Supporting Information

Verticilide: Elucidation of Absolute Configuration and Total Synthesis

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Methods and Material

General.

Unless otherwise noted, all other commercially obtained reagents and solvents were used as received. All reactions were monitored by thin-layer chromatography using E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Flash chromatography was performed with indicated solvents using E. Merck silica gel 60 (partical size 0.040-0.063). ^1H NMR spectra were recorded on JEOL JNM-EX270 (270 MHz) or VXR-300 (300 MHz), and ^{13}C NMR spectra were recorded on JEOL JNM-EX270 (67.5 MHz) or VXR-300 (75 MHz). Chemical shifts are reported relative to internal chloroform (^1H ; $\delta = 7.26$, ^{13}C , $\delta = 77.1$), methanol (^1H , $\delta = 3.31$, ^{13}C , $\delta = 49.2$), pyridine (^1H ; $\delta = 8.73, 7.58, 7.21$, ^{13}C ; $\delta = 149.9, 135.5, 123.5$) as indicated. Melting points were obtained on a YANAGIMOTO MICRO MELTING APPARATUS and are uncorrected. Infrared spectra were recorded on a Horiba FT-210 spectrometer. High resolution mass spectra were acquired on a JEOL JMS-AX505 HA Mass spectrometer. Low resolution mass spectra were acquired on a JEOL JMS-DX300 Mass spectrometer.

Scheme 1. Preparation of (S)-2-hydroxyheptanoic acid (–)-6

• 2-[(4S)-2-Cyclohexylidene-5-oxo-1,3-dioxolan-4yl]acetic Acid

To a suspension of (S)-malic acid (20.0 g, 0.149 mol) in dry ether (149 mL) cooled at 0 °C was added cyclohexanone (18.6 mL, 0.179 mol) and $\text{BF}_3\text{-OEt}_2$ (21.0 mL, 0.164 mmol). The suspension gradually turned into a clean solution, and the mixture was stirred for 1 h at 0 °C. The ice bath was then removed, and the mixture was stirred for 24 h at room temperature. The reaction mixture was diluted with ether (200 mL) and washed with 10% aqueous sodium acetate (70 mL). The combined aqueous layers were extracted with ether (200 mL), and combined organic layers were washed once with brine (70 mL), and dried over MgSO_4 . Flash chromatography (CHCl_3 to CHCl_3 : MeOH = 50 : 1) provided the dioxolanone acid (21.4 g, 67 %).

R_f = 0.33 (CHCl_3 : MeOH = 10 : 1)

[α]_D²⁸ +7.18 (c 1.00, CHCl_3)

IR (KBr) ν cm^{-1} 3205 (COOH), 1801 (C=O), 1736 (COOH)

¹H-NMR (270 MHz, CDCl_3)

δ : 10.0 (brs, 1H, CO₂H), 4.71 (dd, J = 3.92, 6.48 Hz, 1H, -CH-),

2.99 (dd, J = 4.05, 17.6 Hz, 1H, -CH₂-), 2.84 (dd, J = 6.35, 17.0 Hz, 1H, -CH₂-),

1.90-1.37 (m, 10H, C₆H₁₀)

¹³C-NMR (67.5 MHz, CDCl_3)

δ : 175.4, 172.5, 112.6, 70.4, 36.6, 36.5, 35.7, 24.8, 23.3, 23.3

HR-MS (EI+)

m/z : 214.0838 [M]⁺, Calcd for $\text{C}_{10}\text{H}_{14}\text{O}_5$: 214.0841 [M]

• 2-[(4S)-2-Cyclohexylidene-5-oxo-1,3-dioxolan-4yl]acetaldehyde (**3**)

Dioxolanone acid (3.02 g, 14.1 mmol) was dissolved in THF (57 mL), and the mixture was cooled to 0 °C under an atmosphere of N₂. A solution of BH₃-THF 1.0 M solution (21 mL, 21.2 mmol) was added dropwise over a period of 30 min. The mixture was stirred for 1 h at 0 °C and then for 2 h at room temperature. The reaction mixture was cooled to 0 °C, MeOH (20 mL) was added dropwise and the mixture was stirred for 5 min to destroy the remaining borane. The mixture was concentrated at below 35 °C, MeOH (20 mL) was added, and the resulting solution was concentrated. A final concentration from ethyl acetate (20 mL) gave dioxolanone alcohol (5.0 g) as a clear, colorless oil.

