Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information

Total Synthesis of Padanamides A and B

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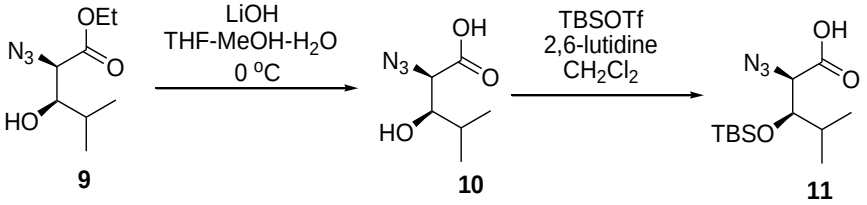
Content

General Experimental:

Commercially available reagents were used without further purification unless otherwise stated. All solvents were distilled prior to use: toluene, benzene, diethyl ether and tetrahydrofuran were distilled from Na/benzophenone; while dichloromethane, dimethylformamide, acetonitrile, triethylamine and diisopropylethylamine were distilled from CaH_2. Methanol was distilled under a N_2 atmosphere from Mg/I_2. All reactions were conducted in oven-dried (120 °C) or flame-dried glasswares under a N_2 atmosphere, and at ambient temperature (20 to 25 °C) unless otherwise stated. All non-aqueous reactions were performed by standard syringe in septa techniques. Evaporation and concentration under reduced pressure was performed at 50-500 mbar. ^{1}H NMR spectra were recorded in $CDCl_3$ (unless stated otherwise) on a Bruker Avance AV500 or 400 at 500 MHz (125 MHz) or 400 MHz (100 MHz), respectively. Chemical shifts are reported as δ values (ppm) referenced to either a tetramethylsilane (TMS) internal standard or the signals due to the solvent residual. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration. Some peptide intermediates exist as rotational conformers, the chemical shift for the minor isomers were indicated using parentheses next to the peak for their major isomers. Mass spectra were measured on ABI Q-star Elite. Optical rotations were measured on a Perkin-Elmer 351 polarimeter at 589 nm with a 100 mm path length cell at 20 °C (reported as follows: concentration (c in g/100 mL), solvent). The reaction progresses were checked on pre-coated thin layer chromatography (TLC) plates. TLC was carried out using pre-coated sheets (Qingdao silica gel 60-F250, 0.2 mm) which, after development, were visualized under UV light at 254nm. Flash column chromatography was performed using the indicated solvents on E. Qingdao silica gel 60 (230-400 mesh ASTM). Yields refer to chromatographically purified compounds, unless otherwise stated.

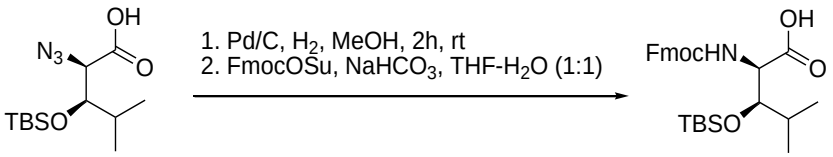
Experimental procedures:



$LiOH{\cdot}H_2O$ (5.5 g, 130.0 mmol) was added to a solution of compound **9** [1] (5.2 g, 25.9 mmol) in THF-MeOH-H_2O (100 mL, 1:1:1) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h before all volatiles were removed in *vacuo*. The residue was diluted with ether (100 mL) and acidified to pH 1 by dropwise addition of $KHSO_4$ (1 M solution in water). Layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed by water (50 mL), brine (50 mL), dried over sodium sulfate (anhydrous) and concentrated in *vacuo*. The residue was purified by chromatography on silica gel (MeOH : CH_2Cl_2, 1 : 10) to give the acid **10** (4.1 g, 90%). $[\alpha]_D^{25}$ + 42.0 (*c* 2.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.04 (d, *J* = 6.0 Hz, l H), 3.73 (dd, *J* = 4.5, 5.5 Hz, 1H), 3.53 (s, 1H), 2.08-2.01 (m, 1H), 1.05 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 64.5, 61.4, 30.7, 19.9, 17.3 ppm; HR-ESIMS m/z: calculated for $C_6H_{10}N_3O_3^-$ $[M-H]^-$: 172.0728, found 172.0725.

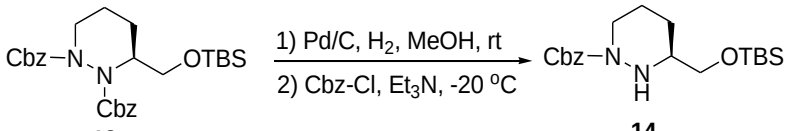
Acid **10** (4.1 g, 23.3 mmol) was dissolved in CH_2Cl_2 (100 mL) at 0 °C. After 2,6-lutidine (13 mL, 110.0 mmol) and TBSOTf (12.5 mL, 55.0 mmol) were sequentially added, the reaction mixture was stirred at 0 °C for 4 h, and then quenched by the addition of a cold solution of HCl (100 mL, 10% in water). Layers were separated and the aqueous phase was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed by a solution of $KHSO_4$ (100 mL, 1 M in water), brine (100 mL), dried over anhydrous sodium sulfate (anhydrous) and concentrated in *vacuo*. The residue was purified by chromatography on silica gel (MeOH : CH_2Cl_2, 1 : 20) to give the desired compound **11** (5.4 g, 80%). $[\alpha]_D^{25}$ +15.7 (*c* 1.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (d, *J* = 4.0 Hz, 1H), 3.88 (dd, *J* = 5.0, 4.5 Hz, 1H), 2.04-1.95 (m, 1H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.94 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDC1_3$) δ 174.6, 78.5, 66.2, 32.2, 30.4, 26.5, 19.5, 18.8, 18.7, -3.78, -3.85 ppm; HR-ESIMS m/z: calculated for $C_{12}H_{24}N_3O_3Si^-$ $[M-H]^-$: 286.1592, found 286.1593.

[1] a) K. J. Hale, S. Manaviazar, V. M. Delisser, *Tetrahedron*, 1994, **50**, 9181-9188; b) P. Saravanan, E. J. Corey *J. Org. Chem.* 2003, **68**, 2760-2764.



11 **12**

Palladium-carbon (0.2 g, 10%) was added to a solution of compound **11** (1.4 g, 5.0 mmol) in methanol (50 mL) under a nitrogen atmosphere. The reaction vessel was sealed and the resulting solution was stirred at room temperature for 14 h under a hydrogen atmosphere. The catalyst was removed by filtration through a pad of celite and washed with methanol (50 mL). The total filtrate was concentrated in *vacuo* to afford the corresponding amine as a white solid. This amine was dissolved in THF-H_2O (60 mL, 1:1) and cooled to 0 ^oC. After $NaHCO_3$ (1.7 g, 20.0 mmol) and FmocOSu (2.5 g, 7.5 mmol) were added, the reaction mixture was allowed to stir at room temperature for 16 h. Volatiles were removed in *vacuo*. The aqueous residue was extracted with ethyl acetate (100 mL) and the organic phase was discarded. The aqueous solution was then diluted with ethyl acetate (100 mL) and adjusted to pH 1 by dropwise addition of $KHSO_4$ solution (1 M in water). Layers were separated, the aqueous phase was further extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate (anhydrous) and concentrated in *vacuo*. The residue was purified by chromatography on silica gel (MeOH : CH_2Cl_2, 1 : 10), to give rise to the desired **12** (2.0 g, 82% over two steps). $[\alpha]_D^{25}$ – 15.8 (*c* 0.7, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) (exists as rotamers) δ 7.79 (d, *J* = 7.5 Hz, 2H), 7.64-7.61 (m, 2H), 7.42 (d, *J* = 7.0 Hz, 2H), 7.35-7.29 (m, 2H), 5.53 (d, *J* = 7.0 Hz, 1H), 4.63 (d, *J* = 5.5 Hz, 1H), 4.44 (d, *J* = 6.5 Hz, 2H), 4.26 (d, *J* = 5.5 Hz, 1H), 3.67-3.64 (m, 1H), 2.05-1.98 (m, 1H), 1.06 (d, *J* = 6.5 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.92 (s, 9H), 0.14-0.08 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDC1_3$) (exists as rotamers) δ 175.4, 156.2, 144.6, 144.4, 142.0, 130.8, 128.4, 127.7, 125.8, 125.7, 120.7, 80.5, 67.8, 57.9, 47.8, 34.0, 32.1, 30.4, 26.6, 26.1, 25.4, 20.1, 18.9, -3.4, -3.6 ppm; HR-ESIMS m/z: calculated for $C_{27}H_{36}NO_5Si^-$ $[M-H]^-$: 482.2368, found 482.2373.

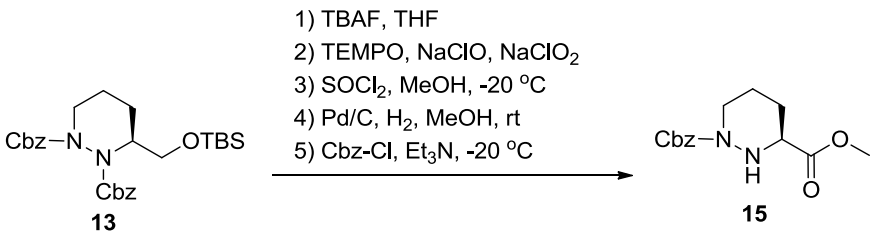


13 **14**

To a solution of **13** [2] (15.2 g, 31.0 mmol) in methanol (100 mL) was added Pd/C (1.0 g, catalytic amount, 10 % palladium on charcoal), the suspension was stirred under hydrogen atmosphere for 72 h. Pd/C was removed by filtration. The filtrate was cooled to -20 ^oC, triethylamine (8.4 mL, 60.0 mmol)

[2] Y. Henmi, K. Makino, Y. Yoshitomi, O. Hara, Y. Hamad, *Tetrahedron: Asymmetry*, 2004, **15**, 3477–3481.

