

MODEL STUDIES TOWARD SCYPHOSTATIN: SYNTHESIS OF (S)-4-BENZYL-3-(p-TOLUENESULFONYL)-2-OXAZOLIDINONE AND ITS EFFECTIVE TRANSFORMATION TO (S)-N-(1-BENZYL-2-HYDROXYETHYL)HEXADECANAMIDE[‡]

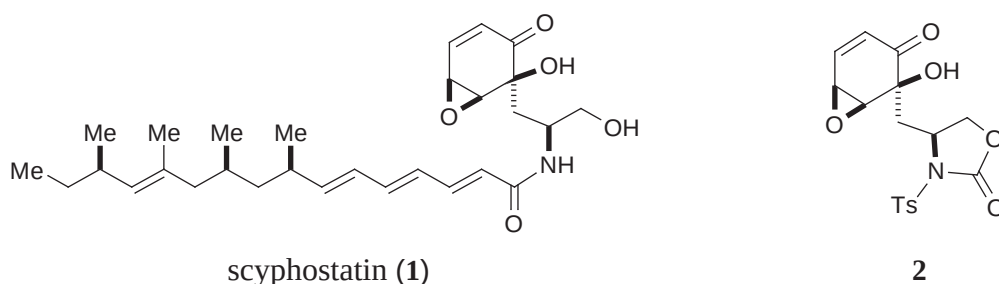
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Abstract – (S)-4-Benzyl-3-(p-toluenesulfonyl)-2-oxazolidinone (**6**) was synthesized as a simplified model substrate for the cyclohexenone subunit (**2**) of scyphostatin (**1**) starting from L-phenylalanine (**3**). Transformation of **6** to (S)-N-(1-benzyl-2-hydroxyethyl)hexadecanamide (**10**) was efficiently achieved to develop a reliable protocol for the construction of the fatty acid-substituted aminopropanol side chain moiety present in **1**; the method involves hydrolysis of the cyclic carbamate moiety, N-palmitoylation of the liberated N-Ts-amido function, and removal of the N-Ts protecting group as the crucial steps.

Scyphostatin (**1**, Figure 1), a potent inhibitor of neutral sphingomyelinase (IC₅₀=1.0 μM) isolated from the mycelial extract of *Trichopeziza mollissima* SANK 13892,² is anticipated to be a promising therapeutic agent for inflammation and immunological and neurological disorders.²⁻⁴ Structurally, this natural product possesses a novel, highly oxygenated cyclohexane ring connected with an unsaturated fatty acid-substituted aminopropanol side chain.^{2,5,6} Its promising biological profiles as well as unique

Figure 1. Structures of scyphostatin (**1**) and the cyclohexenone subunit (**2**)



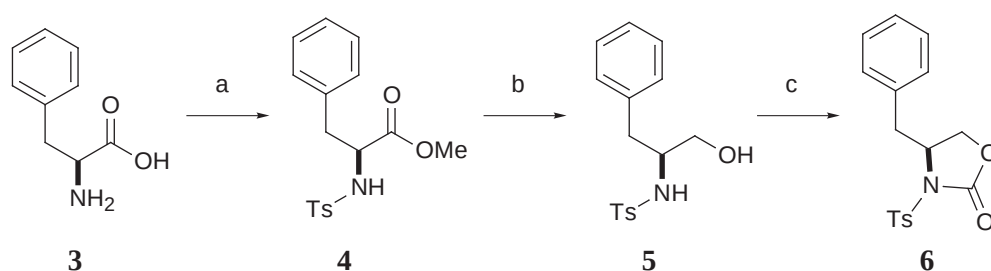
[‡] This paper is dedicated to Professor James P. Kutney of the University of British Columbia on the occasion of his 70th birthday.

structural features make **1** an attractive target for total synthesis, which, however, has not been achieved to date.⁷

During the course of our ongoing project directed toward the total synthesis of **1** and analogues,⁸ we have recently developed an enantioselective route to the key cyclohexenone subunit (**2**) bearing the *N,O*-protected aminopropanol side chain with the requisite asymmetric carbon centers.⁹ In order to forward the projected synthesis to the next phase, we are strongly required to explore a reliable protocol for constructing the fatty acid-substituted aminopropanol side chain moiety present in **1**. Herein we wish to report a synthesis of (*S*)-4-benzyl-3-(*p*-toluenesulfonyl)-2-oxazolidinone (**6**) starting from L-phenylalanine (**3**) (see, Scheme 1) as well as effective transformation of **6** to (*S*)-*N*-(1-benzyl-2-hydroxyethyl)hexadecanamide (**10**) (see, Scheme 2), which represents model studies for the elaboration of the fatty acid-substituted aminopropanol side chain moiety.