The crude dioxolanone alcohol (5.0 g) and 4 Å molecular sieves (10.0 g) was dissolved in CH₂Cl₂ (140 mL) and cooled to 0 °C. Solid pyridinium chlorochromate (6.0 g, 28.3 mmol) was added all at once, and the reaction mixture was stirred for 10 min. The reaction mixture was concentrated and filtered through Celite with ether, giving a clear, dark-orange filtrate. Flash chromatography (hexane : ethyl acetate = 40 : 1 to 10 : 1) provided the dioxolanone aldehyde **3** (1.10 g, 2 steps 40%).

R_f = 0.47 (hexane : ethyl acetate = 1 : 1)

[α]_D²⁹ +2.50 (c 0.70, CHCl₃)

IR (KBr) ν cm⁻¹ 2941, 2864 (CHO), 1793 (C=O), 1728 (CHO)

¹H-NMR (270 MHz, CDCl₃)

δ : 9.77 (s, 1H, -CHO), 4.79 (dd, *J* = 3.65, 6.48 Hz, 1H, 4'-H),

3.08 (dd, *J* = 3.51, 18.1 Hz, 1H, 2-H), 2.90 (dd, *J* = 6.62, 18.1 Hz, 1H, 2-H),

1.95-1.25 (m, 10H, C₆H₁₀)

¹³C-NMR (67.5 MHz, CDCl₃)

δ : 196.4, 171.8, 111.6, 67.8, 44.2, 35.6, 34.5, 23.7, 22.4, 22.3

HR-MS (EI+)

m/z: 198.0907 [M]⁺, Calcd for C₁₀H₁₄O₄: 198.0892 [M]

• (S)-2-Hydroxy heptanoic acid benzyl ester ((-)-6)

A solution of NaHMDS 1.0 M in THF (1.53 mL, 1.53 mmol) was added dropwise over a period of 10 min to a slurry of *n*-propyltriphenylphosphonium bromide (703 mg, 1.83 mmol) in THF (8.0 mL) at 0 °C under N₂, which produced a red solution along with some solid. The reaction mixture was stirred at 0 °C for 5 min and at room temperature for 30 min and then cooled to -78 °C. A solution of aldehyde **3** (201 mg, 1.02 mmol) in THF (2.0 mL) was added dropwise over a period of 15 min. The reaction mixture was stirred at -78 °C for 10 min and then warmed to room temperature. The reaction mixture was diluted with Et₂O and filtered through Celite, giving a white solid **4**. Since the crude solid **4** was unstable, it was used to the next reaction without further purification.

To a solution of the crude **4** in ethyl acetate (10 mL) was added 10% palladium on activated carbon (250 mg) and the suspension was vigorously stirred under an atmosphere of hydrogen. After stirring for 2 h, the catalyst was filtered by a pad of Celite and washed with ethyl acetate. The solvent was removed *in vacuo*. The crude **5** was used next reaction without farther purification.

To a solution of the crude **5** in CH₂Cl₂ (10 mL) was added BnOH (526 μL, 5.09 mmol) and TsOH (20 mg, 0.102 mmol). The reaction mixture was stirred for 48 h at room temperature under N₂. The reaction mixture was diluted with CH₂Cl₂ (50 mL) and twice extracted with saturated aqueous NaHCO₃ (30 mL). The extracts were combined, washed once with brine (40 mL), and dried over MgSO₄. Concentration *in vacuo* afforded a crude as a pale yellow oil. Flash chromatography (hexane : ethyl acetate = 30 : 1 to 8 : 1) provided the (-)-**6** (72 mg, 3 steps 30%) as a colorless oil.

R_f = 0.53 (hexane : ethyl acetate = 2 : 1)

[α]_D²⁴ -18.0 (c 1.08, CHCl₃)

IR (KBr) ν cm⁻¹ 3475 (OH), 3066-3035 (Ph : C-H), 1738 (C=O)

¹H-NMR (270 MHz, CDCl₃)

δ : 7.38-7.31 (m, 5H, Ph), 5.24 (d, *J* = 12.4 Hz, 1H, Ph-CH₂-),

5.19 (d, *J* = 12.2 Hz, 1H, Ph-CH₂-), 4.23 (dd, *J* = 4.32, 7.29 Hz, 1H, 2-H),

1.88-1.56 (m, 2H, 3-H), 1.52-1.14 (m, 6H, 4,5,6-H), 0.87 (t, *J* = 6.48 Hz, 3H, 7-H)

^{13}C -NMR (67.5 MHz, CDCl_3)

δ : 175.1 (1-C), 135.2, 128.5 (x 2), 128.4, 128.2 (x 2) (C₆H₅), 70.5 (2-C), 67.1 (Ph-CH₂-),
34.2 (3-C), 31.4, 24.2, 22.4 (4, 5, 6-C), 13.8 (7-C)

