Evolution of a Strategy for the Synthesis of Structurally Complex Batzelladine Alkaloids. Enantioselective Total Synthesis of the Proposed Structure of Batzelladine F and Structural Revision

*Frederick Cohen and Larry E. Overman**

Supporting Information Part 1 (38 Pages)

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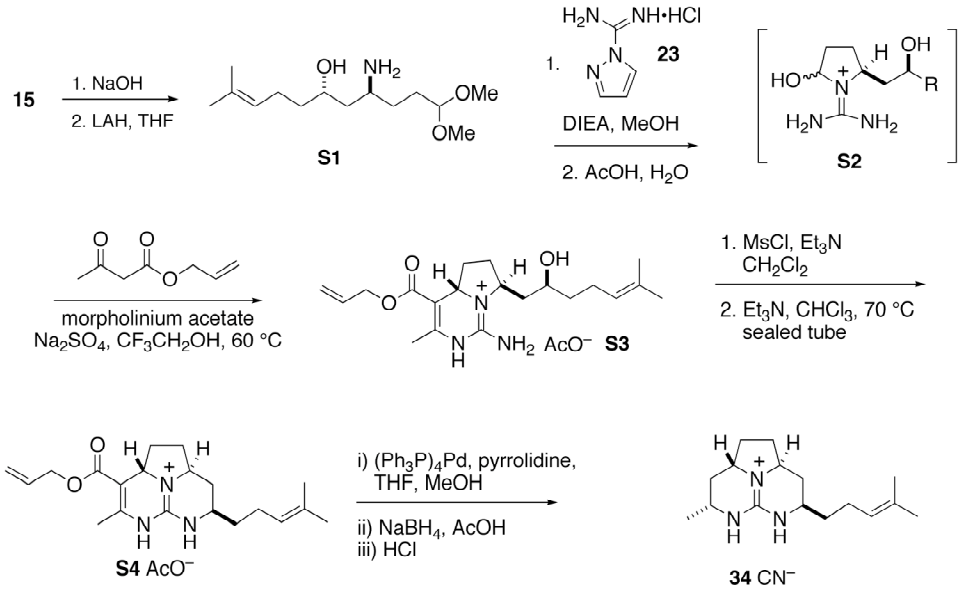
A. Complete Reference 17

Without this basic additive, the bis-dimethyl acetal was isolated in quantitative yield. See: Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chenevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hayatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; RajanBabu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, A. E.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc*. **1981**, *103*, 3210-3213.

B. Reaction Schemes

Scheme S1



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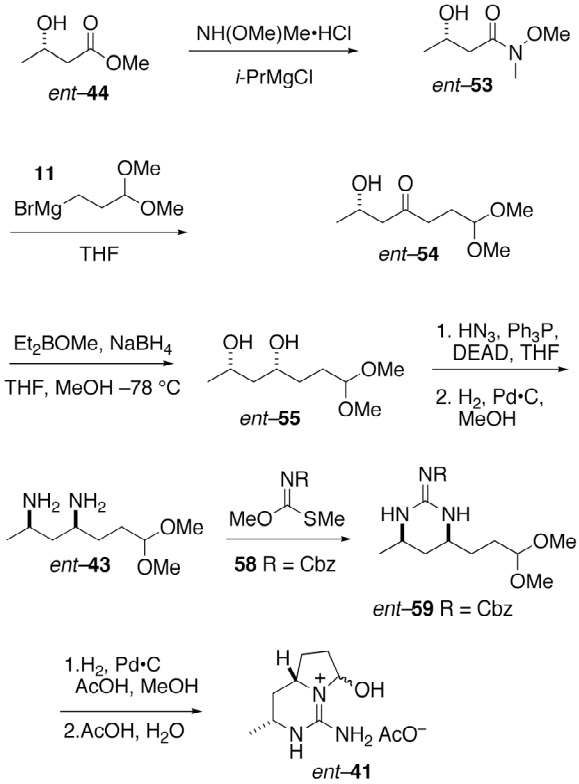

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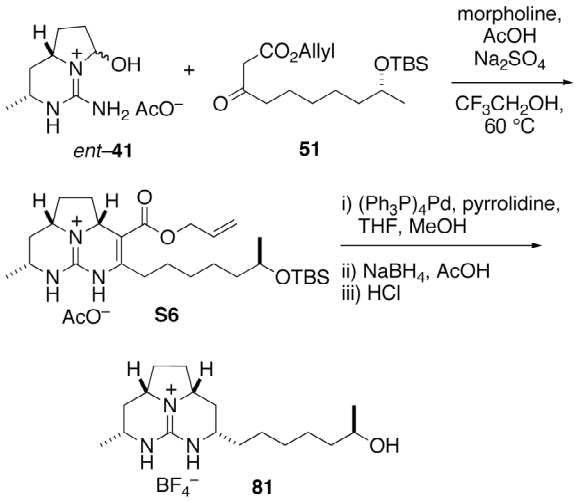

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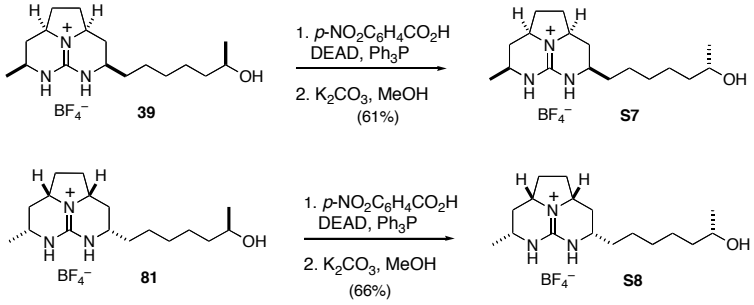

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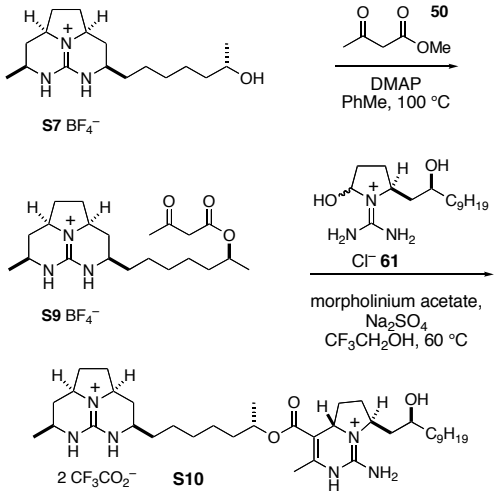

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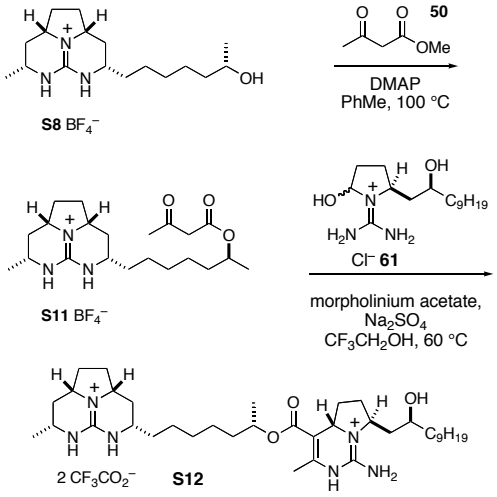

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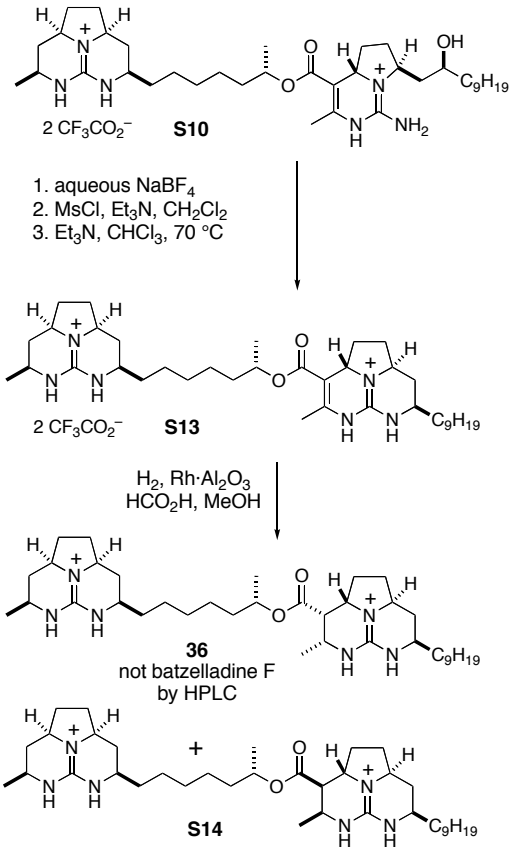
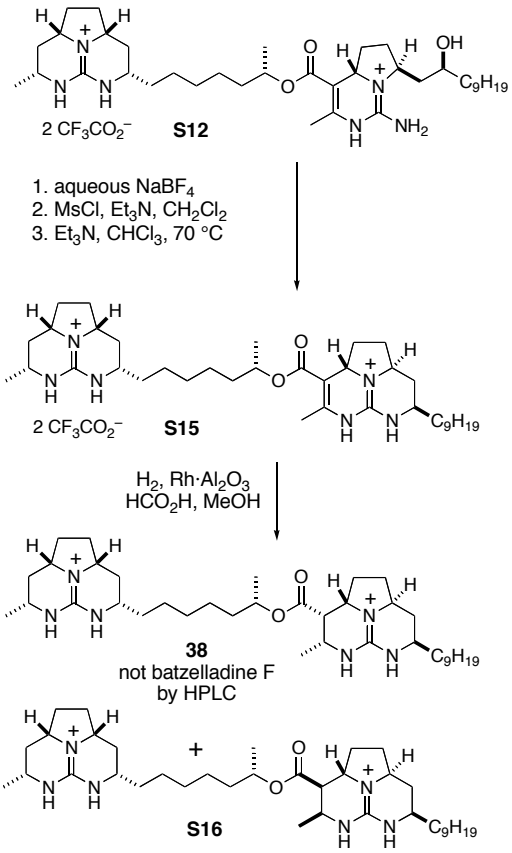
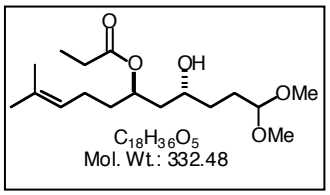


Scheme S8



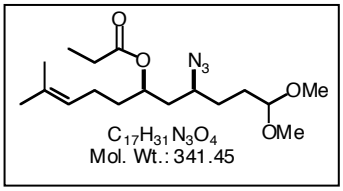
C. Experimental Details and Tabulated Characterization Data for New Compounds[1]

Section I Experimental

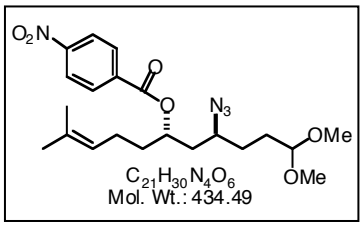


(1*R*)-Propionic acid 1-[(2*R*)-2-hydroxy-5,5-dimethoxypentyl]-5-methylhex-4-enyl ester (13). Following the procedure of Porter,[2] 3-bromopropionaldehyde dimethylacetal (55.0 g, 183 mmol) was added over 2 h to a suspension of Mg (9.50 g, 390 mmol) and I_2 (0.5 g) in THF (550 mL). The internal temperature was maintained below 25 °C by portion-wise addition of ice to an external water bath. The black suspension was stirred for 1 h after addition was complete. This suspension was cooled to 0 °C and added *via* cannula to a solution of amide **10** (9.20 g, 43.0 mmol) and THF (220 mL) at 0 °C over 0.5 h. Following addition, the cooling bath was removed and the reaction was stirred for 3 h, at which time it was poured into ice-cold saturated aqueous $NaHCO_3$ (500 mL). The mixture was diluted with 20% EtOAc–hexanes and the layers were separated. The aqueous layer was extracted with 20% EtOAc–hexanes (3 × 500 mL), the combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 × 250 mL) and brine (1 × 500 mL), dried (K_2CO_3), filtered and concentrated. The residue was chromatographed (SiO_2, gradient elution 15%–20%–25% EtOAc–hexanes containing 1% Et_3N) to give 8.50 g (76%) of ketone **12** as a colorless oil, which was azeotropically dried with toluene to give a colorless residue that was carried on directly. Diagnostic data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11–5.08 (m, 1H), 4.35 (t, *J* = 5.2 Hz, 1H), 4.05–4.01 (m, 1H), 3.00 (d, *J* = 3.5 Hz, 1H), 2.61–2.49 (m, 4H), 2.11–2.04 (m, 2H), 1.92–1.87 (m, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.57–1.50 (m, 1H), 1.43–1.38 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.4, 132.2, 123.7, 103.7, 67.3, 53.33, 53.25, 49.3, 38.1, 36.4, 26.4, 25.7, 24.0, 17.7 ppm; FTIR (film) 3473, 1712 cm^{-1}.

