Supporting Information-1

A Convergent Synthesis of the Proposed Structure of Antitumor Depsipeptide, Stereocalpin A

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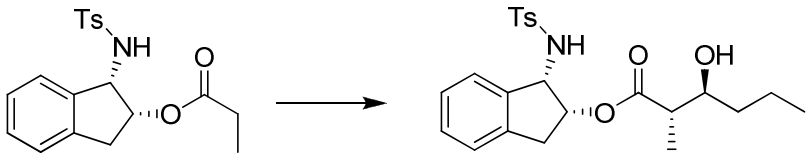
Contents

General Experimental Methods:

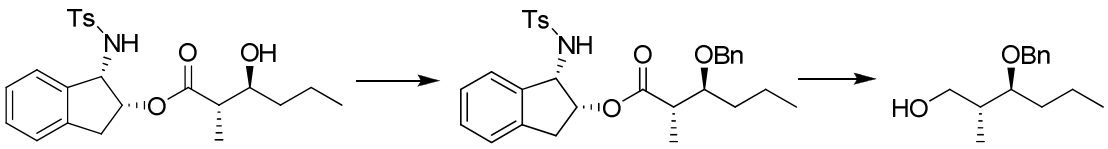
All anhydrous solvents were obtained according to the following procedures: diethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone under argon; toluene, methanol, acetonitrile, and dichloromethane from calcium hydride and benzene from sodium. Other solvents were used without purification. All moisture-sensitive reactions were carried out in flame-dried flasks under argon atmosphere. Reactions were monitored by thin layer chromatography (TLC) using Silicycle 60A-F_{254} silica gel precoated plates. Flash column chromatography was performed using Silicycle 230-400 mesh silica gel. All reactions are carried out under argon and yields refer to chromatographically and spectroscopically pure compounds. FT-IR spectra were recorded with a Mattson Genesis II spectrophotometer. Optical rotations were recorded on a Perkin-Elmer 341 polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Inova-300 (300 and 75 MHz), or Bruker Avance ARX- 400 (400 and 100 MHz) or Bruker DRX500. High and low resolution mass spectra were carried out by the Mass Spectroscopy Center at Purdue University. HPLC analysis and preparative HPLC were performed on Agilent 1100 Series instruments (Agilent 1200 Series Autosampler used for analytical).



6 **7**

(2*S*,3*S*)-((1*S*,2*R*)-1-(4-methylphenylsulfonamido)-2,3-dihydro-1H-inden-2-yl) 3-hydroxy-2-methylhexanoate (7) :

To a solution of (1*S*,2*R*)-1-(4-methylphenylsulfonamido)-2,3-dihydro-1H-inden-2-yl propionate (**6**) (12.93 g, 36 mmol) in CH_2Cl_2 (180 mL) was added $TiCl_4$ (4.34 mL, 39.6 mmol, 1.1 equiv) dropwise at 0 ^oC. The solution was stirred at 0 ^oC for 15 min, followed by the slow addition of diisopropylethylamine (23.8 mL, 137 mmol, 3.8 equiv) slowly. The dark solution was allowed to warm to 23 ^oC and stirred at 23 ^oC for 2 h. In a separate flask, to *n*-butyraldehyde (6.5 mL, 72 mmol, 2 equiv) in CH_2Cl_2 (180 mL) was added $TiCl_4$ (7.9 mL, 2 equiv) slowly, followed by addition of anhydrous acetonitrile (3.8 mL, 2 equiv). The mixture was stirred at -78 ^oC for 5 min, white precipitate was formed. To this solution was added the above enolate solution via a cannula over 15 min. The resulting dark solution was stirred at -78 ^oC for 2 h and quenched with saturated ammonium chloride solution. The aqueous layer was extracted with CH_2Cl_2 and the combined extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (Hexanes/ethyl acetate, 9:1) to afford the desired product **7** (10.1 g, 65% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 1.24 (m, 1H), 1.31 (m, 2H), 1.38 (m, 1H), 2.40 (s, 3H), 2.46 (m, 1H), 2.85(d, *J* = 17.1 Hz, 1H), 3.03 (dd, *J* = 4.9, 17.1 Hz, 1H), 3.06 (s, 1H), 4.87 (dd, *J* = 5.0, 9.5 Hz, 1H), 5.28 (t, *J* = 4.7 Hz, 1H), 6.63 (d, *J* = 9.6 Hz, 1H), 7.12-7.25 (m, 4H), 7.25(d, *J* = 8.2 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 13.6, 13.9, 18.4, 21.5, 36.3, 37.2, 46.1, 60.0, 73.0, 74.6, 124.3, 124.7, 127.0, 127.2, 128.2, 129.7, 137.8, 138.4, 140.1, 143.4, 173.7; FT-IR (film, NaCl) 1093.9, 1161.3, 1335.3, 1461.1, 1733.5 cm^{-1}; $[\alpha]_D^{20}$ +1.8 (*c* 1.0, $CHCl_3$).

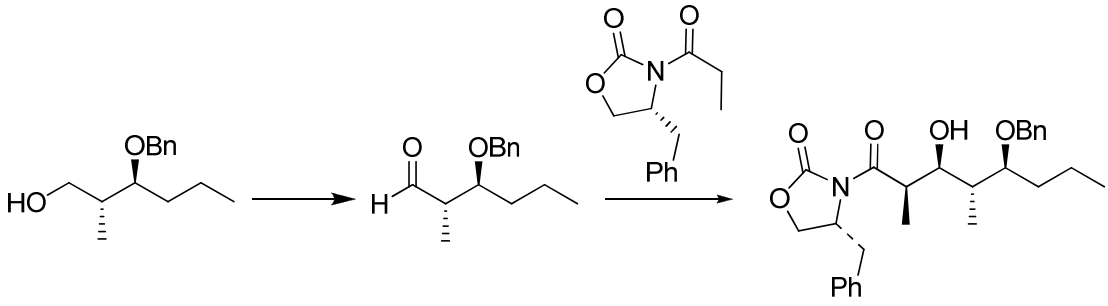


7 **8**

(2*R*,3*S*)-3-(benzyloxy)-2-methylhexan-1-ol (8) : To a mixture of the above alcohol **7** (6.30 g, 14.6 mmol) and benzyl 2,2,2-trichloroacetimidate (4.1 mL, 21.9 mmol, 1.5 equiv) in CH_2Cl_2/cyclohexane(1:2, 135 mL) was added triflic acid (194 μL, 2.19 mmol, 0.15 equiv) dropwise via a syringe. The mixture was stirred at 0 ^oC for 6 h upon which a white precipitate was formed. H_2O (2 mL) was added and the solution was stirred at 23 ^oC for 0.5 h. The white precipitate was filtered off and washed with CH_2Cl_2/hexanes (1:4, 100 mL). The filtrate was washed with saturated sodium bicarbonate solution, brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (Hexanes/ethyl acetate, 95:5 to 9:1) to afford the benzyl protected product (6.59 g, 86% yield) as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.83 (t, *J* = 7.2 Hz, 2H), 1.00 (d, *J* = 6.9 Hz, 3H), 1.27-1.34 (m, 3H), 1.38 (m, 1H), 2.44 (s, 3H), 2.63 (m, 1H), 2.79 (d, *J* = 17.1 Hz, 1H), 3.03 (dd, *J* = 4.9, 17.1 Hz, 1H), 3.47 (m, 1H), 4.39 (d, *J* = 11.5 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.93 (dd, *J* = 4.9, 10.0 Hz, 1H), 5.26 (t, *J* = 4.7 Hz, 1H), 5.79 (d, *J* = 10.0 Hz, 1H), 7.04-7.3 (m, 11H), 7.77 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 14.0, 18.4, 21.5, 33.1, 37.2, 42.8, 59.6, 72.0, 75.0, 80.3, 124.1, 124.8, 126.9, 127.2, 127.5, 128.2, 128.3, 129.7, 138.0, 138.2, 138.5, 139.8, 143.5, 173.4; FT-IR (film, NaCl) 1162.0, 1336.1, 1734.1 cm^{-1}; $[\alpha]_D^{20}$ -42.2 (*c* 1.0, $CHCl_3$).

