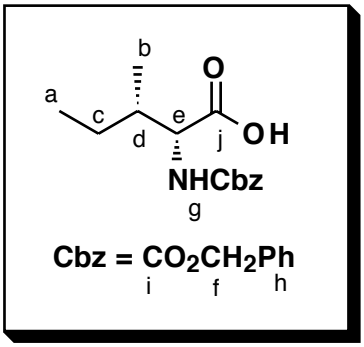
EXPERIMENTAL

General Procedure

All manipulations were conducted under an inert atmosphere (argon or nitrogen). All solvents were reagent grade (used in work–ups, columns and distillations) or HPLC grade (used as reaction solvent). Anhydrous diethyl ether and tetrahydrofuran (THF) were distilled from sodium and benzophenone. The boiling point range of the hexane used was 38.0–55 °C. Methylene chloride (CH_2Cl_2), benzene, toluene, and N,N–dimethyl formamide (DMF) were distilled from calcium hydride (CaH_2). Organic acids and bases are reagent grade. Triethylamine, diisopropylethylamine, morpholine and N–methylmorpholine were distilled from CaH_2. All other reagents were commercial compounds of the highest purity available. Analytical thin–layer chromatography (TLC) was performed on EM Separations Tech./Merck silica gel (60–F254) plates (0.25 mm) precoated with a fluorescent indicator. Visualization was effected using ultraviolet light (254 nm), phosphomolybdic acid (7% w/v) in 95% ethanol. Melting points (mp) were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected. Proton and carbon magnetic resonance spectra (^{1}H–, ^{13}C–NMR) were recorded on a Bruker AM–500 [500MHz] Fourier transform spectrometer, and chemical shifts were expressed in parts per million (ppm) relative to $CHCl_3$ as an internal reference (7.24 ppm for ^{1}H and 77.0 for ^{13}C). Multiplicities are designated as singlet (s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), triplet (t), quartet (q) multiplet (m), and broad singlet (s). Infrared spectra (IR) were obtained on a Perkin–Elmer Model 1600 FT–IR spectrophotometer. Absorptions are reported in wavenumber (cm^{-1}). Optical rotations (in degrees) were measured with a Perkin–Elmer Model 341 polarimeter. High resolution mass spectra (HRMS) were obtained on either a VG 70–70HS, or a Micromass AutoSpect. Elemental Analyses were performed on a Perkin–Elmer 2400 Series II CHNS/O Analyzer at the University of Pennsylvania. Flash column chromatography was carried out on E. Merck silica gel 60 (240–400 mesh) using the solvent systems listed under individual experiments.

Cbz–D–alloisoleucine (8). To a suspension of D–alloisoleucine (**7**) (1.56 g, 11.9 mmol) in 50 mL

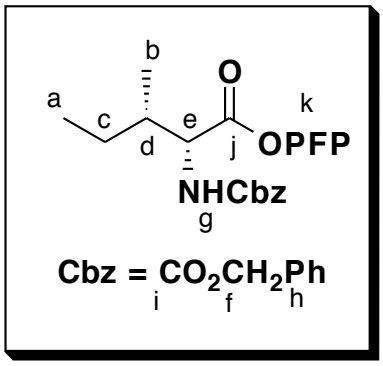
of freshly distilled CH_2Cl_2 at 0 °C, was added Et_3N (5.13 mL, 36.9 mmol) dropwise, followed by the addition of Cbz–succinimide (3.114 g, 12.5 mmol) and the reaction was stirred at 0 °C for 1h, then at rt overnight. The reaction mixure was concentrated, diluted with saturated $NaHCO_3$ solution (20 mL), and washed with ether (2X10 mL). The ether layers were extracted with saturated $NaHCO_3$ solution (10 mL). The combined aqueous layers were cooled to 0 °C, acidified to pH 2 with 1N $KHSO_4$ solution , and extracted with EtOAc (3X20 mL). The EtOAc layers were combined, washed with saturated NaCl solution (20 mL), dried (Na_2SO_4), filtered, and concentrated. Acid **8** (3.13 g, 99%) was obtained as a colorless oil and used directly in the next step without purification.



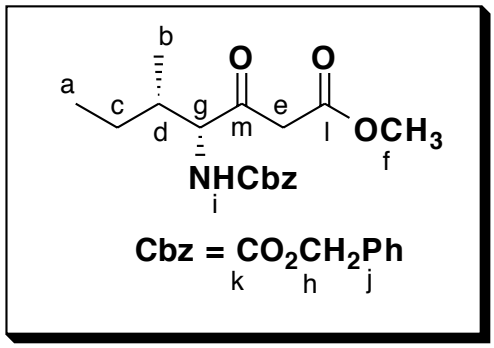
8 : R_f 0.08 (20:80–ethyl acetate:hexane); ^1H NMR (500 MHz, $CDCl_3$) δ **H_a)** 0.86–0.90 (m, 3H), **H_b)** 0.93–0.97 (m, 3H), **H_c)** 1.20–1.27 (m, 1H) and 1.42–1.47 (m, 1H), **H_d)** 1.98–2.09 (m, 1H), **H_e)** 4.47–4.50 (dd, J_1=9.1 Hz, J_2=3.4 Hz, 1H), **H_f)** 5.10 (s, 2H), **H_g)** 5.17–5.19 (d, J=9.1 Hz, 1H), **H_h)** 7.29–7.35 (m, 5H); ^{13}C NMR (500 MHz, $CDCl_3$) δ **C_a)** 11.69, **C_b)** 14.35, **C_c)** 26.20 **C_d)** 37.42, **C_e)** 56.9,6 **C_f)** 67.20, **C_h)** 128.14, 128.24, 128.55, and 135.06, **C_i)** 156.42, **C_j)** 177.41; IR ($CHCl_3$) 2470–3540, 3440, 2980, 2950, 2890, 1720, 1510, 1455, 1405, 1385, 1325–1355, 1230–1280, 1165, 1095, 1040, 1005, 910 cm^{-1}.

