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Enantioselective Total Synthesis of Batzelladine A

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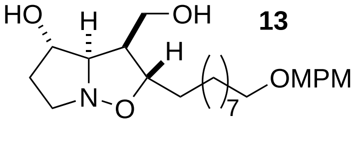
Experimental

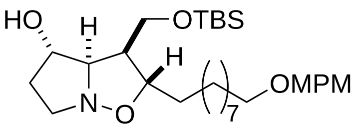
General: Flash chromatography was performed on Silica gel 60 (spherical, particle size 0.040-0.100 mm; Kanto). $[\alpha]_D$ were measured with a JASCO DIP polarimeter 370. IR spectra were measured with a JASCO VALOR-III FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on DELTA-NMR-ECP-500 instrument. Mass spectra were recorded on JEOL JMA-HX110 spectrometer.



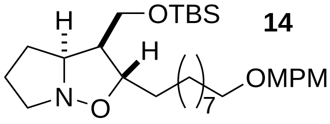
13

(2*S*,3*S*,3a*R*,4*S*)-2-(9-(4-methoxybenzyloxy)nonyl)-3-(hydroxymethyl)-hexahydropyrrolo[1,2-*b*]isoxazol-4-ol (13). A mixture of nitrone **10** (15.2 g, 59.0 mmol) and the olefin **11** (25.9 g, 68.9

mmol) in toluene (100 mL) was heated at 90˚C for 19 h. After cooling, the reaction mixture was concentrated *in vacuo* to give the crude product **12** (42.0 g). The product was difficult to be isolated from the remaining olefin **11** and used without further purification. To a slurry of $LiAlH_4$ (1.53 g, 40.3 mmol) in Et_2O (220 ml), solution of ester **12** (16.6 g, 40% of the above product) in Et_2O (30 ml) was added slowly at 0˚C. After stirring 3 h at the same temperature, the reaction was quenched by sequential addition of H_2O (500 μl), 4N aq. NaOH (500 μl), and H_2O (1 mL). $MgSO_4$ was added and the resulting mixture was stirred for 20 min, filtered through Celite, and the eluant was concentrated to afford a residue (16.4 g) that was used without further purification. A solution of this crude alcohol and CsF (11.4 g, 75.0 mmol) in EtOH (90.0 mL) was refluxed at 90˚C for 13 h. The reaction was concentrated and filtered through Florisil. The filtrate was concentrated and purified on silica gel (50:1 $CHCl_3$-MeOH; 20:1 $CHCl_3$-MeOH) to give 6.63 g (59% for three steps) of diol **13** as a clear viscous oil. $[\alpha]_D^{23}$ = -65.3 (*c* 0.63, $CHCl_3$); IR (neat) 3392, 2929, 2854, 1613, 1586, 1513, 1464, 1361, 1302, 1248 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.44-4.38 (m, 3H), 3.85 (d, J = 8.1 Hz, 2H), 3.80 (s, 2H), 3.58-3.51 (m, 1H), 3.48 (ddd, J = 12.4, 7.7, 4.3 Hz, 1H), 3.42 (t, J = 6.6 Hz, 2H), 3.09 (ddd, J = 12.4, 9.0, 6.8 Hz, 1H), 2.77-2.69 (m, 1H), 2.31-2.23 (m, 1H), 1.82-1.74 (m, 1H), 1.62-1.45 (m, 4H), 1.45-1.20 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) 158.8, 130.3, 129.0, 113.4, 77.8, 74.7, 72.2, 70.5, 69.9, 59.8, 54.93, 54.9, 52.4, 33.1, 29.4, 29.35, 29.2, 29.15, 26.0, 25.9 ppm; HRMS (FAB, MH^+) calcd for $C_{24}H_{40}NO_5$ 422.2906, found 422.2928.

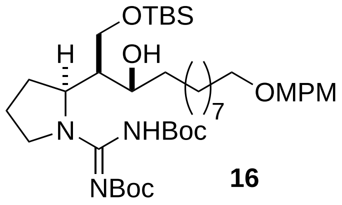


(2*S*,3*S*,3a*R*,4*S*)-2-(9-(4-methoxybenzyloxy)nonyl)-3-((*tert*-butyldimethylsilyloxy)methyl)-hexahydropyrrolo[1,2-*b*]isoxazol-4-ol. TBDMSCl (361 mg, 2.40 mmol) was added to the solution of diol **13** (773.6 mg, 1.84 mmol) and pyridine (20 mL). After 19 h, the mixture was concentrated and purified on silica gel (7:1 hexane-AcOEt to 30:1 $CHCl_3$-MeOH) to afford 799.4 mg (81%) of mono TBS ether as a colorless oil. $[\alpha]^{22}_{\mathrm{D}}$ = -16.4 (*c* 1.18, $CHCl_3$); IR (neat) 3288, 2929, 2856, 2416, 2349, 2285, 1613, 1586, 1513, 1464, 1361, 1302, 1249 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.72 (br, 1H), 4.67 (d, J = 9.4 Hz, 1H), 4.41 (s, 2H), 4.30 (dt, J = 8.1, 4.3 Hz, 1H), 4.09-4.02 (m, 1H), 3.93 (dd, J = 11.1, 4.7 Hz, 1H), 3.83 (dd, J = 11.1, 4.7 Hz, 1H), 3.79 (s, 3H), 3.55-3.48 (m, 1H), 3.42 (t, J = 6.8 Hz, 2H), 2.76-2.68 (m, 1H), 2.33-2.20 (m, 2H), 1.78-1.62 (m, 2H), 1.57 (tt, J = 6.8, 6.8 Hz, 2H), 1.48-1.16 (m, 12H), 0.87 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 158.9, 130.6, 129.0, 113.5, 85.9, 77.9, 77.2, 72.3, 70.0, 58.8, 55.3, 55.1, 49.6, 32.9, 32.6, 29.6, 29.2, 29.1, 29.0, 26.0, 17.9, -5.7, -5.8 ppm; HRMS (FAB, MH^+) calcd for $C_{48}H_{81}N_2O_{10}Si$ 536.3771, found 536.3767.