The above benzyl protected ester (6.59g, 12.6 mmol) was dissolved in anhydrous THF (150 mL) and cooled to 0 ^oC. LAH (719 mg, 18.9 mmol, 1.5 equiv) was added in portions. The grey suspension was stirred at 0 ^oC for 1 h and quenched sequentially with water (0.72 mL), 2 N NaOH (1.44 mL) and water (2.16 mL). The mixture was stirred for 2 h at 23 ^oC and the precipitate was filtered off and washed with ethyl ether. The filtrate was evaporated under vacuum and the crude product was purified by

column chromatography on silica gel (hexanes/ethyl acetate, 2:1) to afford the desired alcohol **9** (2.64g, 94% yield) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.92 (d, *J* = 7.4 Hz, 3H), 0.95 (t, *J* = 7.9 Hz, 3H), 1.38-1.46 (m, 2H), 1.56-1.64 (m, 2H), 1.89-1.94 (m, 1H), 3.43 (dd, *J* = 5.4, 11.6 Hz, 1H), 3.58 (dd, *J* = 6.5, 10.8 Hz, 1H), 3.68 (dd, *J* = 3.9, 10.8 Hz, 1H), 4.47 (d, *J* = 11.2 Hz, 1H), 4.61 (d, *J* = 11.2 Hz, 1H), 7.26-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.4, 17.7, 33.0, 37.8, 66.5, 71.7, 83.9, 127.7, 127.8, 128.4, 138.2; FT-IR (film, NaCl) 1028.1, 1072.4, 1454.2, 1496.1, 2871.5, 2932.3, 2957.8 cm^{-1}; $[\alpha]_D^{25}$ +36.2 (*c* 1.0, $CHCl_3$).



8 **10**

(*R*)-4-benzyl-3-((2*R*,3*S*,4*R*,5*S*)-5-(benzyloxy)-3-hydroxy-2,4-dimethyloctanoyl)oxazolidin-2-one (10) :

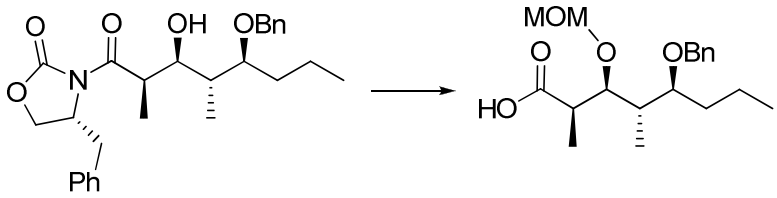
Swern Oxidation:

To a solution of oxalyl chloride (1.1 mL, 12.6 mmol) in CH_2Cl_2 (125 mL) was added DMSO (1.8 mL, 25.2 mmol) dropwise at -78 ^{o}C. The clear solution was stirred at -78 ^{o}C for 5 min, followed by addition of the alcohol **8** (1.4 g, 6.3 mmol) dissolved in CH_2Cl_2 (10 mL) slowly. A white precipitate was formed and the mixture was stirred at -78^{o}C for 15 min. Then anhydrous triethylamine (7 mL, 50 mmol) was added slowly, the precipitate was dissolved immediately. The clear solution was stirred for 0.5 h at -78 ^{o}C and was allowed to warm to 0 ^{o}C and quenched with 0.5 N HCl. The aqueous layer was extracted with CH_2Cl_2 and the combined extracts were washed with saturated $NaHCO_3$ solution, brine and dried over Na_2SO_4. After concentration, the residue was purified by flash column chromatography on silica gel (hexanes/ethyl

ether, 96:4) to afford the desired aldehyde (1.32 g, 99% yield).

Evans' *syn*-aldol reaction:

To the solution of (*R*)-4-benzyl-3-propionyloxazolidin-2-one (**9**) (1.81 g, 7.74 mmol) in CH_2Cl_2 (30 mL) was added di-*n*-butylboron triflate solution (1 M in CH_2Cl_2, 8.5 mL, 8.5 mmol), followed by addition of diisopropylethylamine (1.6 mL, 9.3 mmol). The clear solution was stirred at 0 ^oC for 0.5 h and was cooled to -78 ^oC. To the above enolate solution was added the aldehyde (1.32 g, 5.96 mmol) from above dissolved in CH_2Cl_2 (10 mL) slowly via a syringe. The aldehyde flask was washed with CH_2Cl_2 (5 mL) and was also added to the enolate solution. The mixture was stirred at -78 ^oC for 10 min, then was warmed to 0 ^oC for 1 h. The reaction was quenched with pH = 7 buffer (10 mL) and methanol (15 mL). Then a solution of 30% H_2O_2 (10 mL) and methanol (20 mL) was added slowly to keep the inside temperature below 5 ^oC. The mixture was stirred at 0 ^oC for 1 h after addition. The reaction mixture was diluted with CH_2Cl_2 (40 mL), the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with brine and dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, 85:15) to afford the desired product **10** (2.45 g. 89% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.92 (d, *J* = 7.0 Hz, 3H), 0.96 (t, *J* = 6.9 Hz, 3H), 1.29 (d, *J* = 7.0 Hz, 3H), 1.38-1.48 (m, 1H), 1.51-1.60 (m, 3H), 2.07 (m, 1H), 2.82 (dd, *J* = 9.6, 13.3 Hz, 1H), 3.33 (dd, *J* = 2.9, 13.3 Hz, 1H), 3.77 (m, 1H), 3.82 (s, 1H), 3.97 (m, 1H), 4.21 (m, 2H), 4.57 (s, 2H), 4.73 (m, 1H), 7.21-7.40 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.9, 11.1, 14.4, 18.4, 31.7, 37.5, 37.7, 40.1, 55.4, 66.2, 71.3, 73.7, 81.7, 127.4, 127.5, 127.6, 127.8, 128.0, 128.3, 128.4, 129.0, 129.5, 135.2, 138.6, 153.0, 177.1; FT-IR (film, NaCl) 1210.0, 1386.4, 1453.9, 1699.9, 1779.7 cm^{-1}; $[\alpha]_D^{20}$ -19.0 (*c* 1.0, $CHCl_3$).



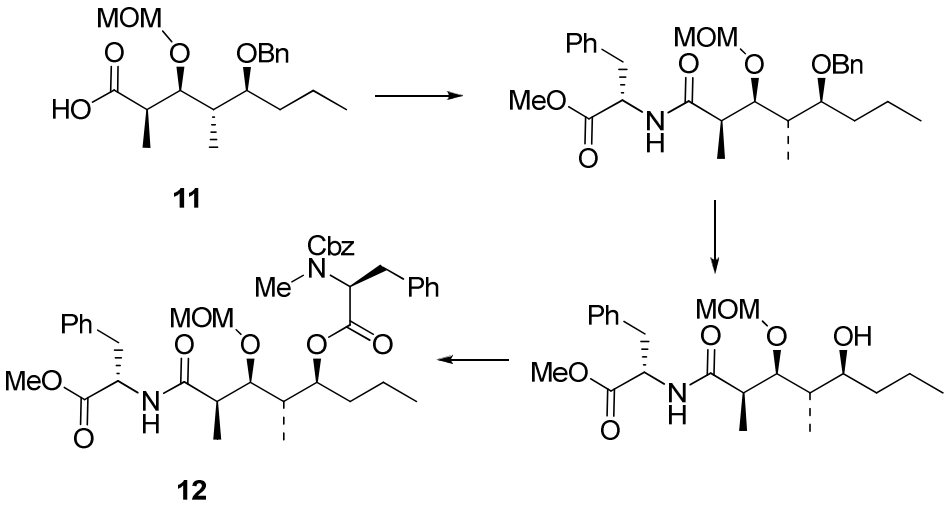
10 **11**

(2*R*,3*S*,4*S*,5*S*)-5-(benzyloxy)-3-(methoxymethoxy)-2,4-dimethyloctanoic acid (7) :

To the solution of the above alcohol **10** (1.41 g, 2.85 mmol) in CH_2Cl_2 (23 mL) was added diisopropylethylamine (5 mL, 28 mmol), chloromethyl methyl ether (1.7 mL, 23 mmol) and DMAP (348 mg, 2.9 mmol). The mixture was allowed to warm to 23 ^oC and stirred at 23 ^oC for 36 h. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic extracts were washed with 0.5 N HCl, saturated $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, 8:2) to afford the desired MOM protected alcohol (949 mg, 67% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 1.29 (d, *J* = 6.8 Hz, 3H), 1.43-1.57 (m, 4H), 2.23 (m, 1H), 2.75 (dd, *J* = 9.8, 13.1 Hz, 1H), 3.27 (m, 1H), 3.33 (s, 3H), 3.56 (m, 1H), 3.86 (dd, *J* = 3.0, 8.4 Hz, 1H), 3.98 (m, 1H), 3.99 (d, *J* = 8.5 Hz, 1H), 4.09 (d, *J* = 8.5 Hz, 1H), 4.03 (d, *J* = 11.7 Hz, 1H), 4.49-4.60 (m, 4H), 7.17-7.37 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.2, 10.3, 14.0, 19.2, 31.5, 37.4, 38.4, 40.8, 55.8, 56.4, 65.9, 70.8, 79.1, 81.2, 98.2, 127.06, 127.14, 127.5, 128.0, 128.7, 129.2, 135.4, 138.9, 153.0, 175.0; FT-IR (film, NaCl) 1028.5, 1209.7, 1382.8, 1699.0, 1778.8 cm^{-1}; $[\alpha]_D^{20}$ -66.6 (*c* 1.0, $CHCl_3$).