The crude Cbz–D–allo–isoleucine (**8**, 3.534 g, 13.3 mmol) was dissolved in anhydrous CH_2Cl_2 (50 mL) and cooled to 0 °C, followed by the sequential additions of PFPOH (2.574 g, 14.0 mmol), EDAC•HCl (3.064 g, 16.0 mmol) and DMAP (0.325 g, 2.7 mmol). The reaction mixture was stirred at 0 °C for half an hour, at rt for an additional 4 h and then diluted with CH_2Cl_2 (50 mL). The organic layer was washed sequentially with 10% HCl (25 mL), 5% $NaHCO_3$ (25 mL) and saturated NaCl (25 mL) solutions. The CH_2Cl_2 layer was dried (Na_2SO_4), filtered and concentrated. The resulting PFP ester **9** was obtained as a colorless oil (5.70 g) and

used directly in the next step. The oil was dissolved in anhydrous THF (25 mL), cooled to –78 °C, and treated with a solution of the lithium enolate of methyl acetate. The enolate was prepared by addition of methyl acetate (3.92 mL, 49.2 mmol) via syringe into a solution of LDA (49.2 mmol in 25 mL anhydrous THF) at –78 °C and the resulting solution was stirred for 1 h. The reaction mixture was stirred for 45 minutes more at the same temperature, and then carefully quenched with saturated aqueous NH_4Cl (50 mL) at –78 °C. After warming to room temperature, the THF was removed on a rotary evaporator and the resulting aqueous solution was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were then washed with 10% aqueous HCl (20 mL), 5% aqueous $NaHCO_3$ (20 mL) and saturated aqueous NaCl (20 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to afford a yellow oil which was purified by flash column chromatography by eluting with EtOAc:Hexane (10:95) to obtain β–keto ester **10** (3.42 g, 80% yield, 2 steps overall) as a colorless oil.



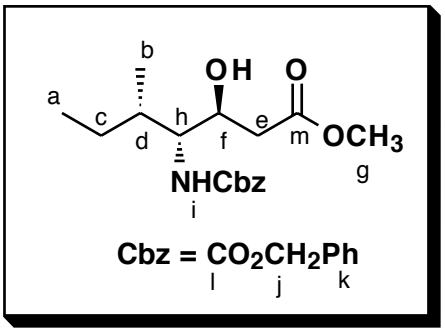
9 : R_f 0.52 (20:80–ethyl acetate:hexane); ^1H NMR (500 MHz, $CDCl_3$) δ **H_a, H_b)** 0.90–1.12 (m, 6H), **H_c)** 1.29–1.39 (m, 1H) and 1.45–1.52 (m, 1H), **H_d)** 2.05–2.15 (m, 1H), **H_e)** 4.79–4.84 (m, 1H), **H_f)** 5.10 (s, 2H), **H_g)** 5.12–5.14 (d, J=9.1 Hz, 1H), **H_h)** 7.29–7.37 (m, 5H); ^{13}C NMR (500 MHz, $CDCl_3$) δ **C_a)** 11.68, **C_b)** 14.25, **C_c)** 26.24 **C_d)** 37.64, **C_e)** 57.09 **C_f)** 67.45, **C_h)** 128.20, 128.35, 128.59, and 135.95, **C_k)** 136.9, 139.0, 140.0 and 142.0, **C_i)** 156.13, **C_j)** 168.87.



10 : R_f 0.42 (35:65–ethyl acetate:hexane); ^1H NMR (500 MHz, $CDCl_3$) δ **H_a)** 0.75–0.79 (m, 3H), **H_b)** 0.90–0.98 (m, 3H), **H_c)** 1.26–1.30 (m, 1H) and 1.42–1.46 (m, 1H), **H_d)** 1.97–1.99 (m, 1H), **H_e)** 3.53 (s, 2H), **H_f)** 3.72 (s, 3H), **H_g)** 4.56–4.58 (d,

J=7.6 Hz, 1H), **H_h)** 5.10 (s, 2H), **H_i)** 5.26–5.28 (d, J=6.4 Hz, 1H), **H_j)** 7.30–7.36 (m, 5H); ^{13}C NMR (500 MHz, $CDCl_3$) δ **C_a)** 11.83, **C_b)** 13.79, **C_c)** 26.83, **C_d)** 36.12, **C_e)** 46.56 **C_f)** 52.46, **C_g)** 63.00, **C_h)** 67.19, **C_j)** 128.10, 128.24, 128.56, and 136.16, **C_k)** 156.42, **C_l)** 166.96, **C_m)** 201.68; IR ($CHCl_3$) 3349.1, 2964.4, 1748.3, 1712.9, 1520.6, 1454.8, 1328.2, 1232.1 cm^{-1}; HRMS m/z calcd for $C_{17}H_{23}NO_5Na$ ($M+Na^+$): 344.1498, found 344.1490; $[\alpha]_D^{20}$ – 27.85 (c 0.53, $CHCl_3$); Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.52; H, 7.22, N, 4.36. Found: C, 63.32; H, 7.15, N, 4.24.

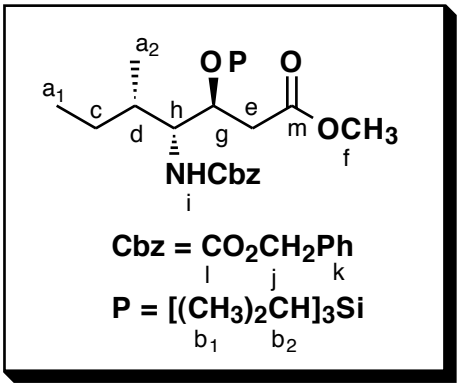
A solution of β–keto ester (**10**, 2.797 g, 8.7 mmol) in HPLC MeOH (30 mL) was cooled to –78 °C, followed by the addition of potassium borohydride (1.644 g, 30.5 mmol) in portions. The reaction mixture was stirred at –78 °C for 10 min, warmed to –20 °C for 30 min, and then to 0 °C for 10 min. The reaction mixure was quenched by the dropwise addition of glacial acetic acid until the aqueous layer was neutral to litmus (not < pH 6). The resulting solution was concentrated in vacuo, dissolved in EtOAc:H_2O (1:1, 50 mL) and separated. The organic phase was washed with saturated aqueous NaCl (10 mL), then dried (Na_2SO_4), filtered, and concentrated. The crude product was obtained as a colorless oil (2.786 g, 99% yield) (11:1 ratio of major : minor according to NMR integration data). Crystallization of the crude oil with ether/hexane afforded the pure major isomer (**11**) as white crystals.



11 : R_f 0.29 (35:65–ethyl acetate:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ **H_a)** 0.83–0.85 (m, 3H), **H_b)** 0.89–0.92 (m, 3H), **H_c)** 1.19–1.23 (m, 1H) and 1.32–1.34 (m, 1H), **H_d)** 1.91–1.93 (m, 1H), **H_e)** 2.45–2.51 (dd, J_1=16.7 Hz, J_2=9.1 Hz, 1H) and 2.58–2.62 (dd, J_1=16.7 Hz, J_2=2.7 Hz, 1H), **H_f)** 3.12–3.14 (d, J=4.5 Hz, 1H), **H_g)** 3.68 (s, 3H), **H_h)** 3.90–3.91 (m, 1H), **H_i)** 4.62–4.65 (d, J=10.0 Hz, 1H), **H_j)** 5.07–5.08 (d, J=5.1 Hz, 2H), **H_k)** 7.29–7.35 (m, 5H); ^{13}C NMR (500 MHz, $CDCl_3$) δ **C_a)** 12.10, **C_b)** 13.64, **C_c)** 27.52, **C_d)** 34.28, **C_e)** 38.74,