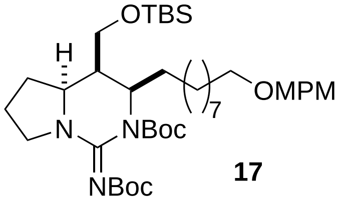
14

(2*S*,3*S*,3a*S*)-2-(9-(4-methoxybenzyloxy)nonyl)-3-((*tert*-butyldimethylsilyloxy)methyl) -hexahydropyrrolo[1,2-*b*]isoxazole (14). To a solution of alcohol (6.35 g, 11.9 mmol) and DMAP (145 mg) in pyridine (120 mL) was added phenyl chlorothionoformate (3.3 ml) at 0˚C. After stirring at rt for 20 h, the reaction mixture was diluted with Et_2O and washed with H_2O, brine. The mixture was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography (20:1 hexane-AcOEt; 10:1 hexane-AcOEt) gave xanthate (4.64 g, 58%) as a yellow oil. The residue was dissolved in toluene (35 ml). To this solution was added $n\mathrm{Bu_3SnH}$ (3.7 ml) and AIBN (113 mg) and refluxed at 110˚C for 30 min. After cooling, the reaction mixture was concentrated *in vacuo* and purified on silica gel (100:1 hexane-AcOEt to 3:1 hexane-AcOEt) to afford **14** (3.36 g, 94%) as a clear oil. $[\alpha]_D^{22}$ = -46.3 (*c* 1.21, $CHCl_3$); IR (neat) 2929, 2855, 1613, 1513, 1464, 1361, 1302, 1249, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, 2H, *J*=8.6Hz), 6.86 (d, 2H, *J*=8.6Hz), 4.41 (s, 2H), 3.78 (s, 2H), 3.72-3.62 (m, 4H), 3.42 (t, 2H, *J*=13.8Hz), 3.22-3.36 (m, 1H), 3.12-3.05 (m, 1H), 2.68-2.59 (m, 1H), 1.96-1.86 (m, 1H), 1.76-1.64 (m, 2H), 1.61-1.52 (m, 5H), 1.50-1.35 (m, 1H), 1.35-1.20 (m, 11H), 0.88 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) 158.9, 130.6, 129.0, 113.5, 78.6, 72.3, 70.0, 68.3, 61.5, 56.7, 55.0, 53.6, 34.5, 29.6, 29.5, 29.4, 29.3, 26.2, 26.0, 25.7, 24.9, 24.6, 18.0, -5.6, -5.7 ppm; HRMS (FAB, MH^+) calcd for $C_{48}H_{81}N_2O_9Si$ 520.3822, found 520.3820.



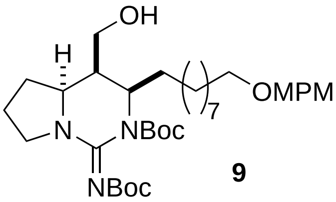
16

16. To a solution of **14** (797 mg, 1.53 mmol) in EtOH (5 ml) was added $Pd(OH)_2/C$ (400 mg). The reaction mixture was stirred at rt under an atomosphere of hydrogen gas (ballon) for 3 h then filtered through Celite and eluted with MeOH. The product was concentrated under reduced pressure to give pyrrolidine. To a solution of pyrrolidine, 1,3-Bis-(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (**15**) (537 mg, 1.85 mmol) and triethylamine (640 μl, 4.62 mmol) in DMF (10 ml) was added $HgCl_2$ (500 mg, 1.85 mmol), and the resulting mixture was stirred for 30 min. The reaction mixture was diluted with AcOEt, and filtered through a pad of Celite. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (6:1 hexane-AcOEt, 5:1 hexane-AcOEt) to give the bis-Boc protected guanidine **16** (830 mg, 71% for two steps).



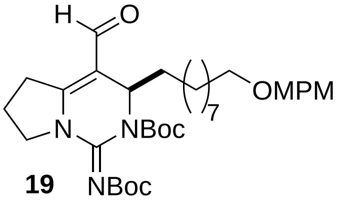
17

(3*R*,4*R*,4a*S*)-*tert*-butyl 3-(9-(4-methoxybenzyloxy)nonyl)-1-(*tert*-butoxycarbonyl)-4-((*tert*-butyldimethylsilyloxy)methyl)-hexahydropyrrolo[1,2-*f*]pyrimidine-2(1*H*)-carboxylate (17). To a solution of **16** (830 mg, 1.09 mmol), PPh_3 (433 mg, 1.65 mmol) in toluene (10 ml) was added DEAD (750μl, 1.65 mmol, 40% in toluene). After stirring 30 min, the reaction was quenched with H_2O and concentrated *in vacuo*. Purification of the residue by flash chromatography (4:1 hexane-AcOEt; 3:2 hexane-AcOEt) gave **17** (860 mg, q.y.) as a clear oil. $[\alpha]_D^{24}$ = -128.9 (*c* 1.68, $CHCl_3$); IR (neat) 2929, 2856, 1732, 1678, 1586, 1513, 1471, 1390, 1365, 1326, 1301, 1249 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.47-4.40 (m, 1H), 4.42 (s, 2H), 3.79 (s, 3H), 3.70-3.47 (m, 6H), 3.42 (t, J = 6.8 Hz, 2H), 2.64-2.56 (m, 1H), 2.00-1.85 (m, 2H), 1.81-1.54 (m, 6H), 1.54-1.18 (m, 12H), 1.48 (s, 9H), 1.47 (s, 9H), 0.89 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 159.2, 159.1, 151.9, 150.0, 130.8, 129.2, 113.7, 81.8, 77.8, 72.5, 70.3, 60.5, 56.7, 55.2, 54.0, 46.7, 43.8, 29.8, 29.6, 29.5, 29.4, 29.3, 28.5, 28.4, 28.2, 28.16, 26.3, 26.2, 25.8, 22.1, 18.0, -5.5, -5.6 ppm; HRMS (FAB, MH^+) calcd for $C_{41}H_{72}N_3O_7Si$ 746.5140, found 746.5143.