HR-MS (FAB, NBA matrix)

m/z : 237.1491 $[\text{M}+\text{H}]^+$, Calcd for $\text{C}_{14}\text{H}_{21}\text{O}_3$: 237.1491 $[\text{M}+\text{H}]$

Scheme 3. Preparation of (*R*)-2-hydroxyheptanoic acid benzyl ester ((+)-6)

• (*R*)-4-Benzyl-3-heptanoyl-2-oxazolidinone (11)

(*R*)-4-Benzyl-2-oxazolidinone **9** (16.0 g, 90.3 mmol) was dissolved in THF (180 mL, 0.5 M). This mixture was cooled to -78 °C, then *n*-butyl lithium 1.54 M solution in hexane (67 mL, 104 mmol) was added dropwise. After stirring for 30 min, *n*-heptanoyl chloride **10** (15.3 mL, 99.3 mmol) was added to this mixture and stirred for 30 min. The reaction mixture was poured into saturated aqueous NaHCO₃ and this mixture was extracted with ethyl acetate (x 2). The combined organic layer was washed with 10% citric acid and brine, dried over MgSO₄, filtered and evaporated *in vacuo*. The crude was purified by column chromatography on silica gel (hexane : ethyl acetate = 20 : 1 to 15 : 1) to provide (*R*)-4-Benzyl-3-heptanoyl-2-oxazolidinone (25.1 g, quant) as a colorless oil.

R_f = 0.39 (hexane : ethyl acetate = 3 : 1)

[α]_D²⁶ -53.3 (c 1.02, CHCl₃)

IR (KBr) ν cm⁻¹ 3078-3022 (Ph : C-H), 1786, 1703 (C=O)

¹H-NMR (270 MHz, CDCl₃)

δ : 7.37-7.19 (m, 5H, Ph-H), 4.72-4.63 (m, 1H, 4-H), 4.25-4.11 (m, 2H, benzyl-H), 3.30 (dd, *J* = 3.2 Hz, 13.5 Hz, 1H, 5-H), 2.93 (dd, *J* = 8.0 Hz, 15.5 Hz, 2H, 2'-H), 2.76 (dd, *J* = 9.6 Hz, 13.2 Hz, 1H, 5-H), 1.75-1.63 (m, 2H, 3'-H), 1.44-1.23 (m, 6H, 4', 5', 6'-H), 0.90 (t, *J* = 6.6 Hz, 3H, 7'-H)

¹³C-NMR (67.5 MHz, CDCl₃)

δ : 173.7 (1'-C), 153.8 (2-C), 135.7, 129.8 (x2), 129.2 (x2), 127.6 (Ph-C), 66.5 (benzyl-C), 55.4 (4-C), 38.2 (5-C), 35.9 (2'-C), 31.9 (3'-C), 29.1 (4'-C), 24.5 (5'-C), 22.8 (6'-C), 14.4 (7'-C)

HR-MS (FAB, NBA matrix)

m/z : 290.1742 [M+H]⁺, Calcd for C₁₇H₂₄NO₃ : 290.1756[M+H]

• (4*R*, 2'*R*)-4-Benzyl-3-(2'-hydroxyheptanoyl)-2-oxazolidinone (13)

A solution of sodium hexamethyldisilazane 1.0 M in THF (33.6 mL, 33.6 mmol) was diluted with THF (200 mL) and cooled to $-78\text{ }^{\circ}\text{C}$ under nitrogen atmosphere. To the resulting solution was added dropwise a solution of (*R*)-4-Benzyl-3-heptanoyl-2-oxazolidinone (8.10 g, 28.0 mmol) in THF (40 mL). After stirring for 1 h at $-78\text{ }^{\circ}\text{C}$, a solution of Davis reagent (11.0 g, 42.0 mmol) in THF (40 mL) was added dropwise to the reaction mixture. After stirring for 1 h at $-78\text{ }^{\circ}\text{C}$, the reaction mixture was poured into 0.5 M CSA (33.0 g, 140 mmol) and this mixture was extracted with ethyl acetate (x 2). The combined organic layer was washed with brine, dried over MgSO_4 , filtered and evaporated *in vacuo*. The crude was purified by column chromatography on silica gel (hexane : ethyl acetate = 30 : 1 to 10 : 1) to provide (4*R*, 2'*R*)-4-Benzyl-3-(2'-hydroxyheptanoyl)-2-oxazolidinone (8.0 g, 94%) as a colorless oil.