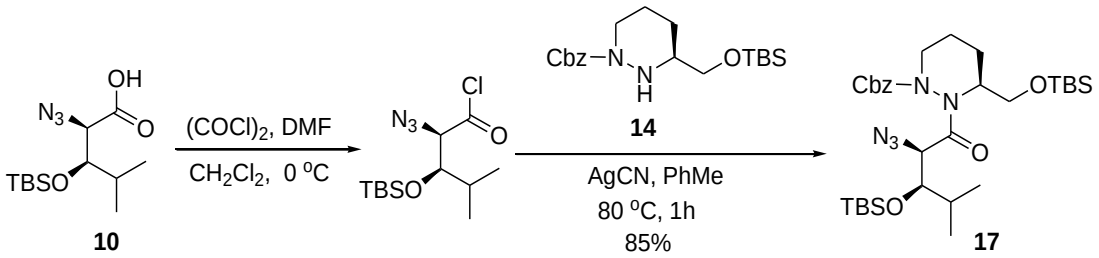
and benzyl chloroformate (6.8 mL, 34.0 mmol) were added. The reaction mixture was stirred at – 20 ^{o}C for 1 h before it was concentrated in *vacuo*. The residue was dissolved in ethyl acetate (700 mL), washed with saturated ammonium chloride (150 mL), brine (150 mL). The organic phase was dried over sodium sulfate (anhydrous), filtered and concentrated. The residue was purified by flash chromatography on silica gel (ethyl acetate : hexanes 1 : 9) to afford **14** (9.6 g, 86%). $[\alpha]_D^{25}$ +3.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ7.30-7.37 (m, 5H), 5.18 (s, 2H), 4.12 (d, 1H, *J* = 6.9 Hz), 3.60 (dd, 1H, *J* = 2.1Hz, *J* = 6.0 Hz), 3.47 (t, 1H, *J* = 5.4 Hz), 3.01 (t, 1H, *J* = 7.2 Hz), 2.88 (s, 1H), 1.68 (d, 1H, *J* = 8.4 Hz), 1.61 (d, 1H, *J* =7.8 Hz), 1.54 (d, 1H, *J* = 7.5 Hz), 1.32 (dq, 1H, *J* = 2.4 Hz, *J* = 7.5 Hz), 0.89 (s, 9H), 0.05 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.9, 136.5, 128.4, 128.0, 127.9, 67.3, 65.3, 58.3, 44.9, 26.3, 25.8, 23.8, 18.2, -5.5, -5.6 ppm; HR-ESIMS m/z: calculated for $C_{19}H_{33}N_2O_3Si^+$ $[M+H]^+$: 365.2255, found 365.2260.



To a solution of **13** (0.22 g, 0.4 mmol) in THF (5 mL) was added TBAF (1.1 mL, 0.9 mmol, 0.8 M in THF). The reaction mixture was stirred at room temperature for 1h. Volatiles were removed in *vacuo* and the residue was dissolved in ethyl acetate (100 mL) and washed with water (30 mL), brine (30 mL). The organic phase was dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. The residue was purified by flash chromatography (ethyl acetate : hexanes, 1 : 1) to produce the corresponding alcohol in quantitative yield. To the above alcohol in MeCN (10 ml) was sequentially added a pH 5.0 phosphonate buffer (10 mL), $NaClO_2$ (0.08 g, 0.9 mmol) and TEMPO (0.006 g, 0.04 mmol). The reaction mixture was then stirred at room temperature for 16 h before it was quenched with cold saturated sodium thiosulfate (15 mL). After the solution was adjusted to pH 3 with sulfuric acid (1.0 M solution in water), it was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (40 mL), dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo* to give rise to the crude acid. The acid, without further purification, was dissolved in methanol (5 mL) at – 20 ^{o}C. After $SOCl_2$ (0.07 mL, 0.9 mmol) was added, the reaction solution was stirred at 0 ^{o}C for 3h. Saturated sodium bicarbonate was employed to adjust the solution to pH 7, and volatiles were removed under reduced pressure. The residue was dissolved in ethyl acetate (100 mL). The solution was

washed with brine (50 mL), and dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. The residue was purified by flash chromatography (ethyl acetate : hexanes, 1 : 2), to afford the corresponding methyl ester (0.13 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50-1.60 (br m, 1H), 1.75-1.83 (br m, 1H), 1.91-1.93 (m, 1H), 2.13 (d, 1H, J = 13.5Hz), 2.90-3.01 (br m, 1H), 3.51 (s, 3H), 3.59-3.70 (m, 1H), 4.24 (d, 1H, J = 11.5Hz), 5.07-5.14 (br m, 4H), 7.27-7.38 (br m, 10H) ppm.

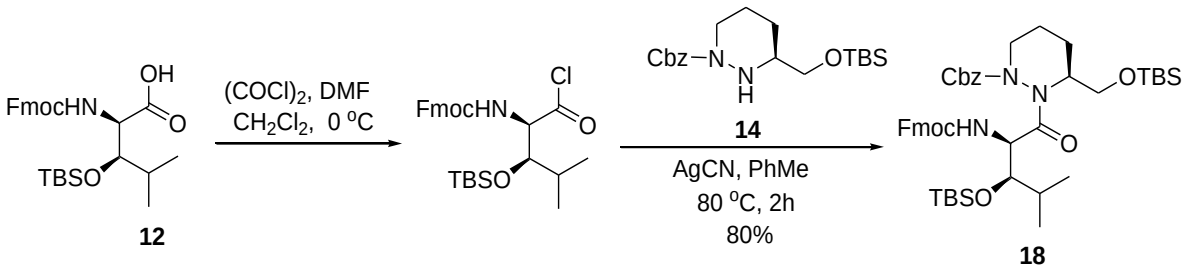
To a solution of the above ester (0.13 g, 0.3 mmol) in methanol (10 mL) was added Pd/C (0.05 g, 10% on charcoal, catalyst), the resulted suspension was exposed to hydrogen (balloon) for 3 days. Catalyst was removed by filtration. To the filtrate was added triethylamine (0.12 mL, 0.9 mmol), followed by CbzCl (0.11 mL, 0.6 mmol), at – 20 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 3h before it was concentrated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate-hexanes, 1 : 1) to produce **15** (0.07 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.57-1.63 (m, 1H), 1.67-1.78 (m, 2H), 2.04-2.08 (m, 1H), 3.11-3.15 (m, 1H), 3.55 (dd, 1H, J = 3.0Hz, 10.0Hz), 3.72 (s, 3H), 4.00 (d, 1H, J = 13.0Hz), 5.18 (s, 2H), 7.30-7.36 (m, 5H) ppm.



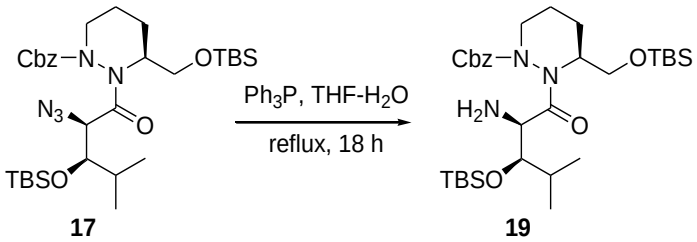
Oxalyl chloride (7.5 mL, 87.0 mmol) was slowly added to a solution of **10** (5.0 g, 17.4 mmol) in dichloromethane (100 mL) at 0 ^{o}C, followed by DMF (0.13 mL, 1.6 mmol) via a syringe. The reaction mixture was stirred at 0 ^{o}C until gas evolution had ceased. Volatiles were removed in *vacuo*. The residue was dissolved in dichloromethane (50 mL) and concentrated in *vacuo*. These procedures were repeated twice to ensure all the acid have been converted to the corresponding acyl chloride.

The acyl chloride was dissolved in toluene (50 mL) and dropwise added to the suspension of **14** (5.5 g, 15.0 mmol) and AgCN (4.0 g, 30.0 mmol) in toluene (50 mL) at 0 ^{o}C. The reaction mixture was allowed to warm to 80 ^{o}C and stirred for 1 h, before it was poured into saturated sodium bicarbonate (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over sodium sulfate (anhydrous) and concentrated in *vacuo* to give the crude product, which was purified by silica gel column chromatography (ethyl acetate : hexanes, 1 : 25) to provide **17** (8.0 g, 85%) as a colorless oil. $[\alpha]_D^{25}$ – 59.3 (*c* 1.36, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) (exists as rotamers) δ 7.40 (br, 5H), 5.25-5.10 (m, 2H), 4.59 (brm, 1H), 4.29-4.18 (m, 1H), 4.00 (br, 1H), 3.94 (d,

J = 8.0 Hz, 1H), 3.77-3.62 (m, 1H), 3.42-3.41 (m, 1H), 3.14-3.05 (m, 1H), 1.98-1.94 (m, 3H), 1.76 (br, 1H), 1.55-1.52 (m, 1H), 0.98-0.95 (m, 6H), 0.86 (s, 9H), 0.77 (s, 9H), 0.13-0.04 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDC1_3$) (exists as rotamers) δ 169.8, 156.3, 135.8, 135.0, 128.7, 128.6, 75.7, 74.7, 68.9, 68.4, 60.6, 58.5, 52.2, 52.1, 46.4, 31.9, 30.4, 29.7, 26.3, 26.1, 25.8, 22.3, 18.5, 18.4, 18.3, 18.2, 16.8, 15.8, -3.7, -4.2, -4.9, -5.0, -5.4, -5.6 ppm; HR-ESIMS m/z: calculated for $C_{31}H_{56}N_5O_5Si_2^+$ $[M+H]^+$: 634.3814, found 634.3804.

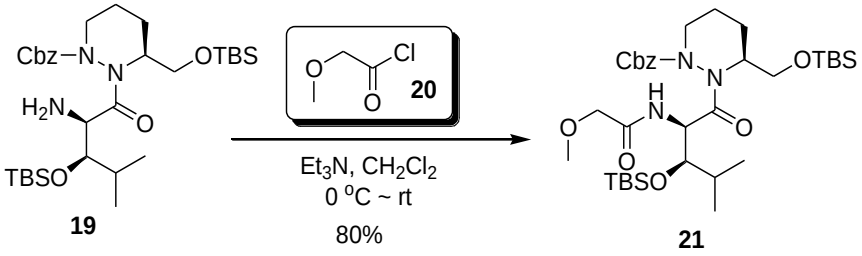


The above reactions were carried out according to procedures described for compound **11**. With **12** (2.0 g, 4.1 mmol) as starting material, compound **18** (2.0 g, 80%) was obtained as a colorless oil. $[\alpha]_D^{25}$ – 20.4 (*c* 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) (exists as rotamers) δ 7.77-7.75 (m, 2H), 7.55-7.50 (m, 2H), 7.42-7.29 (m, 2H), 7.24-7.18 (m, 2H), 5.40-4.97 (m, 4H), 4.60-4.30 (m, 2H), 4.30-4.02 (m, 2H), 3.94-3.35 (m, 3H), 3.24-2.97 (m, 1H), 2.06-1.70 (m, 4H), 1.01-0.81 (m, 24H), 0.12-0.02 (m, 9H), -0.08--0.11 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDC1_3$) (exists as rotamers) δ 175.5, 172.6, 167.7, 156.0, 155.1, 143.8, 141.2, 135.3, 135.2, 132.5, 130.9, 129.9, 129.7, 128.8, 128.5, 128.3, 128.0, 127.6, 127.0, 125.2, 125.0, 119.9, 68.6, 68.2, 66.7, 60.0, 52.1, 51.9, 47.1, 46.1, 38.7, 37.4, 37.1, 36.3, 35.9, 33.7, 33.4, 33.2, 32.7, 32.4, 32.2, 31.9, 31.6, 30.4, 30.3, 30.2, 30.0, 29.8, 29.7, 29.5, 29.5, 29.4, 29.36, 29.2, 29.0, 28.9, 27.2, 26.7, 26.4, 26.2, 25.8, 25.5, 25.2, 23.8, 23.7, 23.4, 23.2, 23.0, 22.7, 22.2, 19.1,18.5, 18.1, 16.9, 14.2, 14.1, 14.0, 11.0, 10.9, -3.6, -5.0.-5.5, -5.7 ppm; HR-ESIMS m/z: calculated for $C_{46}H_{68}N_3O_7Si_2^+$ $[M+H]^+$: 830.4590, found 830.4591.