9

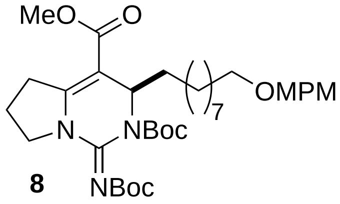
(3*R*,4*R*,4a*S*)-tert-butyl 3-(9-(4-methoxybenzyloxy)nonyl)-1-(*tert*-butoxycarbonyl)-4-(hydroxymethyl)-hexahydropyrrolo[1,2-*f*]pyrimidine-2(1*H*)-carboxylate (9). TBAF hydrate (590 mg, 2.26 mmol) was added to a solution of **17** (860 mg, 1.13 mmol) in THF (15 ml). After 2 h, the solution was diluted with AcOEt and washed with H_2O, saturated NH_4Cl. Organic layer was dried over $MgSO_4$ and concentrated. Resulting oil was purified on silica gel (2:1 hexane-AcOEt; 1:2 hexane-AcOEt) to give **9** (580 mg, 81%) as a colorless oil. $[\alpha]_D^{24}$ = -133.4 (*c* 1.30, $CHCl_3$); IR (neat) 3369, 2975, 2929, 2855, 1729, 1682, 1574, 1514, 1473, 1389, 1366, 1325, 1301, 1249 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, 2H, *J* = 8.6Hz), 6.87 (d, 2H, *J* = 8.6Hz), 4.42 (m, 3H), 3.80 (s, 3H), 3.73 (d, 2H, *J* = 7.3Hz), 3.66-3.58 (m, 2H), 3.54-3.47 (m, 1H), 3.43 (t, 2H, *J* = 6.6Hz), 2.66-2.58 (m, 1H), 2.03-1.94 (m, 2H), 1.83-1.72 (m, 1H), 1.70-1.53 (m, 3H), 1.48 (s, 9H), 1.48 (s, 9H), 1.42-1.20 (m, 14H); ^{13}C NMR (125 MHz, $CDCl_3$) 158.9, 158.8, 151.9, 150.5, 130.5, 129.0, 113.5, 81.8, 77.6, 72.3, 70.0, 59.9, 57.2, 55.0, 54.2, 46.8, 43.4, 29.5, 29.3, 29.2, 29.0, 28.4, 28.3, 27.9, 26.1, 25.9, 21.9 ppm; HRMS (FAB, MH^+) calcd for $C_{35}H_{58}N_3O_7$ 632.4275, found 632.4274.



19

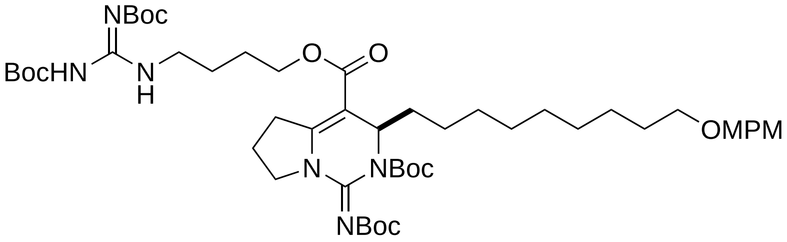
(*R*)-*tert*-butyl 3-(9-(4-methoxybenzyloxy)nonyl)-1-(*tert*-butoxycarbonyl)-4-formyl-6,7-

dihydropyrrolo[1,2-*f*]pyrimidine-2(1*H*,3*H*,5*H*)-carboxylate (19). Solid TPAP (8.4 mg) was added in one portion to a stirred mixture of the alcohol **9** (301 mg, 0.48 mmmol), NMO (225 mg, 1.92 mmol) and powdered 4Å molecular sieves (240 mg) in CH_2Cl_2 (2.0 ml) at rt. After stirring 30min, the reaction mixture was evaporated and the resulting black residue was purified on silica gel (3:1 hexane-AcOEt) to afford α,β-unsaturated aldehyde **19** (143 mg, 47%) as a yellow oil. $[\alpha]_D^{24}$ = -34.3 (*c* 1.01, $CHCl_3$); IR (neat) 2977, 2930, 2855, 1739, 1695, 1651, 1613, 1514, 1457, 1416, 1392, 1368, 1335, 1304 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.26 (d, 2H, *J* = 8.5Hz), 6.87 (d, 2H, *J* = 8.5Hz), 5.26 (dd, 1H, *J* = 8.5, 4.5Hz), 4.42 (s, 2H), 3.97 (ddd, 1H, *J* = 12.1, 7.7, 7.7Hz), 3.85 (ddd, 1H, *J* = 12.1, 8.5, 4.5Hz), 3.80 (s, 3H), 3.42 (t, 2H, *J* = 6.8Hz), 3.15 (ddd, 1H, *J* = 16.5, 8.5, 4.5Hz), 2.98 (ddd, 1H, *J* = 16.5, 8.5, 8.5Hz), 2.22-2.13 (m, 1H), 2.13-2.03 (m, 1H), 1.63-1.55 (m, 2H), 1.52 (s, 9H), 1.49 (s, 9H), 1.40-1.20 (m, 14H); ^{13}C NMR (125 MHz, $CDCl_3$) 158.9, 158.8, 151.9, 150.5, 130.5, 129.0, 113.5, 81.8, 77.6, 72.3, 70.0, 59.9, 57.2, 55.0, 54.2, 46.8, 43.4, 29.5, 29.3, 29.2, 29.0, 28.4, 28.3, 27.9, 26.1, 25.9, 21.9 ppm; HRMS (FAB, MH^+) calcd for $C_{35}H_{54}N_3O_7$ 628.3962, found 628.3959.