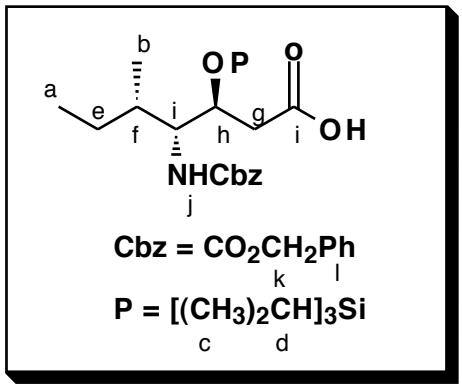
C_f) 52.25, **C_g)** 57.57, **C_h)** 67.39, **C_j)** 69.43, **C_k)** 128.50, 128.61, 128.97 and 136.82, **C_l)** 157.08, **C_m)** 174.09; IR ($CHCl_3$) 3421, 3316, 2951, 1709, 1537, 1443, 1229 cm^{-1}; HRMS m/z calcd for $C_{17}H_{25}NO_5Na$ ($M+Na^+$): 346.1630, found 346.1645; $[\alpha]_D^{20}$ – 10.9 (c 0,595, $CHCl_3$); Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.12; H, 7.80, N, 4.33. Found: C, 63.23; H, 7.85, N, 4.06.

The crude alcohol (0.8636 g, 2.67 mmol), dissolved in CH_2Cl_2 (10 mL) under argon, was cooled to 0 °C. To this solution was added 2,6–lutidine (0.778 mL, 6.68 mmol), followed by the dropwise addition of triisopropylsilyl triflate (i–Pr_3SiOTf, 1.08 mL, 4.01 mmol). The reaction mixture was stirred at 0 °C for 30 min and then at rt for 2 h, at which time it was diluted with CH_2Cl_2 (20 mL). The organic phase was washed with 10% aqueous HCl (15 mL), saturated aqueous $NaHCO_3$ (15 mL), and saturated aqueous NaCl (15 mL). The organic layer was then dried (Na_2SO_4), filtered, and concentrated. The resulting residue was purified by flash column chromatography eluting with ether:hexane (2:98 to 15:85) to obtain the major isomer (**12**) as a colorless oil (1.204 g, 94% yield).



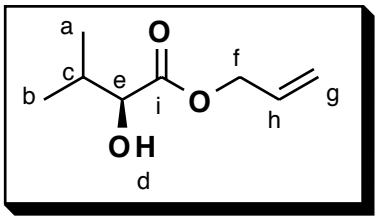
12: R_f 0.65 (35:65–ethyl acetate:hexane); ^1H NMR (500 MHz, $CDCl_3$) δ **H_a)** 0.84–0.91 (m, 6H), **H_b)** 0.99–1.05 (m, 21H), **H_c)** 1.12–1.34 (m, 2H), **H_d)** 1.81–1.84 (m, 1H), **H_e)** 2.54–2.62 (m, 2H), **H_f)** 3.54 (s, 3H), **H_g)** 3.73–3.75 (m, 1H), **H_h)** 4.34–4.36 (m, 1H), **H_i)** 4.69–4.71 (d, J=10.5 Hz, 1H), **H_j)** 5.01–5.04 (d, J=12.3 Hz, 1H) and 5.09–5.11 (d, J=12.3 Hz, 1H), **H_k)** 7.28–7.34 (m, 5H); ^{13}C NMR (500 MHz, $CDCl_3$) δ **C_{a1})** 12.50, **C_{b1})** 12.74, **C_{a2})** 13.97, **C_{b2})** 18.08, **C_c)** 27.44, **C_d)** 34.40, **C_e)** 40.45, **C_f)** 51.54, **C_g)** 58.62, **C_h)** 66.67, **C_j)** 70.49, **C_k)** 128.03, 128.08, 128.46 and 136.67, **C_l)** 156.51, **C_m)** 172.00; IR ($CHCl_3$) 3450, 3359, 2944, 2863, 1728, 1510, 1459, 1434, 1384, 1308, 1232, 1171, 1090 cm^{-1}; HRMS m/z calcd for $C_{26}H_{45}NSiO_5Na$ ($M+Na^+$): 480.3145, found 480.3128; $[\alpha]_D^{20}$ +15.88 (c 0.57, $CHCl_3$); Anal. Calcd for $C_{17}H_{25}NO_5$: C, 65.09; H, 9.46, N, 2.92. Found: C, 64.80; H, 9.41, N, 2.69.

A solution of methyl ester (**12**, 0.84 g, 1.753 mmol) in THF/MeOH (1:1, 20 mL) was cooled to 0 °C, followed by the addition of 1N NaOH solution (20 mL, 11 mmol). The reaction was stirred at 0 °C for 2 h, then at rt overnight. The reaction mixure was concentrated and diluted with H_2O (10 mL), cooled to 0 °C, acidified to pH 2 with 1N $KHSO_4$ solution, and extracted with EtOAc (3X10 mL). The EtOAc layers were combined, washed with saturated NaCl solution (10 mL), dried (Na_2SO_4), filtered and concentrated. Acid **13** (0.7709 g, 95%) was obtained as a white foam and used directly in the next step without purification.



13 : R_f 0.08 (35:65–ethyl acetate:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ **H_a, H_b)** 0.86–1.00 (m, 6H), **H_c)**, **H_d)** 1.06–1.08 (m, 21H), **H_e)** 1.19–1.24 (m, 1H) and 1.64–1.72 (m, 1H), **H_f)** 1.85–1.92 (m, 1H), **H_g)** 2.50–2.80 (m, 2H), **H_h)** 3.60–3.80 (m, 1H), **H_i)** 4.28–4.33 (m, 1H), **H_j)** 4.86–4.88 (d, J=10.4 Hz, 1H), **H_k)** 5.06–5.22 (m, 2H), **H_l)** 7.29–7.45 (m, 5H).

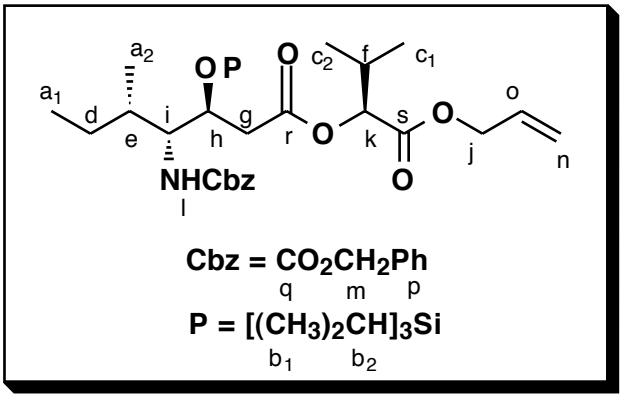
To the hydroxy valine[1] (**15**, 2.0 g, 16.93 mmol) dissolved in redistilled DMF (20 mL), was added anhydrous K_2CO_3 (2.46 g, 17.78 mmol) and phase transfer catalyst Bu_4NI (1.25 g, 3.4 mmol), followed by the dropwise addition of allyl bromide (5.86 mL, 67.72 mmol). The resulting solution was stirred at rt for 1 h and then concentrated in vacuo , diluted with H_2O (20 mL), and extracted with ether (3X20 mL). The combined organic layers were washed sequentially with 10% HCl (15 mL), 5% $NaHCO_3$ (15 mL) and saturated NaCl (10 mL) solutions, dried (Na_2SO_4), filtered and concentrated. The product (**16**) was obtained (2.53 g, 96%) as an orange oil which did not require purification.