As shown in Scheme 1, we initially pursued the synthesis of (*S*)-4-benzyl-3-(*p*-toluenesulfonyl)-2-oxazolidinone (**6**) starting with the commercially available L-phenylalanine (**3**). Thus, treatment of **3** with gaseous hydrogen chloride in methanol provided L-phenylalanine methyl ester hydrochloride,¹⁰ which was then, without purification, reacted with *p*-toluenesulfonyl chloride (TsCl) in the presence of triethylamine, affording the *N*-Ts protected phenylalanine derivative (**4**) in 79% yield for the two steps. After reduction of the methyl ester function in **4** (100%), the resulting phenylalaninol derivative (**5**) was allowed to react with phosgene dimer (trichloromethyl chloroformate) in the presence of triethylamine, resulting in the formation of the desired oxazolidinone (**6**) in 88% yield.

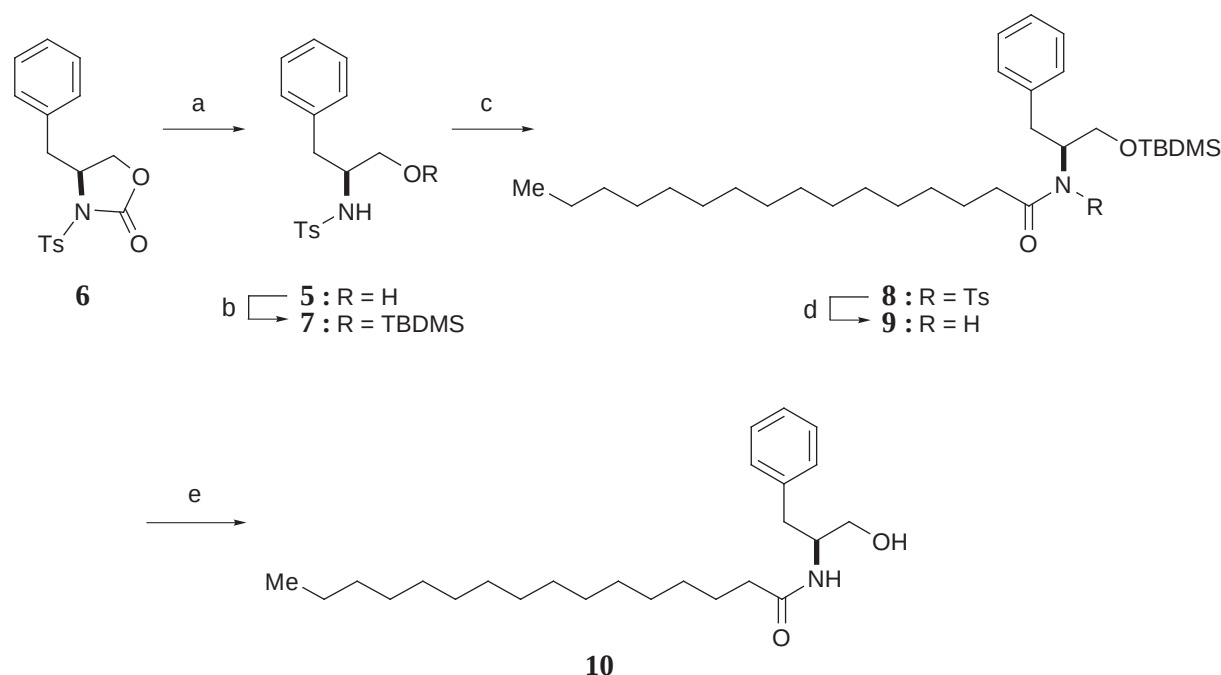
Scheme 1. Synthesis of (*S*)-4-benzyl-3-(*p*-toluenesulfonyl)-2-oxazolidinone (**6**)