R_f = 0.36 (hexane : ethyl acetate = 3 : 1)

[α]_D²⁶ -41.8 (c 1.00, CHCl_3)

IR (KBr) ν cm^{-1} 3500 (OH), 1784, 1693 (C=O)

¹H-NMR (300 MHz, CDCl_3)

δ : 7.38-7.12 (m, 5H, Ph-H), 4.99 (dd, J = 3.5 Hz, 8.0 Hz, 1H, 2'-H),

4.71-4.58 (m, 1H, 4-H), 4.32-4.16 (m, 2H, benzyl-H),

3.30 (dd, J = 3.0 Hz, 13.5 Hz, 1H, 5-H), 2.83 (dd, J = 9.5 Hz, 13.5 Hz, 1H, 5-H),

1.87-1.20 (m, 8H, 3', 4', 5', 6'-H), 0.88 (t, J = 12.0 Hz, 3H, 7'-H)

¹³C-NMR (75 MHz, CDCl_3)

δ : 175.0 (1'-C), 153.1 (2-C), 134.8, 129.4 (x2), 129.0 (x2), 127.4 (Ph-C), 70.8 (2'-C),

66.8 (benzyl-C), 55.5 (4-C), 37.4 (5-C), 34.2 (3'-C), 31.4 (5'-C), 24.9 (4'-C),

22.5 (6'-C), 13.9 (7'-C)

HR-MS (FAB, NBA matrix)

m/z : 306.1711 $[\text{M}+\text{H}]^+$, Calcd for $\text{C}_{17}\text{H}_{24}\text{NO}_4$: 306.1705 $[\text{M}+\text{H}]$

• (4*R*, 2'*R*)-4-Benzyl-3-(2'-*O*-*t*-butyldimethylsilyl heptanoyl)-2-oxazolidinone

To a solution of **13** (25 g, 81.9 mmol) in DMF (410 mL, 0.2 M) was added imidazole (7.3 g, 106.4 mmol) and TBSCl (19 g, 122.8 mmol) and this mixture was stirred at 0 °C. After stirring for 5 min, this reaction mixture was warmed to room temperature and farther stirred for 2 h. The reaction mixture was poured into H₂O and this mixture was extracted with hexane : ethyl acetate = 1 : 1 (x 3). The combined organic layer was washed with H₂O and brine, dried over MgSO₄, filtered and evaporated *in vacuo*. The crude was purified by column chromatography on silica gel (hexane : ethyl acetate = 40 : 1 to 9 : 1) to provide (*R*)-4-Benzyl-3-heptanoyl-2-oxazolidinone (30.1 g, 88%) as a colorless oil.

R_f = 0.53 (hexane : ethyl acetate = 3 : 1)

[α]_D²⁷ -4.58 (c 0.95, CHCl₃)

IR (KBr) ν cm⁻¹ 3072-3019 (Ph : C-H), 1782, 1722 (C=O)

¹H-NMR (300 MHz, CDCl₃)

δ : 7.42-7.24 (m, 5H, Ph-H), 5.41 (dd, *J* = 3.6 Hz, 9.6 Hz 1H, 2'-H),

4.70-4.60 (m, 1H, 4-H), 4.27-4.12 (m, 2H, benzyl-H),

3.43 (dd, *J* = 3.3 Hz, 13.5 Hz, 1H, 5-H), 2.74 (dd, *J* = 9.9 Hz, 13.2 Hz, 1H, 5-H),

1.78-1.25 (m, 8H, 3', 4', 5', 6'-H), 0.97 (s, 9H, -Si-C(CH₃)₃),

0.95 (t, *J* = 9.3 Hz, 3H, 7'-H), 0.15, 0.13 (s, each 3H, -Si-(CH₃)₂)

¹³C-NMR (300 MHz, CDCl₃)

δ : 174.4 (1'-C), 153.0 (2-C), 135.2, 129.4 (x2), 128.9 (x2), 127.3 (Ph-C), 71.3 (2'-C),

66.4 (benzyl-C), 55.5 (4-C), 37.6 (5-C), 35.2 (-Si-C(CH₃)₃), 31.3 (3'-C),

25.8 (x3) (-Si-C(CH₃)₃), 25.1 (4'-C), 22.4 (5'-C), 18.3 (6'-C), 13.9 (7'-C),

-4.70, -5.16 (-Si-(CH₃)₂)

HR-MS (FAB, NBA matrix)

m/z : 420.2550 [M+H]⁺, Calcd for C₂₃H₃₈O₄NSi : 420.2570 [M+H]

• (*R*)-2-*O*-*t*-Butyldimethylsilyl heptanoic acid benzyl ester (**14**)

