HETEROCYCLES, Vol. 56, 2002, pp. 553-560, Received, 8th August, 2001

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‡

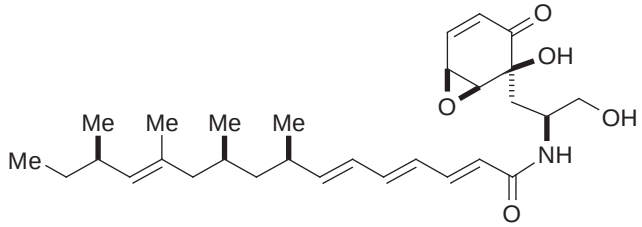
Takashi Izuhara,[1] Wakako Yokota, Munenori Inoue, and Tadashi Katoh*

Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229-0012, Japan

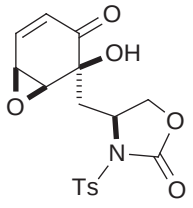
Abstract – (*S*)-4-Benzyl-3-(*p*-toluenesulfonyl)-2-oxazolidinone (**6**) was synthesized as a simplified model substrate for the cyclohexenone subunit (**2**) of scyphostatin (**1**) starting from L-phenylalanine (**3**). Transformation of **6** to (*S*)-*N*-(1-benzyl-2-hydroxyethyl)hexadecanamide (**10**) 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 (IC_{50}=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**)



scyphostatin (**1**)



2

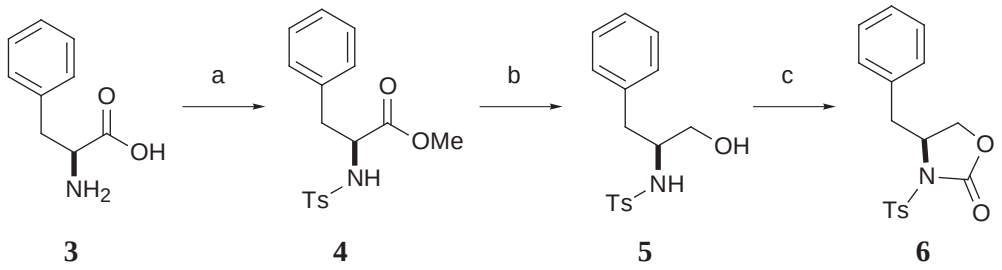
‡ This paper is dedicated to Professor James P. Kutney of the University of British Columbia on the occasion of his 70th birthday.

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**)