(a) i) HCl, MeOH, reflux ; ii) TsCl, Et₃N, THF, rt, 79% (two steps); (b) NaBH₄, LiCl, EtOH-H₂O (2:1), rt, 100 %; (c) Cl₃COCOC₂H₅, Et₃N, THF, 0 °C, 88%

With the oxazolidinone (**6**) serving as a model substrate for the cyclohexenone subunit (**2**) in hand, our next efforts were devoted to transformation of **6** to a fatty acid-substituted aminopropanol derivative (**10**) (Scheme 2). This transformation involves the following three pivotal steps: i) hydrolysis of the cyclic carbamate moiety (**6** → **5**), ii) *N*-palmitoylation of the liberated *N*-Ts-amide function (**7** → **8**), and iii) removal of the *N*-Ts protecting group (**8** → **9**). After several experimentations, the carbamate moiety in **6**

Scheme 2. Transformation of (S)-4-benzyl-3-(*p*-toluenesulfonyl)-2-oxazolidinone (**6**) to (S)-*N*-(1-benzyl-2-hydroxyethyl)hexadecanamide (**10**)



(a) K₂CO₃, MeOH, rt, 100%; (b) TBDMSCl, imidazole, DMF, rt, 100%; (c) NaN(SiMe₃)₂, THF, -78 → -40 °C ; Me(CH₂)₁₄COCl, -40 → 0 °C, 86%; (d) sodium naphthalenide, DME, -70 °C, 65%; (e) TBAF, THF, rt, 85%

could be hydrolyzed readily by exposure to potassium carbonate (2.0 equiv) in methanol at room temperature for 10 min,¹¹ furnishing the *N*-Ts protected phenylalaninol (**5**) in quantitative yield. Protection of the hydroxy group in **5** provided the *tert*-butyldimethylsilyl (TBDMS) ether (**7**) in quantitative yield. Subsequent *N*-palmitoylation was best achieved by initial treatment of **7** with NaN(SiMe₃)₂ (3.0 equiv) in THF at -78 → -40 °C followed by exposure to palmitoyl chloride (2.0 equiv) at -40 → 0 °C, giving rise to the *N*-palmitoyl-*N*-Ts-amide (**8**) in 86% yield. The crucial removal of the *N*-Ts protecting group in **8** turned out to be effected by employing sodium naphthalenide in 1,2-dimethoxyethane (DME) at -70 °C for 5 min,¹² which led to the formation of the *N*-palmitoylamino-propanol derivative (**9**) in 65 % yield. Finally, removal of the TBDMS group in **9** by reaction with tetrabutylammonium fluoride (TBAF) in THF at room temperature, afforded the targeted compound (**10**) in 85% yield. The ¹H NMR spectrum of **10** was identical with that reported¹³ for its (*R*)-enantiomer (*ent*-**10**). In summary, we have performed model studies directed toward scyphostatin (**1**), which involve synthesis of (S)-4-benzyl-3-(*p*-toluenesulfonyl)-2-oxazolidinone (**6**) starting from L-phenylalanine (**3**) and effective transformation of **6** to (S)-*N*-(1-benzyl-2-hydroxyethyl)hexadecanamide (**10**). The explored protocol for the transformation of **6** to **10** should hold great promise for constructing the fatty acid-substituted amino-propanol side chain moiety in **1**. On the basis of these model studies, further efforts toward the total synthesis of **1** and its analogues are currently underway in our laboratories.