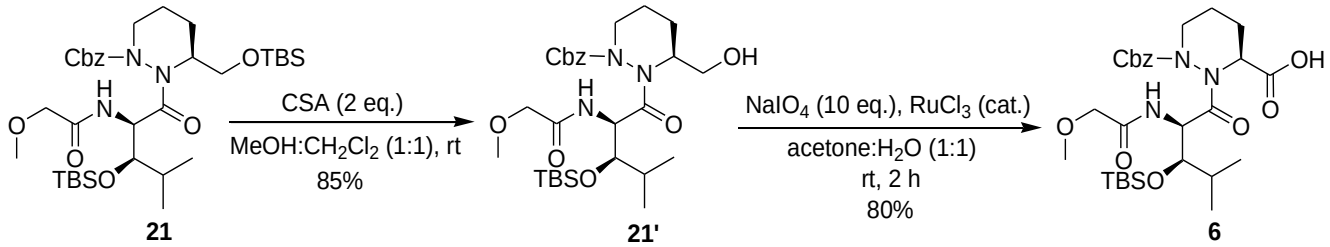


Compound **17** (4.5 g, 7.2 mmol) was dissolved in THF-H_2O (42 mL, 20:1), triphenylphosphine (18.9 g, 72.0 mmol) was added, and then the reaction mixture was stirred and refluxed for 18 h. The residue, after concentration in *vacuo*, was purified by flash chromatography on silica gel (ethyl acetate : hexanes,

1 : 10) to give the product **19** (3.7 g, 85%). $[\alpha]_D^{25}$ – 24.8 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) (exists as rotamers) δ 7.37 (br, 5H), 5.22-5.12 (m, 2H), 4.65 (br, 1H), 4.33-4.17 (m, 1H), 3.71-3.66 (m, 2H), 3.59-3.50 (m, 1H), 3.50-3.44 (m, 1H), 3.16-3.08 (m, 1H), 2.07-1.96 (m, 1H), 1.96-1.94 (m, 2H), 1.79-1.72 (m, 2H), 0.95-0.89 (m, 24H), 0.09-0.06 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDC1_3$) (exists as rotamers) δ 175.5, 174.9, 155.9, 155.2, 134.8, 134.1, 132.8, 132.7, 131.2, 127.8, 127.7, 127.6, 127.4, 127.1, 76.9, 67.6, 59.5, 59.3, 53.0, 52.4, 50.6, 46.2, 45.4, 29.9, 29.7, 28.7, 25.2, 24.9, 21.3, 18.9, 18.6, 18.5, 17.7, 17.5, 17.2, 16.2, 15.4, -4.67, -5.9, -6.4, -6.5 ppm; HR-ESIMS m/z: calculated for $C_{31}H_{58}N_3O_5Si_2^+$ $[M+H]^+$: 608.3910, found 608.3913.

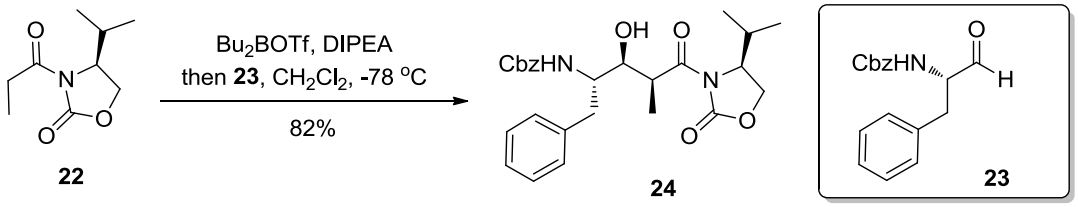


To a solution of compound **19** (3.2 g, 5.3 mmol) in CH_2Cl_2 (50 mL), Et_3N (7.3mL, 52.0 mmol) and methoxyacetyl chloride **20** (2.5 mL, 26.3 mmol) were added sequentially at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1h, then quenched by the addition of saturated $NaHCO_3$ solution (50 mL). Layers were separated and the aqueous phase was extracted with dichloromethane (2 × 200 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate (anhydrous) and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel (ethyl acetate-hexanes, 1 : 5) to give the desired tripeptide **21** (2.9 g, 80%) as an oil. $[\alpha]_D^{25}$ – 2.7 (*c* 0.4, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) (exists as rotamers) δ 7.41-7.32 (m, 5H), 6.98-6.96 (m, 1H), 5.33-5.08 (m, 3H), 4.95-4.93 (m, 1H), 4.57 (br,1H), 4.40-4.13 (m, 1H), 3.91-3.87 (m, 1H), 3.78-3.77 (m, 1H), 3.72-3.69 (m, 1H), 3.64-3.63 (m, 1H), 3.46-3.40 (m, 2H), 3.30-3.25 (m, 3H), 3.18-3.13 (s, 2H), 2.07-1.90 (m, 2H), 1.79-1.78 (m, 2H), 1.56-1.53 (m, 1H), 0.99-0.83 (m, 24H), 0.11-0.03 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDC1_3$) (exists as rotamers) δ 171.2, 167.1, 155.0, 134.6, 127.5, 127.3, 127.0, 126.6, 70.7, 67.6, 59.2, 57.9, 51.2, 51.0, 48.6, 45.2, 30.6, 28.7, 21.3, 18.4, 17.5, 17.1, 15.7, -4.7, -6.0, -6.5, -6.6 ppm; HR-ESIMS m/z: calculated for $C_{34}H_{62}N_3O_7Si_2$ $[M+H]^+$: 680.4121, found 680.4111.

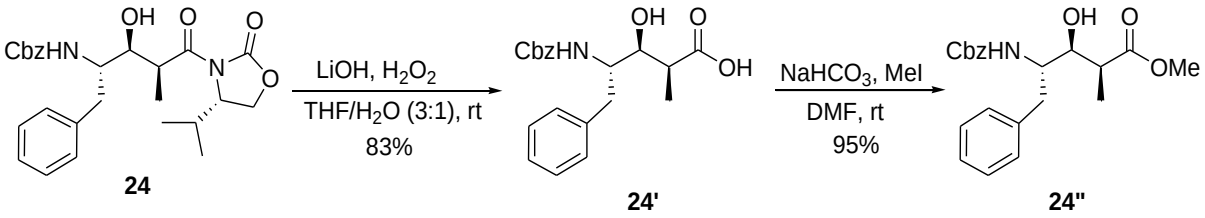


D-Camphorsulfonic acid (1.2 g, 5.0 mmol) was added to a solution of **21** (1.7 g, 2.5 mmol) in CH_2Cl_2-MeOH (40 mL, 1:1) at 0 °C. The reaction mixture was stirred at room temperature for 2 h, then poured into saturated aqueous solution of $NaHCO_3$ (50 mL) and concentrated in *vacuo*. The aqueous residue was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed by brine (100 mL), dried over sodium sulfate (anhydrous) and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel (MeOH : CH_2Cl_2, 1 : 20) to afford alcohol **21'** (1.2 g, 85%) as an oil. $[\alpha]_D^{25}$ + 7.0 (*c* 0.3, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) (exists as rotamers) δ 7.43-7.36 (m, 5H), 6.92-6.81 (m, 1H), 5.36-5.14 (m, 3H), 4.80-4.68 (m, 1H), 4.41-4.22 (m, 1H), 4.02-3.74 (m, 3H), 3.53-3.48 (m, 2H), 3.47 (s, 3H), 3.29-3.23 (m, 1H), 1.84-1.83 (m, 2H), 1.70-1.56 (s, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDC1_3$) (exists as rotamers) δ 172.0, 167.7, 156.9, 134.5, 127.6, 127.5, 127.4, 70.9, 68.4, 59.4, 58.2, 59.4, 58.2, 51.6, 48.4, 46.2, 29.9, 25.2, 24.7, 21.7, 18.7, 18.3, 18.0, 17.5, 15.8, 15.3, -4.6, -5.9, -6.1 ppm; HR-ESIMS m/z: calculated for $C_{28}H_{47}N_3NaO_7Si^+$ $[M+Na]^+$: 588.3075, found 588.3080.

A solution of **21'** (1.2 g, 2.1 mmol) in MeCN-acetone (60 mL, 1:1) was added to a suspension of $NaIO_4$ (4.5 g, 21.0 mmol) and $RuCl_3{\cdot}nH_2O$ (20 mg, 0.1 mmol) in water (30 mL) at ambient temperature. 2 h later, the reaction mixture was filtered through a pad of celite and the filtrate was concentrated in *vacuo*. The aqueous residue was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed by saturated brine (50 mL), dried over sodium sulfate (anhydrous) and concentrated in *vacuo*. The residue was purified by silica gel flash column chromatography (MeOH : CH_2Cl_2, 1 : 10) to afford the desired compound **6** (1.0 g, 80%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) (exists as rotamers) δ 7.37 (brs, 5H), 5.16 (brs, 2H), 5.05 (brs, 1H), 5.00-4.94 (m, 1H), 4.27-4.23 (m, 1H), 3.97-3.80 (m, 3H), 3.41-3.39 (m, 3H), 3.16 (brs, 2H), 2.13 (br, 1H), 2.04-2.00 (m, 1H), 1.85-1.77 (m, 2H), 1.56-1.52 (m, 1H), 0.98 (d, *J* = 7.0 Hz, 6H), 0.89 (brs, 9H), 0.09-0.02 (m, 6H) ppm; ^{13}C NMR (125 MHz, MeOD) (exists as rotamers) δ 179.8, 175.4, 173.5, 161.5, 138.7, 135.0, 133.7, 132.4, 77.5, 74.8, 74.0, 71.6, 62.2, 61.0, 59.5, 42.7, 42.1, 38.9, 36.0, 35.6, 34.2, 33.3, 30.6, 29.0, 27.6, 26.3, 23.9, 23.1, 21.7, 19.6, 17.0, 14.1, -1.6, -2.2 ppm; HR-ESIMS m/z: calculated for $C_{28}H_{44}N_3O_8Si^-$ $[M-H]^-$: 578.2903, found 578.3001.