The above MOM protected alcohol (626 mg, 1.26 mmol) was dissolved in THF (8.0 mL) and H_2O (8.0 mL) and was cooled to 0 ^oC. Hydrogen peroxide solution (30%, 1.1 mL, 10 mmol) and lithium hydroxide hydrate (210 mg, 5 mmol) was added sequentially. The mixture was allowed to warm to 23 ^oC and stirred at 23 ^oC for 12 h. The mixture was partitioned and the organic layer was extracted with 1 N LiOH (2 × 5 mL). The organic layer was dried over Na_2SO_4, concentrated and recrystallized

from Hexanes/EtOAc (8:2) to recover the auxiliary. The aqueous layers were combined and was adjusted to pH = 1 with 1 N HCl and were extracted with CH_2Cl_2 (3 × 20 mL). The extracts were washed with brine and dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude acid was purified by flash column chromatography on silica gel (Hexanes/ethyl acetate, 2:1) to afford the desired acid **11** (347 mg, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (m, 6H), 1.21 (d, *J* = 7.0 Hz, 3H), 1.32 (m, 2H), 1.40-1.49 (m, 2H), 1.53-1.63 (m, 1H), 2.18 (m, 1H), 2.73 (ddd, *J* = 2.2, 6.9, 13.9 Hz, 1H), 3.33 (s, 3H), 3.66 (m, 1H), 3.93 (dd, *J* = 2.3, 9.0 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 4.45-4.64 (m, 3H), 7.26-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.2, 10.7, 14.2, 19.3, 31.4, 37.7, 41.8, 56.1, 71.2, 79.0, 81.7, 97.9, 127.4, 127.8, 128.2, 138.9, 181.0; FT-IR (film, NaCl) 1029.4, 1381.8, 1460.9, 1708.8 cm^{-1}; $[\alpha]_D^{25}$ -28.1 (*c* 1.0, $CHCl_3$).



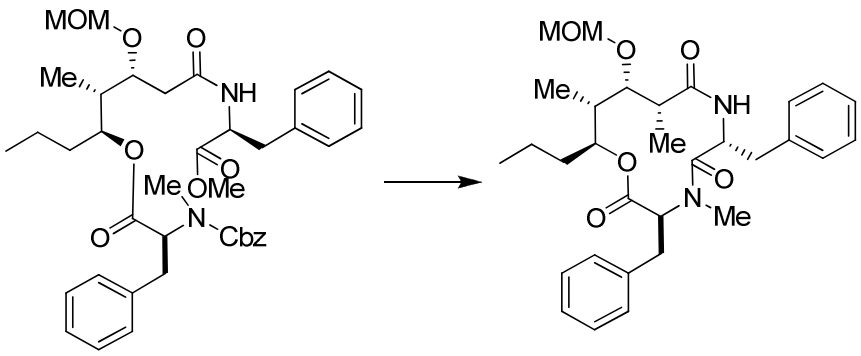
To a 50 mL round bottom flask equipped with a magnetic stirrer bar was added the above acid **11** (118 mg, 0.35 mmol), EDCI (133 mg, 0.7 mmol) and HOBt (71mg, 0.53 mmol). The mixture was cooled to 0 ^{o}C and CH_2Cl_2 (4 mL) was added. The mixture was warmed to 23 ^{o}C for 10 min, then diisopropylethylamine (370 μL, 2.1 mmol), L-phenylalanine methyl ester hydrochloride salt (175 mg, 0.35 mmol) were added sequentially. The mixture was stirred at 23 ^{o}C overnight. Then water was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 and the combined extracts were washed with brine and dried with anhydrous Na_2SO_4. The

solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography on silica gel (Hexanes/ethyl acetate, 8:2) to afford the desired amide (162 mg, 93% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 6.8 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.29-1.37 (m, 2H), 1.44-1.56 (m, 3H), 2.07 (m, 1H), 2.69 (m, 1H), 3.09 (m, 2H), 3.32 (s, 3H), 3.63 (m, 1H), 3.72 (s, 3H), 3.73 (m, 1H), 4.46 (d, *J* = 11.3 Hz, 1H), 4.54-4.86 (m, 3H), 4.84 (m, 1H), 6.35 (d, *J* = 7.2 Hz, 1H), 7.15-7.34 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 12.1, 14.4, 18.9, 32.1, 37.9, 38.3, 43.6, 52.2, 53.1, 56.1, 71.3, 79.6, 82.4, 98.1, 127.1, 127.5, 127.9, 128.3, 128.6, 129.2, 136.0, 138.9, 172.1, 174.7; FT-IR (film, NaCl) 1028.6, 1208.7, 1455.1, 1520.6, 1652.0, 1747.2 cm^{-1}, $[\alpha]_D^{25}$ +0.7 (*c* 1.0, $CHCl_3$), *m/z* (ESI), 522.2 $(M+Na)^+$.

The amide from above (148 mg, 0.3 mmol) was dissolved in EtOAc (4 mL) and CH_3OH (2 mL) and was cooled to 0 °C. $Pd(OH)_2$ (48 mg) was added under Ar. A balloon of H_2 was attached and the mixture was allowed to warm to 23 °C for 4 h. The Pd catalyst was filtered off with the aid of celite and washed with EtOAc/CH_3OH (1:1). The filtrated was carefully evaporated under vacuum at 23 °C and the residue was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, 3:2) to afford the desired alcohol (115 mg, 95% yield). ^{1}H NMR (500 MHz, CDCl3) δ 0.83 (t, *J* = 7.1Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.25-1.32 (m , 2H), 1.45 (m, 1H), 1.54 (m, 1H), 1.69 (m, 1H), 2.61 (m, 1H), 2.97 (br s, 1H), 3.07 (dd, *J* = 7.2, 13.9 Hz, 1H), 3.16 (dd, *J* = 5.6, 14.0 Hz, 1H), 3.34 (m, 1H), 3.35 (s, 3H), 3.73 (s, 3H), 3.88 (dd, *J* = 4.3, 6.7 Hz, 1H), 4.62 (d, *J* = 11.4, 21.6 Hz, 2H), 4.87 (m, 1H), 6.42 (d, *J* = 7.7 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 2H), 7.27 (m, 1H), 7.28 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1, 14.2, 14.3, 18.8, 36.7, 37.8, 42.8, 43.5, 52.3, 53.0, 56.1, 72.7, 81.9, 97.6, 127.2, 128.6, 129.1, 135.9, 172.1, 175.4; FT-IR (film, NaCl) 1031.5, 1211.1, 1455.1, 1538.2, 1650.0, 1745.9, 2872.6, 2951.3 cm^{-1}; $[\alpha]_D^{25}$ + 19.3 (*c* 1.0, $CHCl_3$).