EXPERIMENTAL

General

All reactions involving air- and moisture-sensitive reagent were carried out using oven-dried glass ware and standard syringe-septum cap techniques. Routine monitorings of reaction were carried out using glass-supported Merck silica gel 60 F₂₅₄ TLC plates. Flash column chromatography was performed on Kanto Chemical Silica Gel 60 N (spherical, neutral 40-50 μ m) with indicated solvents. All solvents and reagents were used as supplied with the following exceptions. Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were freshly distilled from sodium/benzophenone under argon. Measurements of optical rotation were performed with JASCO P-1020 automatic digital polarimeter. Melting points were taken on Yanaco MP-3 micro melting point apparatus and are uncorrected. ¹H and ¹³C NMR spectra were measured with a Bruker DRX-500 (500 MHz) spectrometer. Chemical shifts were expressed in ppm using tetramethylsilane (δ =0) as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). IR spectral measurements were carried out with a JASCO FT/IR-5300 spectrophotometer. Low-resolution mass (MS) spectra and high-resolution mass (HRMS) spectra were measured on a Hitachi M80-B spectrometer.

N-(*p*-Toluenesulfonyl)-L-phenylalanine methyl ester (**4**)

Dry hydrogen chloride (HCl) gas was bubbled into a stirred suspension of L-phenylalanine (**3**) (1.00 g, 6.1 mmol) in methanol (30 mL) at 0 °C. Then, the mixture was refluxed for 4 h. After cooling, the mixture was concentrated *in vacuo* to give L-phenylalanine methyl ester hydrochloride as a white solid. Without purification, the crude product was dissolved in THF (20 mL). Triethylamine (2.52 mL, 18 mmol) and a solution of *p*-toluenesulfonyl chloride (1.27 g, 6.7 mmol) in THF (10 mL) was added successively to the above solution at 0 °C under argon. The resulting mixture was stirred for 12 h at rt. The reaction was quenched with water (10 mL), and the mixture was extracted with Et₂O (3 x 80 mL). The combined extracts were washed with 3% aqueous HCl, saturated aqueous NaHCO₃, and brine, then dried over Na₂SO₄. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane–ethyl acetate, 5:2) to give **4** (1.60 g, 79%) as a white solid. Recrystallization from hexane–dichloromethane (3:1) provided colorless needles, mp 100–101 °C and $[\alpha]_D^{20} +11.2^\circ$ (c 0.97, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 2.40 (3H, s), 3.03 (2H, d, J=6.1 Hz), 3.49 (3H, s), 4.20 (1H, dt, J=6.0, 9.1 Hz), 5.03 (1H, d, J=9.1 Hz), 7.07 (2H, dd, J=2.0, 7.3 Hz), 7.20–7.27 (5H, m), 7.63 (2H, d, J=8.3 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 21.52, 39.41, 52.36, 56.61, 127.19 (2 carbons), 127.26, 128.58 (2 carbons), 129.41 (2 carbons), 129.61 (2 carbons), 134.93, 136.66, 143.60, 171.22; IR (KBr) 550, 660, 700, 740, 810, 1090, 1160, 1220, 1340, 1440, 1500, 1600, 1740, 2950, 3280 cm⁻¹; CIMS (isobutane) *m/z* 334 [(M+H)⁺]; *Anal.* Calcd for C₁₇H₁₉NO₄: C, 61.24; H, 5.74; N, 4.20; S, 9.62. Found: C, 61.05; H, 5.85; N, 4.14; S, 9.49.

(*S*)-3-Phenyl-2-(*N*-*p*-toluenesulfonylamino)-1-propanol (**5**)

Sodium borohydride (0.37 g, 9.8 mmol) was added to a stirred solution of **4** (1.60 g, 4.8 mmol) and lithium chloride (0.41 g, 9.7 mmol) in a mixture of ethanol (16 mL) and THF (8 mL) at 0 °C. The mixture

was stirred for 3 h at rt. The reaction was quenched with water (10 mL), and the mixture was extracted with Et₂O (3 x 80 mL). The combined extracts were washed with saturated aqueous NaHCO₃ and brine, and then dried over Na₂SO₄. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane–ethyl acetate, 1:1) to give **5** (1.52 g, 100%) as a colorless syrup: $[\alpha]_D^{20}$ –27.3° (c 1.30, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 2.32 (1H, t, J=5.7 Hz), 2.41 (3H, s), 2.68 (1H, dd, J=7.3, 13.8 Hz), 2.78 (1H, dd, J=7.1, 13.8 Hz), 3.45 (1H, m), 3.53 (1H, m), 3.64 (1H, ddd, J=3.9, 6.1, 11.2 Hz), 5.00 (1H, d, J=7.2 Hz), 6.97 (2H, m), 7.15–7.22 (5H, m), 7.59 (2H, d, J=8.3 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 21.49, 37.75, 56.61, 64.00, 126.67, 126.99 (2 carbons), 128.63 (2 carbons), 129.13 (2 carbons), 129.66 (2 carbons), 136.71, 136.80, 143.36; IR (neat) 550, 580, 670, 700, 750, 810, 890, 980, 1040, 1090, 1160, 1320, 1450, 1490, 1600, 2880, 2930, 3280, 3500 cm⁻¹; CIMS (isobutane) *m/z* 306 [(M+H)⁺]; HREIMS *m/z* calcd for C₁₅H₁₆NO₂S [(M–CH₂OH)⁺], 274.0903, found 274.0900.