Following the procedure of Evans[3] samarium diiodide (100 mL, 0.1 M in THF, 10 mmol) was added over 1 h to a solution of freshly distilled propionaldehyde (9.4 mL, 130 mmol), the hydroxy–ketone prepared above and THF (120 mL) at –15 °C (external bath temperature). The reaction was maintained at this temperature for 1 h following completion of addition. Saturated aqueous $NaHCO_3$ (100 mL) was added and the mixture was poured into a separatory funnel with 20% EtOAc–hexanes (250 mL) and shaken vigorously. The layers were separated and the aqueous layer was extracted with 20% EtOAc–hexanes (2 × 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 × 100 mL), brine (1 × 100 mL), dried (K_2CO_3), filtered and concentrated. The residue was chromatographed (SiO_2, gradient elution 15% to 25% EtOAc–hexanes containing 1% Et_3N) to give 9.50 g (92%) of hydroxy-ester **13** as a colorless oil: ^{1}H NMR (500 MHz, C_6D_6) δ 5.27–5.22 (m, 1H), 5.12–5.09 (m, 1H), 4.35 (t, *J* = 5.6 Hz, 1H), 3.57–3.54 (m, 1H), 3.23 (d, *J* = 3.4 Hz, 1H), 3.15 (s, 6H), 1.80–1.75 (m, 1H), 1.60–1.36 (m, 14H), 0.94 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 175.7, 132.4, 124.3, 105.2, 71.8, 67.5, 52.9, 52.5, 44.1, 35.8, 33.0, 29.8, 28.2, 26.2, 25.0, 18.0, 9.8 ppm; FTIR (film) 3507, 1732 cm^{-1}; $[\alpha]_D^{24} = -11.8$, $[\alpha]_{546}^{24} = -13.3$, $[\alpha]_{435}^{24} = -23.7$, $[\alpha]_{405}^{24} = -28.5$ (*c* 1.30, C_6H_6). Anal. Calcd for $C_{17}H_{32}O_5$: C, 64.53; H, 10.19. Found: C, 64.52; H 10.09.

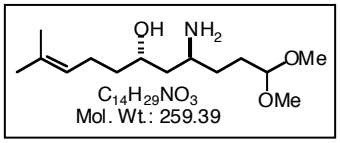


(1*R*)-Propionic acid 1-[(2*S*)-2-azido-5,5-dimethoxypentyl]-5-methylhex-4-enyl ester (14). Diethyl azodicarboxylate (6.8 mL, 43 mmol) was added dropwise to a solution of alcohol **13** (6.93 g, 21.9 mmol), hydrazoic acid (28 mL, 1.5 M in toluene, 43 mmol),[4] triphenylphosphine (11.2 g, 42.7 mmol) and benzene (200 mL) at 0 °C. The reaction was then concentrated, adsorbed onto Celite®, and chromatographed (SiO_2, gradient elution 5% to 10% to 20% EtOAc–hexanes containing 1% Et_3N) to yield 7.10 g (95%) of the title compound as a colorless oil: ^{1}H NMR, (500 MHz, $CDCl_3$) δ 5.10–5.05 (m, 1H,), 5.05–4.95 (m, 1 H), 4.36 (t, *J* = 5.4 Hz, 1H), 3.30 (s, 7H), 1.80–1.75 (m, 1H), 2.33 (q, *J* = 7.6 Hz, 2H), 2.02–1.97 (m, 2H) 1.89–1.83 (m, 1H), 1.76–1.50 (m, 13H), 1.15 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 132.4, 123.1, 104.0, 71.0, 59.5, 52.9, 52.7, 38.6, 34.4, 29.2, 28.8, 27.8, 25.7, 23.8, 17.6, 9.2 ppm; FTIR (film) 2101, 1732 cm^{-1}; $[\alpha]_D^{24}$ = 84.1, $[\alpha]_{546}^{24}$ = 101.9, $[\alpha]_{435}^{24}$ = 162.3, $[\alpha]_{405}^{24}$ = 190.1 (*c* 1.40, $CHCl_3$). Anal. Calcd for $C_{17}H_{31}N_3O_4$: C, 59.80; H, 9.15; N 12.31. Found: C, 59.51; H 9.04; N 12.15.



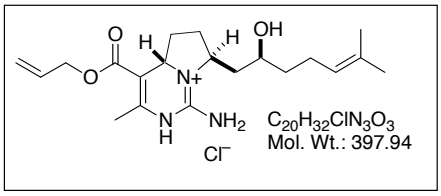
(1*S*)-4-Nitrobenzoic acid 1-[(2*S*)-2-azido-5,5-dimethoxypentyl]-5-methylhex-4-enyl ester (15). A mixture of azido–ester **14** (7.20 g, 23.1 mmol) K_2CO_3 (7.2 g) and MeOH (100 mL) was heated at reflux for 4 h. The reaction was cooled to rt, and most of the solvent was removed under reduced pressure. The residue was partitioned between water (100 mL) and 20% EtOAc–hexanes (300 mL). The layers were separated, and the aqueous layer was extracted with 20% EtOAc–hexanes (1 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was azeotroped from toluene and the resulting alcohol was carried on directly.

Diethyl azodicarboxylate (6.22 mL, 39.3 mmol) was added dropwise to a solution of triphenylphosphine (10.3 g, 39.3 mmol) and toluene (50 mL) at 0 °C. The resulting solution was added dropwise *via* cannula to a mixture of the alcohol prepared above (5.90 g, 20.7 mmol), *p*–nitrobenzoic acid (6.56 g, 39.3 mmol), and toluene (50 mL) at rt. The reaction was concentrated, adsorbed onto Celite®, and chromatographed (SiO_2, gradient elution 5% to 10% to 20% EtOAc–hexanes containing 1% Et_3N) to yield 7.02 g (78%) of the title compound as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.4 Hz, 2H), δ 8.21 (d, *J* = 8.4 Hz, 2H), 5.38–5.33 (m, 1H), 5.10–5.07 (m, 1H), 4.35 (t, *J* = 5.1 Hz, 1H), 3.42–3.38 (m, 1H), 1.95–1.65 (m 11H), 1.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 150.6, 135.7, 132.7, 130.7, 123.6, 122.9, 104.1, 73.2, 59.3, 53.3, 52.9, 39.1, 34.6, 29.9, 29.0, 25.7, 23.9, 17.7; FTIR (film) 2105, 1724, 1529, 1274 cm^{-1}; $[\alpha]_D^{24}$ = 16.1, $[\alpha]_{546}^{24}$ = 20.2, $[\alpha]_{435}^{24}$ = 33.2, (*c* 1.30, $CHCl_3$). Anal. Calcd for $C_{21}H_{30}N_4O_6$: C, 58.06; H, 6.96; N 12.89. Found: C, 58.05; H 7.12; N 12.80.



(6*S*,8*S*)-8-Amino-11,11-dimethoxy-2-methylundec-2-en-6-ol (S1). A mixture of ester **15**, (2.20 g, 5.10 mmol), aqueous NaOH (1 M, 50 mL) and THF (50 mL) was heated at reflux for 24 h. After cooling to rt, the THF was removed under reduced ressure and the organic phase was extracted with 20% EtOAc–hexanes (3 × 20 mL). The combined organic phases were washed with 1 N NaOH (1 ×), brine (1 ×), dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed (SiO_2, 20% EtOAc–hexanes containing 1% Et_3N) to yield 1.38 g (92%) of alcohol as a colorless oil.

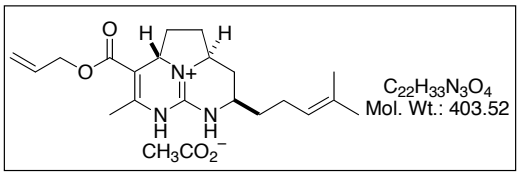
Lithium aluminum hydride (3.2 mL, 1 M in Et_2O, 3.2 mmol) was added to a solution of the azide prepared above (730 mg, 2.60 mmol) and THF (10 mL) at 0 °C. The solution was allowed to warm to rt for 1 h. The solution was cooled to 0 °C, and water (120 μL), 15% NaOH (120 μL) and water (365 μL) were added sequentially. The resulting slurry was stirred vigorously for 12 h, then filtered through a pad of Celite©, washing with CH_2Cl_2. The filtrate was concentrated to provide 630 mg (94%) of amino alcohol **S1** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.13–5.10 (m, 1H), 4.36–4.34 (m, 1H) 3.88–3.85 (m, 1H), 3.29 (s, 6H), 3.12–3.09 (m, 1H), 2.13–1.97 (m, 2H), 1.67–1.37, (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.7, 124.3, 104.4, 69.0, 52.9, 52.8, 49.0, 41.0, 37.7, 32.7, 29.4, 25.7, 24.5, 17.7; FTIR (film) 3358, 2927, 1450, 1382, 1127, 1061 cm^{-1}; $[\alpha]_D^{24}$ = 0.9, $[\alpha]_{546}^{24}$ = 0.9, $[\alpha]_{405}^{24}$ = 2.8 (*c* 1.0, $CHCl_3$); HRMS (FAB) *m/z* 260.2224 (260.2225 Calcd for $C_{14}H_{29}NO_3$, M+H).



(4a*S*,7*S*)-7-[(2*S*-2-Hydroxy-6-methyl-hept-5-enyl]-1-imino-3-methyl-1,2,4a,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidinium-4-carboxylic acid allyl ester acetate (S3). A solution of amino-alcohol **S1** (1.12 g, 4.31 mmol), 1*H*-pyrazole-1-carboxamidine hydrochloride (664 mg, 4.53 mmol), diisoproplyethylamine (800 μL, 4.53 mmol) in MeOH (2.2 mL) was heated at 50 °C for 18 h. The mixture was concentrated under reduced pressure, then placed under high vacuum for 24 h. Aqueous acetic acid (50%, 25 mL) was then added and the mixture was maintained at rt for 24 h, at which time the solvents were removed under reduced pressure at approx 35 °C, followed by drying under high vacuum for 24 h, to afford hemi-aminal **S2**.

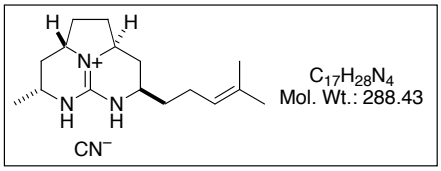
A mixture of guanidine hemi-aminal **S2** (4.31 mmol), allyl acetoacetate (1.8 mL, 12.4 mmol), morpholinium acetate (950 mg, 4.5 mmol), and CF_3CH_2OH (4.5 mL) was heated at 65 °C for 48 h. The mixture was filtered, concentrated and chromatographed (SiO_2, gradient elution 2% to 5% MeOH–$CHCl_3$ containing 1% acetic acid) to yield 880 mg (48%) of the title compound as a light–yellow solid. An analytical sample was converted to the chloride salt by concentrating from PhMe saturated with HCl: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.11 (s, 1H), 5.96–5.86 (m, 1H), 5.30–5.22 (m, 2H), 5.11–5.05 (m, 1H), 4.71–4.58 (m, 3H), 4.46–4.35 (m, 2H), 3.58 (s, 1H), 2.55–2.46 (m, 1H), 2.33 (s, 3H), 2.24–2.13 (m, 1H), 2.13–2.00 (m, 3H), 1.75–1.50 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 151.2, 143.1, 132.5, 131.9, 123.4,

118.8, 101.0, 67.9, 65.2, 57.0, 56.3, 41.6, 37.3, 34.2, 28.3, 25.7, 24.2, 18.0, 17.7; FTIR (film) 3175, 2934, 1681, 1537, 1268 cm^{-1}; $[\alpha]_D^{24} = -32.5$, $[\alpha]_{546}^{24} = -35.8$, $[\alpha]_{435}^{24} = -44.5$, $[\alpha]_{405}^{24} = -38.1$ (*c* 0.7, $CHCl_3$); HRMS (FAB) *m/z* 362.2451 (362.2444 Calcd for $C_{18}H_{28}N_3O_2$, M).



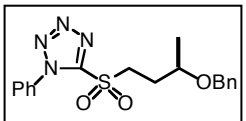
(2a*S*,7*R*,8a*S*)-7-[4-Methylhept-3-enyl]-4-methyl-2,2a,5,7,8,8a-hexahydro-1*H*-5,6,8b-triazaacenaphthylenium-3-carboxylic acid allyl ester chloride (S4). Methanesulfonyl chloride (14 μL, 0.20 mmol) was added to a solution of alcohol **S3** (36 mg, 0.09 mmol, dried azeotropically with toluene), Et_3N (46 μL, 0.34 mmol), and CH_2Cl_2 (2 mL) at 0 °C. The reaction was allowed to warm to rt over 3 hr, then diluted with $CHCl_3$ (50 mL), washed with 1 N HCl (1 × 10 mL). The aqueous phase was extracted with $CHCl_3$ (2 × 5 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed (SiO_2, elution 2% MeOH–$CHCl_3$) to yield the corresponding mesylate, which was carried on directly.