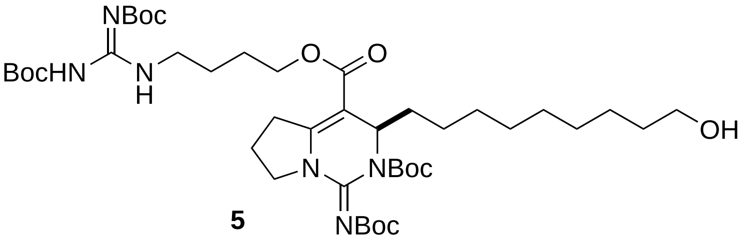


8

(*R*)-2-*tert*-butyl 4-methyl 3-(9-(4-methoxybenzyloxy)nonyl)-1-(*tert*-butoxycarbonyl)-6,7-dihydropyrrolo[1,2-*f*]pyrimidine-2,4(1*H*,3*H*,5*H*)-dicarboxylate (8). To a mixture of aldehyde **19** (61.0 mg, 0.097 mmol) and 2-methyl-2-butene (515 μl) in *t*BuOH (900 μl) was added $NaClO_2$ (105 mg) and $NaH_2PO_4 \cdot 2H_2O$ (106 mg) in water (190 μl) at rt and the mixture was stirred vigorously. After 21h, excess of $TMSCHN_2$ (40% in hexane) was added and the mixture was diluted with AcOEt. The mixture was extracted with AcOEt three times and dried over $MgSO_4$. The solution was concentrated under reduced pressure and purified by flash chromatography(4:1 hexane-AcOEt) to afford **8** (34.1 mg, 0.052 mmol, 53%, 74% from recovered aldehyde) and starting material **19** (16.9 mg, 0.027 mmol, 28%). $[\alpha]_D^{24} = +18.7$ (*c* 1.08, $CHCl_3$); IR (neat) 2979, 2931, 2855, 1740, 1698, 1655, 1612, 1513, 1457, 1438, 1416, 1390, 1368, 1346 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, 2H, *J* = 8.5 Hz), 6.87 (d, 2H, *J* = 8.5 Hz), 5.21 (dd, 1H, *J* = 8.5, 4.5 Hz), 4.43 (s, 2H), 3.80 (s, 3H), 3.76-3.69 (m, 1H), 3.74 (s, 3H), 3.48 (ddd, 1H, *J* = 11.5, 8.0, 8.0 Hz), 3.42 (t, 2H, *J*=6.8Hz), 3.23 (ddd, 1H, *J* = 17.8, 8.2, 4.2 Hz), 2.92 (ddd, 1H, *J* = 17.8, 9.0, 9.0 Hz), 2.10-1.90 (m, 2H), 1.60-1.00 (m, 16H), 1.51 (s, 9H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 165.7, 158.8, 152.0, 150.8, 144.8, 131.5, 130.7, 129.2, 113.7, 102.9, 83.1, 79.6, 72.4, 70.2, 55.2, 53.0, 51.2, 48.8, 33.6, 31.2, 29.7, 29.6, 29.4, 29.37, 29.1, 28.7, 28.3, 28.2, 28.1, 26.2, 24.7, 21.3 ppm; HRMS (FAB, MH^+) calcd for $C_{36}H_{56}N_3O_8$ 658.4067, found 658.4064.

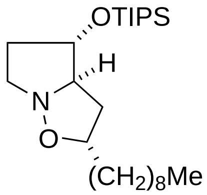


(*R*)-4-(4-(2,3-bis(*tert*-butoxycarbonyl)guanidino)butyl) 2-*tert*-butyl 3-(9-(4-methoxybenzyloxy)nonyl)-1-(*tert*-butoxycarbonyl)-6,7-dihydropyrrolo[1,2-*f*]pyrimidine-2,4(1*H*,3*H*,5*H*)-dicarboxylate. To a methyl ester **8** (57.6 mg, 0.088 mmol), *n*PrSLi (71.9 mg) in HMPA (2.1 ml) was added at rt and stirred for 80 min. Reaction mixture was poured into ice-Et_2O, and washed seven times with water. Aqueous layer was acidified to pH3 with 0.1N HCl aq. and extracted with Et_2O. After washed with HCl aq. (pH3) seven times, combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give carboxylic acid. To a mixture of the crude carboxylic acid, guanidine alcohol **4** (117 mg, 0.35 mmol) and BOPCl (56 mg) in CH_2Cl_2 was added Et_3N at rt. After stirring 12 h, the reaction mixture was diluted with AcOEt and resulting solution was poured into H_2O. The mixture was extracted with AcOEt twice and dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography (6:1 hexane-AcOEt; 4:1 hexane-AcOEt) gave ester (45.3 mg, 0.047 mmol, 54% in two steps) as a yellow oil. $[\alpha]_D^{24}$ = +28.3 (c 0.88, $CHCl_3$); IR (neat) 3332, 2979, 2931, 2856, 1739, 1731, 1723, 1715, 1704, 1695, 1643, 1633, 1622, 1614, 1514, 1455, 1415, 1391, 1368, 1331 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.50 (brs, 1H), 8.34 (brs, 1H), 7.27 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.21 (dd, J = 8.6, 4.3 Hz, 1H), 4.42 (s, 2H), 4.25-4.05 (m, 2H), 3.95 (ddd, J = 11.5, 8.1, 7.7 Hz, 1H), 3.80 (s, 3H), 3.73 (ddd, J = 12.4, 8.6, 3.3 Hz, 1H), 3.46 (dd, J = 12.4, 6.8 Hz, 2H), 3.42 (t, J = 6.8 Hz, 2H), 3.22 (ddd, J = 17.5, 8.6, 4.3 Hz, 1H), 2.15-2.03 (m, 1H), 2.01-1.93 (m, 1H), 1.78-1.64 (m, 4H), 1.62-1.53 (m, 2H), 1.51 (s, 9H), 1.50 (s, 9H), 1.49 (s, 9H), 1.48 (s, 9H), 1.41-1.19 (m, 14H); ^{13}C NMR (125 MHz, $CDCl_3$) 165.1, 163.6, 159.0, 158.8, 156.1, 153.3, 152.0, 150.8, 144.7, 130.8, 129.1, 113.7, 103.0, 83.1, 83.0, 79.6, 79.3, 72.5, 70.2, 63.6, 55.2, 53.0, 48.8, 40.4, 33.7, 31.2, 29.8, 29.6, 29.5, 29.46, 29.2, 28.3, 28.2, 28.1, 28.0, 26.3 26.2, 25.8, 24.8, 21.4 ppm; HRMS (FAB, MH^+) calcd for $C_{50}H_{81}N_6O_{12}$ 957.5912, found 957.5919.