16 : R_f 0.50 (25:75–ethyl acetate:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ **H_a)** 0.71–0.86 (d, J=6.8 Hz, 3H), **H_b)** 0.92–1.00 (d, J=7.0 Hz, 3H), **H_c)** 2.04–2.10 (m, 1H), **H_d)** 2.65–2.66 (d, J=6.1 Hz, 1H), **H_e)** 4.03–4.05 (dd,

J_1=5.9 Hz, J_2=3.5 Hz, 1H), **H_f)** 4.62–4.70 (m, 2H), **H_g)** 5.24–5.27 (dd, J_1=10.4 Hz, J_2=1.1 Hz, 1H) and 5.31–5.35 (dd, J_1=17.2 Hz, J_2=3.5 Hz, 1H), **H_h)** 5.86–5.94 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ **C_a)** 15.93, **C_b)** 18.76, **C_c)** 32.17, **C_e)** 66.04, **C_f)** 75.03, **C_g)** 119.12, **C_h)** 131.48, **C_i)** 174.62; IR ($CHCl_3$) 3521–3458, 2964, 2880, 1735, 1646, 1462, 1367, 1257, 1204, 1136, 1073, 1026, 983, 931 cm^{-1}.

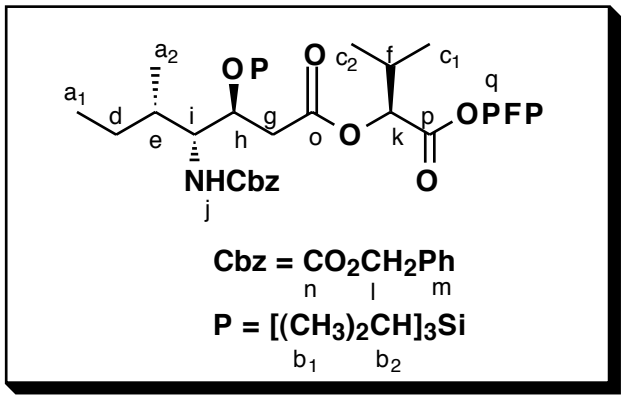
The isostatine acid (**13**, 0.6827 g, 1.47 mmol), dissolved in freshly distilled toluene (2.5 mL) under argon, was cooled to 0 °C, and was subjected to the sequential dropwise additions of the allyl ester (**16**, 0.232 g, 1.47 mmol) in toluene (2.5 mL), DCC (0.333 g, 1.61 mmol), and DMAP (0.036 g, .29 mmol). The reaction mixture was stirred at 0 °C for 2 h and then at rt overnight. It was then quenched with MeOH/AcOH (1:2) in EtOAc (2 mL), stirred for 20 min, then concentrated. The residue was dissolved in ether (10 mL) and the solid was removed by filtration. The filtrate was washed with 10% citric acid (10 mL), 5% $NaHCO_3$ (10 mL) and brine (10 mL) solutions. The organic layer was dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by flash column chromatography eluting with ether:hexane (2:98 to 12:88) to provide the coupled product (**17**) as a colorless oil (0.5774 g, 65% yield).



17: R_f 0.55 (20:80–ethyl acetate:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ **H_a, H_b, H_c)** 0.85–1.08 (m, 33H), **H_d)** 1.16–1.19 (m, 1H) and 1.34–1.36 (m, 1H), **H_e)** 1.80–1.82 (m, 1H), **H_f)** 2.18–2.21 (m, 1H), **H_g)** 2.68–2.73 (m, 2H), **H_h)** 3.78–3.82 (m, 1H), **H_i)** 4.37–4.42 (m, 1H), **H_j)** 4.55–4.64 (m, 2H), **H_k)** 4.77–4.78 (d, J=4.4 Hz, 1H), **H_l)** 4.86–4.88 (d, J=10.7 Hz, 1H), **H_m)** 5.07 (s, 2H), **H_n)** 5.21–5.23 (dd, J_1=9.4 Hz, J_2=0.9 Hz, 1H) and 5.28–5.32 (dd, J_1=17.0 Hz, J_2=1.2 Hz, 1H), **H_o)** 5.83–5.87 (m, 1H), **H_p)** 7.27–7.34 (m, 5H); ^{13}C NMR (500 MHz, $CDCl_3$) δ **C_{a1})** 12.69, **C_{b1})** 12.93, **C_{a2})** 14.14, **C_{c1})** 17.25, **C_{b2})** 18.12, **C_{c2})**

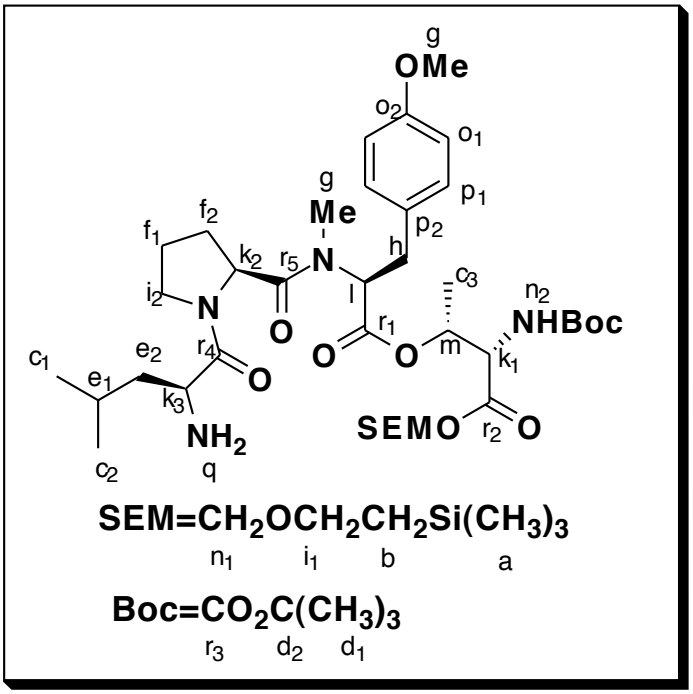
18.78, **C_d)** 26.33, **C_e)** 29.98, **C_f)** 34.48, **C_g)** 40.28, **C_h)** 58.15, **C_j)** 66.69, **C_k)** 68.67, **C_m)** 70.66, **C_j)** 76.74, **C_n)** 118.82, **C_p)** 128.01, 128.40, 128.47 and 136.75, **C_o)** 131.63, **C_q)** 156.48, **C_r)** 169.13, **C_s)** 170.78; IR ($CHCl_3$) 3380. 2964, 2867, 1743, 1508, 1463, 1374, 1201, 1129, 994, 882 cm^{-1}; HRMS m/z calcd for $C_{33}H_{55}NSiO_7Na$ ($M+Na^+$): 628.364552, found 628.365878; Anal. Calcd for $C_{33}H_{55}NSiO_7$: C, 65.41; H, 9.16. Found: C, 65.09; H, 9.05.