The mesylate prepared above was transferred to a sealable tube, and azeotroped with toluene (2 ×). Chloroform (6 mL, filtered through basic Al_2O_3) and Et_3N (0.6 mL) were added and the solution was heated at 70 °C for 48 h. After cooling to rt, the solvent was removed under reduced pressure, and the residue was chromatographed (SiO_2, gradient elution 2% to 5% MeOH–$CHCl_3$ containing 1% acetic acid) to yield 25 mg (74%) of cyclic guanidine **S4** as a light-yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95–5.85 (m, 1H), 5.31–5.21 (m, 2H), 5.07–5.05 (m, 1H), 4.65–4.57 (m, 2H), 4.10 (dd, *J* = 11.0, 4.4 Hz, 1H), 3.67–3.60 (m, 1H), 3.50–3.44 (m, 1H), 2.64–2.59 (m, 1H), 2.33–2.26 (m, 5H), 2.15–2.09 (m, 2H), 1.98 (s, 3H), 1.70–1.60 (m, 4H) 1.60–1.50 (m, 4H), 2.20–1.15 (m 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 164.9, 149.7, 132.5, 132.2, 122.8, 118.5, 102.5, 64.9, 55.2, 54.1, 51.4, 34.6, 32.8, 31.9, 25.6, 24.0, 23.6, 17.7, 17.6; FTIR (film) 2926, 2689, 1693, 1620, 1404 cm^{-1}; $[\alpha]_D^{24} = -32.6$, $[\alpha]_{546}^{24} = -29.4$, $[\alpha]_{435}^{24} = 10.5$, $[\alpha]_{405}^{24} = 61.1$ (*c* 0.7, $CHCl_3$).



(2a*S*,4*R*,7*R*,8a*S*)-4-[4-Methylhept-3-enyl]-7-methyl-2,2a,3,4,5,7,8,8a-octahydro-1*H*-5,6,8b-triazaacenaphthyleium cyanide (34). A solution of ester **S4** (21 mg, 0.05 mmol), $(PPh_3)_4Pd$ (1 mg, 0.001 mmol), pyrrolidine (1 drop), THF (0.5 mL) and MeOH (0.5 mL) was maintained at rt for 1 h. The reaction was concentrated, and MeOH (0.25 mL), acetic acid (0.25 mL), and $NaBH_3CN$ (16 mg, 0.26 mmol) were added. After 1h at rt, the solvents were removed under reduced pressure and the residue was purified by preparative TLC (SiO_2, elution with 5% MeOH–$CHCl_3$, 1% AcOH) to yield 10 mg (67%) of the title compound as a colorless oil: ^{1}H NMR (500 MHz, CD_3OD) δ 5.11–5.09 (m, 1H), 3.65–3.56 (m, 3H), 3.54–3.46 (m, 1H), 2.37–2.24 (m, 2H), 2.24–2.16 (m, 2H), 2.11–2.05 (m, 2H), 1.66 (s, 3H), 1.65–1.51 (m, 6H),

1.40–1.30 (m, 2H), 1.30–1.20 (m, 4H); ^{13}C NMR (125 MHz1:1 C_6D_6–$CDCl_3$) δ 176.8, 150.4, 132.8, 123.3, 54.8, 54.7, 51.5, 47.7, 35.8, 35.3, 33.2, 30.8, 30.7, 25.9, 24.1, 23.1, 21.4, 17.9; FTIR (film) 3312, 2916, 2355, 1633, 1328 cm^{-1}; $[\alpha]_D^{24}$ = –38.0, $[\alpha]_{546}^{24}$ = –48.7, $[\alpha]_{435}^{24}$ = –83.7, $[\alpha]_{405}^{24}$ = –102.8 (*c* 0.5, MeOH); HRMS (FAB) *m/z* 262.2283 (262.2283 Calcd for $C_{16}H_{28}N_3$, M).

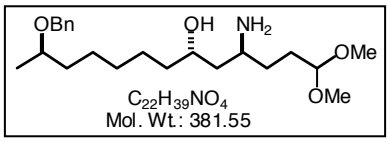


$C_{18}H_{20}N_4O_3S$
Mol. Wt.: 372.44

5-[(3*R*)-3-Benzyloxybutane-1-sulfonyl]-1-phenyl-1*H*-tetrazole (20) A solution of alcohol **18** (1.12 g, 6.21 mmol), *p*-toluenesulfonyl chloride (1.24 g, 6.52 mmol), Et_3N (1.75 mL, 12.4 mmol), 4-dimethylamino pyridine (catalytic), and CH_2Cl_2 (30 mL) was maintained under N_2 for 8 hrs. The mixture was diluted with CH_2Cl_2 (70 mL), washed with 1 N HCl (2 × 30 mL) and saturated aqueous $NaHCO_3$ (1 × 30 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to yield the resulting tosylate, which was carried on directly.

The tosylate prepared above was combined with 1-phenyl-1*H*-tetrazole-5-thiol (1.21 g, 6.82 mmol), K_2CO_3 (4.30 g, 31.0 mmol) and MeCN (30 mL) and heated at 50 °C for 12 h. After cooling to rt, the mixture was partitioned between water (100 mL) and 20% EtOAc–hexanes (100 mL). The layers were separated, and the aqueous layer was extracted with 20% EtOAc–hexanes (3 × 30 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 × 30 mL), dried (Na_2SO_4), filtered, and concentrated to yield the sulfide, which was carried on directly.

The sulfide prepared above was combined with *m*–CPBA (3.50 g, 14.2 mmol), CH_2Cl_2 (30 mL) and pH 7.0 buffer (30 mL), and stirred vigorously for 24 h. The reaction was quenched with 10% aqueous $Na_2S_2O_3$ (50 mL) and stirred vigorously for 1 hr. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with 10% aqueous $Na_2S_2O_3$ (1 × 50 mL), saturated aqueous $NaHCO_3$ (1 × 50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed (SiO_2, elution with 20% EtOAc–hexanes) to yield 1.67 g (85%) of the title compound as a colorless oil which solidified upon standing at –20 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.55 (m, 5H) 7.40–7.26 (m, 5H) 4.60 (d, *J* = 13.4 Hz 1H), 4.42 (d, *J* = 13.4 Hz 1H), 3.95–3.85 (m, 1H), 3.80–3.70 (m, 3H), 1.27 (d, *J* = 6.7 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 138.1, 133.0, 131.4, 129.6, 128.4, 127.7, 125.1, 72.1, 70.4, 52.7, 28.9, 19.3 ppm; FTIR (film) 1497, 1340, 1151 cm^{-1}; $[\alpha]_D^{24}$ = –19.9, $[\alpha]_{546}^{24}$ = –20.8, $[\alpha]_{405}^{24}$ = –44.8, (*c* 1.30, $CHCl_3$). Anal. Calcd for $C_{18}H_{20}N_4O_3S$: C, 58.05; H, 5.41; N 15.04. Found: C, 58.03; H 5.52; N 15.07.



$C_{22}H_{39}NO_4$
Mol. Wt.: 381.55

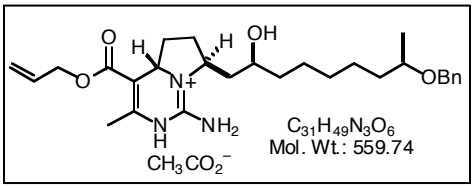
(4*S*,6*S*,12*R*)-4-Amino-12-benzyloxy-1,1-dimethoxytridecan-6-ol (22). Ozone was bubbled through a mixture of olefin **15** (935 mg, 2.15 mmol), $NaHCO_3$ (100 mg), CH_2Cl_2 (7 mL), and MeOH (7 mL) at –78 °C until the solution turned blue. Excess O_3 was purged with N_2, and Me_2S (1.5 mL) was added at –78 °C. The reaction was allowed to warm to rt and maintained at that temperature for 5 h, at which time the mixture was filtered and the filtrate concentrated to provide aldehyde **16**. This residue was azeotropically dried with C_6H_6 (3 × 5 mL) and carried on

directly. Diagnostic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.9 (s, 1H), 8.31 (d, J = 8.4 Hz, 2H), δ 8.21 (d, J = 8.4 Hz, 2H), 5.45–5.35 (m, 1H), 4.35 (t, J = 5.1 Hz, 1H), 3.42–3.38 (m, 1H), 3.30 (s, 6H), 2.62–2.54 (m, 2H), 2.20–2.00 (m, 2H), 2.00–1.90 (m, 1H), 1.80–1.50 (s, 7H).

Following the procedure of Kocienski,[5] a solution of LHMDS (2.7 mL, 1.0 M THF, 2.7 mmol) was added dropwise to a solution of sulfone **20** (1.0 g, 2.7 mmol) in THF (8 mL) at –50 °C. The resulting orange solution was maintained at –50 °C for 1 h, whereupon crude aldehyde **16** in THF (2 mL) was added dropwise. After 1 h at –50 °C, the reaction was allowed to warm to rt overnight. The reaction was then quenched with water (1 mL) and the resulting mixture was stirred until all the solids had dissolved. This solution was partitioned between saturated aqueous $NaHCO_3$ (50 mL) and 20% EtOAc–hexanes (50 mL). The layers were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 10 mL). The combined aqueous phases were extracted with 20% EtOAc–hexanes (3 × 10 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed (SiO_2, elution with 20% acetone–hexanes containing 1% Et_3N) to yield 1.05 g of olefin **21** as a 3:2 mixture of isomers, which was carried on directly. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52–5.48 (m, 2H).

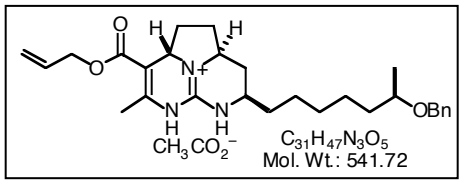
A mixture of the olefin prepared above, THF (20 mL), and aqueous 1 M NaOH (20 mL) was heated at reflux with vigorous stirring for 24 h. After cooling to rt, the layers were separated, and the aqueous layer was extracted with 20% EtOAc–hexanes (3 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (3 × 10 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed (SiO_2, elution with 20% EtOAc–hexanes containing 1% Et_3N) to yield 660 mg of the azido alcohol as a colorless oil, which was carried on directly.

The azido-olefin prepared above was combined with 5% Pd(en)·C (170 mg)[6] and MeOH (25 mL), and maintained under H_2 (50 psi) for 24 h. The mixture was filtered through Celite® with MeOH. The filtrate was concentrated to yield 600 mg (73%) of amino-alcohol **22** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.24 (m, 5H), 4.53, (d, J = 11.8 Hz, 1H), 4.45 (d, J = 11.8 Hz, 1H), 4.36 (t, J = 5.5 Hz, 1H), 3.89–3.86 (m, 1H), 3.52–3.48 (m, 1H), 3.31 (s, 6H), 3.13–3.05 (m, 1H), 1.70–1.20 (m, 16H), 1.18 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 128.3, 127.6, 127.3, 104.5, 74.9, 70.3, 69.3, 53.0, 52.9, 49.0, 41.1, 37.7, 36.6, 32.6, 29.8, 29.5, 25.9, 25.5, 19.6 ppm; FTIR (film) 3357, 1126, 1067 cm^{-1}; $[\alpha]_D^{24}$ = –66.5, $[\alpha]_{546}^{24}$ = –80.1, $[\alpha]_{435}^{24}$ = –130.7, (*c* 0.90, MeOH); HRMS (FAB) *m/z* 382.2958, (382.2957 Calcd for $C_{22}H_{40}NO_4$,M+H).

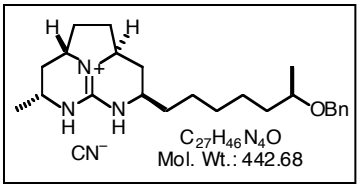


(4a*S*,7*S*)-7-[(2*S*,8*R*)-8-Benzyloxy-2-hydroxynonyl]-1-imino-3-methyl-1,2,4a,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidinium-4-carboxylic acid allyl ester acetate (25). A solution of amino-alcohol **22** (270 mg, 0.70 mmol), 1*H*-pyrazole-1-carboxamidine hydrochloride (108 mg, 0.74 mmol), diisoproplyethylamine (130 μL, 0.74 mmol) in MeOH (350 μL) was heated at 50 °C for 4 h. The mixture was concentrated under reduced pressure, then placed under high vacuum for 24 h. Aqueous acetic acid (50%, 3 mL) was then added and the mixture was maintained at rt for 56 h, at which time the solvents were removed under reduced pressure at approx 35 °C, followed by drying under high vacuum for 48 h, to afford hemi-aminal **24**.