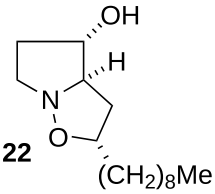
5

(*R*)-4-(4-(2,3-bis(*tert*-butoxycarbonyl)guanidino)butyl) 2-*tert*-butyl 1-(*tert*-butoxy)carbonyl)-3-(9-hydroxynonyl)-6,7-dihydropyrrolo[1,2-*f*]pyrimidine-2,4(1*H*,3*H*,5*H*)-dicarboxylate (5). To a solution of ester (108.0 mg, 0.113 mmol) in CH_2Cl_2 (1.6 ml) and H_2O (180 μl) was added DDQ (77 mg) at rt and stirred for 1 h. The reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with AcOEt three times. Organic layer was washed with H_2O, brine and dried over $MgSO_4$. The solution was concentrated under reduced pressure and purified on silica gel (3:1 hexane-AcOEt; 2:1 hexane-AcOEt) to afford **5** (62.2 mg, 66%) as a clear oil. $[\alpha]_D^{24}$ = +23.2 (*c* 1.52, $CHCl_3$); IR (neat) 3329, 2979, 2930, 2856, 1739, 1722, 1698, 1641, 1614, 1456, 1416, 1392, 1368, 1332 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.49 (br, 1H), 8.34 (br, 1H), 5.21 (dd, *J* = 8.5, 4.7 Hz, 1H), 4.16 (dt, *J* = 12.4, 5.1 Hz, 2H), 3.95 (ddd, *J* = 11.5, 8.1, 7.7 Hz, 1H), 3.73 (ddd, *J* = 12.4, 8.6, 4.3 Hz, 1H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.46 (dd, *J* = 12.4, 6.9 Hz, 2H), 2.92 (ddd, *J* = 18.0, 9.0, 9.0 Hz, 1H), 2.12-1.96 (m, 2H), 1.78-1.41 (m, 8H), 1.51 (s, 9H), 1.49 (s, 9H), 1.48 (s, 9H), 1.48 (s, 9H), 1.41-1.18 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) 165.2, 163.6, 158.9, 156.2, 153.3, 152.1, 150.8, 144.8, 103.0, 83.2, 83.1, 79.7, 79.4, 63.6, 63.0, 53.0, 48.8, 40.5, 33.6, 32.8, 31.2, 29.7, 29.4, 29.3, 29.26, 29.0, 28.3, 28.1, 28.0, 26.3, 25.9, 25.7, 24.7, 21.4 ppm; HRMS (FAB, MH^+) calcd for $C_{42}H_{73}N_6O_{11}$ 837.5337, found 837.5337.



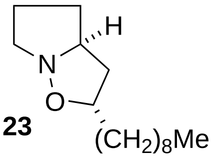
(2*S*,3a*R*,4*S*)-2-nonyl-4-(triisopropylsilyloxy)-hexahydropyrrolo[1,2-*b*]isoxazole. A mixture of nitrone **10** (9.0 g, 35.0 mmol) and 1-undecene (**21**) (27.0 g, 175.0 mmol) in toluene (200 mL) was heated at 90˚C for 9 h. After cooling, the reaction mixture was concentrated *in vacuo* and purified on silica gel (16:1 hexane-AcOEt, 8:1 hexane-AcOEt) to afford oxazolidine (10.77 g, 75%) as a clear oil. $[\alpha]_D^{22}$ = +3.6 (*c* 0.88, $CHCl_3$); IR (neat) 2927, 2865, 1465, 1381, 1368 cm^{-1}; ^1H NMR (500 MHz,

$CDCl_3$) δ 4.12 (ddd, J = 5.6, 3.0, 3.0 Hz, 1H), 3.90 (m, 1H), 3.60 (ddd, J = 8.1, 3.0, 3.0 Hz, 1H), 3.37 (ddd, J = 12.4, 8.1, 6.4 Hz, 1H), 3.18 (ddd, J = 12.4, 6.4, 4.7 Hz, 1H), 2.15-2.02 (m, 3H), 1.78-1.68 (m, 1H), 1.68-1.56 (m, 1H), 1.43-1.20 (m, 18H), 1.13-0.95 (m, 18H), 0.93-0.20 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 78.7, 76.6, 73.9, 55.2, 40.1, 34.2, 33.7, 31.5, 29.2, 29.14, 29.1, 28.9, 26.0, 22.3, 17.5, 13.7, 11.6 ppm; HRMS (FAB, MH^+) calcd for $C_{24}H_{50}NO_2Si$ 412.3611, found 412.3622.



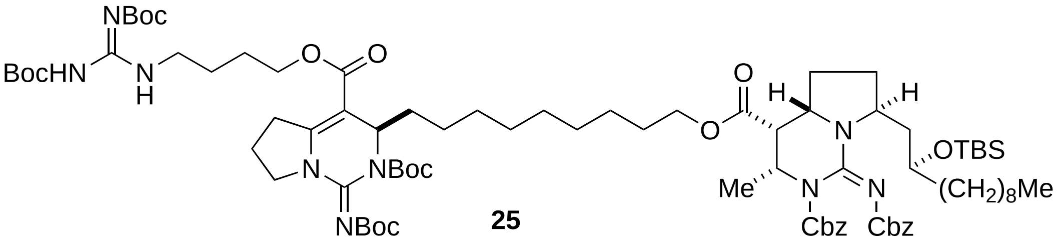
22

(2*S*,3a*R*,4*S*)-2-nonyl-hexahydropyrrolo[1,2-*b*]isoxazol-4-ol (22). The mixture of oxazolidine (10.73 g, 10.0 mmol) and CsF (11.9 g) in EtOH (20 ml) was refluxed at 90˚C for 9 h. After cooling, the solution was poured into H_2O and extracted with AcOEt twice. The solution was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by flash chromatography ($CHCl_3$, 200:1 $CHCl_3$-MeOH to 9:1 $CHCl_3$-MeOH) to give **22** (6.71 g, q.y.) as a clear oil. $[\alpha]_D^{22}$ = -18.7 (c 0.69, $CHCl_3$); IR (neat) 3362, 2926, 2855, 1466 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.12-4.06 (m, 1H), 3.94-3.87 (m, 1H), 3.59-3.54 (m, 1H), 3.43-3.36 (m, 1H), 3.16-3.09 (m, 1H), 2.15-2.00 (m, 3H), 1.75-1.67 (m, 1H), 1.65-1.55 (m, 1H), 1.47-1.20 (m, 14H), 0.86 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 76.7, 72.7, 55.0, 40.0, 33.3, 33.26, 31.5, 29.3, 29.2, 29.17, 29.0, 26.0, 22.3, 13.7 ppm; HRMS (FAB, MH^+) calcd for $C_{15}H_{30}NO_2$ 256.2277, found 256.2288.