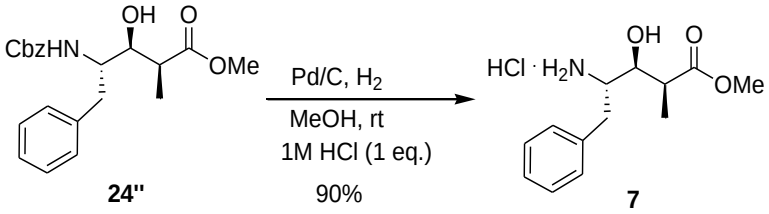


To a stirred solution of oxazolidinone **22** (5.8 g, 31.5 mmol) in CH_2Cl_2 (30 mL) was added Bu_2BOTf (34.6 mmol) and DIPEA (6.6 mL, 37.7 mmol) at 0 °C. After stirring for 1h, the solution was cooled to –78 °C and maintained at -78 °C for 30 min. A solution containing **23** (9.4 g, 33.0 mmol) in CH_2Cl_2 (30 mL) was added and the solution was allowed to slowly warm to room temperature overnight. The reaction was quenched by the addition of pH 7 buffer solution (10 mL) followed by MeOH (20 mL) at 0 °C and then sequentially added H_2O_2 (20 mL), MeOH (20 mL) at the same temperature. After stirring for 1 h at 0 °C, volatiles were removed and then H_2O (30 mL) was added to the reaction mixture. The mixture was extracted with ethyl acetate (3 × 100 mL). The combined extracts were dried over anhydrous sodium sulfate (anhydrous), filtered, and concentrated in *vacuo*. The organic residue was purified by column chromatography on silica gel (ethyl acetate : hexanes, 2 : 5) to afford **24** (13.2 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.20(m, 10 H), 5.12 (d, J = 11.6 Hz, 1H), 5.03 (br s, 1 H), 4.97 (d, J = 12.2 Hz, 1H), 4.48 (ddd, J = 2.4, 6.7, 7.9 Hz, 1 H), 4.38 (t, J = 8.6 Hz, 1H), 4.16 (dd, J = 1.8, 8.6 Hz, 1 H), 4.06 (br q, J = 7.6 Hz, 1H), 3.98-3.89 (m, 2H), 2.92 (d, J = 7.6 Hz, 2H), 2.32-2.26 (m, 1H), 2.24-2.16 (m, 1H), 1.35 (d, J = 6.4 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHZ, $CDC1_3$) δ 175.8, 156.7, 154.0, 137.8, 136.4, 129.1, 128.5, 128.0, 126.5, 73.4, 66.9, 63.9, 58.5, 53.7, 40.9, 38.8, 29.7, 29.1, 17.9, 15.2, 15.0 ppm; HR-ESIMS m/z: calculated for $C_{26}H_{33}N_2O_6^+$ $[M+H]^+$: 469.2333, found 469.2336.



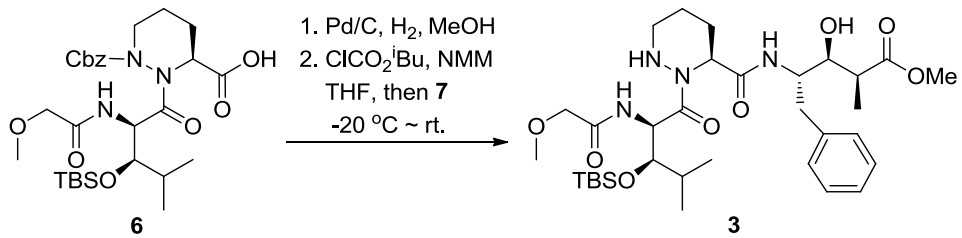
To a cold (0 °C) solution of **24** (4.2 g, 9.0 mmol) in THF-H_2O (50 mL, 3:1) was added H_2O_2 (9 mL, 30% solution in water) and LiOH-H_2O (0.8 g, 18.6 mmol). The reaction mixture was stirred at 0 °C for 2 h, and quenched by the addition of Na_2SO_3 (50 mL, 1.5 N in water). The solution was adjusted to pH 9-10 with saturated aqueous solution of $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 75 mL). The organic layers were discarded, while the aqueous phase was then acidified to pH 1 with dilute HCl (1.0 N) and

extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed by water (50 mL), brine (50 mL), dried over sodium sulfate (anhydrous) and concentrated in *vacuo* to yield the corresponding carboxylic acid **24'**. The crude acid **24'** was subsequently dissolved in DMF (20 mL) at 0 ^{o}C, after $NaHCO_3$ (7.6 g, 90.0 mmol) and MeI (2.8 mL, 45.0 mmol) were added, the reaction mixture was allowed to stir at room temperature for 16 h. The reaction was then diluted with ethyl acetate (300 mL) and washed by water (50 mL), saturated aqueous solution of NH_4Cl (50 mL) and brine (50 mL). The organic phase was dried over sodium sulfate (anhydrous) and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate : hexanes, 2 : 5) to afford **24''** (2.6 g, 79% over two steps). $[\alpha]_D^{25}$ – 19.5 (*c* 0.9, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.21 (m, 10H), 5.09 (s, 2H), 5.06 (s, 1H), 3.95-3.88 (m, 1H), 3.82-3.81 (m, 1H), 3.64 (s, 3H), 3.09 (d, *J* = 6.0 Hz, 1H), 3.01-2.89 (m, 2H), 2.70-2.59 (m, 1H), 1.22 (d, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDC1_3$) δ 175.8, 156.4, 137.9, 136.5, 129.3, 128.5 (2C), 128.1, 128.0, 126.5, 72.2, 66.8, 54.6, 51.9, 42.9, 38.9, 13.0 ppm; HR-ESIMS m/z: calculated for $C_{21}H_{26}NO_5^+$ $[M+H]^+$: 372.1805, found 372.1816.



24" **7**

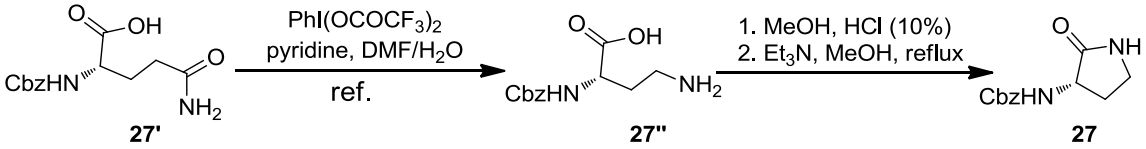
Compound **24''** (2.6 g, 7.1 mmol) was dissolved in methanol-HCl (1.0 N) (60 mL, 7 : 1), after palladium-carbon (10%, 500 mg) was added under a nitrogen atmosphere. The vessel was sealed and the atmosphere was changed to hydrogen and the resulting mixture was stirred at room temperature for 14 h. Palladium-carbon was removed by filtration and washed with methanol. The filtrate was concentrated in *vacuo* to give **7** (2.0 g, 99%) as a white solid. $[\alpha]_D^{25}$ – 13.8 (*c* 0.4, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 7.41-7.29 (m, 5H), 3.75-3.80 (m, 1H), 3.63 (s, 3H), 3.48-3.43 (m, 1H), 3.07-2.99 (m, 2H), 2.82-2.67 (m, 1H), 1.17 (d, *J* = 6.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, MeOD) δ 174.8, 135.6, 129.2, 129.0, 128.6, 128.1, 127.1, 68.9, 54.6, 51.1, 42.7, 36.2, 11.7 ppm.



6 **3**

Carboxylic acid **6** (0.2 g, 0.3 mmol) was dissolved in methanol (15 mL), after palladium-carbon (50 mg,

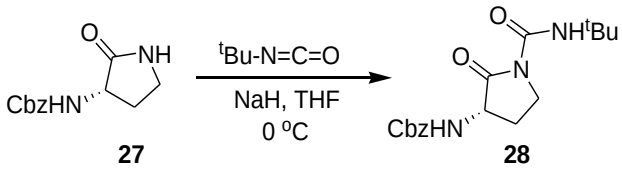
10% on carbon) was added, the reaction vessel was sealed and changed to hydrogen atmosphere. The resulting mixture was stirred at room temperature for 2 h. Palladium-carbon was removed by filtration, the filtrate was concentrated in *vacuo* to give the corresponding amine (**26**) as an oil in quantitative yield. This amine (**26**) was dissolved in THF (20 mL) at -20 ^{o}C, *N*-methylmorpholine (0.37 mL, 3.3 mmol) and isobutylchloroformate (0.05 mL, 0.4 mmol) were dropwise added sequentially. The reaction mixture was stirred at -20 ^{o}C for 1h, then a solution of compound **7** (0.2 g, 0.7 mmol) and *N*-methylmorpholine (0.1 mL, 1.0 mmol) in THF (10 mL) was dropwise added. The reaction mixture was stirred at -20 ^{o}C for 2 h and then allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of aqueous solution of NH_4Cl (50 mL). Volatiles were removed in *vacuo* and the aqueous residue was extracted by ethyl acetate (3 × 100 mL). The combined organic layers were washed by aqueous solution of $KHSO_4$ (50 mL, 1.0 M), saturated aqueous solution of $NaHCO_3$ (50 mL) and brine (50 mL), dried over sodium sulfate (anhydrous) and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (MeOH : CH_2Cl_2, 1 : 40) to afford **3** (0.16 g, 71% over two steps) as an oil. $[\alpha]_D^{25}$ – 25.0 (*c* 0.2, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.19 (m, 5H), 5.22-5.20 (m, 1H), 5.06 (d, *J* = 4.4 Hz, 1H), 4.68-4.61 (m, 1H), 4.17 -4.10 (m, 1H), 3.96-3.82 (m, 3H), 3.68 (s, 3H), 3.47(s, 3H), 3.15-3.04 (m, 2H), 2.65-2.59 (m, 2H), 2.54-2.40 (m, 3H), 1.84-1.76 (m, 1H), 1.65 (br, 2H), 1.51-1.42 (m, 2H), 1.27 (d, *J* = 2.0 Hz, 3H), 1.03 (d, *J* = 6.4 Hz, 3H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.96 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDC1_3$) δ 175.6, 171.1, 170.2, 168.3, 139.0, 129.3, 128.6, 128.5, 126.5, 74.6, 72.9, 71.3, 59.4, 54.7, 52.2, 51.9, 51.7, 47.8, 43.5, 37.8, 31.7, 29.7, 25.9, 25.8, 23.1, 21.3, 21.0, 18.2, 16.3, -4.6, -5.1 ppm; HR-ESIMS m/z: calculated for $C_{33}H_{56}N_4NaO_8Si^+$ $[M+Na]^+$: 687.3760, found 687.3767.