To a solution of isostatine–Hiv–Allyl ester (**17**, 0.2315 g, 0.38 mmol) in dry THF (3 mL) was added $Pd(PPh_3)_4$ (0.044 g, 0.038 mmol) in a dark hood, followed by the dropwise addition of redistilled morpholine (0.33 mL, 3.8 mmol). The mixture was stirred at rt overnight. The reaction mixure was concentrated and diluted with CH_2Cl_2 (5 mL), washed with 1N HCl (5 mL) and H_2O (5 mL). The organic layer was dried (Na_2SO_4), filtered, and the methylene chloride removed. The residue was dissolved in ether (5 mL), filtered and concentrated. Acid **6** (0.218 g, quantitative yield) was obtained as a white foam and used directly in the next step without purification. The crude acid (**6**) was dissolved in dry CH_2Cl_2 (1 mL) and cooled to 0 °C, followed by the sequential addition of PFPOH (0.074g, 0.40 mmol), EDAC•HCl (0.088 g, 0.46 mmol) and DMAP (0.0093 g, 0.076 mmol). The reaction was stirred at 0 °C for half an hour, and then at rt for an additional 4 h and diluted with CH_2Cl_2 (10 mL). The organic layer was washed sequentially with 10% HCl (5 mL), 5% $NaHCO_3$ (5 mL) and saturated NaCl (5 mL) solutions. The CH_2Cl_2 layer was dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by flash column chromatography eluting with ether:hexane (3:97 to 7:93) to obtain the PFP ester (**19**) as a colorless oil (0.2315 g, 83% yield, two steps overall).



19: R_f 0.57 (20:80–ethyl acetate:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ **H_a, H_b, H_c)** 0.86–1.09 (m, 33H), **H_d)** 1.18–1.20 (m, 1H) and 1.27–1.29 (m, 1H), **H_e)** 1.84–1.86 (m, 1H), **H_f)** 2.31–2.36 (m, 1H), **H_g)** 2.69–2.72 (m, 1H) and 2.80–2.85 (m, 1H), **H_h)** 3.79–3.82 (m, 1H), **H_i)** 4.38–4.42 (m, 1H), **H_j)** 4.78–4.80 (d, J=10.7 Hz, 1H), **H_k)** 4.97–4.98 (d, J=4.4 Hz, 1H), **H_l)** 5.00–5.06 (m, 2H), **H_m)** 7.25–7.29 (m, 5H); ^{13}C NMR (500 MHz, $CDCl_3$) δ **C_{a1})** 12.72, **C_{b1})** 12.95, **C_{a2})** 14.07, **C_{c1})** 17.20, **C_{b2})** 18.09, **C_{c2})** 18.45, **C_d)** 27.52, **C_e)** 30.19, **C_f)** 34.40, **C_g)** 40.12, **C_h)** 58.17, **C_j)** 65.82, **C_k)** 66.74, **C_l)** 70.47, **C_m)** 127.92, 128.18, 128.33 and 136.57, **C_q)** 138.83, 140.06, 140.65 and 141.97, **C_n)** 156.56, **C_o)** 165.68, **C_p)** 170.76; IR ($CHCl_3$) 3480, 2962, 2868, 1793, 1730, 1516, 1464, 1381, 1214, 1094, 995, 880 cm^{-1}; HRMS m/z calcd for $C_{36}H_{50}NF_5SiO_7Na$ ($M+Na^+$): 754.3174, found 754.3191.

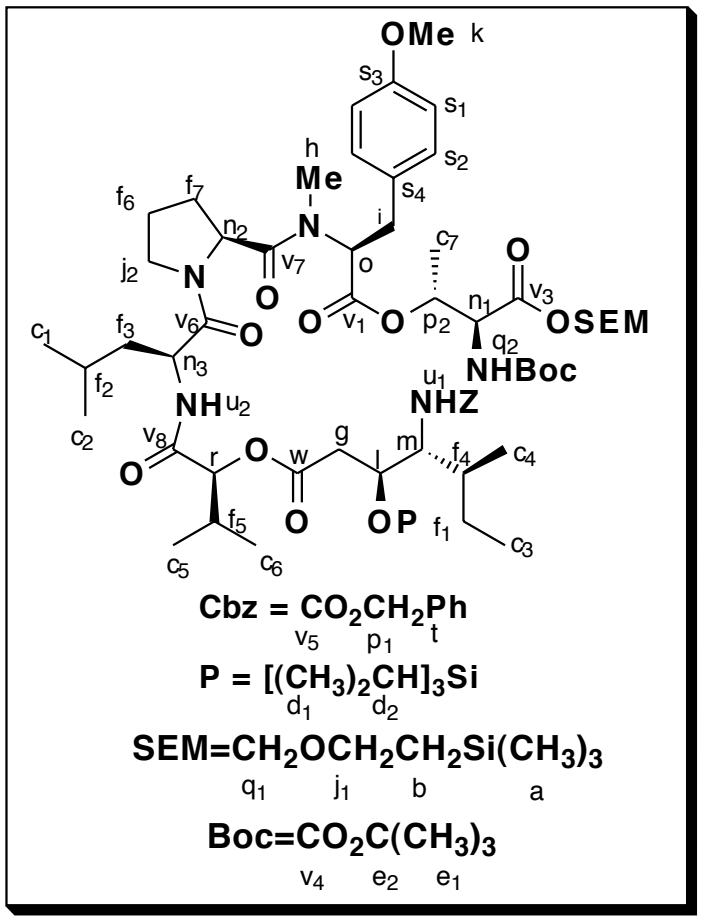
Leucylprolyl–N,O–dimethyltyrosine–N–Boc–O–SEM–threonine (18). The fully protected tetrapeptide[1] (**5**, 0.6653 g, 0.74 mmol), dissolved in HPLC MeOH (10 mL), was added to the suspension of 10% Pd/C (0.1996 g) in CH_3OH/EtOAc (1:1, 20 mL) and the reaction was shaken for 5 h in a Parr apparatus. The slurry was filtered through Celite and the filter cake washed with excess solvent mixture. The filtrate was dried (Na_2SO_4), filtered, and concentrated to provide a free amine (**18**, 0.552 g, 98% yield) as a white solid, which was used immediately in the next step.