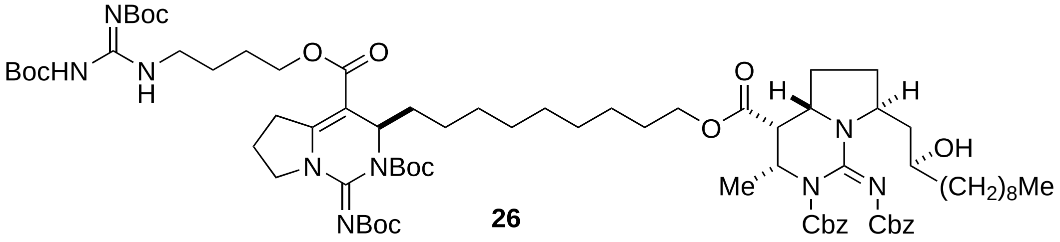
23

(2*S*,3a*S*)-2-nonyl-hexahydropyrrolo[1,2-*b*]isoxazole (23). To a solution of alcohol **22** (5.40 g, 21 mmol) and DMAP (180 mg) in pyridine (100 ml) was added phenyl chlorothionoformate (5.8 ml) at rt. After stirring for 5 h, the reaction mixture was concentrated under reduced pressure and diluted with AcOEt. The solution was washed with H_2O twice and organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane; 12:1 hexane-AcOEt) gave xanthete as a yellow oil. To a solution of xanthate in toluene (100 ml), *n*Bu_3SnH (17 ml) and AIBN (345 mg) was added and refluxed at 110˚C for 20 min. The solution was concentrated under reduced pressure and purified by silicagel column chromatography (hexane, 6:1 hexane-AcOEt to 1:2 hexane-AcOEt) to afford **23** (2.56 g, 10.1 mmol, 51% in two steps). $[\alpha]_D^{23}$ = -34.1 (*c* 1.19, $CHCl_3$); IR (neat) 2926, 2855, 1465 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.97 (m,1H), 3.70 (m, 1H), 3.10 (m, 2H), 2.03-1.90 (m, 4H), 1.84-1.20 (m, 18H), 0.83 (t, J = 6.8Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 76.4, 64.8, 57.0, 42.5, 33.9, 31.8, 31.7, 29.62, 29.57, 29.45, 29.21, 26.4, 24.3, 22.6, 14.0 ppm; HRMS (FAB, MH^+) calcd for $C_{15}H_{30}NO$ 240.2327, found 240.2383.



25

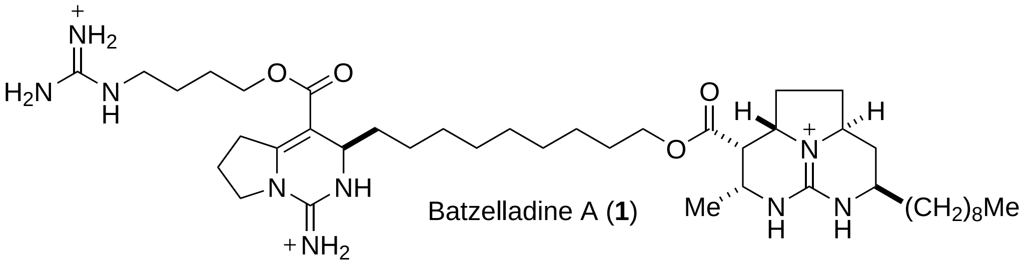
(*R*)-4-(4-(2,3-bis(*tert*-butoxycarbonyl)guanidino)butyl) 2-*tert*-butyl 3-(9-((3*R*,4*S*,4a*S*,7*S*,*Z*)-1-(benzyloxycarbonyl)-7-((*S*)-2-(*tert*-butyldimethylsilyloxy)undecyl)-2-(carbonyl)-3-methyl-octahydropyrrolo[1,2-*f*]pyrimidine-4-carbonyloxy)nonyl)-1-(*tert*-butoxycarbonyl)-6,7-dihydropyrrolo[1,2-*f*]pyrimidine-2,4(1*H*,3*H*,5*H*)-dicarboxylate (25). TBAF hydrate (44 mg) was added to a solution of **24** (44 mg, 0.052 mmol) in THF (1 ml) at 0˚C and stirred at the temperature for 100 min. The reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with AcOEt twice. Combined organic layer was washed with saturated NH_4Cl solution, H_2O and brine. The solution was concentrated *in vacuo* and purified by column chromatography (4:1 hexane-AcOEt; 2:1 hexane-AcOEt) to afford alcohol (37.7 mg, 0.051 mmol, 99%) as a clear oil. To a solution of alcohol (12.8 mg, 0.017 mmol) in acetone (500 μl) was added Jones reagent (2drops) and stirred at 0˚C for 40 min. The mixture was added excess of isopropanol and poured into AcOEt. The solution was washed with brine four times and the aqueous layer was reextracted with AcOEt. Combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give the crude carboxylic acid **7**. To a mixture of crude carboxylic acid **7** and **5** (13.2 mg, 0.016 mmol) in CH_2Cl_2 (400 μl) was added EDCI (11.0 mg) and DMAP (1.0 mg) at 0˚C. After stirring at the temperature for 3 h, the reaction mixture was poured into H_2O and extracted with Et_2O twice. The solution was washed with saturated $NaHCO_3$ solution, brine, H_2O and dried over $MgSO_4$. The solution was evaporated and purified by column chromatography (8:4:1 CH_2Cl_2-hexane-AcOEt; 16:8:3 CH_2Cl_2-hexane-AcOEt) to afford **25** (14.8 mg, 0.0094 mmol, 60%) as a clear oil. $[\alpha]_D^{24}$ = -52.4 (*c* 0.57, $CHCl_3$); IR (neat) 3334, 2928, 2855, 1736, 1725, 1696, 1639, 1612, 1456, 1415, 1390, 1368, 1330, 1287, 1248 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.50 (br, 1H), 8.34 (br, 1H), 7.36-7.20 (m, 10H), 5.21 (dd, J = 8.6, 4.7 Hz, 1H), 5.15 (d, *J* = 12.4, 1H), 4.97 (d, *J* = 12.8, 1H), 4.90 (d, *J* = 12.4, 1H), 4.87 (d, *J* = 12.4, 1H), 4.48 (m, 1H), 4.25-4.10 (m, 3H), 4.10-4.02 (m, 1H), 4.05 (t, *J* = 6.8 Hz, 2H), 3.96 (ddd, *J* = 11.5, 8.1, 7.7 Hz, 1H), 3.90- 3.82 (m, 1H), 3.77-3.70 (m, 1H), 3.46 (dd, *J* = 12.4, 6.4 Hz, 2H), 3.27-3.17 (m, 2H), 2.92 (ddd, *J* = 18.0, 9.0, 9.0 Hz, 1H), 2.30-2.21 (m, 2H), 2.18-1.92 (m, 2H), 1.90-1.45 (m, 14H), 1.51 (s, 9H), 1.50 (s, 9H), 1.49 (s, 9H), 1.48 (s, 9H), 1.45-1.20 (m, 29H), 0.95-0.80 (m, 12H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) 169.9, 165.1, 163.6, 160.0, 158.9, 156.2, 153.3, 152.9, 152.0, 150.8, 150.2, 144.8, 137.2, 135.6, 128.3, 128.1, 128.06, 128.0, 127.4, 103.0, 83.1, 83.0, 79.6, 79.3, 71.1, 68.1, 66.8, 65.5, 63.6, 58.5, 56.3, 53.0, 52.4, 50.3, 48.8, 40.6, 40.4, 37.4, 33.7, 31.9, 31.3, 29.9, 29.7, 29.6, 29.5, 29.46, 29.3, 29.2, 28.8, 28.3, 28.27, 28.2, 28.1, 28.0, 27.4, 26.3, 25.9, 25.8, 24.8, 24.4, 22.7, 21.4, 16.4, 14.1, -4.3, -4.4 ppm; HRMS (FAB, MH$^+$) calcd for $C_{84}H_{134}N_9O_{17}Si$ 1569.9697, found 1569.9678.