Compound **27''**[3] (2.0 g, 7.9 mmol) was dissolved in anhydrous methanol-HCl (50 mL, 10% in weight). The solution was stirred for 16 h at room temperature and then concentrated in *vacuo* to afford the corresponding methyl ester as a highly hydroscopic colorless solid (1.8 g, 75%). The methyl ester (1.8 g, 5.9 mmol) was re-dissolved in methanol (50 mL). After triethylamine (10 mL) was added, the reaction mixture was refluxed for 16 h. All volatiles were removed in *vacuo*, and the residue was purified by silica gel flash chromatography (ethyl acetate, 100%) to give the desired product **27** (1.1 g, 78%) as an

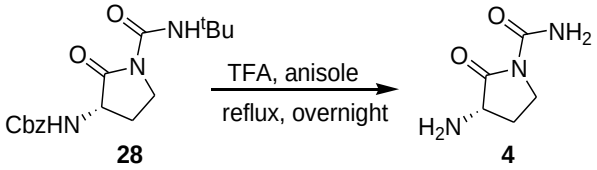
[3] P. de Macedo, C. Marrano, J.W. Keillor, *Bioorg. Med. Chem.*, 2002**, 10**, 355–360.

oil. $[\alpha]_D^{25}$ – 16.7 (*c* 0.9, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.35 (m, 5H), 6.10 (br, 1H), 5.42 (s, 1H), 5.14 (s, 2H), 4.29-4.21 (m, 1H), 3.40-3.35 (m, 2H), 2.74 (br,1H), 2.08-1.94 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDC1_3$) δ 175.5, 156.5, 136.2, 128.5, 128.2, 128.1, 67.0, 51.9, 39.0, 29.9 ppm; HR-ESIMS m/z: calculated for $C_{12}H_{15}N_2O_3^+$ $[M+H]^+$: 235.1077, found 235.1087.



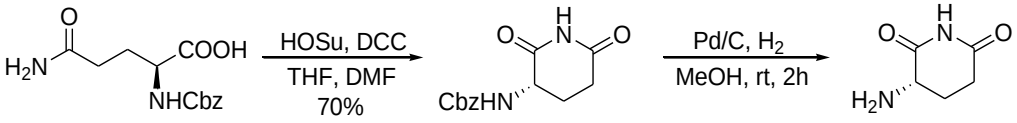
27 **28**

NaH (0.4 g, 10.0 mmol, 60% disperse in mineral oil) was added to a solution of **27** (1.0 g, 4.3 mmol) in THF (50 mL) at 0 °C. 30 min later, *tert*-butylisocyanate (0.6 mL) was added dropwise. The solution was stirred at 0 °C for 2 h, then quenched by addition of saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate (anhydrous) and concentrated in *vacuo*. The residue was purified by chromatography on silica gel (ethyl acetate : hexanes, 1 : 2) to give the desired **28** (0.9 g, 60%). $[\alpha]_D^{25}$ – 4.3 (*c* 0.5, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.36-7.35 (m, 5H), 5.31 (s, 1H), 5.14 (s, 2H), 4.45 (br, 1H), 3.99-3.92 (m, 1H), 3.54-3.51 (m, 1H), 2.59-2.54 (m, 1H), 1.94-1.85 (m, 1H), 1.38 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDC1_3$) δ 174.0, 156.2, 150.8, 136.2, 128.7, 128.3, 67.5, 54.7, 51.2, 41.7, 29.0, 26.3 ppm; HR-ESIMS m/z: calculated for $C_{17}H_{24}N_3O_4^+$ $[M+H]^+$: 334.1761, found 334.1760.



28 **4**

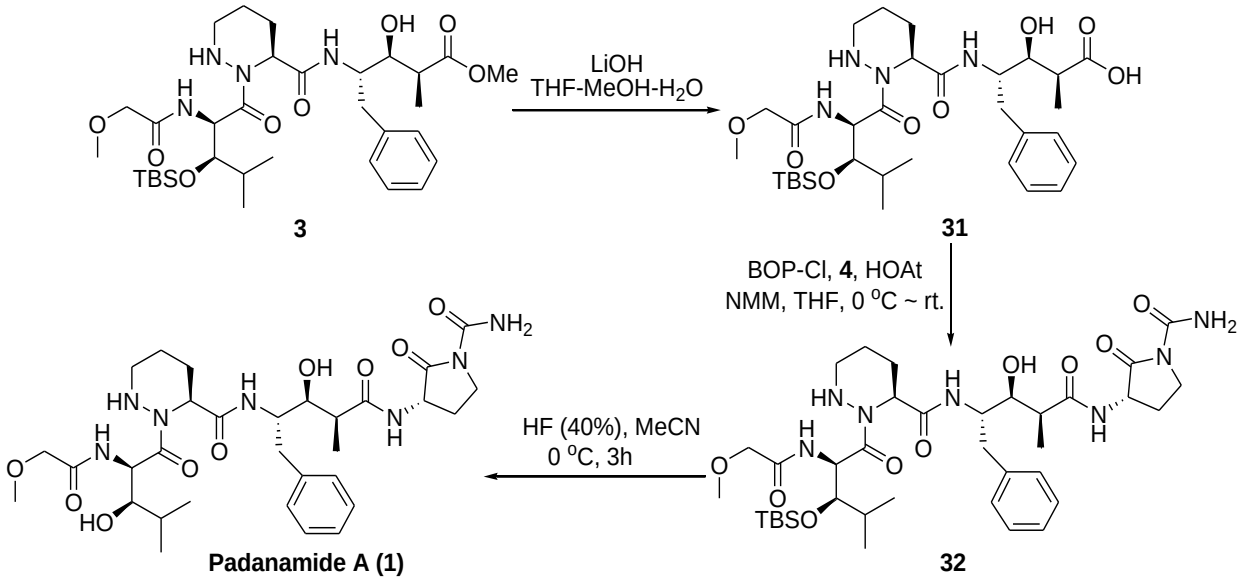
TFA (10 mL) and anisole (1 mL) were added to compound **28** (0.8 g, 3.4 mmol), the reaction mixture was refluxed for 16 h. The reaction mixture was concentrated in *vacuo*, the residue was purified by chromatography on silica gel (MeOH-CH_2Cl_2, 1 : 9) to give the desired compound **4** (0.4 g, 80%) as an oil. $[\alpha]_D^{25}$ – 10.8 (*c* 1.0, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (brs, 1H), 5.24 (brs, 1H), 4.01-3.95 (m, 1H), 3.76-3.54 (m, 2H), 2.52-2.37 (m, 1H), 1.89-1.80 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDC1_3$) (exists as rotamers) δ 177.9, 176.3, 152.9, 61.9, 54.8, 41.9, 41.5. 34.0, 29.7, 27.8, 25.2 ppm; HR-ESIMS m/z: calculated for $C_5H_{10}N_3O_2^+$ $[M+H]^+$: 144.0768, found 144.0772.



29 **30** **5**

Cbz-*L*-Glutamine **29** (10.0 g, 35.0 mmol) and *N*-hydroxysuccinimide (4.2 g, 35.0 mmol) were dissolved in THF-DMF (30 mL, 5:1). The solution was cooled to -78 ^{o}C, then DCC (7.5 g, 35.0 mmol) was added in one portion. The reaction mixture was allowed to gradually warm to room temperature and stirred overnight. The precipitate was removed by filtration, and the filtrate was concentrated in *vacuo*. The residue was taken up in $CHCl_3$ (50 mL) and heated to reflux for 3 h. After being cooled to room temperature, volatiles were removed in *vacuo*. The residue was dissolved in ethyl acetate (300 mL) and washed by H_2O (100 mL) and brine (100 mL). The organic phase was dried over sodium sulfate (anhydrous), filtered, and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate-hexanes, 1 : 1) to afford the desired product **30** (6.4 g, 70%) as an oil. $[\alpha]_D^{25}$ – 64.5 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (brs, 1H), 7.39-7.35 (m, 5H), 5.70 (d, *J* = 4.8 Hz, 1H), 5.16 (s, 2H), 4.41-4.37 (m, 1H), 2.84-2.64 (m, 2H), 2.56-2.53 (m, 1H), 1.96-1.85 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDC1_3$) δ 171.4, 171.2, 156.1, 135.9, 128.6, 128.3, 128.2, 67.3, 52.2, 31.2, 25.3 ppm; HR-ESIMS m/z: calculated for $C_{13}H_{14}N_2NaO_4^+$ $[M+Na]^+$: 285.0846, found 285.0844.

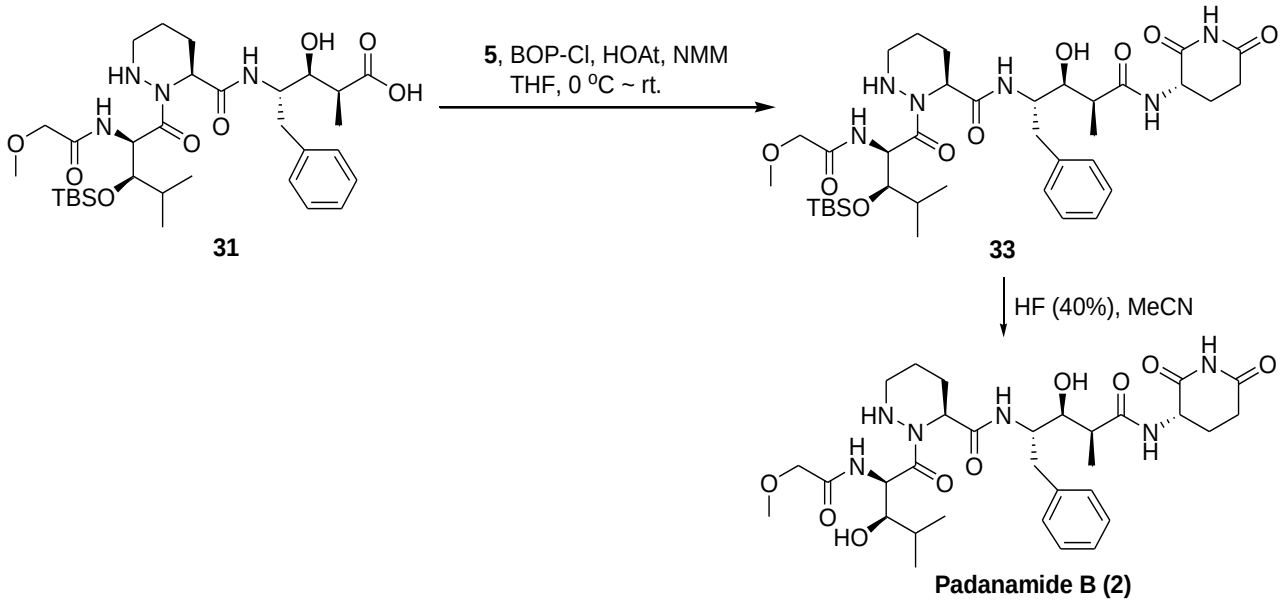
Palladium-carbon (200 mg, 10% on carbon) was added to a solution of **30** (5.0 g, 19.0 mmol) in methanol (50 mL). The reaction vessel was sealed and changed to hydrogen atmosphere, and stirred at room temperature for 4 h. Palladium-carbon was removed by filtration, the filtrate was concentrated in *vacuo* to give **5** (2.3 g, 95%) as a white solid, which was not further purified and used directly in next step of coupling reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (br, 1H), 3.58 (dd, *J* = 4.8, 12.0 Hz, 1H), 2.86-2.79 (m, 1H), 2.70-2.61 (m, 1H), 2.32-2.26 (m, 1H), 1.93-1.82 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDC1_3$) δ 174.9, 172.0, 52.0, 31.3, 26.9 ppm; HR-ESIMS m/z: calculated for $C_5H_9N_2O_2^+$ $[M+H]^+$: 129.0659, found 129.0647.