To a solution of BnOH (17.2 mL, 166.4 mmol) in THF (400 mL) was added *n*-butyl lithium 1.57 mol/L in hexane (97.5 mL, 153.0 mmol) and this mixture was stirred at -78 °C. After stirring for 5 min, this reaction mixture was added **23** (27.9 g, 66.5 mmol) in THF (44 mL) and stirred for 30 min at -78 °C, for 30 min at 0 °C and for 10 min at room temperature. The reaction mixture was poured into saturated aqueous NH₄Cl at 0 °C and this mixture was extracted with ethyl acetate (x 2). The combined organic layer was washed with H₂O and brine, dried over MgSO₄, filtered and evaporated *in vacuo*. The crude was purified by column chromatography on silica gel (hexane : ethyl acetate = 50 : 1 to 35 : 1) to provide **14** (19.9 g, 85%) as a colorless oil.

R_f = 0.69 (hexane : ethyl acetate = 3 : 1)

[α]_D²⁷ +34.5 (c 0.96, CHCl₃)

IR (KBr) ν cm⁻¹ 3072-3033 (Ph : C-H), 1751 (C=O)

¹H-NMR (300 MHz, CDCl₃)

δ : 7.40-7.27 (m, 5H, Ph-H), 5.20 (d, *J* = 12.0 Hz, 1H, benzyl-H),
5.13 (d, *J* = 12.5 Hz, 1H, benzyl-H), 4.26 (t, *J* = 6.0 Hz, 1H, 2-H),
1.80-1.70 (m, 2H, 3-H), 1.48-1.20 (m, 6H, 4, 5, 6-H), 0.92 (s, 9H, -Si-C(CH₃)₃),
0.89 (t, *J* = 6.0 Hz, 3H, 7-H), 0.07, 0.06 (s, each 3H, -Si-(CH₃)₂)

¹³C-NMR (75.0 MHz, CDCl₃)

δ : 173.4 (1-C), 135.7, 128.3 (x 2), 128.2 (x 2), 128.1 (Ph-C), 72.1 (2-C),
66.2 (Ph-CH₂-), 35.0 (3-C), 31.3, 24.6, 22.3 (4, 5, 6-C), 13.8 (7-C), 25.6 (x3)
(-Si-C(CH₃)₃), 18.1 (-Si-C(CH₃)₃), -5.06, -5.53 (-Si-(CH₃)₂)

HR-MS (FAB, NBA matrix)

m/z : 351.2343 [M+H]⁺, Calcd for C₂₀H₃₅O₃Si: 351.2355 [M+H]

• **(R)-2-Hydroxy heptanoic acid benzyl ester {(+)-6} (H.A. benzyl ester)**

14 (18.9 g, 0.054 mol) was added 4M HCl/ dioxane (270 mL, 0.2 M) and stirred at room temperature. After stirring for 3 h, this reaction mixture was added toluene and evaporated *in vacuo*. The crude was purified by column chromatography on silica gel (hexane : ethyl acetate = 30 : 1 to 20 : 1) to provide **(+)-6** (11.8 g, 93%) as a colorless oil.

R_f = 0.46 (hexane : ethyl acetate = 2 : 1)

[α]_D²⁶ +16.7 (c 1.01, CHCl₃)

IR (KBr) ν cm⁻¹ 3456 (OH), 3091-3033 (Ph : C-H), 1732 (C=O)

¹H-NMR (300 MHz, CDCl₃)

δ : 7.45-7.28 (m, 5H, Ph-H), 5.24 (d, *J* = 12.0 Hz, 1H, benzyl-H),

5.19 (d, *J* = 12.0 Hz, 1H, benzyl-H), 4.23 (dd, *J* = 3.75, 7.20 Hz, 1H, 2-H),

1.88-1.56 (m, 2H, 3-H), 1.52-1.18 (m, 6H, 4, 5, 6-H), 0.87 (t, *J* = 6.75 Hz, 3H, 7-H)

¹³C-NMR (75 MHz, CDCl₃)

δ : 175.3 (1-C), 135.2, 128.6 (x2), 128.5 (x2), 128.3 (Ph-C), 70.5 (2-C), 67.2 (Ph-CH₂-),

34.3 (3-C), 31.4, 24.3, 22.4 (4, 5, 6-C), 13.9 (7-C)

HR-MS (FAB, NBA matrix)

m/z : 237.1502 [M+H]⁺, Calcd for C₁₄H₂₁O₃ : 237.1491 [M+H]

Scheme 4. Total synthesis of verticilide (1)

• *N*-Boc-*N*-MeAla-H.A. benzyl ester (**16**)