26

(*R*)-4-(4-(2,3-bis(*tert*-butoxycarbonyl)guanidino)butyl) 2-tert-butyl 1-(*tert*-butoxycarbonyl)-3-(9-((3*R*,4*S*,4a*S*,7*S*)-7-((*S*)-2-hydroxyundecyl)-1-imino-3-methyl-octahydropyrrolo[1,2-*f*]pyrimidine-4-carbonyloxy)nonyl)-6,7-dihydropyrrolo[1,2-*f*]pyrimidine-2,4(1*H*,3*H*,5*H*)-dicarboxylate (26). To the solution of **25** (41.7 mg 0.027 mmol) in THF (300 μl) in a polypropyrene tube was added HF-Py complex (100 μl) at 0˚C. After stirred at the temperature for 4 h, saturated NaHCO$_3$ solution (500 μl) and solid NaHCO$_3$ (100 mg) was added. The mixture was dried over MgSO$_4$ and filtered through Celite and washed with AcOEt. The solution was concentrated under reduced pressure and purified by silicagel column chromatography (4:1 hexane-AcOEt; 2:1 hexane-

AcOEt) to afford **26** (31.0 mg, 0.021 mmol, 80%). $[\alpha]_D^{24}$ = -66.3 (*c* 1.11, $CHCl_3$); IR (neat) 3331, 2978, 2929, 2855, 1738, 1732, 1695, 1641, 1614, 1576, 1456, 1416, 1390, 1368, 1329 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.50 (br, 1H), 8.54 (br, 1H), 7.36-7.16 (m, 10H), 5.20 (dd, *J* = 8.5, 4.7 Hz, 1H), 5.14 (d, *J* = 12.4 Hz, 1H), 5.00 (d, *J* = 12.8 Hz, 1H), 4.82 (d, *J* = 12.4 Hz, 1H), 4,78 (d, *J* = 12.4 Hz, 1H), 4.62-4.53 (m, 1H), 4.42-4.35 (m, 1H), 4.23-4.09 (m, 3H), 4.06 (dt, *J* = 6.8, 3.4 Hz, 2H), 4.00-3.90 (m, 2H), 3.77-3.69 (m, 1H), 3.51 (br, 1H), 3.45 (dd, *J* = 12.4, 6.8 Hz, 2H), 3.27-3.16 (m, 2H), 2.91 (ddd, *J* = 18.0, 9.0, 9.0 Hz, 1H), 2.42-2.23 (m, 2H), 2.12-1.91 (m, 2H), 1.91-1.38 (m, 14H), 1.50 (s, 9H), 1.49 (s, 9H), 1.48 (s, 9H), 1.48 (s, 9H), 1.38-1.07 (m, 29H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 169.9, 165.1, 163.6, 159.3, 158.9, 156.2, 153.7, 153.3, 152.7, 152.0, 150.8, 144.8, 136.9, 135.1, 128.4, 128.1, 128.0, 127.9, 127.5, 127.47, 127.4, 103.0, 83.2, 83.1, 79.6, 79.3, 68.2, 66.4, 66.3, 65.8, 63.6, 56.9, 56.5, 53.2, 53.0, 51.0, 48.8, 44.4, 40.4, 37.0, 33.7, 31.9, 31.3, 30.0, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.7, 28.5, 28.3, 28.2, 28.1, 28.0, 27.0, 26.3, 26.25, 25.8, 25.79, 24.8, 22.7, 21.4, 16.5, 14.1 ppm; HRMS (FAB, MH$^+$) calcd for $C_{62}H_{108}N_9O_{13}$ 1454.8802, found 1454.8811.