To a suspension of Cbz-*N*-Me-$_L$-phenylalanine (130 mg, 0.41 mmol) and DCC (85 mg,

0.41 mmol) in CH_2Cl_2 (7.5 mL) was added DMAP (5 mg, 0.041 mmol) at 0 ^oC. The mixture was stirred at 0 ^oC for 10 min, followed by addition of the above alcohol (109 mg, 0.27 mmol) dissolved in CH_2Cl_2 (1 mL) dropwise via a syringe at 0 ^oC. The mixture was stirred at 0 ^oC for 1.0 h. Then H_2O (1 mL) was added and the solution was kept stirring for another 10 min. Hexanes (20 mL) was added and the white precipitate was filtered off and the precipitate was washed with hexanes/CH_2Cl_2 (2:1, 30 mL). The filtrate was washed with saturated $NaHCO_3$ solution and brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, 2 : 1) to afford the desired ester **12** (164 mg, 86% yield) which contains more than two rotamers. ^1H NMR (100 MHz, CD_3OD) δ 0.80 (d, *J* = 7.9 Hz, 1.2 H), 0.82 (d, *J* = 7.5 Hz, 1.8 H), 0.89 (t, *J* = 7.4 Hz, 1.2 H), 0.92 (t, *J* = 7.2 Hz, 1.8 H), 1.08 (d, *J* = 5.6 Hz, 1.2 H), 1.11 (d, *J* = 6.4 Hz, 1.8 H), 1.24-1.41 (m, 3H), 1.54 (m, 1H), 1.93 (m, 1H), 2.56 (t, *J* = 6.8 Hz, 0.4 H), 2.62 (t, *J* = 6.8 Hz, 0.6 H), 2.82 (s, 3H), 3.00 (dd, *J* = 9.4, 13.9 Hz, 1H), 3.10 (m, 0.8H), 3.20 (m, 1.2 H), 3.28 (m, 1H), 3.33 (s, 1.2 H), 3.34 (s, 1.8 H), 3.60 (t, *J* = 6.0 Hz, 1H), 3.69 (s, 3H), 4.36 (d, *J* = 7.0Hz, 0.4H), 3.37 (d, *J* = 7.0Hz, 0.6H), 4.47 (d, *J* = 7.0 Hz, 1H), 4.64 (m, 1H), 4.90-4.97 (m, 2H), 5.07 (s, 2H), 7.14-7.33(m, 15H), 8.12 (d, *J* = 7.5 Hz, 1H); FT-IR (film, NaCl) 1029.0, 1217.4, 1455.7, 1669.9, 1701.8, 1739.0, 2890.7, 2989.9, 3028.7 cm^{-1}; $[\alpha]_D^{25}$ -25.8 (*c* 0.5, $CHCl_3$), *m/z* (ESI), 727.1 $(M+Na)^+$.



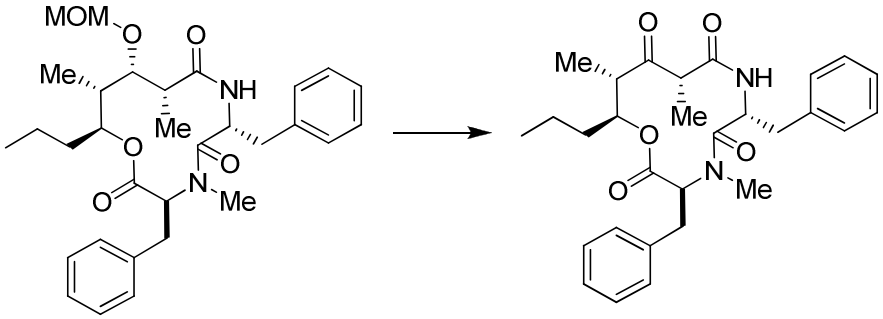
12 **13**

The ester **12** (135 mg, 0.192 mmol) was dissolved in *tert*-butanol/H_2O (2:1, 4.5 mL). The solution was cooled to 0 ^oC and 1 M LiOH solution (0.29 mL, 0.29 mmol, 1.5 equiv) was added. The mixture was stirred at 0 ^oC for 2 h. Then 1 N HCl (0.4 mL) was added and the solution was diluted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 96:4) to afford the desired acid (97.4 mg, 90% yield). The acid contains two rotamers. ^1H NMR(400 MHz, CD_3OD) δ 0.75 (d, *J* = 8.2 Hz, 1.2 H), 0.77 (d, *J* = 8.2 Hz, 1.8H), 0.89 (m, 3H), 1.04 (d, *J* = 7.6 Hz, 1.2 H), 1.06 (d, *J* = 7.4 Hz, 1.8 H), 1.21-1.38 (m, 4H), 1.46-1.49 (m, 1 H), 1.86 (m, 1H), 2.51-2.60 (m, 1H), 2.78 S, 3 H), 2.97 (dd, *J* = 9.7, 14.1 Hz, 1H), 3.03-3.11 (m, 1H), 3.20-3.37 (m, 2H), 3.28 (s, 3H), 3.53 (t, *J* = 6.0 Hz, 1H), 4.29 (m, 1H), 4.42 (d, *J* = 6.8 Hz, 1H), 4.62 (dd, *J* = 4.8, 9.2 Hz, 1H), 4.84 (m, 1H), 4.88-5.10 (m, 3H), 7.11-7.31 (m, 15 H); ^{13}C NMR (100 MHz, CD_3OD) "M" for major rotamer, "m" for minor rotamer, δ 11.6 (m), 12.1 (M), 12.9 (m), 13.1 (M), 14.6, 19.4 (M), 19.5 (m), 32.8 (m), 33.0 (M), 35.6 (M), 36.0 (m), 38.2, 41.0, 44.0 (m), 44.2 (M), 56.6, 62.3 (m), 62.5 (M), 68.2 (M), 68.6 (m), 77.2 (M), 77.3 (m), 82.8 (m), 83.2 (M), 99.2, 127.3 (m), 127.8 (M), 128.5 (M), 128.9 (m), 129.0, 129.1, 130.0, 130.3, 137.6 (m), 138.1 (m), 138.7 (M), 138.8 (M), 157.9 (m), 158.1 (M), 171.6, 177.3.

The above acid (181 mg, 0.27 mmol) was dissolved in EtOAc/MeOH (1:1, 8 mL) and was cooled to 0 ^oC. $Pd(OH)_2$ (40 mg) was added under Ar. A balloon of H_2 was

attached and the mixture was allowed to warm to 23 ^{o}C and stirred at 23 ^{o}C vigorously for 1 h. The catalyst was removed by filtration on celite and washed with ethyl acetate. After concentration, the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 93:7) to afford the desired *seco* amino acid (130 mg, 90% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 0.40 (d, *J* = 7.1 Hz, 3H), 0.85 (t, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), l.17-1.37 (m, 5H), 2.35 (m, 1H), 2.49 (s, 3H), 2.93 (dd, *J* = 9.4, 13.3 Hz, 2H), 3.17 (m, 2H), 3.23 (s, 3H), 3.24 (m, 1H), 3.30 (m, 1H), 3.89 (dd, *J* = 5.5, 9.3 Hz, 1H0, 4.09 (d, *J* = 6.9 Hz, 1H), 4.28 (d, *J* = 6.9 Hz, 1H), 4.45 (m, 1H), 5.13 (m, 1H), 7.09-7.26 (m, 10H); ^{13}C NMR (100 MHz, CD_3OD) δ 10.8, 11.2, 14.4, 20.2, 31.4, 33.3, 38.3, 38.9, 40.8, 43.9, 56.7, 57.1, 64.3, 78.0, 83.2, 99.2, 127.6, 128.5, 129.3, 129.9, 130.4, 130.5, 136.4, 139.5, 171.6, 176.6.

To the above *seco* amino acid (20.1 mg, 0.0361 mmol) dissolved in CH_2Cl_2 (30 mL) and DMF (6 mL) was added HATU (28 mg, 0.072 mmol), HOAt (10 mg, 0.072 mmol) and diisopropylethylamine (25 uL, 0.14 mmol) at 0 ^{o}C. The mixture was allowed to warm to 23 ^{o}C for 20 h. Then H_2O (10 mL) was added to quench the reaction. The aqueous layer was extracted with EtOAc. The combined extracts were washed with brine and dried over Na_2SO_4. The volatile solvent was removed by a rotavapor under vacuum and DMF was removed by vacuum distillation with oil bath at 35 ^{o}C. The crude product was purified by flash column chromatography on silica gel (Hexanes/ethyl acetate, 2:1) to afford the cyclic depsipeptide **13** as a white solid (18.5 mg, 95% yield). ^{1}H NMR (100 MHz, DMSO-d_6, 120 ^{o}C) δ 0.90 (t, *J* = 7.5 Hz, 3H), 0.93 (d, *J* = 7.5 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 1.31 (m, 3H), 1.62 (m, 2H), 2.56 (m, 1H), 2.68 (m, 1H), 2.79 (s, 3H), 3.01 (dd, *J* = 9.9, 14.6 Hz, 1H), 3.27 (dd, *J* = 4.9, 14.8 Hz, 1H), 3.31 (s, 3H), 3.92 (dd, *J* = 1.7, 8.9 Hz, 1H), 4.59 (dd, *J* = 6.5, 13.8 Hz, 2H), 4.92 (m, 1H), 4.89 (dd, *J* = 6.4, 11.0 Hz, 1H), 5.27 (dd, 4.7, 9.5 Hz, 1H), 7.01-7.30 (m, 10H); FT-IR (film, NaCl) 1027.7, 1215.1, 1279.4, 1455.2, 1613.8, 1681.8, 1735.0 cm^{-1}; $[\alpha]_D^{25}$ 0 (*c* 1.0, $CHCl_3$), HRMS (ESI) $[M+Na]^+$ calcd for $C_{31}H_{42}N_2O_6Na$, 561.2941, found 561.2957.