(S)-4-Benzyl-3-(p-toluenesulfonyl)-2-oxazolidinone (6)

Trichloromethyl chloroformate (0.39 mL, 2.0 mmol) was added dropwise to a stirred solution of **5** (598 mg, 2.0 mmol) containing triethylamine (1.36 mL, 9.8 mmol) in THF (15 mL) at 0 °C under argon. After 2 h, the reaction was quenched with saturated aqueous NaHCO₃ (10 mL), and the mixture was extracted with Et₂O (3 x 70 mL). The combined extracts were washed with 3% aqueous HCl, saturated aqueous NaHCO₃, and brine, then dried over Na₂SO₄. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane–ethyl acetate, 2:1) to give **6** (572 mg, 88%) as a white solid. Recrystallization from hexane–dichloromethane (4:1) afforded colorless prisms, mp 137–138 °C and $[\alpha]_D^{20}$ +50.3° (c 0.95, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 2.46 (3H, s), 2.83 (1H, dd, J=10.2, 13.4 Hz), 3.53 (1H, dd, J=3.6, 13.4 Hz), 4.09 (1H, dd, J=3.3, 9.0 Hz), 4.15 (1H, t, J=8.4 Hz), 4.67 (1H, m), 7.21 (2H, d, J=7.2), 7.25–7.39 (5H, m), 8.01 (2H, d, J=8.4 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 21.70, 39.74, 57.97, 66.57, 127.53, 128.47 (2 carbons), 129.07 (2 carbons), 129.42 (2 carbons), 129.83 (2 carbons), 134.59, 135.15, 145.67, 152.00; IR (neat) 540, 580, 620, 670, 700, 740, 810, 1090, 1130, 1170, 1370, 1450, 1490, 1600, 1780 cm⁻¹; EIMS *m/z* 331 (M⁺); *Anal.* Calcd for C₁₇H₁₇NO₄S: C, 61.61; H, 5.17; N, 4.23; S, 9.68. Found: C, 61.58; H, 5.26; N, 4.15; S, 9.62.

Hydrolysis of the cyclic carbamate (6) to the phenylalaninol derivative (5)

Potassium bicarbonate (42.0 mg, 0.30 mmol) was added to a stirred solution of **6** (50.0 mg, 0.15 mmol) in methanol (3 mL) at rt. After 10 min, the mixture was diluted with Et₂O (30 mL), and the organic layer was washed with saturated aqueous NaHCO₃ and brine, and dried over Na₂SO₄. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane–ethyl acetate, 1:1) to give **5** (46.0 mg, 100%). The ¹H NMR spectrum of this material was identical with that of an authentic sample recorded for the preparation of (S)-3-phenyl-2-(N-p-toluenesulfonylamino)-1-propanol (**5**).