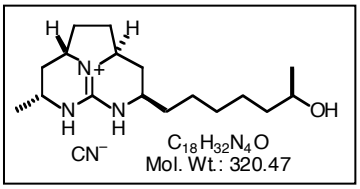
The hemi–aminal prepared above was combined with allyl acetoacetate (190 μL, 1.4 mmol), morpholinium acetate (310 mg, 2.10 mmol) and Na_2SO_4 (300 mg, 2.10 mmol) in CF_3CH_2OH (1.5 mL). The resulting mixture was heated at 60 °C for 48 h. The mixture was filtered, concentrated, and the residue was chromatographed (SiO_2, gradient elution 2% to 5% MeOH–$CHCl_3$ containing 1% acetic acid) to yield 150 mg (39%) of the title compound as a light–yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.23 (m, 5H), 5.89–5.88 (m 1H), 5.34–5.23 (m, 2H), 4.70–4.59 (m, 2H), 4.55 (d, *J* = 11.8 Hz, 1H), 4.44 (d, *J* = 11.8 Hz, 1H), 4.36–4.28 (m 2H), 3.57–3.45, (m, 2H), 2.50–2.45 (m, 1H), 2.36 (s, 3H), 2.19–2.08 (m, 1H), 1.99 (s, 3H), 1.70, 1.20 (m, 14H), 1.18 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 165.1, 151.7, 145.1, 139.0, 132.1, 128.1, 127.4, 127.2, 118.3, 100.1, 74.7, 70.1, 67.5, 64.8, 56.8, 55.9, 41.9, 37.6, 36.4, 34.3, 29.6, 28.2, 25.4, 25.3, 24.3, 19.5, 17.3 ppm; FTIR (film) 3175, 1684, 1558, 1409, 1270 cm^{-1}; $[\alpha]_D^{24}$ = –66.5, $[\alpha]_{546}^{24}$ = –80.1, $[\alpha]_{435}^{24}$ = –130.7, (*c* 0.80, $CHCl_3$); HRMS (FAB) *m/z* 484.3173 (484.3175 Calcd for $C_{29}H_{42}N_3O_4$, M).



(2a*S*,7*R*,8a*S*)-7-[(6*R*)-6-Benzyloxyheptyl]-4-methyl-2,2a,5,7,8,8a-hexahydro-1*H*-5,6,8b-triazaacenaphthylenium-3-carboxylic acid allyl ester acetate (26). Methanesulfonyl chloride (54 μL, 0.70 mmol) was added over 20 min to a solution of alcohol **25** (182 mg, 0.33 mmol, dried azeotropically with toluene) and Et_3N (185 μL, 1.32 mmol) in CH_2Cl_2 (6 mL) at 0 °C. The reaction was maintained at that temperature for 2 h, then diluted with $CHCl_3$ (50 mL), and washed with 1 N HCl (3 × 20 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 10 mL), dried (Na_2SO_4), filtered, concentrated and the residue was filtered through SiO_2 with 2% MeOH–$CHCl_3$. This mesylate was concentrated in a sealed tube, then dried azeotropically with toluene (3 × 1 mL). Chloroform (33 mL, filtered through basic Al_2O_3) and Et_3N (3.3 mL) were added, and N_2 was bubbled through the solution for 15 min. The tube was sealed, wrapped in foil, and heated at 70 °C for 2 d. After cooling to rt, the mixture was concentrated, and chromatographed (SiO_2, gradient elution 2% to 5% MeOH–$CHCl_3$ containing 1% acetic acid), to yield 135 mg (78%) of tricycle **26** containing a mixture of counter-ions, which was generally carried on directly. An analytical sample was obtained by preparative TLC (SiO_2, elution 4% MeOH–$CHCl_3$ containing 1% acetic acid): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.23 (m, 5H), 5.99–5.89 (m 1H), 5.33–5.23 (m, 2H), 4.69–4.60 (m, 2H), 4.55 (d, *J* = 11.8 Hz, 1H), 4.43 (d, *J* = 11.8 Hz, 1H), 4.11 (dd, *J* = 11.2, 3.6 Hz, 1H), 3.69–3.36 (m 1H), 3.51–3.42 (m, 2H), 2.69–2.59 (m 1H), 2.35 (s, 3H), 2.33–2.27 (m, 2H), 2.00 (s 3H), 1.95–1.75 (m, 2H), 1.70–1.45 (m, 3H), 1.45–1.20 (m 8H), 1.20–1.13 (m 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 150.0, 164.8, 149.6, 139.1, 132.1, 128.2, 127.6, 127.3, 118.6, 102.6, 74.8, 70.3, 65.0, 55.2, 54.2, 51.8, 36.5, 34.8, 32.8, 31.9, 32.8, 29.4, 25.5, 25.3, 24.0, 19.6, 17.8 ppm; FTIR (film), 1684, 1652 cm^{-1}; $[\alpha]_D^{24}$ = –29.5, $[\alpha]_{546}^{24}$ = –30.3, $[\alpha]_{435}^{24}$ = –7.8, $[\alpha]_{405}^{24}$ = 28.8 (*c* 0.80, $CHCl_3$); HRMS (FAB) *m/z* 466.3073 (466.3070 Calcd for $C_{29}H_{40}N_3O_3$,M).

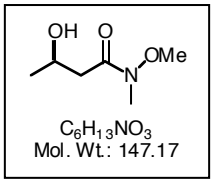


(2a*S*,4*R*,7*R*,8a*S*)-4-[(6*R*)-6-Benzyloxyheptyl]-7-methyl-2,2a,3,4,5,7,8,8a-octahydro-1*H*-5,6,8b-triazaacenaphthylenium cyanide (28). A solution of ester **26** (135 mg, 0.260 mmol), $(PPh_3)_4Pd$ (6 mg, 0.005 mmol), pyrrolidine (100 μL, 1.3 mmol), THF (1 mL) and MeOH (1 mL) was maintained at rt for 1h. The reaction was concentrated, and MeOH (0.5 mL), acetic acid (0.5 mL), and $NaBH_3CN$ (82 mg, 1.3 mmol) were added. After 1h at rt, the solvents were removed under reduced pressure, and the residue was chromatographed (SiO_2, gradient elution 2% to 5% MeOH–$CHCl_3$ containing 1% acetic acid), to yield 89 mg (85%) of tricyclic guanidine **28**: ^{1}H NMR (500 MHz, 1:1 $CDCl_3$–C_6D_6) δ 8.21 (brs, 1H), 8.10 (brs, 1H), 7.21–7.05 (m 5H), 4.38 (d, *J* = 11.8 Hz, 1H), 4.26 (d, *J* = 11.8 Hz, 1H), 3.36–3.30 (m, 1H), 3.20–3.15 (m, 1H), 3.10–3.05 (m, 1H), 2.93–2.89 (m 2H), 1.87–1.60 (m, 3H), 1.50–1.40 (m, 2H), 1.35–0.95 (m, 16H), 0.89–0.70 (m, 3H); ^{13}C NMR (125 MHz, 1:1 $CDCl_3$–C_6D_6) δ 180.0, 150.3, 139.6, 75.1, 70.5, 54.9, 54.8, 51.8, 47.5, 37.0, 35.8, 35.2, 33.2, 30.8, 29.8, 25.7, 25.6, 19.9; ^{13}C NMR (125 MHz, CD_3OD) δ 180.0, 151.5, 140.3, 129.3, 129.0, 128.6, 76.3, 71.5, 56.5, 56.4, 53.1, 37.6, 36.8, 36.5, 31.8, 30.6, 26.4, 26.2, 21.7, 19.9; FTIR (film), 3298, 2331, 1633 cm^{-1}; $[\alpha]_D^{24}$ = –80.0, $[\alpha]_{546}^{24}$ = –94.3, $[\alpha]_{435}^{24}$ = –164.3, $[\alpha]_{405}^{24}$ = –200.8 (*c* 0.80, $CHCl_3$); HRMS (FAB) *m/z* 384.3025 (384.3015 Calcd for $C_{24}H_{38}N_3O$, M).



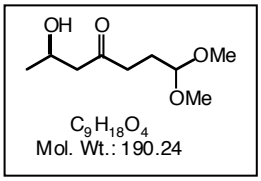
(2a*S*,4*R*,7*R*,8a*S*)-4-[(6*R*)-6-Hydroxyheptyl]-7-methyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylenium cyanide (29). A mixture of benzyl ether **29** (25 mg, 0.061 mmol), 10% Pd·C (15 mg), acetic acid (4 drops) and MeOH (2 mL) was maintained under 75 psi of H_2 for 2 d. The mixture was filtered through Celite®, and concentrated. The residue was chromatographed (SiO_2, gradient elution 5% to 10% MeOH–$CHCl_3$ containing 1% acetic acid), to yield 14 mg (72%) of **29**, as a colorless oil: ^{1}H NMR (500 MHz, CD_3OD) δ 3.71–3.66 (m, 1H), 3.65–3.58 (m, 3H), 3.54–3.48 (m, 1H), 2.35–2.15 (m, 4H) 2.04–1.90 (brs 2H), 1.70–1.50 (m, 4H), 1.48–1.30 (m, 10H), 1.25 (d, *J* = 6.4 Hz, 3H), 1.13 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD, DEPT90) δ 151.5, 68.5, 56.5, 56.4, 53.1, 48.9, 40.0, 36.8, 34.3, 31.8, 30.6,[7] 26.7, 26.2, 23.5, 21.7; FTIR (film), 3272, 2360, 1634 cm^{-1}; $[\alpha]_D^{24}$ = –42.6, $[\alpha]_{546}^{24}$ = –56.1, $[\alpha]_{435}^{24}$ = –94.7, $[\alpha]_{405}^{24}$ = –114.6 (*c* 0.55, $CHCl_3$); HRMS (FAB) *m/z* 294.2541 (294.2545 Calcd for $C_{17}H_{32}N_3O$, M).

Section II Experimental



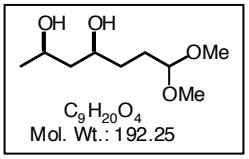
3*R*-Hydroxy-*N*-methoxy-*N*-methylbutyramide (53). Following the general procedure of Williams,[8] a solution of *i*-PrMgCl (127 mL of a 2.0 M in THF, 254 mmol) was added to a –30 °C mixture of ester **44**[9] (6.00 g, 51.0 mmol), *N,O*-dimethylhydroxyamine hydrochloride (12.4 g, 127 mmol), and THF (150 mL) over 40 min. The solution was maintained at –30 °C for 30 min, then at 0 °C for 3 h, then poured into cold, saturated aqueous NH_4Cl (500 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (6 × 50 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and partially concentrated. The residue was filtered through SiO_2 with EtOAc, concentrated and the residue placed under vacuum (0.5 mm) for 1 h to provide 6.00 g (80%) of the title compound as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.24–4.17 (m, 1H), 3.88 (s, 1H), 3.70 (s, 3H), 3.19 (s, 1H), 2.65 (d, *J* = 16.9 Hz, 1H), 2.40 (dd, *J* = 16.9, 9.5 Hz, 1H), 1.21 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 63.7, 60.9, 39.4, 31.4, 22.1; IR (film) 3438, 2970, 1650, 1389, 1000, cm^{-1}; $[\alpha]_D^{24}$ = –67.2 (*c* 0.95, $CHCl_3$); HRMS (EI+) *m/z* 147.0897 (147.0896 Calcd for $C_6H_{13}NO_3$, M+Na).

3*S*-Hydroxy-*N*-methoxy-*N*-methylbutyramide (*ent*–53). Following the procedure for preparing **53**, ester *ent*–**44** (6.00 g 50.8 mmol) was converted to 6.67 g (89%) of amide *ent*–**53**; $[\alpha]_D^{24}$ = 60.8 (*c* 0.55, $CHCl_3$).



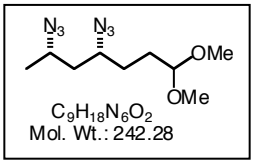
6*R*-Hydroxy-1,1-dimethoxyheptan-4-one (54). A 0 °C solution of Grignard reagent **11**[10] (140 mL, 0.5 M in THF, 70 mmol) was added to a 0 °C solution of amide **53** (1.50 g, 10.2 mmol) and THF (60 mL) over 10 min. The solution was maintained at 0 °C for 30 min, then 1 h at rt. The solution was cooled to 0 °C, then poured into cold saturated aqueous NH_4Cl (500 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (6 × 50 mL), the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed (SiO_2, gradient elution with 20–30–100% EtOAc–hexanes containing 1% Et_3N) to provide 1.80 g (91%) of the title compound as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (t, *J* = 5.4 Hz, 1H), 4.22–4.19 (m, 1H), 3.25 (s, 6H), 3.12 (s, 1H) 2.61–2.47 (m, 4H), 1.91–1.87 (m, 2H), 1.17 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.3, 103.7, 63.9, 53.3, 50.7, 38.0, 26.4, 22.4; IR (film) 3448, 2966, 1709, 1374, 1127, 1057 cm^{-1}; $[\alpha]_D^{24}$ = –51.9, $[\alpha]_{546}^{24}$ = –62.6, $[\alpha]_{435}^{24}$ = –103, $[\alpha]_{405}^{24}$ = –124 (*c* 0.8., $CHCl_3$).

6*S*-Hydroxy-1,1-dimethoxyheptan-4-one (*ent*–54). Following the procedure for preparing **54**, amide *ent*–**53** (6.67 g, 45.3 mmol) yielded 5.82 g (68%) of ketone *ent*–**54** as a colorless oil.