To a solution of (+)-**6** (4.85 g, 20.5 mmol) and alanine **15** (4.80 g, 23.6 mmol) in CH₂Cl₂ (200 mL, 0.1 M) was added EDCI (4.71 g, 24.6 mmol) and DMAP (125 mg, 1.03 mmol) and this mixture was stirred at 0 °C. After stirring for 30 min, this reaction mixture was warmed to room temperature and further stirred for 1 h. The reaction mixture was poured into H₂O and this mixture was extracted with CHCl₃ (x 2). The combined organic layer was washed with saturated aqueous NaHCO₃ and brine, dried over MgSO₄, filtered and evaporated *in vacuo*. The crude was purified by column chromatography on silica gel (hexane : ethyl acetate = 15 : 1 to 10 : 1) to provide ester **16** (8.64 g, quant) as a colorless oil.

R_f = 0.54 (hexane : ethyl acetate = 3 : 1)

[α]_D²⁷ -13.1 (c 1.66, CHCl₃)

IR (KBr) ν cm⁻¹ 1749, 1699 (C=O)

¹H-NMR (300 MHz, pyridine, temp : 60 °C)

δ : 7.62-7.30 (m, 5H, Ph-H), 5.22 (d, *J* = 12.2 Hz, 1H, -CO₂CH₂Ph),
5.11 (d, *J* = 12.4 Hz, 1H, -CO₂CH₂Ph), 5.03 (t, *J* = 6.08 Hz, 1H, heptanoic acid : 2-H),
4.87, 4.57 (m, 1H, Ala : 2-H), 3.00 (brs, 3H, Ala : -*N*-CH₃),
2.00-1.88 (m, 2H, heptanoic acid : 3-H), 1.56 {brs, 9H, Boc : (CH₃)₃C-},
1.48 (d, *J* = 7.50 Hz, 3H, Ala : 2-CH₃), 1.32-1.16 (m, 6H, heptanoic acid : 4, 5, 6-H),
0.86 (t, *J* = 6.00 Hz, 3H, heptanoic acid : 7-H)

¹³C-NMR (100 MHz, CDCl₃, temp : rt)

δ : 172.1 (Ala : 1-C), 169.9, 169.7 (heptanoic acid : 1-C), 155.9, 155.3 (Boc : C=O),
135.2, 128.6 (x2), 128.4 (x2), 128.3 (Ph-C), 80.2, 79.8 {Boc : (CH₃)₃C-},
72.7 (heptanoic acid : 2-C), 67.0 (-CO₂CH₂Ph), 54.3, 53.1 (Ala : 2-C),
31.2 (heptanoic acid : 3-C), 31.0 (heptanoic acid : 4-C), 30.0 (Ala : -*N*-CH₃),
28.3 (x3) {Boc : (CH₃)₃C-}, 24.6 (heptanoic acid : 5-C), 22.3 (heptanoic acid : 6-C),
15.2, 14.6 (Ala : 2-CH₃), 13.9 (heptanoic acid : 7-C)

HR-MS (FAB, NBA matrix+NaI)

m/z : 444.2366 [M+Na]⁺, Calcd for C₂₃H₃₅NO₆Na: 444.2362 [M+Na]

• ***N*-Boc-*N*-MeAla-H.A.-*N*-MeAla-H.A. benzyl ester (**19**)**

To a solution of **16** (4.30 g, 10.1 mmol) in ethyl acetate (50 mL, 0.2 M) was added 10 % palladium on activated carbon (430 mg) and the suspension was vigorously stirred under an atmosphere of hydrogen. After stirring for 1 h, the catalyst was filtered by a pad of Celite and washed with ethyl acetate. The solvent was removed *in vacuo*. The crude **17** was used next reaction without farther purification.

On the one hand, **16** (4.26 g, 10.1 mmol) was added 4M HCl/ dioxane (20 mL) and stirred at room temperature. After stirring for 1 h, this reaction mixture was added toluene and evaporated *in vacuo*. The crude **18** was used next reaction without farther purification.

The crude of **17** and **18** was dissolved in CH₂Cl₂ (50 mL, 0.2 M). The reaction mixture was added DIPEA (5.27 mL, 30.3 mmol) and PyBrop (7.06 g, 15.2 mmol) at 0 °C. After stirring for 1 h, the reaction mixture was poured into 10% citric acid at 0 °C and this mixture was extracted with CHCl₃ (x 2). The combined organic layer was washed with saturated aqueous NaHCO₃ and brine, dried over MgSO₄, filtered and evaporated *in vacuo*. The crude **19** was purified by column chromatography on silica gel (hexane : ethyl acetate = 10 : 1 to 3 : 1) to provide **19** {6.26 g, 98% (3 steps)} as a colorless oil.