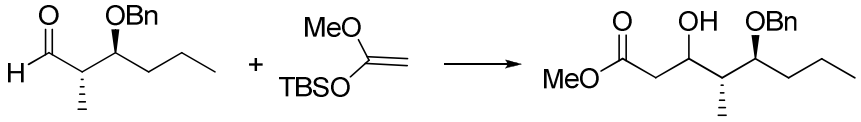


13 **14**

To the solution of cyclic depsipeptide **13** (18.9 mg, 0.034 mmol) in CH_2Cl_2 (2.0 mL) was added triethyl amine (19 μL, 0.14 mmol, 4 equiv). The solution was cooled to -78 ^oC and bromodimethylboron (34 μL, 0.34 mmol) was added dropwise via a syringe. The solution was stirred at -78 ^oC for 2 h. The mixture was allowed to warm to 23 ^oC and quenched with THF (2 mL) and saturated $NaHCO_3$ solution (3mL). The mixture was stirred for 30 min and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel ($CHCl_3$/CH_3OH, 97:3) to afford the crude product.

The above alcohol was dissolved in CH_2Cl_2 (5 mL) and $NaHCO_3$ (4 mg, 0.052 mmol, 2 equiv) and Dess-Martin reagent (22 mg, 0.052 mmol, 2 equiv). The mixture was stirred at 23 ^oC for 1 h and quenched with saturated $NaHCO_3$ (2 mL) and saturated $Na_2S_2O_3$ solution (2 mL). The aqueous layer was extracted with CH_2Cl_2 and the combined extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the crude product was purified by column chromatography on silica gel (Hexanes/Et_2O, 1:1) to afford the product **14** (9.8 mg, 58% yield for two steps) as a white solid. The product contains two rotamers. ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.4 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 0.8H), 1.04 (d, *J* = 6.8 Hz, 2.2H), 1.22-1.40 (m, 3H), 1.28 (d, *J* = 6.8 Hz, 0.8H), 1.43 (d, *J* = 6.8 Hz, 2.2H), 1.53 (m, 1H), 1.91 (m, 0.7H), 2.31 (m, 0.3H), 2.77 (s, 2.2H), 2.77-2.83 (m, 1.5H), 2.93 (s, 0.8H), 3.00 (m, 0.5H), 3.21 (dd, *J* = 10.6, 13.4 Hz, 0.7H), 3.28 (q, *J* =

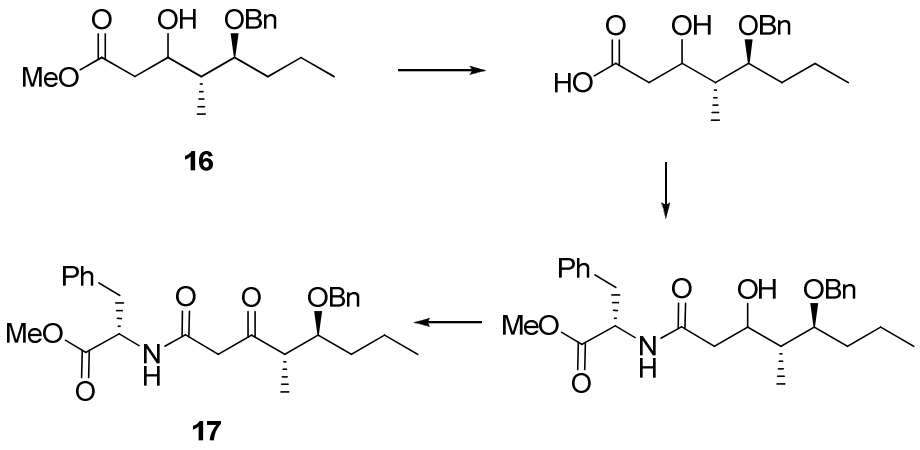
6.8 Hz, 0.7H), 3.41-3.48 (m, 2.5H), 4.61 (m, 0.5H), 4.99 (m, 0.7H), 5.16 (m, 0.3H), 5.22 (m, 0.7H), 5.50 (d, *J* = 3.5 Hz, 0.3H), 5.64 (dd, *J* = 4.3, 12.7 Hz, 0.7H), 6.48 (d, *J* = 10.2 Hz, 0.7H), 6.87-7.35 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) "M" for major rotamer, "m" for minor rotamer, δ 12.5 (m), 12.8(M), 13.9 (m), 14.3(M), 14.7(m), 15.0(M), 16.4(M), 17.7(m), 31.0, 31.87(m), 31.91(M), 33.5(M), 34.1(M), 34.4(m), 34.6(m), 36.6, 41.7(M), 42.5(m), 50.6, 56.8(M), 57.9(m), 58.2(M), 58.9(m), 62.1(m), 76.9 (M), 77.8 (m), 135.8 (m), 136.0 (M), 136.4 (M), 137.2 (m), 167.6 (M), 167.7 (m), 169.0 (m), 170.2 (M), 171.0 (m), 173.8 (M), 207.7 (M), 211.1 (m); FT-IR (film, NaCl) 1227.9, 1260.2, 1455.3, 1497.6, 1525.1, 1621.2, 1681.2, 1737.1, 2935.2, 2960.1 cm^{-1}; $[\alpha]_D^{25}$ -61.2 (*c* 0.56, CH_2Cl_2); HRMS (ESI) $[M+Na]^+$ calcd for $C_{29}H_{36}N_2O_5Na$ 515.2522, found 515.2528.



15 **16**

(2*S*,3*S*)-3-(benzyloxy)-2-methylhexanal (207 mg, 0.94 mmol) derived from alcohol **9** by Swern oxidation was dissolved in CH_2Cl_2 (10 mL) and was cooled to -78 ^{o}C with dry ice/acetone bath. To the above solution was added 1-methoxy-1-*tert*-butyldimethylsiloxy ethene (**15**) (180 mg, 0.94 mmol), followed by addition of borontrifluoride etherate (47 μL, 0.38 mmol) dropwise via a syringe. The mixture was stirred at -78 ^{o}C for 1 h and quenched with saturated $NaHCO_3$ solution. The mixture was warmed to 23 ^{o}C and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 4:1) to afford the desired hydroxyl ester **16** (201 mg, 72% yield, dr = 5:1). The two diastereomers were carried on without complete separation. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.4 Hz, 3H), 1.00 (d, *J* = 7.1 Hz, 3H), 1.40 (m, 2H), 1.68 (m, 2H), 1.74 (m, 1H), 2.36 (dd, *J* = 4.8, 15.3 Hz, 1H), 2.56 (dd, *J* = 9.0, 15.3 Hz, 1H), 3.42 (d, *J* = 2.5 Hz, , 1H), 3.50 (dd,

J = 5.8, 11.1 Hz, 1H), 3.70 (s, 3H), 4.43 (m, 1H), 4.49 (d, *J* = 11.1 Hz, 1H), 4.63 (d, *J* = 11.1 Hz, 1H), 7.29 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 14.4, 18.4, 33.5, 39.4, 51.7, 67.8, 72.5, 83.4, 127.8, 127.9 128.5, 138.2, 172.9.

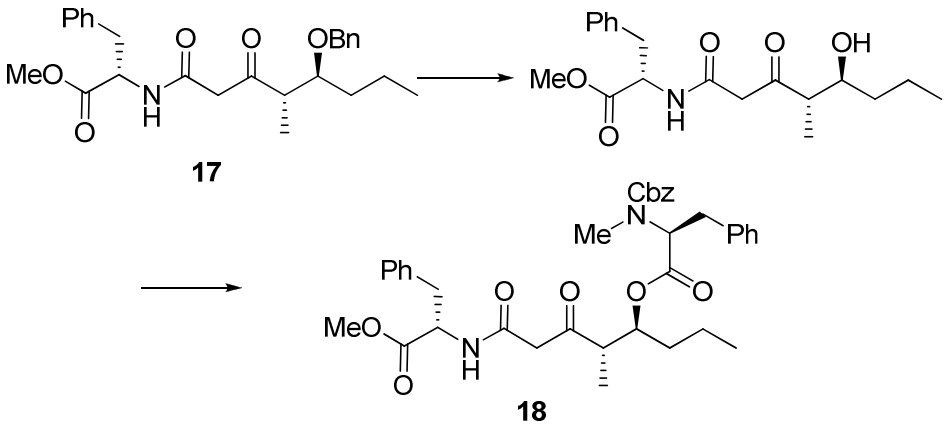


To the solution of hydroxyl ester **16** (209 mg, 0.68 mmol) in THF/H_2O (3/3 mL) was added 30% hydrogen peroxide (615 μL, 5.4 mmol) and lithium hydroxide (114 mg, 2.7 mmol). The solution was stirred at 0 ^{o}C for 3 h. Then THF was removed via vacuum. The aqueous layer was acidified to pH = 1 with 1 N HCl. The aqueous layer was extracted with CH_2Cl_2 and washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and residue was passed through a quick column to afford the acid (165 mg, 87% yield).