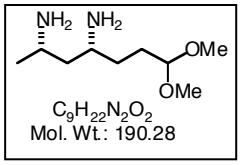
(2*R*,4*S*)-7,7-Dimethoxyheptane-2,4-diol (55). Following the procedure of Shapiro,[11] a solution of Et_2BOMe (13.3 mL, 1.0 M in THF, 13.3 mmol) was added to a solution of ketone **54** (2.20 g, 11.6 mmol), THF (130 mL), and MeOH (35 mL) at –78 °C. After 30 min, $NaBH_4$ (850 mg, 14 mmol) was added, and the mixture was stirred at –78 °C for 1 h. Methanol (50 mL) was added followed by 1 N NaOH (30 mL), and the mixture was maintained at 25 °C for 1 h. This mixture was cooled to 0 °C and 30% H_2O_2 (15 mL) was added dropwise, and the reaction was allowed to warm to rt overnight. Brine (50 mL) was added and the mixture was concentrated to approximately 100 mL prior to extraction with CH_2Cl_2 (6 × 50 mL), Et_2O (3 × 50 mL), and CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated to provide 2.20 g (97%) of the title compound as a clear oil which was used without further purification. An analytical sample was obtained by chromatography (SiO_2, gradient elution with 75–100% EtOAc–hexanes containing 1% Et_3N): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (t, J = 5.3 Hz, 1H), 4.06–4.02 (m, 1H), 3.88–3.84 (m, 1H), 3.49 (s, 1H), 3.31 (s, 6H), 3.29 (s, 1H), 1.76–1.71 (m, 2H), 1.56–1.48 (m, 4H), 1.19 (d, J = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.7, 72.6, 68.9, 53.3, 53.0, 44.8, 32.8, 28.7, 24.1; IR (film) 3386, 2936, 1451, 1376, 1129, 1057, cm^{-1}; $[\alpha]_D^{24}$ = –14.8, $[\alpha]_{546}^{24}$ = –20.1, $[\alpha]_{435}^{24}$ = –32.5, $[\alpha]_{405}^{24}$ = –38.4 (*c* 0.85, C_6H_6); HRMS (CI) *m/z* 215.1125 (215.1259 Calcd for $C_9H_{20}O_4Na$, M+Na).

(2*S*,4*R*)-7,7-Dimethoxyheptane-2,4-diol (*ent*–55). Following the procedure for preparation of **55**, ketone *ent*–**54** (5.82 g, 30.6 mmol) yielded 4.57 g (78%) of diol *ent*–**55**, as a colorless oil.



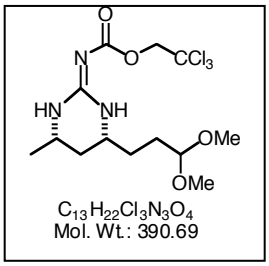
(2*S*,6*R*)-4,6-Diazido-1,1-dimethoxyheptane (S5) Diethyl azodicarboxylate (4.0 mL, 25 mmol) was added dropwise to a 0 °C solution of diol **55** (1.22 g, 6.34 mmol), hydrozoic acid (10.6 mL, 2.7 M in toluene, 29 mmol), triphenylphosphine (6.65 g, 25.4 mmol) and THF (60 mL) over 20 min. After an additional 20 min, hexanes (100 mL) was added, and the residue was filtered through SiO_2 with 10% Et_2O-hexanes. The solution was concentrated and the residue was chromatographed (SiO_2, gradient elution with 5–10% Et_2O–hexanes) to provide 1.26 g (82%) of the title compound as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (t, J = 5.5 Hz, 1H), 3.63–3.58 (m, 1H), 3.42–3.37 (m, 1H), 3.31 (s, 6H), 1.81–1.42 (m, 6H), 1.31 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.1, 59.4, 54.7, 53.2, 52.9, 40.4, 29.0, 28.9, 19.2; IR (film) 2930, 2100, 1251, 1130, cm^{-1}; $[\alpha]_D^{24}$ = 29.4, $[\alpha]_{546}^{24}$ = 32.1, $[\alpha]_{435}^{24}$ = 55.4, $[\alpha]_{405}^{24}$ = 67.3 (*c* 1.1, C_6H_6); HRMS (CI) *m/z* 211.1305 (211.1307 Calcd for $C_8H_{15}N_6O$, M–MeOH).

(2*R*,6*S*)-4,6-Diazido-1,1-dimethoxyheptane (*ent*-S5). Following the above procedure, diol *ent*-**55** (4.56 g, 23.7 mmol) yielded 5.0 g (87%) of the title compound as a colorless oil.

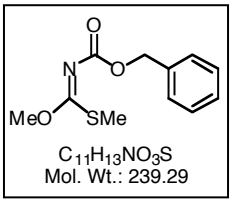


(2*S*,4*R*)-7,7-Dimethoxyheptane-2,4-diamine (43). A mixture of bis-azide **S5** (1.89 g, 7.8 mmol), 10% Pd·C (200 mg) and MeOH (20 mL) was maintained under 60 psi of H_2 for 24 h. The mixture was filtered through Celite and the filtrate was concentrated to provide 1.46 g (98%) of the title compound as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.36 (t, *J* = 5.6 Hz, 1H), 3.32 (s, 6H), 3.07–3.04 (m, 1H), 2.83–2.80 (m, 1H) 1.72–1.57 (m, 6H), 1.51–1.40 (m, 2H), 1.32–1.26 (m, 2H), 1.08 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 104.6, 53.0, 52.7, 50.0, 47.6, 45.7, 33.9, 29.0, 24.8; IR (film) 3359, 3279, 2951, 1126, 1055, cm^{-1}; $[\alpha]_D^{24} = -4.0$, $[\alpha]_{546}^{24} = -3.4$, $[\alpha]_{435}^{24} = -9.6$, $[\alpha]_{405}^{24} = -7.7$ (*c* 0.70, MeOH); HRMS (FAB) *m*/*z* 191.1761 (191.2912 Calcd for $C_9H_{23}N_2O_2$, M+H).

(2*S*,4*R*)-7,7-Dimethoxyheptane-2,4-diamine (*ent*–43). Following the procedure for preparation of **43**, bis azide *ent*–**S5** (500 mg, 2.1 mmol) yielded 390 mg (100%) of *ent*–**43** as a colorless oil.

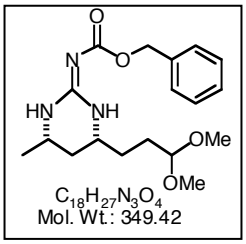


[(4*R*,6*S*)-4-(3,3-Dimethoxy-propyl)-6-methyltetrahydropyrimidine-2-ylidene]-carbamic acid 2,2,2-trichloroethyl ester (57). A solution of diamine **43** (1.0 g, 5.2 mmol), reagent **56**[12] (1.5 g, 5.5 mmol), and CH_2Cl_2 (20 mL) was maintained for 24 h. The solvent was removed under a stream of air in a fume hood (*stench!*) then concentrated. The residue was chromatographed (SiO_2, elution with 5% *i*-PrOH–hexanes with 1% Et_3N) to provide 1.67 g (82%) of the title compound as a colorless oil which solidifies upon standing: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30–8.14 (m, 2H), 4.66 (d, *J* = 12.1 Hz, 1H), 4.58 (d, *J* = 12.1 Hz, 1H), 4.28 (t, *J* = 4.8 Hz, 1H), 3.57–3.52 (m, 1H), 3.45–3.37 (m, 1H), 3.25 (s, 6H), 1.96 (dt, *J* = 13.0, 3.4 Hz), 1.67–1.50 (m, 4H), 1.26–1.17 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5, 158.9, 103.9, 96.1, 74.3, 53.0, 52.8, 49.3, 45.2, 35.3, 30.1, 28.0, 21.4; IR (film) 3250, 3155, 2935, 1633, 1556, 1391 cm^{-1}; $[\alpha]_D^{24} = 14.7$, $[\alpha]_{546}^{24} = 17.5$, $[\alpha]_{435}^{24} = 31.8$, $[\alpha]_{405}^{24} = 39.3$ (*c* 1.2, $CHCl_3$); HRMS (FAB) *m*/*z* 390.0751 (390.0754 Calcd for $C_{13}H_{23}Cl_3N_3O_4$, M+H).



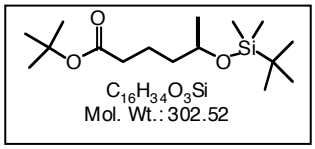
Benzyl *N*-[methoxy-(methylthio)methylene]carbamate (58). Benzyl chloroformate (3.4 mL, 24 mmol) was added dropwise to a 0 °C suspension of KSCN (2.40 g, 24.7 mmol) in THF (120 mL). The cooling bath was removed and the mixture was stirred vigorously for 5 h. Methanol (1.6 mL, 39.5 mmol) was then added dropwise, and the mixture was stirred for 18 h.

Potassium carbonate (6.6 g, 47 mmol) was then added, followed by dimethyl sulfate (2.4 mL, 25 mmol) and the mixture was stirred for 24 h. The pale-yellow suspension was filtered, concentrated, and the residue was chromatographed (SiO_2, gradient elution 10–20% Et_2O–hexanes) to yield 1.66 g (30%) of the title compound as colorless oil, which solidifies upon standing at –20 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.25 (m, 5H), 5.19 (s, 2H), 3.95 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 136.0, 128.5, 128.4, 128.2, 68.1, 58.5, 57.7, 13.9. Further characterization was precluded by this compound's stench and instability.



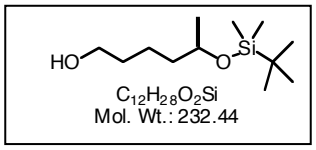
4*R*,6*S*)-2-[Benzyloxycarbonylamino]-4-[(3,3)-dimethoxypropyl]-6-methyl-3,4,5,6-tetrahydopyrimidine (59). Reagent **58** (290 mg, 1.21 mmol) was added to a solution of diamine **43** (209 mg, 1.1 mmol) and CH_2Cl_2 (5 mL). The solution was maintained for 24 h, then the solvent was removed under a stream of air in the hood (*stench*!), and residual volatiles removed under reduced pressure. The residue was chromatographed (SiO_2, gradient elution with 5–10% *i*-PrOH–hexanes, 1% Et_3N) to yield 317 mg (82%) of the title compound as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.29 (m, 5H), 7.25–7.05 (broad d, 2H), 5.08 (s, 2H), 4.35 (t, J = 5.5 Hz, 1H), 3.56–3.50 (m, 1H), 3.45–3.41 (m, 1H), 3.32 (s, 6H), 1.98 (broad d, J = 13 Hz, 1H), 1.69–1.55 (m, 5H), 1.32–1.23 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 158.8, 137.6, 128.2, 127.8, 127.5, 104.1, 66.0, 53.1, 53.1, 53.0, 49.6, 45.4, 35.8, 30.5, 28.3, 21.5; FTIR (film) 3245, 3154, 2952, 1621, 1556, 1454, 1392, 1325, 1241, 1074 cm^{-1}; $[\alpha]_D^{24}$ = 5.6, $[\alpha]_{546}^{24}$ = 10.3, $[\alpha]_{435}^{24}$ = 15.5, $[\alpha]_{405}^{24}$ = 19.6 (*c* 1.0, MeOH); HRMS (FAB) *m*/*z* 350.2083 (350.2080 Calcd for $C_{18}H_{29}N_3O_4$, M+H).

(4*S*,6*R*)-2-[Benzyloxycarbonylamino]-4-[(3,3)-dimethoxypropyl]-6-methyl-3,4,5,6-tetrahydopyrimidine (*ent*–59). Following the procedure for preparation of **59**, diamine *ent*–**43** (393 mg, 2.1 mmol) yielded 460 mg (64%) of guanidine *ent*–**59** as a colorless oil: $[\alpha]_D^{24}$ = –5.7, $[\alpha]_{546}^{24}$ = –7.0, $[\alpha]_{435}^{24}$ = –12.9, $[\alpha]_{405}^{24}$ = –16.1 (*c* 0.8, MeOH).