Batzelladine A (**1**)

Batzelladine A (**1**): To a solution of **26** (14.4 mg, 0.0099 mmol) in AcOEt (200 μl) was added catalytic amount of Pd/C. The reaction mixture was stirred at rt under an atmosphere of hydrogen gas (baloon) for 3 h then filtered and washed with AcOEt. The solution was concentrated under reduced pressure to afford alcohol. To a solution of alcohol and PPh_3 (25.2 mg) in toluene (300 μl) was added DEAD (44 μl, 40% in toluene). After stirring 5 h, the reaction was quenched with H_2O and concentrated *in vacuo*. The residue was roughly chromatographed (AcOEt, 20:1 $CHCl_3$-MeOH, 1:1 $CHCl_3$-MeOH) to give crude tricyclic guanidine. The crude tricyclic guanidine was dissolved in 50%TFA in CH_2Cl_2 (500 μl). After 30 min, the solution was concentrated under reduced pressure and purified by HPLC (50% MeCN aq. 0.1% TFA) to give batzelladine A (**1**) (2.52 mg, 0.0023 mmol, 24% in three steps) $[\alpha]_D^{25} = +4.29$ (*c* 0.25, MeOH); IR (neat) 2925, 2854, 1732, 1697, 1683, 1648, 1637, 1558, 1347, 1092 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 4.39 (t, J = 6.1 Hz, 1H), 4.21 (t, J = 6.4 Hz, 2H), 4.13 (t, J = 6.7 Hz, 2H), 3,93 (m, 1H), 3.83 (m, 2H), 3.66 (m, 1H), 3.52 (m, 1H), 3.32 (m, 1H), 3.22 (t, J = 7.3 Hz, 2H), 3.12 (dd, J = 4.6, 3.5 Hz, 1H), 2.98 (m, 1H), 2.35 (m, 1H), 2.28-2.17 (m, 3H), 2.10 (m, 1H), 1.76 (m, 2H), 1.72-1.52 (m, 9H), 1.48-1.23 (m, 29H), 1.27 (t, J = 6.7 Hz, 3H), 0.89 (t, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) 170.7, 166.2, 158.7, 153.1, 152.7, 151.5, 103.3, 66.0, 65.1, 57.7, 57.3, 53.2, 51.2, 49.9, 48.8, 45.6, 42.0, 37.5, 36.9, 34.2, 33.0, 31.9, 31.4, 29.7, 29.3, 27.0, 26.6, 26.2, 25.2, 23.7, 22.9, 18.4, 14.4; HRMS (FAB, MH^+) calcd for $C_{42}H_{74}N_9O_4$ 768.5864, found 768.5866.

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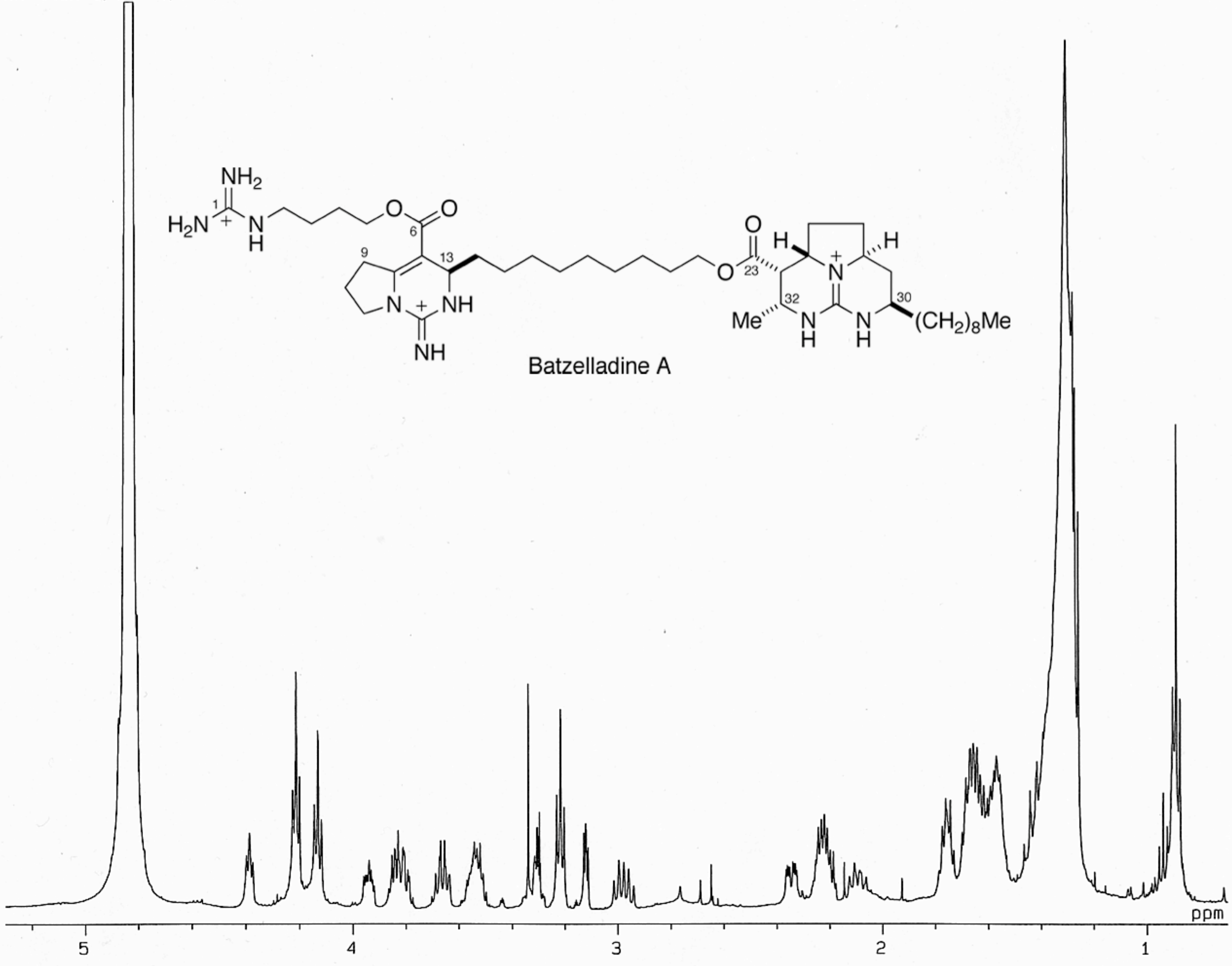

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