R_f = 0.35 (hexane : ethyl acetate = 2 : 1)

[α]_D²⁵ −27.0 (c 1.01, CHCl₃)

IR (KBr) ν cm^{−1} 1743, 1697, 1668 (C=O)

¹H-NMR (300 MHz, CDCl₃)

δ : 7.38-7.26 (m, 5H, Ph-H), 5.18 (d, *J* = 12.3 Hz, 1H, -CO₂CH₂Ph),
5.08 (d, *J* = 12.3 Hz, 1H, -CO₂CH₂Ph), 5.00 (t, *J* = 5.70 Hz, 2H, heptanoic acid : 2-H),
5.04-4.84, 4.80-4.60 (m, each 1H, Ala : 2-H), 3.02-2.72 (m, 6H, Ala : -*N*-CH₃),
1.90-1.56 (m, 4H, heptanoic acid : 3-H), 1.43 {brs, 9H, Boc : (CH₃)₃C-},
1.56-1.10 (m, 6H, Ala : 2-CH₃), 1.80-1.10 (m, 12H, heptanoic acid : 4, 5, 6-H),
0.90-0.78 (m, 6H, heptanoic acid : 7-H)

HR-MS (FAB, NBA matrix+NaI)

m/z : 657.3751 $[M+Na]^+$, Calcd for $C_{34}H_{54}N_2O_9Na$: 657.3727 $[M+Na]$

• ***N*-Boc-*N*-MeAla-H.A.-*N*-MeAla-H.A.-*N*-MeAla-H.A.-*N*-MeAla-H.A. benzyl ester**
(22)

To a solution of **19** (4.63 g, 7.29 mmol) in ethyl acetate (35 mL, 0.2 M) was added 10 % palladium on activated carbon (450 mg) and the suspension was vigorously stirred under an atmosphere of hydrogen. After stirring for 1.5 h, the catalyst was filtered by a pad of Celite and washed with ethyl acetate. The solvent was removed *in vacuo*. The crude **20** was used next reaction without farther purification.

On the one hand, **19** (4.62 g, 7.27 mmol) was added 4M HCl/ dioxane (20 mL) and stirred at room temperature. After stirring for 1.5 h, this reaction mixture was added toluene and evaporated *in vacuo*. The crude **21** was used next reaction without farther purification.

The crude of **20** and **21** was dissolved in CH₂Cl₂ (73 mL, 0.1 M). The reaction mixture was added DIPEA (3.80 mL, 21.8 mmol) and PyBrop (5.03 g, 10.9 mmol) at 0 °C. After stirring for 30 min, this reaction mixture was warmed to room temperature and farther stirred for 1.5 h. The reaction mixture was poured into 10% citric acid at 0 °C and this mixture was extracted with CHCl₃ (x 2). The combined organic layer was washed with saturated aqueous NaHCO₃ and brine, dried over MgSO₄, filtered and evaporated *in vacuo*. The crude **22** was purified by column chromatography on silica gel (hexane : ethyl acetate = 5 : 1 to 1 : 1) to provide **22** {7.80 g, quant (3 steps)} as a colorless oil.

R_f = 0.37 (hexane : ethyl acetate = 1 : 1)

[α]_D²⁵ –39.4 (c 1.01, CHCl₃)

IR (KBr) ν cm⁻¹ 1743, 1693, 1664 (C=O)

¹H-NMR (300 MHz, CDCl₃)

δ : 7.42-7.26 (m, 5H, Ph-H), 5.30-5.06 (m, 2H, -CO₂CH₂Ph),

5.26-5.14, 5.06-4.98 (m, 4H, heptanoic acid : 2-H),

5.10-4.88, 4.78-4.60 (m, 4H, Ala : 2-H), 3.12-2.78 (m, 12H, Ala : -N-CH₃),

2.10-1.60 (m, 8H, heptanoic acid : 3-H), 1.44 {brs, 9H, Boc : (CH₃)₃C-},
1.42-1.20 (m, 12H, Ala : 2-CH₃), 1.60-1.16 (m, 24H, heptanoic acid : 4, 5, 6-H),
0.92-0.78 (m, 12H, heptanoic acid : 7-H)

HR-MS (FAB, NBA matrix+NaI)

m/z: 1083.6445 [M+Na]⁺, Calcd for C₅₆H₉₂N₄O₁₅Na: 1083.6457 [M+Na]

• **verticilide (1)**

To a solution of **22** (7.28 g, 6.86 mmol) in ethyl acetate (70 mL) was added 10 % palladium on activated carbon (728 mg) and the suspension was vigorously stirred under an atmosphere of hydrogen. After stirring for 2 h, the catalyst was filtered by a pad of Celite and washed with ethyl acetate. The solvent was removed *in vacuo*. The crude was used next reaction without farther purification.