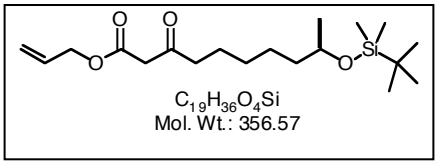


(5*R*)-5-(*tert*-Butyldimethylsiloxy)-hexanoic acid *tert*-butyl ester (46). *t*-Butyl acetate (5.1 mL, 22.5 mmol) was added dropwise to a solution of LDA (38 mmol) in THF (76 mL) at –78 °C. The solution was maintained at –78 °C for 30 min, then DMPU (20 mL) was added, followed quickly by a solution of iodide **45**[13] (6.4 g, 20.5 mmol) and THF (5 mL). The heterogeneous mixture was allowed to warm to 0 °C over 3 h. The mixture was then poured into brine (250 mL) and the layers separated. The aqueous layer was extracted with Et_2O (3 × 50 mL), the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (SiO_2, elution with 5% EtOAc–hexanes) to provide 9.5 g of a mixture of esters **46** and **47**, which was carried on without further purification. An analytical sample of the title compound was obtained by further chromatography (SiO_2, elution with 5% EtOAc–hexanes) colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (app. sextet, J = 6.1 Hz, 1H), 2.20 (t, J = 7.5

Hz, 2H), 1.67–1.53 (m, 2H), 1.48–1.36 (m, 11H), 1.11 (d, J = 6.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 79.9, 68.3, 39.0, 35.6, 28.1, 25.9, 23.8, 21.5, 18.1, –4.4, –4.8; IR (film) 2930, 2858, 1731, 1255, 1155 cm^{-1}; $[\alpha]_D^{24}$ = –10.4, $[\alpha]_{546}^{24}$ = –13.1, $[\alpha]_{435}^{24}$ = –22.0, $[\alpha]_{405}^{24}$ = –27.2 (*c* 0.85, $CHCl_3$). HRMS (CI–isobutane) *m/z* 303.2361 (303.2355 Calcd for $C_{16}H_{35}O_3Si$, M+H).



5*R*-(*tert*-Butyldimethylsiloxy)-hexan-1-ol (48). Lithium aluminum hydride (31 mL of a 1.0 M solution in Et_2O, 31 mmol) was added dropwise to a solution of esters **46** and **47** (9.50 g, 16.8 mmol) and THF (60 mL) at 0 °C. The cooling bath was removed and the reaction was maintained for 12 h. The solution was cooled to 0 °C, and water (1.2 mL), 15% NaOH (1.2 mL), and water (3.6 mL) were added sequentially, with vigorous stirring. The mixture was stirred for 12 h, then filtered through Celite© with EtOAc. The filtrate was concentrated, and the residue was chromatographed (SiO_2, gradient elution with 20–40% EtOAc–hexanes) to provide 3.97 g (50% for 2 steps) of the title compound as colorless oil whose spectral data match those reported[14] $[\alpha]_D^{24}$ = –14.6 (c 0.92 $CHCl_3$) (lit for the enantiomer: $[\alpha]_D^{24}$ = 14 (c 1.05 $CHCl_3$)).

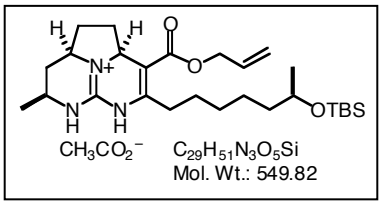


(9*R*)-9-(*tert*-Butyldimethylsiloxy)-3-oxodecanoic acid allyl ester (52). Following the general procedure of Corey,[15] solid I_2 (4.55 g, 17.9 mmol) was added in three portions over 30 min to a solution of alcohol **48** (3.97 g, 17.1 mmol), triphenylphosphine (4.70 g, 17.9 mmol), imidazole (1.28 g, 18.8 mmol), Et_2O (30 mL) and acetonitrile (10 mL) at 0 °C. The mixture was then allowed to warm to rt for 30 min before hexanes (50 mL) was added and the mixture filtered through a plug of SiO_2 topped with a layer of basic Al_2O_3 with 5% Et_2O-hexanes. The solution was concentrated to provide 5.85 g (100%) of iodide **49**, which was used without further purification.

Following the general procedure of Weiler,[16] methyl acetoacetate (1.8 mL, 17 mmol) was added dropwise to a suspension of NaH (820 mg, 18 mmol, washed 1 × 5 mL hexanes) in THF (60 mL) at 0 °C. *n*-Butyllithium (75 mL of 2.5 M solution in hexanes, 18 mmol) was then added dropwise, and the yellow solution maintained at 0 °C for 10 min. Iodide **49** was then added dropwise, and the reaction maintained at 0 °C for 1 h. The reaction was poured into cold 1 NH_4Cl (200 mL) and the layers separated. The aqueous layer was extracted with Et_2O (3 × 50 mL), the combined organic phases where washed with brine (1 × 100 mL), dried ($MgSO_4$), filtered, concentrated, and the residue was chromatographed (SiO_2, gradient elution with 5–10% EtOAc–hexanes) to provide 3.86 g of β-keto ester **51** which was carried on directly.

The ester prepared above (3.86 g, 11.7 mmol), DMAP (1.43 g, 11.7 mmol) and allyl alcohol (12 mL) were heated at 100 °C for 22 h. The solution was partitioned between 0.1 N HCl (200 mL) and MTBE (75 mL). The aqueous layer was extracted with MTBE (2 × 75 mL), the combined organic layers were washed with brine (1 × 100 mL), dried (Na_2SO_4), filtered, concentrated, and the residue residue was chromatographed (SiO_2, gradient elution with 5–10% EtOAc–hexanes) to provide 3.72 g (65%, 3 steps) of the title compound as a colorless oil: ^{1}H

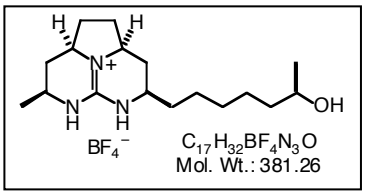
NMR (500 MHz, $CDCl_3$) δ 5.96–5.86 (m, 1H), 5.34 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.26 (dt, *J* = 10.4, 1.1 Hz, 1H), 4.36 (d, *J* = 5.8 Hz, 2H), 3.77–3.72 (m, 1H), 3.47 (s, 2H), 2.53 (t, *J* = 7.3 Hz, 2H), 1.63–1.55 (m, 3H), 1.45–1.24 (m, 6H), 1.10 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7, 166.9, 131.5, 118.9, 68.5, 65.9, 49.2, 43.1, 39.5, 29.1, 25.9, 25.5, 23.8, 23.5, 18.2, –4.4, –4.7; IR (film) 2931, 2657, 1748, 1720, 1255 cm^{-1}; $[\alpha]_D^{24}$ = –8.60, $[\alpha]_{546}^{24}$ = –10.6, $[\alpha]_{435}^{24}$ = –17.0, $[\alpha]_{405}^{24}$ = –23.0 (*c* 0.79, $CHCl_3$). Anal. Calcd for $C_{19}H_{36}O_4Si$: C, 64.00; H, 10.18. Found C, 64.20; H, 10.12.



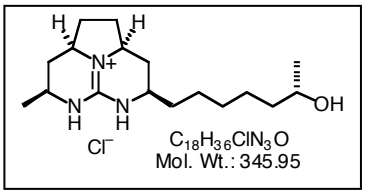
(2a*S*,7*S*,8a*R*)-3-Allyloxycarbonyl-4-[(6*R*)-6-(*tert*-butyldimethylsiloxy)heptyl]-7-methyl-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b-triazaacenaphthylenium acetate (60). A mixture of guanidine **59** (231 mg, 0.66 mmol), 10% Pd·C (50 mg), acetic acid (42 μL, 0.73 mmol) and MeOH (5 mL) was maintained under an atmosphere of H_2 (60 psi) for 12 h. The mixture was filtered through Celite with MeOH, and the filtrate was concentrated to yield 170 mg (93%) of the free guanidinium acetate as a colorless oil, which was carried on directly. Diagnostic data: ^1H NMR (400 MHz, CD_3OD) δ 4.39 (t, *J* = 5.5 Hz, 1H), 3.56–3.51 (m, 1H), 3.49–3.43 (m, 1H), 3.33 (s, 6H), 2.10 (dt, *J* = 14.0, 3.5 Hz), 1.92 (s, 3H), 1.71–1.55 (m, 4H), 1.27–1.19 (m, 4H).

The guanidinium salt prepared above was combined with 50% aqueous acetic acid (3 mL) and maintained at rt for 2 d. The solvents were removed, and the residue was dried thoroughly under high vacuum to provide bicyclic hemi-aminal **41**, which was carried on directly. Diagnostic data: ^1H NMR (400 MHz, CD_3OD) δ 5.46–5.35 (m, 1H).

This sample of guanidine hemi-aminal **41** was combined with β-keto ester **52** (660 mg, 1.84 mmol), morpholinium acetate (90 mg, 0.61 mmol), Na_2SO_4 (90 mg) and trifluoroethanol (1.2 mL), and heated at 60 °C for 2 d. The mixture was filtered, concentrated, and the residue was chromatographed (SiO_2, gradient elution with 2–5% MeOH–$CHCl_3$ with 1% AcOH) to provide 270 mg of the title compound (81%) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 5.96–5.86 (m, 1H), 5.34–5.23 (m, 2H), 4.66–4.58 (m, 2H), 4.42 (dd, *J* = 9.8, 5.7 Hz, 1H), 3.77–3.72 (m, 1H), 3.70–3.63 (m, 1H), 3.57–3.50 (m, 1H), 2.85–2.60 (m, 2H), 2.55–2.48 (m, 1H), 2.32–2.24 (m, 1H), 2.12–2.05 (m, 1H), 2.00 (s, 3H), 1.66–1.50 (m, 4H), 1.45–1.20 (m, 10H), 1.09 (d, *J* = 6.1 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 165.0, 147.0, 132.2, 118.5, 99.1, 68.7, 65.1, 57.0, 55.5, 45.4, 39.7, 35.7, 33.2,, 29.5, 28.7, 27.0, 25.9, 25.7, 23.8, 23.7, 19.5, 18.2, –4.5, –4.7; IR (film) 2930, 2857, 1696, 1626, 1538, 1258 cm^{-1}; $[\alpha]_D^{24}$ = –82.1, $[\alpha]_{546}^{24}$ = –100, $[\alpha]_{435}^{24}$ = –194, $[\alpha]_{405}^{24}$ = –253 (*c* 0.67, $CHCl_3$); HRMS (FAB) *m*/*z* 490.3465 (490.3465 Calcd for $C_{27}H_{48}N_3O_3Si$, M).

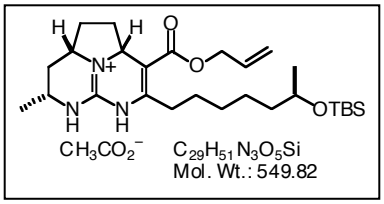


(2a*S*,4*R*,7*S*,8a*R*)-4-[(6*R*)-6-Hydroxyheptyl]-7-methyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylenium tetrafluoroborate (39). A solution of ester **60** (88 mg, 0.16 mmol), $(PPh_3)_4Pd$ (4 mg, 0.0032 mmol), pyrrolidine (70 μL, 0.80 mmol), THF (1 mL) and MeOH (1 mL), was maintained at rt and monitored by ESMS. After 2 h, the reaction was concentrated and the residue was dissolved in AcOH (2 mL). Solid $NaBH_4$ (30 mg, 0.80 mmol) was added, and the solution was maintained at rt overnight. The solvent was removed under reduced pressure and the residue treated with 2 N HCl (10 mL) for 1 d. The solution was diluted with water (10 mL) and extracted with $CHCl_3$ (6 × 5 mL). The combined organic layers were washed with saturated aqueous $NaBF_4$ (3 × 5 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed (SiO_2, gradient elution with 5–10% MeOH–$CHCl_3$) to provide 38 mg (66%) of guanidine **39** as a colorless oil: ^{1}H NMR (500 MHz, CD_3OD) δ 3.77–3.66 (m, 3H), 3.57–3.50 (m, 1H), 3.45–3.38 (m, 1H), 2.29–2.17 (m, 4H), 1.72–1.64 (m, 2H), 1.61–1.53 (m, 2H), 1.46–1.33 (m, 9H), 1.30–1.20 (m, 5H), 1.13 (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 151.1, 68.5, 57.54, 57.48, 51.6, 47.3, 40.0, 36.4, 35.8, 34.6, 31.1, 31.0, 30.6, 26.7, 26.2, 23.6, 20.7; $[\alpha]_D^{24}$ = 7.6, $[\alpha]_{546}^{24}$ = 9.5, $[\alpha]_{435}^{24}$ = 17.4, $[\alpha]_{405}^{24}$ = 21.4 (*c* 0.95, MeOH); HRMS (FAB) *m/z* 294.2539 (294.2545 Calcd for $C_{17}H_{32}N_3O$).



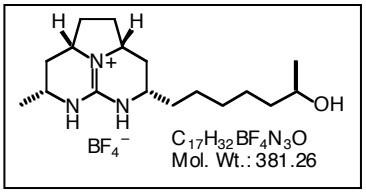
(2a*S*,4*R*,7*S*,8a*R*)-4-[(6*S*)-6-Hydroxyheptyl]-7-methyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylenium chloride (S7). Diethyl azodicarboxylate (68 μL, 0.43 mmol) was added dropwise to a solution of alcohol **39** (82 mg, 0.22 mmol, azeotroped 3 × with C_6H_6), *p*-nitrobenzoic acid (72 mg, 0.43 mmol), triphenylphosphine (113 mg, 0.43 mmol) and THF (2 mL) over 10 min. The mixture was chromatographed (SiO_2, gradient elution with 2–5% MeOH–$CHCl_3$, 1% AcOH) to provide the corresponding *p*-nitrobenzoate ester, contaminated with triphenylphosphine oxide and reduced DEAD. Diagnostic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19–5.14 (m, 1H); ESI *m/z* 443, 276.