(S)-N-[1-Benzyl-2-(tert-butyldimethylsiloxy)ethyl]-p-toluenesulfonamide (7)

tert-Butyldimethylsilyl chloride (285 mg, 1.9 mmol) was added to a stirred solution of **5** (289 mg, 0.95 mmol) and imidazole (193 mg, 2.8 mmol) in DMF (10 mL) at rt. After 12 h, the mixture was diluted with Et₂O (100 mL), and the organic layer was washed with 3% aqueous HCl, saturated aqueous NaHCO₃, and brine, then dried over Na₂SO₄. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane–ethyl acetate, 7:1) to give **7** (397 mg, 100%) as a colorless syrup: $[\alpha]_D^{20}$ –11.0° (c 1.22, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ –0.22 (6H, d, J=11.7 Hz), 0.87 (9H, s), 2.40 (3H, s), 2.78 (2H, m), 3.34 (1H, dd, J=4.9, 10.1 Hz), 3.41–3.46 (2H, m), 4.75 (1H, d, J=7.9 Hz), 7.04 (2H, dd, J=1.5, 7.7 Hz), 7.16–7.23 (5H, m), 7.64 (2H, d, J=8.3 Hz); ¹³C NMR (125 MHz, CDCl₃) δ –5.59, –5.54, 18.19, 21.46, 25.83 (3 carbons), 37.93, 56.08, 62.98, 126.49, 126.93 (2 carbons), 128.46 (2 carbons), 129.32 (2 carbons), 129.60 (2 carbons), 137.33, 137.73, 143.15; IR (neat) 550, 590, 670, 700, 740, 780, 810, 840, 970, 1050, 1090, 1160, 1260, 1330, 1420, 1470, 1500, 1600, 2860, 2880, 2930, 2950, 3030, 3060, 3290 cm^{–1}; CIMS (isobutane) *m/z* 420 [(M+H)⁺]; HREIMS *m/z* calcd for C₂₁H₃₀NO₃SSi [(M–Me)⁺], 404.1717, found 404.1726.

(S)-N-Hexadecanoyl-N-[1-benzyl-2-(*tert*-butyldimethylsiloxy)ethyl]-*p*-toluenesulfonamide (8)

Sodium bis(trimethylsilyl)amide in THF (1.0 M solution, 2.91 mL, 2.9 mmol) was added dropwise to a stirred solution of **7** (408 mg, 0.97 mmol) in THF at –78 °C under argon. The mixture was gradually warmed up to –40 °C over 1 h, and then a solution of palmitoyl chloride (0.54 mL, 1.8 mmol) in THF (2 mL) was added dropwise to the above mixture at –40 °C. After the resulting mixture was warmed to 0 °C over 1 h, the stirring was further continued for 1 h at 0 °C. The mixture was diluted with Et₂O (100 mL), and the organic layer was washed with saturated aqueous NaHCO₃ and brine, and dried over Na₂SO₄. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane–ethyl acetate, 15:1) to give **8** (551 mg, 86%) as a colorless syrup. Since this material contains a small amount of impurities, further purification of **8** was performed using preparative TLC for obtaining an analytical sample: $[\alpha]_D^{20}$ –19.2° (c 1.10, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 0.02 (6H, s), 0.85 (9H, s), 0.88 (3H, t, J=6.9 Hz), 1.07–1.34 (24H, br), 1.43 (2H, br), 2.27–2.37 (1H, br), 2.39 (3H, s), 2.46 (1H, m), 3.17 (1H, dd, J=6.8, 13.8 Hz), 3.29 (1H, dd, J=8.3, 13.8 Hz), 3.88 (1H, dd, J=6.1, 10.2 Hz), 4.16 (1H, br), 4.69 (1H, m), 7.13–7.30 (7H, m), 7.51 (2H, d, J=7.2 Hz); ¹³C NMR (125 MHz, CDCl₃) δ –5.44, –5.41, 14.13, 18.30, 21.56, 22.70, 24.71, 25.89 (3 carbons), 28.91, 29.24, 29.37, 29.42, 29.62 (2 carbons), 29.67 (2 carbons), 29.70 (2 carbons), 29.71 (2 carbons), 31.93, 63.29, 64.82, 126.55, 127.62 (2 carbons), 128.62 (2 carbons), 129.47 (2 carbons), 129.60 (2 carbons), 137.77, 138.80, 144.08, 174.48; IR (neat) 550, 590, 670, 700, 750, 780, 810, 840, 960, 1090, 1160, 1260, 1360, 1470, 1600, 1700, 2850, 2930 cm^{–1}; CIMS (isobutane) *m/z* 658 [(M+H)⁺]; HREIMS *m/z* calcd for C₃₄H₅₄NO₄SSi [(M–*tert*-Bu)⁺], 600.3543, found 600.3555.