$LiOH{\cdot}H_2O$ (63 mg, 1.5 mmol) was added to a solution of compound **3** (0.1 g, 0.2 mmol) in THF-MeOH-H_2O (10 mL, 1 : 1 : 1) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, then allowed to warm to room temperature within 3 h. Volatiles were removed in *vacuo*, and the aqueous solution was diluted with ether (50 mL) and adjusted to pH 2 by dropwise addition of $KHSO_4$ (1.0 M in water). Layers were separated, the aqueous phase was extracted with ethyl acetate (2 × 200 mL). The combined organic phases were washed by brine (2 × 50 mL), dried over sodium sulfate (anhydrous) and concentrated in *vacuo* to give the acid **31** as an oil. Acid **31**, BOP-Cl (0.4 g, 1.5 mmol) and HOAt (0.2 g, 1.5 mmol) were dissolved in THF (20 mL) at 0 °C. After *N*-methylmorpholine (0.3 mL, 3.0 mmol) and amine **4** (0.1 g, 0.8 mmol) in THF (10 mL) were added sequentially, the reaction mixture was stirred at 0 °C for 2 h and then allowed to warm to room temperature and stirred overnight. Volatiles were removed in *vacuo* and the residue was dissolved in ethyl acetate (200 mL) and washed successively with $KHSO_4$ (1.0 M in water, 50 mL), saturated aqueous solution of $NaHCO_3$ (50 mL) and brine (50 mL). The organic phase was then dried over sodium sulfate (anhydrous) and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (MeOH : CH_2Cl_2, 1 : 20) to afford **32** (0.06 g, 50% over two steps) as an oil. $[\alpha]_D^{25}$ – 32.0 (*c* 0.2, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.25 (m, 5H), 5.33 (m, 1H), 5.22 (s, 1H), 4.96 (m, 1H), 4.87 (d, *J* = 4.0 Hz, 1H), 4.45 (s, 1H), 4.02 (d, *J* = 9.0 Hz, 1H), 3.93-3.88 (m, 3H), 3.74 (d, *J* = 9.5 Hz, 1H), 3.63-3.61 (m, 1H), 3.46 (s, 3H), 3.19 (t, *J* = 11.5 Hz, 1H), 3.08 (m, 1H), 2.80 (m, 1H), 2.61-2.45 (m, 2H), 2.25-2.02 (m, 8H), 1.78 (d, J = 2.5 Hz, 1H), 1.39-1.28 (m, 10H), 1.00 (d, *J* = 6.5 Hz, 1H), 0.97 (d, *J* = 6.5 Hz, 1H), 0.94 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDC1_3$) δ 175.6,

175.5, 171.5, 170.4, 152.8, 139.0, 129.4, 128.5, 126.4, 77.2, 75.4, 73.8, 71.5, 59.4, 54.5, 53.9, 52.1, 51.5, 47.4, 45.7, 41.8, 37.0, 31.6, 29.3, 27.2, 25.8, 25.0, 23.7, 20.8, 20.7, 18.2, 16.4, 14.7, -4.7, -5.0 ppm; HR-ESIMS m/z: calculated for $C_{37}H_{62}N_7O_9Si^+$ $[M+H]^+$: 776.4373, found 776.4366.

Aqueous HF (0.25 mL, 40% w/w) was added to a solution of compound **32** (15 mg, 0.02 mmol) in MeCN (5 mL) in a Teflon tube at 0 °C. The resulting solution was stirred at this temperature for 3 h before it was diluted with ethyl acetate (100 mL) and washed by saturated aqueous solution of $NaHCO_3$ (50 mL) and brine (50 mL). The organic phase was dried over sodium sulfate (anhydrous) and concentrated in *vacuo*. The residue was purified by silica gel flash chromatography (MeOH-CH_2Cl_2, 1 : 20) to provide padanamide A **1** (8.8 mg, 70%) as an oil. $[\alpha]_D^{25}$ – 11.4 (c 0.2, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.18 (d, J = 8.0 Hz, 1H), 7.75 (br, 1H), 7.59 (d, J = 9.0 Hz, 1H), 7.43 (br, 1H), 7.25-7.16 (m, 1H), 5.52 (t, J = 9.0 Hz, 1H), 5.08 (d, J = 6.7 Hz, 1H), 4.97 (dd, J = 5.4, 2.0 Hz, 1H), 4.80 (d, J = 6.0 Hz, 1H), 4.53 (dd, J = 8.4, 6.0 Hz, 1H), 4.39 (m, 1H), 4.14 (bq, J = 9.0 Hz, 1H), 3.82 (d, J = 15.0 Hz, 2H), 3.72 (t, J = 9.6 Hz, 1H), 3.45 (m, 3H), 3.30 (s, 3H), 2.80 (m, 3H), 2.25 (m, 1H), 2.14 (m, 1H), 2.08 (bd, J = 11.5 Hz, 1H), 1.95 (m, 2H), 1.65 (br, 2H), 1.35 (m, 2H), 1.05 (d, J = 6.5 Hz, 1H), 0.89 (d, J = 6.5 Hz, 1H), 0.84 (d, J = 6.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 175.0, 174.7, 172.8, 170.8, 168.9, 153.2, 139.5, 129.6, 128.6, 126.4, 75.7, 72.3, 71.7, 59.1, 53.2, 52.7, 51.5, 50.6, 46.5, 43.6, 42.0, 38.2, 29.8, 26.1, 23.9, 21.2, 20.6, 16.1, 15.3 ppm; HR-ESIMS m/z: calculated for $C_{31}H_{47}N_7NaO_9^+$ $[M+Na]^+$: 684.3327, found 684.3342.



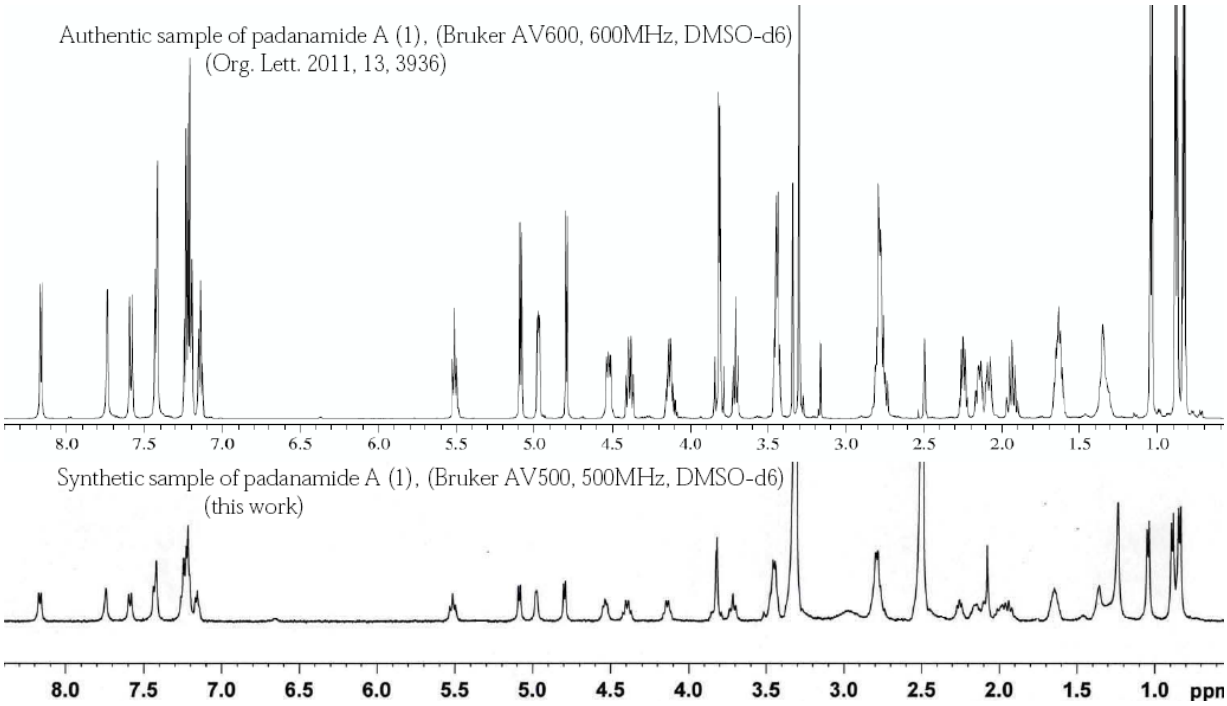
31 **33** **Padanamide B (2)**

Acid **31** (prepared as shown above) BOP-Cl (0.4 g, 1.5 mmol) and HOAt (0.2 g, 1.5 mmol) were dissolved in THF (20 mL) at 0 °C. After *N*-methylmorpholine (0.3 mL, 3 mmol) and amine **5** (0.1 g,