The ester prepared above was combined with K_2CO_3 (120 mg) and MeOH (2 mL), and stirred overnight. The MeOH was removed under reduced pressure and the residue was dissolved in 1 N HCl (10 mL) and extracted with $CHCl_3$ (6 × 3 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed (SiO_2, gradient elution with 5–10% MeOH–$CHCl_3$, 1% AcOH) to provide 45 mg (61%) of **S7** as a colorless oil. $[\alpha]_D^{24}$ = 18.0, $[\alpha]_{546}^{24}$ = 21.2, $[\alpha]_{435}^{24}$ = 36.5, $[\alpha]_{405}^{24}$ = 44.1 (*c* 0.75, MeOH).

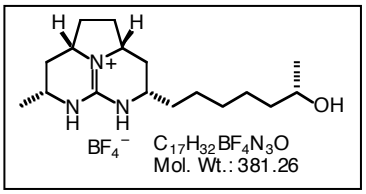


(2a*R*,7*R*,8a*S*)-3-Allyloxycarbonyl-4-[(6*R*)-6-(*tert*-butyldimethylsiloxy)heptyl]-7-methyl-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b-triazaacenaphthylenium acetate (S6). A mixture of guanidine *ent*-**41** (1.35 mmol) was combined with β-ketoester **52** (1.44 g, 4 mmol), morpholinium acetate (200 mg, 1.35 mmol), Na_2SO_4 (200 mg) and trifluoroethanol (2.7 mL) was

maintained at 60 °C for 2 d. The mixture was filtered, concentrated, and the residue was chromatographed (SiO_2, gradient elution with 2–5% MeOH–$CHCl_3$ with 1% AcOH) to provide 500 mg of the title compound (81% for two steps) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89–5.87 (m, 1H), 5.34–5.22 (m, 2H), 4.68–4.58 (m, 2H), 4.41 (dd, *J* = 9.8, 5.6 Hz, 1H), 3.79–3.71 (m, 1H), 3.71–3.60 (m, 1H), 3.60–3.49 (m, 1H), 2.85–2.36 (m, 2H), 2.56–2.47 (m, 1H), 2.34–2.20 (m, 1H), 2.18–2.05 (m, 1H), 2.04 (s, 3H), 1.70–1.51 (m, 4H), 1.46–1.20 (m, 10H) 1.10 (d, *J* = 6.1 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 165.0, 147.0, 132.2, 118.5, 99.1, 68.7, 64.9, 57.0, 55.6, 45.4, 39.6, 35.7, 33.2, 30.7, 29.5, 28.7, 27.0, 25.9, 25.7, 23.8, 22.3, 19.4, 18.1, –4.5, –4.7; FTIR (film) 2934, 2860, 1687, 1625, 1405, 1254 cm^{-1}; $[\alpha]_D^{24}$ = 47.9, $[\alpha]_{546}^{24}$ = 57.6, $[\alpha]_{435}^{24}$ = 111.6, $[\alpha]_{405}^{24}$ = 144.9 (*c* 0.75, $CHCl_3$); HRMS (ESI) *m/z* 490.3455. (490.3465 Calcd for $C_{27}H_{48}N_3O_3Si$, M).



(2a*R*,4*S*,7*R*,8a*S*)-4-[(6*R*)-6-Hydroxyheptyl]-7-methyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylenium tetrafluoroborate (81). A solution of ester **S6** (400 mg, 0.74 mmol), $(PPh_3)_4Pd$ (10 mg, 0.009 mmol), pyrrolidine (300 μL, 3.7 mmol), THF (2 mL) and MeOH (2 mL) was maintained at rt and monitored by ESMS. After 2 h, the reaction was concentrated, and the residue was dissolved in AcOH (5 mL). Solid $NaBH_4$ (140 mg, 3.7 mmol) was added in 3 portions over 45 min at rt. The mixture was then maintained at rt overnight, 1 N HCl (5 mL) was added, and the resulting mixture was stirred for 1 d at rt. This mixture was diluted with water (10 mL) and extracted with $CHCl_3$ (6 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed (SiO_2, gradient elution with 2–5–10% MeOH–$CHCl_3$, 1% AcOH) and the fractions containing the product were combined, concentrated, and azeotroped with heptane. This residue was dissolved in $CHCl_3$ (20 mL), washed with with saturated aqueous $NaBF_4$ (3 × 5 mL), dried (Na_2SO_4), filtered, and concentrated to provide 142 mg (50%) of tricyclic guanidine **81** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77–3.66 (m, 3H), 3.57–3.50 (m, 1H), 3.45–3.38 (m, 1H), 2.29–2.17 (m, 4H), 1.72–1.64 (m, 2H), 1.61–1.53 (m, 2H), 1.46–1.33 (m, 9H), 1.30–1.20 (m, 5H), 1.13 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 68.5, 57.54, 57.48, 51.6, 47.3, 40.0, 36.4, 35.8, 34.6, 31.1, 31.0, 30.6, 26.7, 26.2, 23.6, 20.7; $[\alpha]_D^{24}$ = –15.4, $[\alpha]_{546}^{24}$ = –18.5, $[\alpha]_{435}^{24}$ = –31.7, $[\alpha]_{405}^{24}$ = –38.2 (*c* 0.77, MeOH); HRMS (FAB) *m/z* 294.2546 (294.2545 Calcd for $C_{17}H_{32}N_3O$, M)

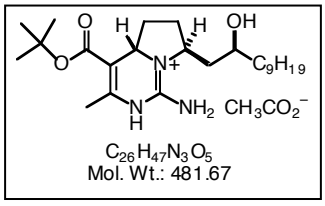


(2a*R*,4*S*,7*R*,8a*S*)-4-[(6*S*)-6-Hydroxyheptyl]-7-methyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylenium tetrafluoroborate (S8). Diethyl azodicarboxylate (80 μL, 0.50 mmol) was added dropwise to a solution of alcohol **81** (94 mg, 0.25 mmol, azeotroped 3 × with C_6H_6), *p*-nitrobenzoic acid (84 mg, 0.50 mmol), triphenylphosphine (131 mg, 0.50 mmol) and

THF (2 mL) over 10 min. The mixture was chromatographed (SiO_2, gradient elution with 2–5% MeOH–$CHCl_3$, 1% AcOH) to provide the corresponding *p*-nitrobenzoate ester, contaminated with triphenylphosphine oxide and reduced DEAD. Diagnostic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19–5.14 (m, 1H); ESI *m/z* 443, 276.

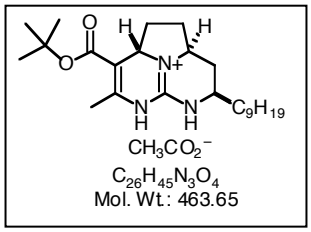
The ester prepared above was combined with K_2CO_3 (300 mg) and MeOH (5 mL), and stirred overnight. The MeOH was removed under reduced pressure and the residue was dissolved in 1 N HCl (20 mL) and extracted with $CHCl_3$ (6 × 3 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed (SiO_2, gradient elution with 5–10% MeOH–$CHCl_3$, 1% AcOH). The fractions containing the product were combined, concentrated, and azeotroped with heptane. The residue was dissolved in $CHCl_3$, (20 mL) and washed with saturated aqueous $NaBF_4$ (3 × 5 mL), dried (Na_2SO_4), filtered, and concentrated to provide 62 mg (66%) of tricyclic guanidine **S8** as a colorless oil: $[\alpha]_D^{24} = -6.7$, $[\alpha]_{546}^{24} = -7.7$, $[\alpha]_{435}^{24} = -14.2$, $[\alpha]_{405}^{24} = -18.7$ (*c* 1.20, MeOH).

Section III Experimental



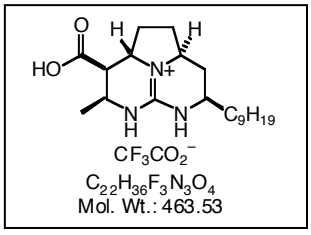
(4a*S*,7*S*)-4-*tert*-Butoxycarbonyl-7-((2*S*)-2-hydroxyundecyl)-1-imino-3-methyl-1,2,4a,5,6,7-hexahydropyrrolo-[1,2-*c*]pyrimidinium acetate (62) A mixture of guanidine **61** (3.46 mmol), *tert*-butyl acetoacetate (1.7 mL, 10.4 mmol), morpholinium acetate (1.0 mg, 6.9 mmol), Na_2SO_4 (500 mg) and 2,2,2-trifluoroethanol (7.0 mL) was heated at 60 °C for 2 d. After cooling to rt, the mixture was filtered and concentrated. The residue was chromatographed (SiO_2, gradient elution with 2.5–5% MeOH–$CHCl_3$ with 1% AcOH) to provide 875 mg 52%) of bicyclic guanidine **62** as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40–4.33 (m, 1H), 4.23 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.56–3.50 (m, 1H), 2.51–2.44 (m, 1H), 2.29 (s, 3H), 2.17–2.09 (m, 1H), 1.97 (s, 3H), 1.68–1.54 (m, 4H), 1.50–1.44 (m, 11H), 1.40–1.33 (m, 1), 1.30–1.20 (m, 14H), 0.86 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 151.6, 142.8, 102.2, 81.1, 67.9, 56.8, 56.3, 41.7, 37.7, 34.3, 31.9, 29.6, 29.5, 29.3, 28.3, 25.5, 23.7, 22.7, 17.5, 14.1; IR (film) 2927, 2855, 1711, 1681, 1556 cm^{-1}; $[\alpha]_D^{24} = -52.0$, $[\alpha]_{546}^{24} = -62.1$, $[\alpha]_{435}^{24} = -95.0$, $[\alpha]_{405}^{24} = -81.4$ (*c* 1.0, $CHCl_3$); HRMS (FAB) *m/z* 422.3387 (422.3383 Calcd for $C_{24}H_{44}N_3O_3$, M).

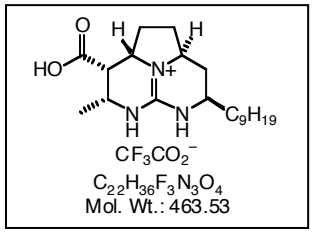
This material was converted to the BF_4^- salt by dissolving the acetate salt in $CHCl_3$ (50 mL) and washing with saturated aqueous $NaBF_4$ (3 × 10 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated.



(2a*S*,7*R*,8a*S*)-3-*tert*-Butoxycarbonyl-4-methyl-7-nonyl-1,2,2a,5,6,7,8,8a-octahydro-5,6,8a-triazaacenaphthylinium acetate (63). Methanesulfonyl chloride (210 μL, 1.4 mmol, freshly distilled) was added over 1 h to a 0 °C solution of alcohol **62** (640 mg, 0.31 mmol, dried azeotropically 2 × with toluene), Et_3N (700 μL, 5.0 mmol), and CH_2Cl_2 (25 mL). The reaction was then diluted with $CHCl_3$ (50 mL), and washed with 0.1 N HCl (3 × 5 mL). The combined aqueous layers were extracted with $CHCl_3$ (3 × 5 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated. The residue was filtered through SiO_2 with 2% MeOH–$CHCl_3$, to provide the corresponding mesylate as a yellow oil, which was carried on directly.

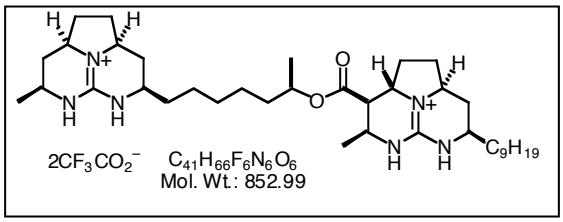
The mesylate prepared above was dried azeotropically with toluene (2 ×2 mL), then combined with $CHCl_3$ (90 mL, filtered through basic Al_2O_3) and Et_3N (10 mL) in a heavy-walled sealable tube. The solution was sparged with N_2 for 15 min, sealed, wrapped in foil, and heated at 75 °C for 3 d. After cooling to rt, the solution was concentrated, and the residue was chromatographed (SiO_2, gradient elution with 2.5–5% MeOH–$CHCl_3$ with 1% AcOH) to provide 360 mg (62% for 2 steps) of tricyclic guanidine **63**, with a mixture of counter-ions as a yellow oil. An analytical sample of the acetate salt was obtained by preparative TLC (SiO_2, 5% MeOH–$CHCl_3$ with 1% AcOH): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.05 (dd, *J* = 11.1, 4.6 Hz, 1H), 3.67–3.60 (m, 1H), 3.47–3.40 (m, 1H), 2.59 (dt, *J* = 12.6, 5.2 Hz, 1H), 2.31–2.27 (m, 5H), 2.00 (s, 3H), 1.92–1.80 (m, 2H), 1.70–1.60 (m, 1H), 1.60–1.44, (m, 10H), 1.35–1.14 (m, 15H), 0.87 (t, *J* = 7.1 Hz), 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 164.5, 149.7, 147.9, 104.3, 80.9, 55.3, 54.1, 34.9, 32.9, 32.0, 31.8, 31.7, 29.5, 29.4, 29.3, 29.2, 28.4, 25.6, 24.6, 22.6, 17.6, 14.1; IR (film) 2927, 2855, 1686, 1619, 1403, 1325 cm^{-1}; $[\alpha]_D^{24}$ = –35.3, $[\alpha]_{546}^{24}$ = –36.0, $[\alpha]_{435}^{24}$ = –95.0, $[\alpha]_{405}^{24}$ = –19.8 (*c* 0.55, $CHCl_3$); HRMS (FAB) *m/z* 422.3387 (422.3383 Calcd for $C_{24}H_{44}N_3O_3$, M).