To a solution of the above acid (165 mg, 0.59 mmol) in DCM/DMF (5/1 mL) was added EDCI (225mg, 1.2 mmol), HOBt (120mg, 0.89 mmol). The suspension became clear after several minutes. Then sodium bicarbonate (400mg, 4.7 mmol) and $_{L}$-Phenylalanine methyl ester HCl salt (191 mg, 0.89 mmol) was added sequentially. The mixture was stirred at 23 ^{o}C for 2 h. Saturated ammonium chloride solution was added to quench the reaction and the organic layer was extracted with ethyl acetate and the combined organic extracts were washed with brine and dried over Na_2SO_4. After concentration under vacuum, the residue was purified by column chromatography on silica gel (Hexanes/ethyl acetate, 8:2) to afford the desired amide (255mg, 98% yield) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (t, *J* = 7.0 Hz,

3H), 1.00 (d, *J* = 6.9 Hz, 3H), 1.38-1.42 (m, 2H), 1.61 (m, 1H), 1.71 (m, 2H), 2.14 (dd, *J* = 2.0, 5.2 Hz, 1H), 2.44 (dd, *J* = 10.3, 15.2 Hz, 1H), 3.08 (dd, *J* = 6.6, 13.8 Hz, 1H), 3.17 (dd, *J* = 5.8, 13.8 Hz, 1H), 3.50 (dd, *J* = 5.8, 10.9Hz, 1H), 3.73 (s, 3H), 3.84 (m, 1H), 4.24 (d, *J* = 8.9 Hz, 1H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.65 (d, *J* = 11.8 Hz, 1H), 4.91 (dd, *J* = 6.4,13.9 Hz, 1H), 6.91-7.61 (m, 10H);^{13}C NMR (125 MHz, $CDCl_3$ major) δ 11.6, 14.4, 18.4, 33.5, 37.9, 39.9, 41.2, 68.2, 83.5, 127.1, 127.9, 128.5, 129.3, 136.1, 138.0, 172.0; FT-IR (film, NaCl) 1213.6, 1364.8, 1534.2, 1647.9, 1744.0 cm^{-1}.

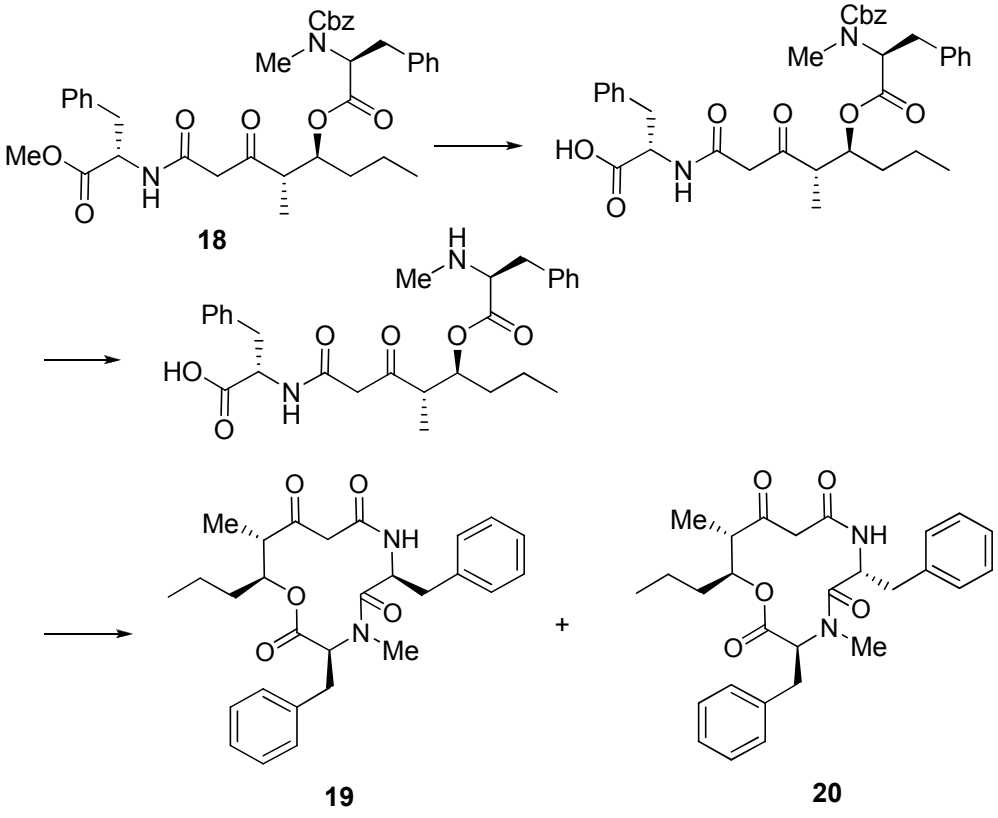
To the above amide (255 mg, 0.58 mmol) dissolved in CH_2Cl_2 (12 mL) was added solid sodium bicarbonate (97 mg, 1.1 mmol) and Dess-Martin reagent (368 mg, 0.87 mmol). The mixture was stirred at 23 ^oC for 1 h and quenched with 1:1 saturated $NaHCO_3/Na_2S_2O_3$ solution. The aqueous layer was extracted with CH_2Cl_2 and washed with brine, dried over Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by column chromatography on silica gel (Hexanes/ethyl aceate, 8:2) to afford the ketone **17** (181mg, 72% yield) as a white semisolid. ^{1}H NMR (500 MHz, $CDCl_3$) δ, 0.96 (t, *J* = 7.2 Hz, 3H), 1.05 (d, *J* = 7.0 Hz, 3H), 1.41-1.58 (m, 4H), 2.92 (m, 1H), 3.05 (dd, *J* = 6.9, 13.9 Hz, 1H), 3.14 (dd, *J* = 4.5, 11.4 Hz, 1H), 3.46 (s, 2H), 3.68 (m, 2H), 3.72 (s, 3H), 4.39 (d, *J* = 11.2 Hz, 1H), 4.52 (d, *J* = 11.2 Hz, 1H), 4.86 (dd, *J* = 6.9, 13.2 Hz, 1H), 7.10-7.50 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 14.1, 17.3, 32.6, 37.7, 48.8, 50.1, 52.1, 53.3, 71.8, 80.6, 126.9, 127.6, 127.8, 129.1, 135.8, 137.9, 165.6, 171.5, 209.2; FT-IR (film, NaCl) 1214.9, 1361.1, 1530.9, 1672.2, 1716.0, 1745.6, 2956.5; $[\alpha]_D^{25}$ +77.4 (*c* 1.0, $CHCl_3$).



The ketone **17** (124 mg, 0.28 mmol) was dissolved in MeOH (4 mL) and EtOAc (4 mL) and was cooled to 0 ^{o}C. The air in it was flushed out with argon and $Pd(OH)_2$ was added under Ar. A balloon of H_2 was attached and the mixture was warmed to 23 ^{o}C and stirred for 3 h. The catalyst was filtered off over celite and washed with ethyl acetate. After careful concentration, the residue was purified by column chromatography on silica gel (hexanes/ethyl acetate, 6:4) to afford the desired alcohol (93.4 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 6.3 Hz, 3H), 1.03 (d, *J* = 7.1 Hz, 3H), 1.29 (m, 2H), 1.48 (m, 2H), 2.64 (m, 1H), 2.79 (br, 1H), 3.04 (dd, *J* = 6.7, 13.8 Hz, 1H), 1.13 (dd, *J* = 5.7, 13.9 Hz, 1H), 3.44 (s, 2H), 3.67 (s, 3H), 3.69 (m, 1H), 4.82 (dd, *J* = 6.6, 13.4 Hz, 1H), 7.08-7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 13.9, 18.3, 36.6, 37.7, 48.7, 52.2, 53.4, 73.3, 127.0, 128.5, 129.2, 135.8, 165.8, 171.7, 210.1; FT-IR (film) 1217.5, 1363.6, 1455.7, 1539.5, 1653.2, 1716.8, 1744.9, 2957.1 cm^{-1}; $[\alpha]_D^{25}$ +55.6 (*c* 1.05, $CHCl_3$).