(S)-N-[1-Benzyl-2-(*tert*-butyldimethylsiloxy)ethyl]hexadecanamide (9)

Sodium naphthalenide in 1,2-dimethoxyethane (DME) (0.2 M solution, 3.88 mL, 0.78 mmol) was added to a stirred solution of **8** (170 mg, 0.26 mmol) in DME (6 mL) at –70 °C under argon. After 5 min, the reaction was quenched with water (3 mL). The mixture was poured into Et₂O (60 mL), and the organic

layer was washed with saturated aqueous NaHCO₃ and brine, and dried over Na₂SO₄. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane–ethyl acetate, 5:1) to give **9** (84.0 mg, 65%) as a white amorphous solid; $[\alpha]_{\text{D}}^{20}$ –20.9° (c 1.12, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 0.05 (6H, d, J=6.7 Hz), 0.88 (3H, t, J=7.0 Hz), 0.93 (9H, s), 1.22–1.30 (24H, br), 1.57 (2H, t, J=7.1 Hz), 2.14 (2H, t, J=7.2 Hz), 2.85 (2H, m), 3.51 (2H, d, J=3.0 Hz), 4.21 (1H, m), 5.68 (1H, d, J=8.6 Hz), 7.18–7.30 (5H, m); ¹³C NMR (125 MHz, CDCl₃) δ –5.51, –5.39, 14.13, 18.27, 22.70, 25.74, 25.90 (3 carbons), 29.21, 29.37, 29.48, 29.64, 29.67 (2 carbons), 29.69, 29.70 (2 carbons), 31.93, 37.01, 37.08, 51.23, 62.70, 126.37, 128.39 (2 carbons), 129.40 (2 carbons), 138.19, 172.42; IR (neat) 510, 700, 740, 780, 840, 1120, 1260, 1380, 1470, 1500, 1550, 1640, 2850, 2930, 3030, 3070, 3290 cm^{–1}; CIMS (isobutane) *m/z* 504 [(M+H)⁺]; HREIMS *m/z* calcd for C₂₇H₄₈NO₂Si [(M-*tert*-Bu)⁺], 446.3454, found 446.3436.

(S)-N-(1-Benzyl-2-hydroxyethyl)hexadecanamide (10)

Tetrabutylammonium fluoride in THF (1.0 M solution, 0.22 mL, 0.22 mmol) was added dropwise to a stirred solution of **9** (73.0 mg, 0.15 mmol) in THF (3 mL) at rt. After 2 h, the mixture was concentrated *in vacuo* to provide a residue, which was purified by column chromatography (hexane–ethyl acetate, 1:2) to give **10** (48.0 mg, 85%) as a white solid. Recrystallization from hexane–dichloromethane (3:1) afforded colorless needles, mp 98–99 °C [lit.,¹³ mp 100–101 °C for the (*R*)-enantiomer (*ent*-**10**)] and $[\alpha]_{\text{D}}^{20}$ –15.9° (c 0.98, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 0.88 (3H, t, J=7.0 Hz), 1.21–1.32 (24H, br), 1.54 (2H, br), 2.13 (2H, dt, J=3.1, 7.5 Hz), 2.68 (1H, t, J=5.4 Hz), 2.87 (2H, ddd, J=7.6, 13.8, 29.3), 3.61 (1H, dt, J=5.3, 11.0 Hz), 3.71 (1H, ddd, J=3.4, 5.6, 11.0 Hz), 4.17 (1H, m), 5.60 (1H, d, J=6.9 Hz), 7.19–7.34 (5H, m); ¹³C NMR (125 MHz, CDCl₃) δ 14.12, 22.70, 25.69, 29.16, 29.33, 29.37, 29.46, 29.62, 29.66 (2 carbons), 29.69, 29.71 (2 carbons), 31.93, 36.85, 37.00, 52.98, 64.81, 126.76, 128.70 (2 carbons), 129.16 (2 carbons), 137.57, 174.02; IR (KBr) 510, 530, 630, 700, 730, 750, 960, 1060, 1090, 1120, 1190, 1220, 1230, 1250, 1270, 1380, 1460, 1470, 1560, 1650, 2850, 2920, 2960, 3030, 3090, 3300 cm^{–1}; EIMS *m/z* 389 (M⁺); *Anal.* Calcd for C₂₅H₄₃NO₂: C, 77.07; H, 11.12; N, 3.60. Found: C, 76.72; H, 11.50; N, 3.61. The ¹H NMR spectrum of this material was identical with that reported¹³ for its (*R*)-enantiomer (*ent*-**10**).