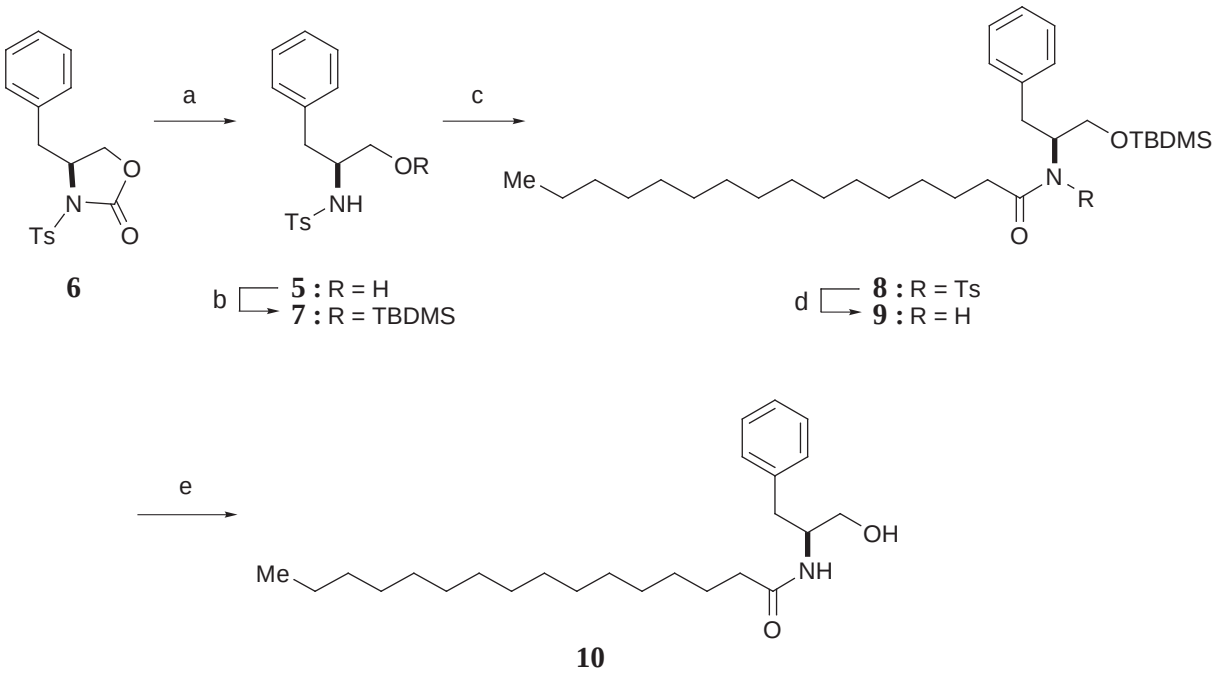


3 **4** **5** **6**

(a) i) HCl, MeOH, reflux ; ii) TsCl, Et_3N, THF, rt, 79% (two steps); (b) $NaBH_4$, LiCl, EtOH–H_2O (2:1), rt, 100 %; (c) $Cl_3COCOCl$, Et_3N, 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) K_2CO_3, MeOH, rt, 100%; (b) TBDMSCl, imidazole, DMF, rt, 100%; (c) $NaN(SiMe_3)_2$, THF, –78 → –40 °C ; $Me(CH_2)_{14}COCl$, –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 $NaN(SiMe_3)_2$ (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 ^{1}H NMR spectrum of **10** was identical with that reported[13] 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 F_{254} TLC plates. Flash column chromatography was performed on Kanto Chemical Silica Gel 60 N (spherical, neutral 40-50 μm) 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. ^{1}H and ^{13}C 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 Et_2O (3 x 80 mL). The combined extracts were washed with 3% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, then dried over Na_2SO_4. 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° (c 0.97, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{17}H_{19}NO_4$: 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 Et_2O (3 x 80 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, and then dried over Na_2SO_4. 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, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{15}H_{16}NO_2S$ $[(M–CH_2OH)^+]$, 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 $NaHCO_3$ (10 mL), and the mixture was extracted with Et_2O (3 x 70 mL). The combined extracts were washed with 3% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, then dried over Na_2SO_4. 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, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{17}H_{17}NO_4S$: 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 Et_2O (30 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. 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 Et_2O (100 mL), and the organic layer was washed with 3% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, then dried over Na_2SO_4. 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, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{21}H_{30}NO_3SSi$ $[(M–Me)^+]$, 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 Et_2O (100 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. 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, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125MHz, $CDCl_3$) 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 $C_{34}H_{54}NO_4SSi$ $[(M–tert\text{-}Bu)^+]$, 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 Et_2O (60 mL), and the organic

layer was washed with saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. 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; $[\alpha]_D^{20}$ –20.9° (c 1.12, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{27}H_{48}NO_2Si$ $[(M–tert\text{-}Bu)^+]$, 446.3454, found 446.3436.

(*S*)-*N*-(1-Benzyl-2-hydroxyetyl)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 $[\alpha]_D^{20}$ –15.9° (c 0.98, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz,$CDCl_3$) 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 $C_{25}H_{43}NO_2$: 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 reported[13] for its (*R*)-enantiomer (*ent*-**10**).

ACKNOWLEDGMENT

We thank Drs. H. Kogen and T. Ogita, Sankyo Co., Ltd., for their constant encouragement and valuable suggestion. This work was supported in part by Sankyo Co., Ltd.

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 elucidation[2] 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] Hoye *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. Hoye 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-phenyl-alanine (**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.