To the solution of Cbz-*N*-Me-$_L$-phenyl alanine (162 mg, 0.52 mmol) in CH_2Cl_2 (5.2 mL) at 0 ^{o}C was added DCC (107 mg, 0.52 mmol). White precipitate was formed immediately. The suspension was stirred at 0 ^{o}C for 10 min. DMAP (4 mg, 0.033 mmol, 0.1 equiv) was added, followed by the alcohol from above (111 mg, 0.32 mmol) dissolved in CH_2Cl_2 (1 mL). The mixture was stirred at 0 ^{o}C for 1 h. H_2O (0.5 mL) was added and the mixture was stirred for 0.5 h. Hexanes (10 mL) was added and the precipitate was removed by filtration. And the filtrate was washed with saturated sodium bicarbonate solution, brine and dried over anhydrous sodium sulfate. After

concentration under vacuum, the residue was purified by column chromatography on silica gel (hexanes/ethyl acetate, 8:2) to afford the desired ester **18** (193 mg, 94% yield). The product contains two major rotamers with CD_3OD as the NMR solvent. ^1H NMR (500 MHz, CD_3OD) δ 0.87-0.97(m, 3H), 1.03-1.13 (m, 3H), 1.24-1.38 (m, 2H), 1.47-1.63 (m, 2H), 2.45 (m, 0.5H), 2.78 (m, 3H), 2.83-3.20 (m, 3.5 H), 3.23-3.36 (m, 2H), 3.61-3.63 (m, 3H), 4.74 (m, 1H), 4.85-4.99 (m, 1H), 5.02-5.09 (m, 2H), 5.10-5.20 (m, 1H), 7.07-7.35 (m, 15H); ^{13}C NMR (500 MHz, CD_3OD) (major rotamer) δ 11.3, 13.0, 17.6, 31.4, 32.9, 33.8, 34.5, 37.1, 49.0, 51.3, 53.9, 60.7, 66.9, 75.6, 126.3, 126.5, 127.1, 127.7, 127.8, 128.2, 128.7, 128.9, 136.5, 136.7, 136.9, 137.3, 156.9, 167.1, 170.1, 171.8, 172.2, 206.0; FT-IR (film, NaCl), 1216.3, 1454.5, 1703.3, 1741.9 cm^{-1}; $[\alpha]_D^{25}$ +11.9 (*c* 1.04, $CHCl_3$).



The ester **18** (193 mg, 0.3 mmol) was dissolved *t*-butanol/H_2O (2:1, 3.0 mL) and was cooled to 0 ^oC. To this solution was added lithium hydroxide monohydrate (19 mg, 0.45 mmol) and the mixture was stirred at 0 ^oC for 2 h. Then the solution was diluted with ethyl acetate (10 mL) and 2 N HCl (0.4 mL) to acidify the reaction. The solution

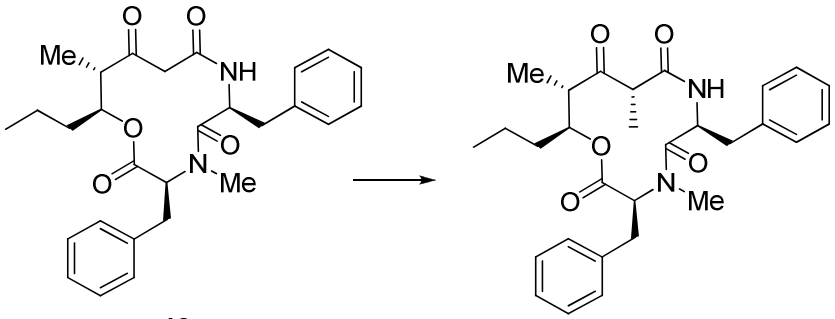
was washed with brine and dried over Na_2SO_4. The solvent was evaporated under vacuum and the crude product was purified by flash column chromatography on silica gel (CH_2Cl_2/CH_3OH, 96:4) to afford the desired acid (179 mg, 94% yield) as a white solid. The acid contains two major rotamers with CD_3OD as the NMR solvent. ^1H NMR (400 MHz, CD_3OD) δ 0.83-0.90 (m, 3H), 0.98 (d, *J* = 7.0 Hz, 3H), 1.13-1.32 (m, 2H), 1.40-1.54 (m, 2H), 2.72 (s, 3H), 2.76-3.05 (m, 3H), 3.19-3.28 (m, 1H), 3.31 (s, 2H), 4.66 (m, 1H), 4.79-5.14 (m, 4H), 7.10-7.31 (m, 15H); ^{13}C NMR (100 MHz, CD_3OD) "M" for major rotamer, "m" for minor rotamer, δ 12.6 (m), 12.9 (M), 14.3, 19.0 (M), 19.2 (m), 30.8 (M), 30.9 (m), 32.9 (M), 33.2 (m), 35.2, 35.6 (m), 35.9 (M), 38.6, 49.9 (M), 50.7, 62.1, 68.3 (M), 68.6 (m), 76.6 (m), 77.0 (M), 127.8, 128.5, 128.7, 129.0, 129.2, 129.4, 129.5, 129.6, 130.1, 130.3, 130.5, 137.6, 138.2, 138.5, 138.7, 157.7 (m), 158.2 (M), 168.4, 171.5, 207.2 (m), 207.6 (M).

To the above acid (178 mg, 0.28 mmol) dissolved in methanol (4 mL) and ethyl acetate (4 mL) was added $Pd(OH)_2$ (44 mg) under Ar at 0 ^oC. A balloon of H_2 was attached and the mixture was allowed to 23 ^oC and stirred at 23 ^oC for 2 h. The Pd catalyst was filtered off over celite and washed with ethyl acetate and methanol. The filtrate was concentrated under vacuum and the crude product was purified by flash column chromatography on silica gel (CH_2Cl_2/CH_3OH, 95:5 to 85:15) to afford the desired *seco* amino acid (102 mg, 73% yield) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 0.84 (t, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 7.2 Hz, 3H), 1.10-1.22 (m, 2H), 1.40-1.49 (m, 2H), 2.49 (s, 3H), 2.87 (m, 1H), 2.94-3.16 (m, 4H), 3.21 (d, J = 11.9 Hz, 1H), 3.30(s, 2H), 3.94 (t, *J* = 7.6 Hz, 1H), 4.54 (m, 1H), 5.13 (m, 1H), 7.12-7.32 (m, 10H); ^{13}C NMR (100 MHz, CD_3OD) δ 12.5, 14.2, 19.1, 33.2, 33.7, 37.4, 39.0, 50.4, 57.5, 64.2, 77.2, 127.4, 128.5, 129.3, 129.5, 129.9, 130.5, 136.2, 139.3, 168.0, 170.1, 207.3.

The *seco* amino acid from above (41 mg, 0.082 mmol) was dissolved in dichloromethane (34 mL) and DMF (6.8 mL) and was cooled to 0 ^oC. To this solution were added HATU (62 mg, 0.16 mmol, 2 equiv), HOAt (22 mg, 0.16 mmol, 2 equiv)

and diisopropylethylamine (57 μL, 0.33 mmol, 4 equiv). The solution was warmed up to 23 °C and stirred at 23 °C for 36 h. Water was added to quench the reaction, the aqueous was extracted with ethyl acetate and the combined extracts were washed with brine and dried over Na_2SO_4. The solution was concentrated under vacuum and residue was purified by flash chromatography on silica gel (hexane/Et_2O, 1:1) to afford cycloamide **19** (18.4 mg, 47% yield) as a white solid and epimerized cycloamide **20** (3.2 mg, 8% yield) as a white solid. Cycloamide **19**: ^{1}H NMR(500 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.4 Hz, 3H), 1.18 (d, *J* = 6.7 Hz, 3H), 1.26-1.38 (m, 2H), 1.55-1.63 (m, 1H), 1.71-1.77 (m, 1H), 2.78-2.94 (m, 3H), 2.85 (s, 3H), 3.03 (m, 1H), 3.29 (s, 2H), 3.38 (dd, *J* = 2.7, 14.5 Hz, 1H), 4.32 (m, 1H), 4.99-5.04 (m, 2H), 6.16 (d, *J* = 8.3 Hz, 1H), 6.88 (d, *J* = 7.1 Hz, 2H), 7.12-7.31 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.3, 17.8, 30.1, 33.9, 34.1, 37.1, 49.0, 50.5, 53.0, 61.9, 78.4, 126.4, 127.1, 128.4, 128.6, 128.7, 128.8, 128.9, 136.8, 137.0, 162.4, 169.0, 205.9; FT-IR (film, NaCl) 1218.9, 1454.0, 1651.6, 1740.2 cm^{-1}; $[\alpha]_D^{25}$ -164.4 (*c* 1.04, CH_2Cl_2), HRMS (ESI) $[M+Na]^+$ calcd for $C_{28}H_{34}N_2O_5Na$ 501.2365, found 501.2362.