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REFERENCES AND NOTES

1. Graduate student from Department of Electronic Chemistry, Tokyo Institute of Technology, Nagatsuta, Yokohama 226-8502, Japan.
2. M. Tanaka, F. Nara, K. Suzuki-Konagai, T. Hosoya, and T. Ogita, *J. Am. Chem. Soc.*, 1997, **119**, 7871.
3. F. Nara, M. Tanaka, T. Hosoya, K. Suzuki-Konagai, and T. Ogita, *J. Antibiotic*, 1999, **52**, 525.

4. F. Nara, M. Tanaka, S. Masuda-Inoue, Y. Yamamoto, H. Doi-Yoshioka, K. Suzuki-Konagai, S. Kumakura, and T. Ogita, *J. Antibiotic*, 1999, **52**, 531.
5. Initial structure elucidation² only determined the relative and absolute stereochemistries of the cyclohexenone moiety in **1**. Recently, Kogen *et al.* in the Sankyo research group elucidated the relative and absolute configurations of the three stereocenters within the C-20 unsaturated fatty acid moiety, see: S. Saito, N. Tanaka, K. Fujimoto, and H. Kogen, *Org. Lett.*, 2000, **2**, 505.
6. Subsequently to the Kogen's report,⁵ Hoyer *et al.* presented the enantioselective synthesis of the C-20 unsaturated fatty acid moiety in **1**, which led to alternative proof of its stereostructure including absolute configuration, see: T. R. Hoyer and M. A. Tennakoon, *Org. Lett.*, 2000, **2**, 1481.
7. Recently, a synthetic study toward the cyclohexenone moiety of **1** was reported by Gurjar *et al.*, see: M. K. Gurjar and S. Hotha, *Heterocycles*, 2000, **53**, 1885.
8. T. Izuhara and T. Katoh, *Tetrahedron Lett.*, 2000, **41**, 7651.
9. T. Izuhara and T. Katoh, *Org. Lett.*, 2001, **3**, 1653.
10. L-Phenylalanine methyl ester hydrochloride is commercially available from Aldrich; nevertheless, from the economical point of view, we conducted the preparation of this compound from L-phenylalanine (**3**) following the reported protocol, see: A. McKillop, R. J. K. Taylor, R. J. Watson, and N. Lewis, *Synthesis*, 1994, 31.
11. Alternatively, exposure of the oxazolidinone (**6**) to *tert*-BuOK (2.0 equiv) in *tert*-BuOH–THF (5:1) at room temperature for 10 min, provided the *N*-Ts protected aminopropanol derivative (**5**) in 90 % yield.
12. For examples for the cleavage of *N*-Ts-amides by the use of sodium naphthalenide, see: (a) J. M. McIntosh and L. C. Matassa, *J. Org. Chem.*, 1988, **53**, 4452. (b) C. H. Heathcock, T. A. Blumenkopf, and K. M. Smith, *J. Org. Chem.*, 1989, **54**, 1548. (c) Y. Ban, S. Nakajima, K. Yoshida, M. Mori, and M. Shibasaki, *Heterocycles*, 1994, **39**, 657. (d) T. Katoh, E. Itoh, Y. Yoshino, and S. Terashima, *Tetrahedron*, 1997, **53**, 10229.
13. The (*R*)-enantiomer (*ent*-**10**) has been previously synthesized by direct acylation of D-alaninol with palmitic acid in the presence of 1,3-dicyclohexylcarbodiimide (DCC), see: C. Bennion, S. Connolly, N. P. Gensmantel, C. Hallam, C. G. Jackson, W. U. Primrose, G. C. Roberts, D. H. Robinson, and P. K. Slaich, *J. Med. Chem.*, 1992, **35**, 2939.