18: R_f 0.03 (40:60–acetone:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ **H_a)** –0.001 (s, 9H), **H_b)** 0.64–0.86 (m, 2H), **$H_{c1, c2}$)** 0.88–0.96 (m, 6H), **H_{c3})** 1.19–1.21 (d, J=6.3 Hz) and 1.33–1.34 (d, J=6.3 Hz, 3H, RI), **H_d)** 1.44 (s, 9H), **H_e)** 1.63–1.92 (m, 3H), **H_f)** 1.92–2.01 and 2.08–2.24 (m, 4H), **H_g)** 2.73 (s, 3H), **H_h)** 2.86–2.96 (m) and 3.10–3.19 (m, 2H), **H_i)** 3.45–3.72 (m, 4H), **H_j)** 3.75 (s, 3H), **H_k)** 4.34–4.69 (m, 3H), **H_l)** 4.78–4.81 (dd, J_1=8.0 Hz, J_2=3.3 Hz, 1H), **H_m)** 5.01–5.10 (m, 1H), **H_n)** 5.17–5.52 (m) and 7.58–7.60 (d, J=9.7 Hz, 3H), **H_{o1})** 6.77–6.83 (m, 2H), **H_{p1})** 7.00–7.10 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ **C_a)** –1.46, **C_b)** 16.87, **C_{c3})** 17.96, **C_{c1})** 22.00, **C_{c2})** 23.19, **C_{e1})** 23.76, **C_{f1})** 25.14, **C_d and C_g)** 28.16 (overlap), **C_{f2})** 29.31, **C_h)** 33.65, **C_{e2})** 39.31, **C_{i2})** 47.34, **C_{k3})** 50.54, **C_j)** 55.37, **C_{k2})** 55.46, **C_l)** 58.66, **C_{k1})** 62.25, **C_m)** 68.16, **C_{i1})** 72.36, **C_{d2})** 81.15, **C_{n1})** 89.83, **C_{o1})** 114.39, **C_{p1})** 128.75, **C_{p2})** 128.75, **C_{p2})** 130.47, **C_{r3})** 157.04, **C_{p2})** 158.84, **C_{r4})** 168.15, **C_{r5})** 168.95, **C_{r1})** 169.57, **C_{r2})** 173.13; IR ($CHCl_3$) 3285, 2951, 1740, 1709, 1641, 1511, 1448, 1365, 1250, 1161 cm^{-1}; HRMS m/z calcd for $C_{37}H_{63}N_4SiO_{10}$ ($M+H^+$): 751.4314, found 751.4343; $[\alpha]_D^{20}$ – 44.68 (c 1.03, $CHCl_3$); Anal. Calcd for $C_{37}H_{62}N_4SiO_{10}$: C, 59.17; H, 8.33; N, 7.46. Found: C, 59.17; H, 8.35; N, 7.26.

The PFP ester (**19**, 0.2855 g, 0.39 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and cooled to 0 °C. DIEA (0.17 mL, 0.98 mmol) was added dropwise to the solution and the mixture was stirred at 0 °C for 20 min, followed by the addition of amine **18** in CH_2Cl_2 (1.5 mL) through a syringe, and DMAP (0.0095 g, 0.078 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at rt for an additional 1 h, at which time the reaction was quenched with saturated NH_4Cl solution (3 mL) at 0 °C, diluted with CH_2Cl_2 (10 mL), then

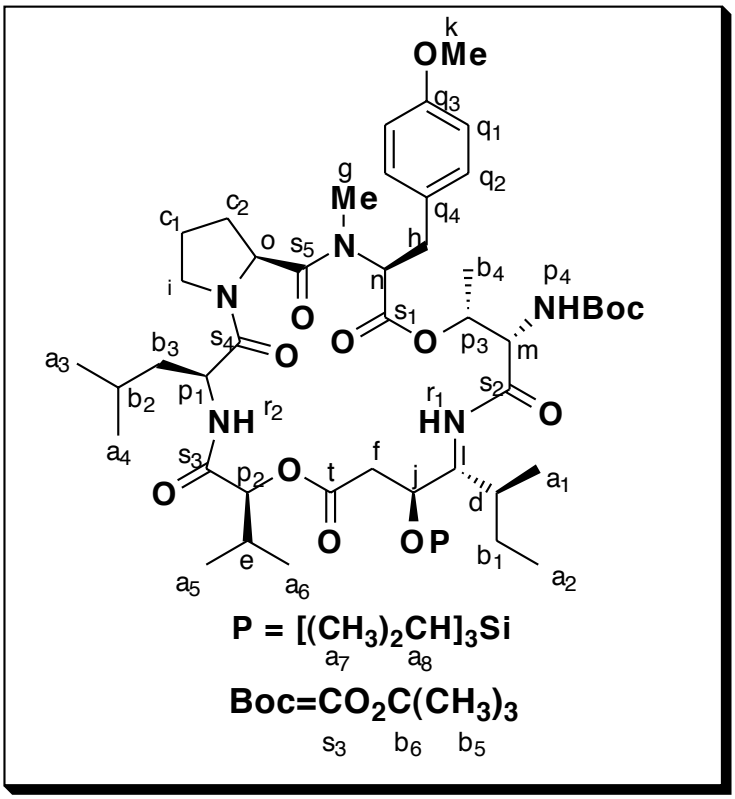
separated at rt. The aqueous layer was extracted with CH_2Cl_2 (3X10 mL), and the combined organic layers were washed sequentially with 10% HCl (10 mL), 5% $NaHCO_3$ (10 mL), brine (10 mL), and dried (Na_2SO_4), filtered and concentrated. The fully protected linear precursor (**20**) (0.4861 g, 96%) was obtained as a white foam and did not require purification.