Cycloamide **20** : ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.3 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.30-1.38 (m, 1H), 1.48-1.70 (m, 2H), 1.91-1.98 (m, 1H), 2.77 (s,3H), 2.81-2.88 (m, 2H), 2.91-3.04 (m, 1H), 3.10-3.25 (m, 1H), 3.39-3.46 (m, 2H), 3.57 (m, 1H), 5.05 (m,1H), 5.22 (m, 1H), 5.66 (dd, *J* = 5.7, 12.6 Hz, 1H), 6.23 (s, 1H), 6.89-7.34 (m, 10 H).



19 **1**

The cyclic depsipeptide **19** (6.2 mg, 0.013 mmol) was dissolved in anhydrous DMF (1.0 mL). To this solution was added cesium carbonate (8.4 mg, 0.026 mmol, 2 equiv) and methyl iodide (8 μL, 0.13 mmol, 10 equiv). The solution was stirred at 23 °C for 1 day. Then methyl acetate (1 mL) was added, followed by addition of 1 N NaH_2PO_4

solution (1 mL). The aqueous layer was extracted with ethyl acetate (3 × 1 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated under vacuum. The crude product was further purified by flash column chromatography on silica get (Hexane/Et_2O, 3:2 to 1:1) to afford the desired product (3.2 mg, 50% yield) as a white solid, along with the recovered starting material (3 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.5 Hz, 3H), 1.17 (d, *J* = 6.5 Hz, 3H), 1.21 (d, *J* = 6.5 Hz, 3H), 1.30-1.38 (m, 2H), 1.57-1.63 (m, 1H), 1.69-1.78 (m, 1H), 2.73 (dd, *J* = 0.5, 2.5 Hz), 2.83 (s, 3H), 2.88-2.93 (m, 2H), 3.01 (br m, 1H), 3.36 (dd, *J* = 2.3, 14.1 Hz, 1H), 3.37 (m, 1H) 3.89 (br, 1H), 4.83(m, 1H), 4.99(m, 1H), 5.79 (d, *J* = 8.7 Hz, 1H), 6.84(d, *J* = 10 Hz, 2 H), 7.15-7.32 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7 (br), 13.9, 15.0, 17.9, 29.6, 30.1, 34.0, 36.6, 46.0 (br), 51.3 (br), 54.9 (br), 61.9, 78.3, 126.3, 127.0, 128.2, 128.7, 128.74, 129.0, 137.0, 137.4, 166.2, 169.0, 169.8, 210.0; FT-IR (film, NaCl) 1220.3, 1260.9, 1454.3, 1633.8, 1683.2, 1739.6, 2934.9 cm^{-1}; $[\alpha]_D^{25}$ -224.5 (*c* 0.36, CH_2Cl_2); HRMS (ESI) $[M+Na]^+$ calcd for $C_{29}H_{36}N_2O_5Na$ 515.2522, found 515.2526.

Model for stereoselective methylation of 19

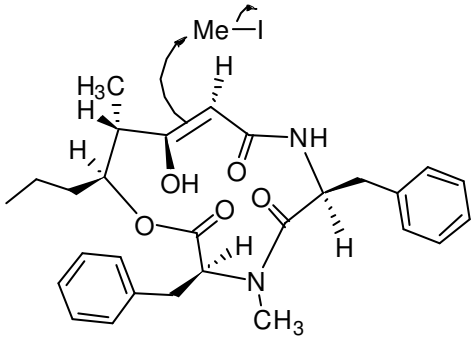
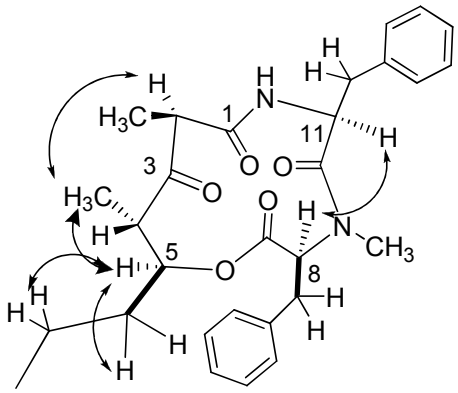


Figure 1 Proposed model for methylation step

The last methylation step has an excellent stereoselectivity. By calculation and model study, we found out that, this high stereoselectivity can be explained in figure 1. The enolate derived from **19** and cesium carbonate has *se* face totally blocked by the macrocycle ring system and two Phe residues, leaving only the *re* face open. The corresponding enolate can only attack the methyl iodide from *re* face, to form the desire product.

NOESY analysis for the synthetic 1

After careful NOESY analysis, we can confirm that C2-H (δ 3.37), C4-Me (δ 1.17) are on the same side of the ring, as shown in the following figure. NOESY correlations also suggests that C5-H (δ 4.99) and C4-Me (δ 1.17), C8-H (δ 4.83) of N-Me-L-Phe and C11-H (δ 3.89) of L-Phe are one the same side of the macrocycle ring. All these correlations are consistent with the natural Stereocalpin A NMR data.



^{1}H NMR comparison of Synthetic 1 and natural Stereocalpin A

Synthetic **1**	Natural Stereocalpin A
0.94 (t, *J* = 7.5 Hz, 3H)	0.89 (t, *J* = 7.3 Hz, 3H)
1.17 (d, *J* = 6.5 Hz, 3H)	0.99 (d, *J* = 7.0 Hz, 3H)
1.30-1.38 (m, 2H)	1.18 (m, 2H)
1.57-1.63 (m, 1H)	1.27 (m, 1H)
1.21 (d, *J* = 6.5 Hz, 3H)	1.30 (d, *J* = 7.3 Hz, 3H,)
1.69-1.78 (m, 1H)	1.48 (m, 1H)
3.01 (br s, 1H)	2.57 (m, 1H)
2.73 (dd, *J* = 2.5, 0.5 Hz, 1H)	2.80 (dd, *J* = 14.3, 8.8 Hz, 1H,)
3.36 (dd, *J* = 14.1, 2.3 Hz, 1H)	2.99 (dd, *J* = 14.2, 4.0 Hz, 1H,)
2.83 (s, 3H)	3.05 (s, 3H)
2.88-2.93 (m, 2H)	3.11 (m, 1H)
	3.14 (m, 1H)
3.37 (m, 1H)	3.87 (q, *J* = 7.0 Hz, 1H)
3.89 (br s, 1H)	4.66 (dd, *J* = 9.9, 5.9 Hz, 1H)
4.83 (m, 1H)	4.97 (m, 1H)
4.99 (m, 1H)	5.30 (m, 1H)
5.79 (d, *J* = 8.7 Hz, 1H)	5.80 (d, *J* = 9.9 Hz, 1H)
6.84 (d, *J* = 10 Hz, 2H)	7.06-7.32 (m, 10H)
7.15-7.32 (m, 8H)	

^{13}C NMR comparison of Synthetic 1 and natural Stereocalpin A

Synthetic **1**	Natural Stereocalpin A
13.7 (br)	10.4
13.9	13.9
15.0	15.0
17.9	18.9
29.6	30.0
30.1	32.8
34.0	36.0
36.6	38.4
46.0 (br)	48.8
51.3 (br)	50.9
54.9 (br)	52.4
61.9	58.9
78.3	76.3
126.3	126.6
127.0	127.3
128.2	128.2
128.7	128.7
128.74	128.9
129.0	129.6
137.0	135.8
137.4	137.0
166.2	167.0
169.0	169.9
169.8	170.6
210.0	210.7