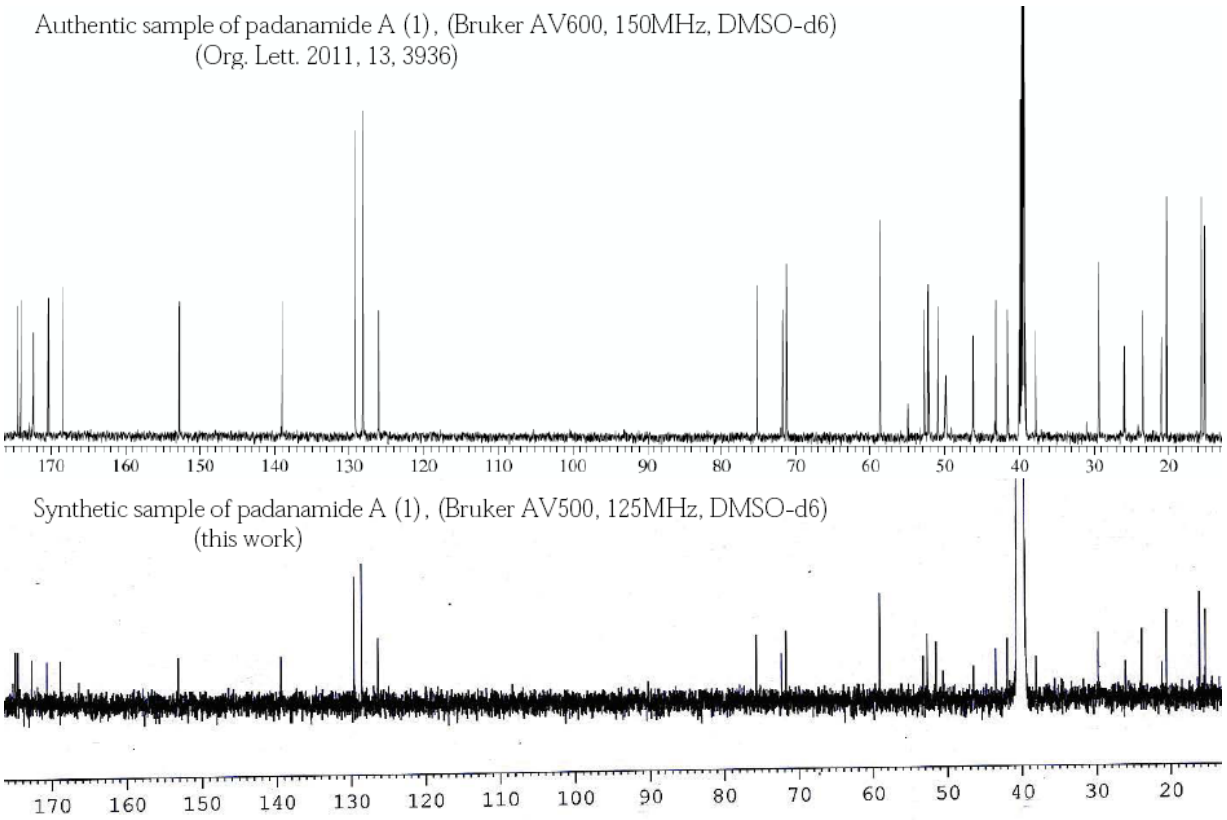
0.75 mmol) in THF (10 mL) were added sequentially, the reaction mixture was stirred at 0 ^{o}C for 2 h and then allowed to warm to room temperature and stirred overnight. Volatiles were removed in *vacuo*, the residue was dissolved in ethyl acetate (200 mL) and washed successively with $KHSO_4$ (50 mL, 1.0 M), saturated aqueous solution of $NaHCO_3$ (50 mL) and brine (50 mL). The organic phase was then dried over sodium sulfate (anhydrous) and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1 : 30) to afford **33** (0.06 g, 54% over two steps) as an oil. $[\alpha]_D^{25}$ – 14.0 (*c* 0.2, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.74-7.66 (m, 1H), 7.63-7.55 (m, 1H), 7.28-1.24 (m, 2H), 7.23-7.21 (m, 1H), 5.38-5.35 (m, 2H), 5.32-5.29 (m, 2H), 4.88-4.80 (m, 2H), 4.47 (br, 1H), 4.25-4.22 (m, 1H), 3.92-3.86 (m, 3H), 3.75-3.67 (m, 1H), 3.45 (s, 3H), 3.25-3.17 (m, 1H), 3.10-3.03 (m, 1H), 2.79-2.68 (m, 2H), 2.66-2.48 (m, 2H), 2.42-2.21 (m, 3H), 2.15-2.00 (m, 3H), 1.69-1.63 (m, 2H), 1.32-1.27 (m, 2H), 1.00-0.84 (m, 18H), 0.10 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDC1_3$) δ 175.7, 172.2, 171.6, 171.4, 170.3, 139.0, 129.9, 129.4, 128.5, 126.4, 77.2, 75.4, 73.7, 71.6, 59.4, 54.5, 54.2, 51.4, 49.5, 47.5, 45.9, 38.7, 36.8, 35.9, 33.7, 27.2, 24.5, 20.9, 18.2, 16.4, 14.9, 11.0, -4.6, -5.0 ppm; HR-ESIMS m/z: calculated for $C_{37}H_{60}N_6NaO_9Si^+$ $[M+Na]^+$: 783.4083, found 783.4077.

Aqueous HF (0.25 mL, 40% w/w) was added to a solution of compound **33** (20 mg, 0.03 mmol) in MeCN (5 mL) in a Teflon tube at 0 °C. The resulting solution was stirred at this temperature for 3 h before it was diluted with ethyl acetate (200 mL) and washed by saturated aqueous solution of $NaHCO_3$ (100 mL) and brine (50 mL). The organic phase was dried over sodium sulfate (anhydrous) and concentrated in *vacuo*. The residue was purified by silica gel flash chromatography (MeOH-CH_2Cl_2, 1 : 20) to provide padanamide B **2** (12 mg, 75%) as an oil. $[\alpha]_D^{25}$ – 20.7 (*c* 0.2, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.86 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.41(d, *J* = 9.0 Hz, 1H), 7.24 (m, 4H), 7.16 (s, 1H), 5.51 (t, *J* = 9.0 Hz, 1H), 5.13 (d, *J* = 6.5 Hz, 1H), 4.95 (dd, *J* = 5.6, 2.1 Hz, 1H), 4.79 (d, *J* = 6.0 Hz, 1H), 4.52 (t, *J* = 7.4 Hz, 1H), 4.47 (ddd, 1H), 4.21 (m, 1H), 3.82 (d, *J* = 14.9 Hz, 1H), 3.81 (d, *J* = 14.9 Hz, 1H), 3.50 (ddd, *J* = 8.9, 6.5, 1.7 Hz, 1H), 3.42 (m, 1H), 3.30 (s, 3H), 2.84-2.73 (m, 5H), 2.29 (m, 1H), 2.08-1.92 (m, 4H), 1.63 (s, 2H), 1.36 (m, 2H), 1.06 (d, *J* = 6.5 Hz, 1H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.1, 172.9, 172.7, 172.3, 170.3, 168.4, 139.1, 129.1, 128.1, 125.9, 75.1, 72.0, 71.2, 58.5, 53.2, 50.9, 49.9, 49.0, 46.0, 43.2, 37.0, 30.9, 29.2, 25.6, 24.0, 20.8, 20.1, 25.6, 24.0, 20.8, 20.1, 15.5, 14.9 ppm; HR-ESIMS m/z: calculated for $C_{31}H_{46}N_6NaO_9^+$ $[M+Na]^+$: 669.3218, found 669.3217.

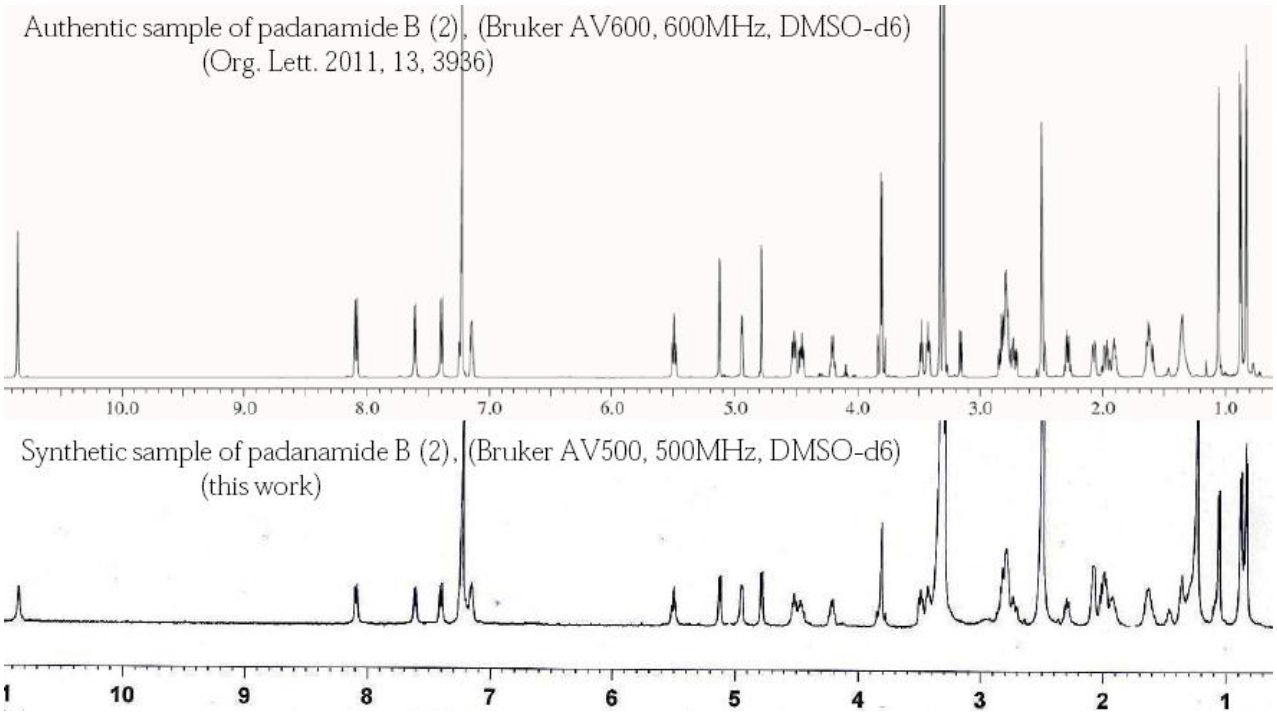
^{1}H NMR of Padanamide A (1)