To a crude of previous reaction was added 4M HCl/ dioxane (70 mL) and stirred at room temperature. After stirring for 30 min, this reaction mixture was added toluene and evaporated *in vacuo*. The crude was used next reaction without farther purification.

A crude of previous reaction was dissolved in CH₂Cl₂ (1.19 L, 0.005 M). The reaction mixture was added DIPEA (2.60 mL, 14.9 mmol) and PyBop (3.73 g, 7.16 mmol) at 0 °C. After stirring for 2 h, this reaction mixture was warmed to room temperature and farther stirred for 1 h. The reaction mixture was poured into 10% citric acid at 0 °C and this mixture was extracted with CHCl₃ (x 2). The combined organic layer was washed with saturated aqueous NaHCO₃ and brine, dried over MgSO₄, filtered and evaporated *in vacuo*. The crude was purified by column chromatography on silica gel (CHCl₃ to CHCl₃ : MeOH = 100 : 1) to provide verticilide (**1**) {4.80 g, 94% (3 steps)} as a colorless oil.

R_f = 0.28 (CHCl₃ : MeOH = 9 : 1)

[α]_D²⁵ −39.2 (c 1.01, MeOH)

IR (KBr) ν cm^{−1} 1743, 1666 (C=O)

¹H-NMR (300 MHz, CD₃OD + KSCN)

δ : 5.47-5.37 (m, 4H, Ala : 2-H), 5.37-5.27 (m, 4H, heptanoic acid : 2-H)

3.07 (s, 12H, Ala : N-CH₃), 1.90-1.76 (m, 8H, heptanoic acid : 3-H)

1.50 (d, *J* = 7.0 Hz, 12H, Ala : 2-CH₃), 1.42-1.24 (brs, 24H, heptanoic acid : 4, 5, 6-H),

0.90 (brs, 12H, heptanoic acid : 7-H)

¹³C-NMR (75 MHz, CD₃OD + KSCN)

δ : 173.1 (x 4), 172.4 (x 4), 73.9 (x 4), 53.7 (x 4), 32.5 (x 4), 31.9 (x 4), 31.6 (x 4)
25.8 (x 4), 23.4 (x 4), 14.8 (x 4), 14.3 (x 4)

HR-MS (FAB, NBA matrix+NaI)

m/z: 875.5372 [M+Na]⁺, Calcd for C₄₄H₇₆O₁₂N₄Na: 875.5357 [M+Na]

[illegible]

^{13}C -NMR of 2-[(4*S*)-2-Cyclohexylidene-5-oxo-1, 3-dioxolan-4yl]acetic Acid (67.5 MHz, CDCl_3)

¹H-NMR of **3** (270 MHz, CDCl₃)

^{13}C -NMR of **3** (67.5 MHz, CDCl_3)

^1H -NMR of (-)-**6** (270 MHz, CDCl_3)

^{13}C -NMR of (-)-**6** (67.5 MHz, CDCl_3)

^1H -NMR of **11** (300 MHz, CDCl_3)

^{13}C -NMR of **11** (75 MHz, CDCl_3)

$^1\text{H-NMR}$ of **13** (300 MHz, CDCl_3)

^{13}C -NMR of **13** (75 MHz, CDCl_3)

^1H -NMR of (4R, 2'R)-4-Benzyl-3-(2'-O-*t*-butyldimethylsilyl heptanoyl)-2-oxazolidinone (300 MHz, CDCl_3)

^{13}C -NMR of (4*R*, 2'*R*)-4-Benzyl-3-(2'-*O*-*t*-butyldimethylsilyl heptanoyl)-2-oxazolidinone (75 MHz, CDCl_3)

$^1\text{H-NMR}$ of **14** (300 MHz, CDCl_3)

^{13}C -NMR of **14** (75 MHz, CDCl_3)

^{13}C -NMR of **16** (100 MHz, CDCl_3)

¹H-NMR of **19** (300 MHz, CDCl₃)

^{13}C -NMR of **19** (75 MHz, CDCl_3)

$^1\text{H-NMR}$ of **22** (300 MHz, CDCl_3)

^{13}C -NMR of **22** (75 MHz, CDCl_3)

¹H-NMR of verticilide (**1**) (300 MHz, CD₃OD)

^{13}C -NMR of verticilide (1) (75 MHz, $\text{CD}_3\text{OD} + \text{KSCN}$)