20: R_f 0.47 (05:95–acetone:CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ **H_a)** –0.0008 (s, 9H), **H_b)** 0.73–0.83 (m, 2H), **H_c)** 0.85–0.92 (m, 9H), **H_d)** 0.92–1.08 (m, 21H), **H_e)** 1.45 (s, 9H), **H_f)** 1.13–2.19 (m, 11H), **H_g)** 2.43–2.46 (m, 1H) and 2.54–2.58 (m, 1H), **H_h)** 2.64 and 2.88 (s, 3H, RI), **H_i)** 3.09–3.17 (m, 2H), **H_j)** 3.44–3.73 (m, 4H), **H_k)** 3.75 (s, 3H), **H_l)** 3.79–3.89 (m, 1H), **H_m)** 4.38–4.45 (m, 1H), **H_n)** 4.21–4.35 (m, 3H), **H_o)** 4.70–4.81 (m, 1H), **H_p)** 4.96–5.06 (m, 3H), **H_q)** 5.18–5.43 (m, 3H) and 8.32–8.34 (d, J=9.0 Hz, 3H), **H_r)** 5.46–5.48 (d, J=6.1 Hz, 1H), **H_{s1})** 6.74–6.83 (m, 2H), **H_{s2})** 6.95–7.11 (m, 2H), **H_t)** 7.25–7.38 (m, 5H), **H_u)** 7.75–7.77 (d, J=8.5 Hz) and 8.85–8.87 (d, J=10.1 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ **C_a)** –1.45, **C_{c3})** 11.73, **C_{d1})** 12.73, **C_{c4})** 14.47, **C_b)** 16.54, **C_{c5})** 17.73, **C_{c7})** 17.99, **C_{d2})** 18.14, **C_{c6})** 18.92, **C_{c1})** 21.40, **C_{c2})** 23.54, **C_{f2})** 24.42, **C_{f1})** 25.13, **C_{e1})** 28.21, **C_h)** 28.27, **C_{f6})** 29.20, **C_{f4})** 29.67, **C_{f7})** 30.13, **C_i)** 33.59, **C_{f5})** 34.86, **C_{f3})** 39.58, **C_g)** 39.73, **C_{j2})** 46.87, **C_{n3})** 49.04, **C_k)** 55.13, **C_{n2})** 55.39, **C_o)** 58.94, **C_{n1})** 62.24, **C_l)** 66.42, **C_{p2})** 68.12, **C_{p1})** 70.96, **C_{j1})** 72.25, **C_{e2})** 80.39, **C_{q1})** 89.85,

C_{s1}) 113.92 and 114.37, **C_t)** 127.70, 127.76, 127.86, 128.35, 128.45, 128.81, 128.91 and 137.01, **C_{s2})** 130.44, **C_{s3})** 130.86, **C_{v4})** 156.39, **C_{v5})** 158.40, **C_{s4})** 158.82, **C_{v7})** 169.20, **C_{v6})** 169.75, **C_{v3})** 169.97, **C_{v1})** 170.58, **C_{v8})** 171.77, **C_w)** 173.85; IR ($CHCl_3$) 3275, 2952, 2868, 1735, 1704, 1636, 1511, 1454, 1380, 1365, 1250, 1167, 1110, 1047 cm^{-1}; HRMS m/z calcd for $C_{67}H_{111}N_5Si_2O_{16}Na$ ($M+Na^+$): 1320.7462, found 1320.7520; $[\alpha]_D^{20}$ – 44.56 (c 1.13, $CHCl_3$); Anal. Calcd for $C_{67}H_{111}N_5Si_2O_{16}$: C, 61.95; H, 8.62; N, 5.40. Found: C, 61.75; H, 8.59; N, 5.15.

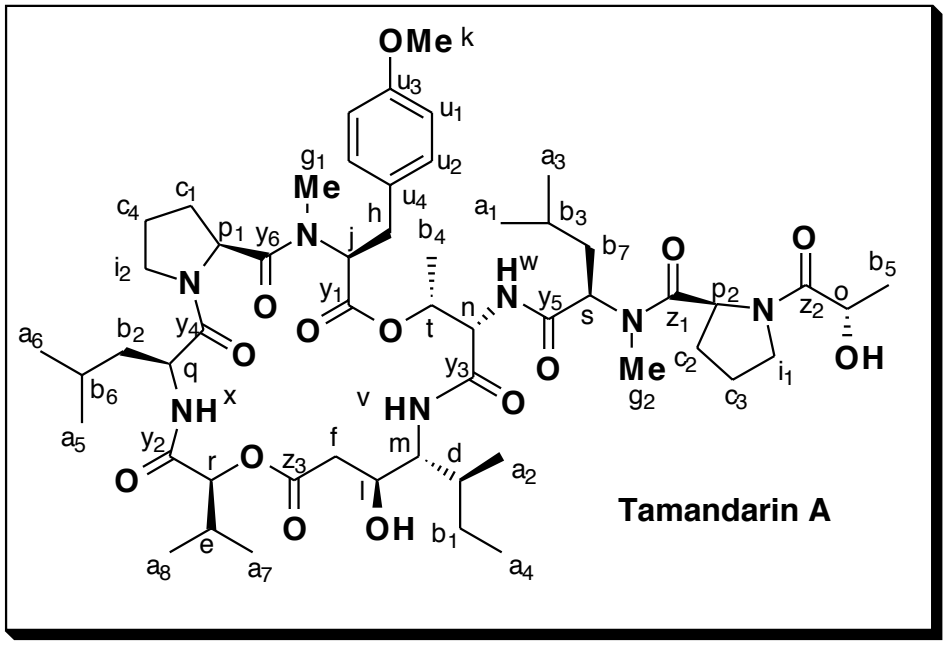
To the fully protected linear precursor (**20**, 0.3505 g, 0.27 mmol) dissolved in CH_2Cl_2 (5 mL), and cooled to 0 °C, was added $MgBr_2 \cdot Et_2O$ (0.21 g, 0.81 mmol). The reaction was stirred at 0 °C for 2 h and at rt for another 4 h. The reaction mixure was diluted with CH_2Cl_2 (10 mL), washed with 10% HCl (10 mL) and brine (10 mL) solutions. The organic layer was dried (Na_2SO_4), filtered and concentrated. The resulting acid (0.3195 g) was obtained as a white foam and used directly in the next step. The crude acid, dissolved in HPLC MeOH (10 mL), was added to the suspension of 10% Pd/C (0.096 g) in CH_3OH/EtOAc (1:1, 20 mL) and the reaction was shaken for 5 h in a Parr apparatus. The slurry was filtered through Celite and the filter cake washed with excess solvent mixture. The filtrate was dried (Na_2SO_4), filtered, and concentrated to provide an amino acid linear precursor free at both termini as a white foam (0.296 g), which was used directly in the next step. The crude amino acid linear precursor was dissolved in redistilled DMF (27 mL), and cooled to 0 °C. HATU (0.123 g, 0.32 mmol) was then added, followed by the dropwise addition of DIEA (0.141 mL, 0.81 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at rt overnight. The reaction mixture was concentrated in vacuo and diluted with EtOAc (10 mL), washed sequentially with 10% HCl (10 mL), 5% $NaHCO_3$ (10 mL) and brine (10 mL), and dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography eluting with acetone:hexane (5:95 to 15:85) to obtain the protected macrocycle (**21**) (0.173 g, 63%, three steps overall) as a white foam.