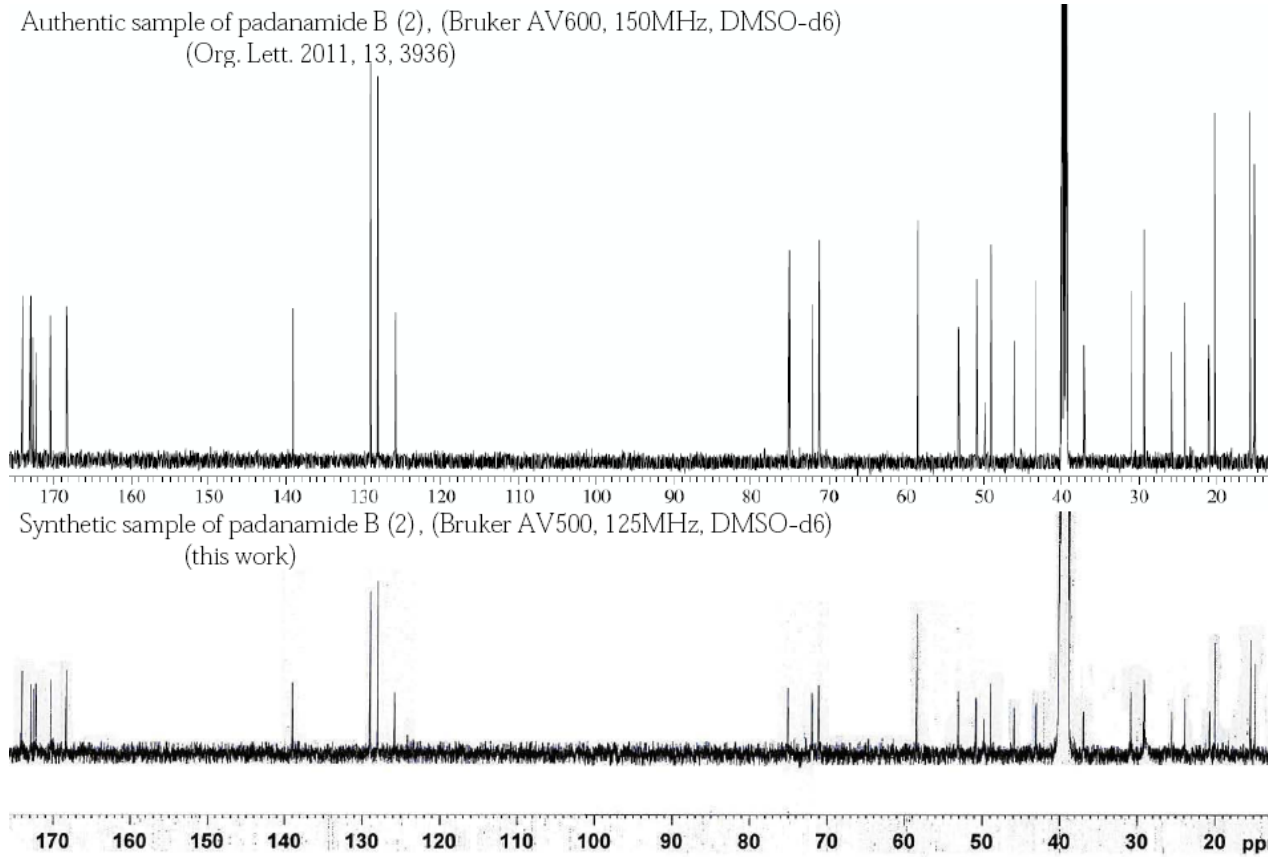
^{13}C NMR of Padanamide A (1)



^{1}H NMR of Padanamide B (2)



^{13}C NMR of Padanamide B (2)



		Padanamide A*					Padanamide B		
Residue	Position	δ_1	$\Delta\delta = \delta_2-\delta_1$	δ_2	$\Delta\delta = \delta_2-\delta_3$	δ_3	δ_4	$\Delta\delta = \delta_5-\delta_4$	δ_5
Hleu	1	172.3	0.0	172.8	-0.1	173	172.3	0	172.3
	2	49.8	0.3	50.6	0.3	50.4	49.7	0.2	49.9
	3	75.1	0.0	75.7	0.1	75.7	75.1	0	75.1
	4	29.2	0.1	29.8	0.1	29.8	29.1	0.1	29.2
	Me (5)	20.1	0.0	20.6	-0.1	20.8	20.1	0	20.1
	Me (6)	15.5	0.1	16.1	0.1	16.1	15.5	0	15.5
Pip	1	170.4	-0.1	170.8	-0.1	171	170.4	-0.1	170.3
	2	50.9	0.1	51.5	0.1	51.5	50.8	0.1	50.9
	3	25.8	-0.2	26.1	-0.3	26.5	25.7	-0.1	25.6
	4	20.8	-0.1	21.2	-0.1	21.4	20.8	0	20.8
	5	46.0	0.0	46.5	-0.1	46.7	46	0	46
Ahmpp	1	174.1	0.1	174.7	0.0	174.8	174	0.1	174.1
	2	43.0	0.1	43.6	0.0	43.7	43.2	0	43.2
	3	71.7	0.1	72.3	0.0	72.4	72	0	72
	4	52.7	0.0	53.2	0.0	53.3	53.2	0	53.2
	5	37.7	0.0	38.2	-0.0	38.3	37	0	37
	6	139.0	0.0	139.5	-0.3	139.9	139.1	0	139.1
	7,11	129.1	0.0	129.6	-0.1	129.8	129.1	0	129.1
	8,10	128.1	0.0	128.6	-0.1	128.8	128.1	0	128.1
	9	125.9	0.0	126.4	-0.1	126.6	125.9	0	125.9
	2-Me	15.0	-0.2	15.3	-0.3	15.7	15	-0.1	14.9
Apoc/Apd	2	174.5	0.0	175.0	-0.1	175.2	172.7	0	172.7
	3	52.2	0.0	52.7	0.0	52.8	49	0	49
	4	23.3	0.1	23.9	0.1	23.9	24	0	24
	5	41.5	0.0	42.0	0.0	42.1	30.9	0	30.9
	6	152.7	0.0	153.2	-0.1	153.4	173	-0.1	172.9
Maa	1	168.4	0.0	168.9	0.0	169	168.3	0.1	168.4
	2	71.2	0.0	71.7	0.0	71.8	71.1	0.1	71.2
	2-OMe	58.5	0.1	59.1	0.0	59.2	58.5	0	58.5

Notes:

δ_1: ^{13}C value of padanamide A from D. E. Williams, D. S. Dalisay, B. O. Patrick, T. Matainaho, K. Andrusiak, R. Deshpande, C. L. Myers, J. S. Piotrowski, C. Boone, M. Yoshida, R. J. Andersen, *Org. Lett.* 2011, **13**, 3936–9.

δ_2: ^{13}C value of padanamide A for synthetic sample.

δ_3: ^{13}C value of padanamide A from S. J. Nam, C. A. Kauffman, P. R. Jensen, W. Fenical, *Tetrahedron*, 2011, **67**, 6707-12.

δ_4: ^{13}C value of padanamide B from D. E. Williams, D. S. Dalisay, B. O. Patrick, T. Matainaho, K. Andrusiak, R. Deshpande, C. L. Myers, J. S. Piotrowski, C. Boone, M. Yoshida, R. J. Andersen, *Org. Lett.* 2011, **13**, 3936–9.

δ_5: ^{13}C value of padanamide B for synthetic sample.

*: $\Delta\delta$ were corrected after elimination of systematic errors.

Biological evaluation:

Materials and Methods

Cell lines. All cancer cell lines were obtained from American Type Culture Collection (Manassas, VA, USA), and were cultured in DMEM containing supplements (10% FCS, penicillin/streptomycin, and L-glutamine) except Jurkat. Jurkat cells were cultured in RMPI medium containing 10% FCS, penicillin/streptomycin, and L-glutamine.

Effects of Padanamide A and B on cancer cell line proliferation. Cells were seeded into 96-well plates and incubated overnight. Padanamide A or Padanamide B were added in serial dilutions in the medium containing 1% FCS and the plates were incubated for another 72 hours. Cell proliferation was measured by 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay using CellTiter96 Aqueous solution (Promega Co., Madison, WI) according to the manufacturer's protocol. The absorbance at 490 nm was measured using an ELISA plate reader (Molecular Devices). Cell proliferation was expressed as percentage of control and IC_{50} were determined using Prism5 (GraphPad, CA, USA).

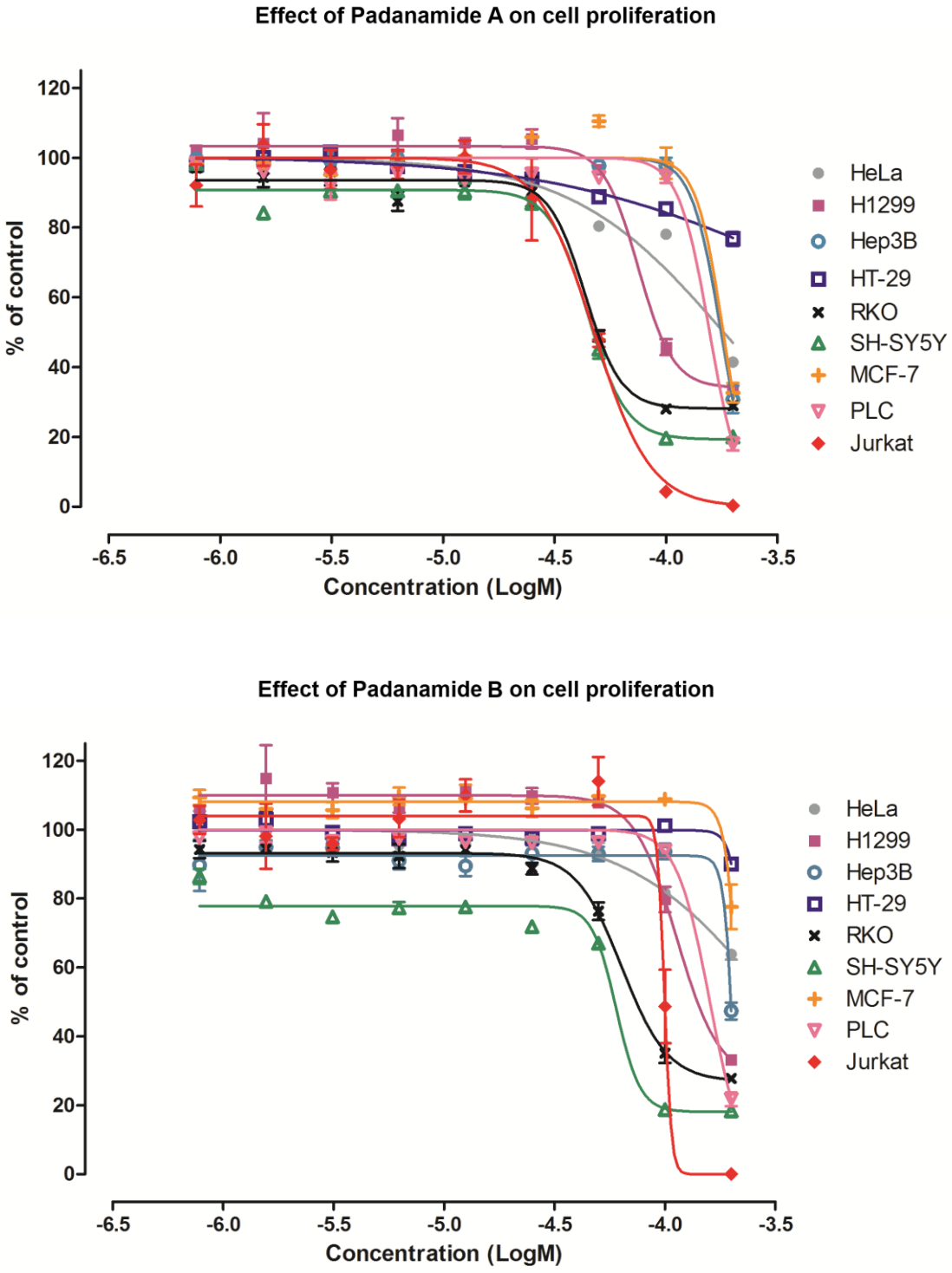


Figure: Effect of padanamides A (**1**) and B (**2**) on cell proliferation of various cancer cell lines. Each point represents the mean ± SE from six determinations.