.

4.9. D-*erythro*-Sphingosine 1a

To a stirred solution of **7** (0.3 g, 0.9 mmol) in dry THF (30 mL) at −78°C under an N_2 atmosphere was added $Zn(BH_4)_2$ (0.1M in THF, 1.8 mL, 1.8 mmol) dropwise. After 5 h, the reaction mixture was cautiously quenched with water (30 mL), adjusted to pH ~1 with 1N aqueous HCl, washed with *n*-hexane and then adjusted to pH ~10 with 1N aqueous NaOH. The mixture was extracted with chloroform (3×30 mL), and the extract was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Recrystallization from $CHCl_3$/Et_2O/*n*-hexane (1:1:4) gave **1a** as a white solid (0.2 g, 75%, 90% d.e. based on ^1H NMR). D-*erythro*-Sphingosine **1a**: mp 79–82°C. $[\alpha]_D^{25}=-1.5$ (*c* 0.52, $CHCl_3$). {lit.[10d] mp 81–82°C. $[\alpha]_D^{25}=-2.8$ (*c* 1.0, $CHCl_3$)}. ^1H NMR ($CDCl_3$) δ 0.86 (3H, t, $J=6.9$ Hz), 1.20–1.37 (22H, m), 2.05 (1H, q, $J=6.7$ Hz), 2.87 (1H, q, $J=5.5$ Hz), 3.66 (2H, m), 4.05 (1H, t, $J=6.2$ Hz), 5.47 (1H, dd, $J=15.4$, 7.1 Hz), 5.75 (1H, dt, $J=15.4$, 6.7 Hz). ^{13}C NMR ($CDCl_3$) δ 14.5, 23.1, 29.6, 29.7, 29.8, 29.9, 30.0, 30.1, 32.3, 32.8, 56.5, 64.5, 75.9, 129.7, 135.2.

4.10. D-*erythro*-Sphingosine-*N*,*O*,*O*-triacetate 8a

In the same manner as described for **8b**, compound **8a** was prepared in 97% yield. D-*erythro*-Sphingosine-*N*,*O*,*O*-triacetate **8a**: mp 101–102°C. $[\alpha]_D^{25}=-13.2$ (*c* 1.04, $CHCl_3$). {lit.[10c] mp 102.5–103°C, $[\alpha]_D^{25}=-13.0$ (*c* 1.08, $CHCl_3$)}. ^1H NMR ($CDCl_3$) δ 0.85 (3H, t, $J=$ 6.4 Hz), 1.20–1.35 (22H, m), 1.95–2.04 (11H, m), 4.02 (1H, dd, $J=11.5$, 3.9 Hz), 4.26 (1H, dd, $J=11.5$, 6.1 Hz), 4.40 (1H, m), 5.25 (1H, pseudo t, $J=6.1$ Hz), 5.36 (1H, dd, $J=15.2$, 7.4 Hz), 5.62–5.80 (2H, m). ^{13}C NMR ($CDCl_3$) δ 14.5, 21.2, 21.5, 23.0, 23.7, 29.2, 29.6, 29.7, 29.8, 30.0, 30.1, 32.3, 32.7, 51.0, 63.0, 124.5, 13 7.8, 170.1, 170.4, 171.4.

4.11. L-*erythro*-Sphingosine 1c

In the same manner as described for **1a**, **1c** was prepared from commercially available D-serine methyl ester HCl. L-*erythro*-Sphingosine **1c**: mp 80–82°C. $[\alpha]_D^{25}=+2.1$ (*c* 0.53, $CHCl_3$). {lit.[10d] mp 81–82°C. $[\alpha]_D^{24}=+2.8$ (*c* 0.6, $CHCl_3$)}. Its spectroscopic data were identical to the literature data.[10b]

4.12. D-*threo*-Sphingosine 1d

In the same manner as described for **1b**, **1d** was prepared from commercially available D-serine methyl ester HCl. D-*threo*-Sphingosine, **1d**: mp 85–87°C. $[\alpha]_D^{25}=-2.15$ (*c* 0.48, $CHCl_3$). {lit.[10c] mp 85–87°C. $[\alpha]_D^{25}=-2.65$ (*c* 1.13, $CHCl_3$)}. Its spectroscopic data were identical to the literature data.[10c]

Acknowledgements

Financial support from the Korea Science and Engineering Foundation and the Ministry of Education/ BSRI Fund is gratefully acknowledged.

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