21: R_f 0.55 (30:70–acetone:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ **H_a)** 0.78–1.07 (m, 39H), **H_b)** 1.21–1.48 (m, 17H), **H_c)** 1.56–1.92 (m, 4H), **H_d and H_e)** 1.95–2.11 (m, 2H), **H_f)** 2.43–2.44 (m, 1H) and 3.11–3.17 (m, 1H), **H_g)** 2.53 (s, 3H), **H_h)** 2.89–3.02 (m, 1H) and 3.30–3.34 (m, 1H), **H_i)** 3.49–3.52 (m, 1H) and 3.60–3.62 (m, 1H), **H_j)** 3.66–3.70 (m, 1H), **H_k)** 3.77 (s, 3H), **H_l)** 4.14–4.19 (m, 1H), **H_m)** 4.37–4.43 (m, 1H), **H_n)** 4.46–4.48 (d, J=7.6 Hz, 1H), **H_o)** 4.55–4.86 (m, 1H), **H_p)** 4.88–4.91 (m) and 7.60–7.66 (m, 4H), **H_{q1})** 6.82–6.83 (d, J=8.5 Hz, 2H), **H_{q2})** 7.06–7.07 (d, J=8.5 Hz, 2H), **H_r)** 7.41–7.48 (m, 2H); HRMS m/z calcd for $C_{53}H_{89}N_5SiO_{12}Na$ ($M+Na^+$): 1038.6175, found 1038.6166.

A solution of protected macrocycle (**21**, 167 mg, 0.165 mmol) in HPLC EtOAc (20 mL) was cooled to –30 °C. Gaseous HCl was introduced at such a rate that the temperature of the mixture was maintained between –10 °C to –20 °C at saturation. After stirring for 30 min at this temperature, the reaction mixture was stirred at 0 °C for 1 h. The solution was then purged with N_2 for about 30 min, maintaining the temperature at 0 °C. After concentrating the solution, the residue was triturated and washed by decantation with three 5.0 mL portions of tert–butyl methyl ether:hexane (1:4). The product was collected by filtration and dried in vacuo to provide the hydrochloride salt (127.5 mg, quantitative yield) as a white solid, which was used directly in the final step. To a mixture of the macrocycle amine salt (63.3 mg, 0.082 mmol) and side chain (**4**) (37.7 mg, 0.12 mmol) in CH_2Cl_2 (0.50 mL) at 0 °C was added BOP (53.1 mg, 0.12 mmol) and NMM (0.035 mL, 0.32 mmol).

After 30 min at 0 °C, the reaction mixture was allowed to warm to rt and stir overnight. The solution was then treated with saturated aqueous NaCl (2 mL) and extracted with EtOAc (10 mL). The organic layer was washed with 10% aqueous HCl (5 mL), 5% aqueous $NaHCO_3$ (5 mL), saturated aqueous NaCl (5 mL), dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified by flash column chromatography eluting with MeOH:CH_2Cl_2 (2:98 to 5:95) to obtain tamandarin A (**1**) (0.0471 g, 56% two steps overall) as a yellow–greenish solid.



1 : R_f 0.57 (10:90–MeOH:CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ **$H_{a)}$** 0.86–1.08 (m, 24H), **H_b, H_c, H_d, H_e)** 1.19–2.30 (dd, J_1=17.1 Hz, J_2=7.9 Hz, 1H) and 3.29–3.33 (d, J=17.0 Hz, 1H), **H_{g1})** 2.62 (s, 3H), **H_{g2})** 3.14 (s, 3H), **$H_{h)}$** 3.16–3.21 (dd, J_1=14.4 Hz, J_2=11.1 Hz, 1H) and 3.41–3.45 (m, 1H), **H_i and H_j)** 3.59–3.80 (m, 5H), **$H_{k)}$** 3.82 (s, 3H), **$H_{l)}$** 3.90–3.95 (m, 1H), **$H_{m)}$** 4.03–4.08 (m, 1H), **$H_{n)}$** 4.29–4.30 (m, 1H), **$H_{o)}$** 4.37–4.42 (m, 1H), **$H_{p1)}$** 4.67–4.69 (m, 1H), **$H_{p2)}$** 4.74–4.77 (m, 1H), **$H_{q)}$** 4.89–4.93 (m, 1H), **$H_{r)}$** 5.06 (d, J=4.3 Hz, 1H), **$H_{s)}$** 5.31–5.35 (q, J_1=11.6 Hz, J_2=3.3 Hz, 1H), **$H_{t)}$** 5.44–5.46 (m, 1H), **$H_{u1)}$** 6.86–6.88 (d, J=8.3 Hz, 2H), **$H_{u2)}$** 7.09–7.11 (d, J=8.3 Hz, 2H), **$H_{v)}$** 7.37–7.39 (d, J=9.1 Hz, 1H), **$H_{w)}$** 7.48–7.50 (d, J=5.1 Hz, 1H), **$H_{x)}$** 7.78–7.80 (d, J=9.7 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ **$C_{a4)}$** 11.78, **$C_{a2)}$** 14.07, **$C_{b4)}$** 16.52, **$C_{a8)}$** 17.55, **$C_{a7)}$** 18.93, **$C_{b5)}$** 20.28, **$C_{a6)}$** 20.90, **$C_{a1)}$** 21.32, **$C_{a3)}$** 23.47, **$C_{a5)}$** 23.79, **C_{b3}, C_{b4}, $C_{b6)}$** 24.83 and 24.90 (overlap), **$C_{c3)}$** 25.98, **$C_{b1)}$** 27.33, **$C_{c1)}$** 27.96, **$C_{c2)}$** 28.40, **$C_{e)}$** 30.11, **$C_{g2)}$** 31.26, **$C_{d)}$** 33.55, **$C_{h)}$** 33.93, **$C_{b7)}$**

35.73, **C_{g1})** 38.70, **C_{b2})** 39.41, **C_f)** 39.65, **C_{i2})** 46.66, **C_{i1})** 47.02, **C_q)** 48.28, **C_m)** 54.91, **C_k and C_s)** 55.27 (overlap), **C_{p2})** 56.71, **C_{p1})** 56.97, **C_n)** 57.90, **C_j)** 66.07, **C_0)** 66.22, **C_l)** 68.98, **C_t)** 70.70, **C_r)** 78.87, **C_{u1})** 114.08, **C_{u2})** 130.07, **C_{u3})** 130.33, **C_{u4})** 156.62, **C_{y1})** 168.52, **C_{y2})** 169.57, **C_{y3})** 170.11, **C_{y4})** 170.35, **C_{y5})** 170.59, **C_{y6})** 171.09, **C_{z1})** 172.67, **C_{z2})** 173.84, **C_{z3})** 174.53; IR ($CHCl_3$) 3330, 2952, 2876, 1735, 1629, 1508, 1447, 1243, 1168, 1024, 843 cm^{-1}; HRMS m/z calcd for $C_{54}H_{85}N_7O_{14}Na$ ($M+Na^+$): 1078.6052, found 1078.6044; $[\alpha]_D^{20}$ – 43.93 (c 1.05, $CHCl_3$).

(1) Li, W.–R.; Ewing, W. R.; Harris, B. D.; Joullié, M. M. J. Am. Chem. Soc. **1990**, 112, 7659–7672.