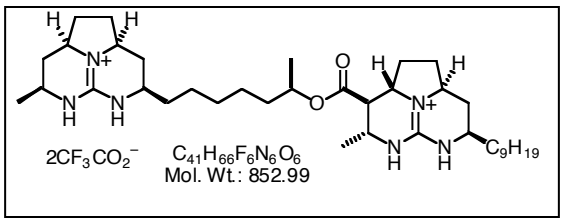


(2a*S*,3*R*,4*S*,7*R*,8a*S*)-3-Carboxy-4-methyl-7-nonyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylinium trifluoroacetate (65) and (2a*S*,3*S*,4*R*,7*R*,8a*S*)-3-Carboxy-4-methyl-7-nonyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylinium trifluoroacetate (64). A mixture of olefin **63** (110 mg, 0.24 mmol), 5% Rh·Al_2O_3 (90 mg), MeOH (10 mL) and formic acid (90%, 12 drops) was maintained under 75 psi of H_2 for 24 h. The mixture was filtered through Celite and concentrated. The residue was dissolved in formic acid (98%, 5 mL), and the solution maintained at rt for 24 h. The reaction was concentrated, and the residue was purified by HPLC (5 μm C_{18}, step gradient 40–50% MeCN-H_2O with 0.1% TFA) to provide 33 mg (30%) of **64** and 53 mg (48%) of **65**. Data for **64**: ^{1}H NMR (500 MHz, CD_3OD) δ 3.95–3.90 (m, 1H), 3.85–3.78 (m, 1H), 3.60–3.50 (m, 2H), 3.04 (dd, *J* = 4.7, 3.3 Hz, 1H), 2.34 (ddd, *J* = 12.9, 5.0, 2.4 Hz, 1H), 2.26–2.15 (m, 2H), 1.75–1.50 (m, 4H), 1.45–1.20 (m, 18H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 172.6, 151.6, 57.7, 57.3, 53.1, 51.6, 45.7, 36.9, 34.3, 33.0, 31.5, 30.6,[17] 30.4, 29.4, 26.2, 23.7, 18.5, 14.4; $[\alpha]_D^{24}$ = –21.4, $[\alpha]_{546}^{24}$ = –44.2, $[\alpha]_{435}^{24}$ = –65.3, $[\alpha]_{405}^{24}$ = –79.4 (*c* 0.45, MeOH); HRMS (ESI) *m/z* 350.2820 (350.2808 Calcd for $C_{20}H_{36}N_3O_2$, M).

Data for **65**: ^{1}H NMR (500 MHz, CD_3OD) δ 4.04 (dq, *J* = 6.2 Hz, 1H), 3.78–3.73 (m, 1H), 3.65–3.56 (m, 1H), 3.53–3.46 (m, 1H), 2.84 (dd, *J* = 10.8, 5.8 Hz, 1H), 2.49 (dd, *J* = 5.9 Hz, 1H), 2.32 (ddd, *J* = 12.9, 4.9, 2.4 Hz, 1H), 2.21 (dd, *J* = 5.7 Hz, 1H), 1.70–1.50 (m, 5H), 1.40–1.20 (m, 20H), 1.19 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 172.3, 151.0, 57.1, 53.2, 53.1, 48.8, 48.5, 36.9, 34.1, 33.0, 31.7, 31.6, 30.7, 30.6, 30.5, 30.4, 26.2, 23.7, 19.5, 14.4; $[\alpha]_D^{24} = -71.6$, $[\alpha]_{546}^{24} = -88.6$, $[\alpha]_{435}^{24} = -154.3$, $[\alpha]_{405}^{24} = -186.5$ (*c* 0.75, MeOH); HRMS (ESI) *m/z* 350.2802 (350.2808 Calcd for $C_{20}H_{36}N_3O_2$, M).

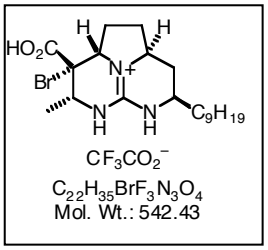


(2a*S*,3*R*,4*S*,7*R*,8a*S*,1´*R*,2a´´*S*,4´´*R*,7´´*S*,8a´´*R*)-4-Methyl-7-nonyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b,-triazaacenaphthylenium-3-carboxylic acid 1´-methyl-6´-(7´´-methyl-1´´,2´´,2a´´,3´´,4´´,5´´,6´´,7´´,8´´,8a´´-decahydro-5´´,6´´,8b´´-triazaacenaphthylenium-4´´-yl)hexyl ester bis triflouroacetate (66). A mixture of acid **65** (3.0 mg, 0.008 mmol), alcohol **39** (3.5 mg, 0.009 mmol), 2-chloro-1-methylpyridinium iodide (10 mg, 0.04 mmol), DMAP (10 mg, 0.08 mmol), and MeCN (0.5 mL) was heated at 55 °C for 4 h. After cooling to rt, the mixture was filtered through a 0.45 μm filter, concentrated, and the residue was purified by HPLC (5 μm C_{18}, 60% MeCN-H_2O with 0.1% TFA) to provide 3.2 mg (48%) of **66** as a colorless oil: ^{1}H NMR (500 MHz, CD_3OD) δ 5.01–4.95 (m, 1H), 4.03 (m, 1H), 3.82–3.70 (m, 3H), 3.65–3.58 (m, 1H), 3.55–3.46 (m, 2H), 3.44–3.39 (m, 1H), 2.88 (dd, *J* = 10.8, 5.7 Hz, 1H), 2.47–2.43 (m, 1H), 2.33 (ddd, *J* = 12.8, 4.8, 2.3 Hz, 1H), 2.27–2.19 (m, 5H), 1.70–1.50 (m, 10H), 1.40–1.20 (m, 30H), 1.16 (d, *J* = 6.6 Hz, 3H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.7, 150.7, 150.6, 73.5, 57.5, 57.1, 53.2, 52.9, 51.5, 47.3, 36.9, 36.8, 36.7, 35.8, 34.8, 34.1, 33.1, 31.7, 31.6, 31.1, 31.0, 30.7, 30.5,[18] 30.4, 26.5, 26.3, 26.2, 23.8, 20.8, 20.1, 19.6, 14.5; FTIR (film) 3200, 3127, 2930, 2860, 1679, 1637, 1200, 1177, 1131 cm^{-1}; $[\alpha]_D^{24} = -40.1$, $[\alpha]_{546}^{24} = -48.7$, $[\alpha]_{435}^{24} = -83.4$, $[\alpha]_{405}^{24} = -101.2$ (*c* 0.4, MeOH); HRMS (ESI) *m/z* 625.5179 (625.5169 Calcd for $C_{37}H_{65}N_6O_2$, M–H).



(2a*S*,3*R*,4*R*,7*R*,8a*S*,1´*R*,2a´´*S*,4´´*R*,7´´*S*,8a´´*R*)-4-Methyl-7-nonyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b,-triazaacenaphthylenium-3-carboxylic acid 1´-methyl-6´-(7´´-methyl-1´´,2´´,2a´´,3´´,4´´,5´´,6´´,7´´,8´´,8a´´-decahydro-5´´,6´´,8b´´-triazaacenaphthylenium-4´´-yl)hexyl ester bis triflouroacetate (68). A mixture of acid **64** (3.0 mg, 0.008 mmol), alcohol **39** (3.0 mg, 0.008 mmol), 2-chloro-1-methylpyridinium iodide (10 mg, 0.04 mmol), DMAP (10 mg, 0.08 mmol), and MeCN (0.4 mL) was heated at 100 °C in a sealed vial for 24 h. After cooling to rt, the mixture was filtered through a 0.45 μm filter, concentrated, and the residue was purified by HPLC (5 μm C_{18}, gradient elution 40-60% MeCN–H_2O with 0.1% TFA) to provide 3.8 mg (57%) of **68** as a colorless oil: ^{1}H NMR (500 MHz, CD_3OD) δ 5.02–4.95 (m, 1H), 3.77–3.70 (m,

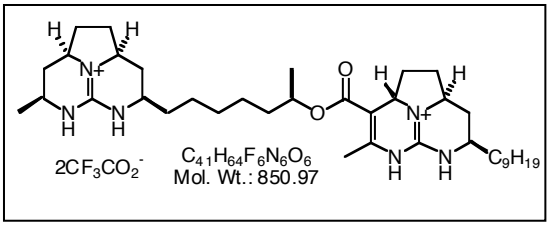
4H), 3.70–3.60 (m, 1H), 3.55–3.45 (m, 2H), 3.43–3.38 (m, 1H), 2.38 (dd, *J* = 10.3, 10.3 Hz, 1H), 2.35–2.29 (m, 1H), 2.28–2.10 (m, 6H), 1.80–1.50 (m, 10H), 1.40–1.20 (m, 31H), 0.91 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 170.5, 150.6, 73.6, 58.3, 57.5, 57.4, 56.7, 53.1, 52.4, 51.5, 51.2, 47.3, 36.8, 36.77, 36.72, 35.8, 34.8, 34.2, 33.1, 31.7, 31.14, 31.1, 30.9, 30.7, 30.5,[18] 30.3, 26.5, 26.3, 26.2, 23.8, 20.8, 20.3, 20.2, 14.5; FTIR (film) 3196, 3123, 2930, 2860, 1679, 1637, 1200, 1177, 1131 cm^{-1}; $[\alpha]_D^{24} = -23.5$, $[\alpha]_{546}^{24} = -27.7$, $[\alpha]_{435}^{24} = -45.2$, $[\alpha]_{405}^{24} = -53.5$ (*c* 0.2, MeOH); HRMS (ESI) *m/z* 625.5175 (625.5169 Calcd for $C_{37}H_{65}N_6O_2$ M–H).

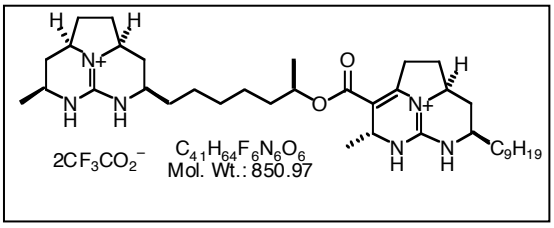


(2a*R*,3*S*,4*R*,7*R*,8a*S*)-3-Bromo-3-carboxy-4-methyl-7-nonyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylinium trifluoroacetate (74). *N*-bromosuccinimide (21 mg, 0.12 mmol) was added to a solution of olefin **63** (50 mg, 0.12 mmol) and MeOH (2 mL), and maintained at rt for 1 h. The solvent was removed under reduced pressure to yield α-bromo-ester **71** as a yellow oil. Diagnostic data: ^{1}H NMR (400 MHz, CD_3OD) δ 4.32 (dd, *J* = 9.9, 6.0 Hz, 1H), 3.74–3.65 (m, 1H), 3.62–3.53 (m, 1H), 3.37 (s, 3H), 2.55–2.48 (m, 1H), 2.42–2.35 (m, 1H), 2.30–2.20 (m, 1H), 1.91 (s, 3H), 1.80–1.70 (m, 1H), 1.70–1.57 (m, 3H), 1.55–1.25 (m, 28H), 0.89 (t, *J* = 6.9 Hz, 1H).

The hemi-aminal from above was dissolved in AcOH (5 mL) and $NaBH_3CN$ (36 mg, 0.58 mmol) was added with stirring. Additional portions of $NaBH_3CN$ (36 mg, 0.58 mmol) were added at approximately 8 h intervals over 2 d. The resulting slurry was poured into 1 N HCl (50 mL) and allowed to stand for 1 h. The aqueous layer was extracted with $CHCl_3$ (3 × 10 mL), and the combined organic layers washed with 1 N HCl (1 × 10 mL), dried (Na_2SO_4), filtered and concentrated to a colorless oil. This oil was dissolved in 98% formic acid (5 mL) and allowed to stand for 2 d. The solvent was removed under reduced pressure, and the residue was filtered through a 0.45 μm filter with MeOH, and concentrated. The residue was purified by HPLC (5 μm C_{18}, 55% MeCN–H_2O with 0.1% TFA) to provide 31 mg (50%) of the title compound as a colorless oil: ^{1}H NMR (500 MHz, CD_3OD) δ 4.08 (dd, *J* = 9.6, 6.2 Hz, 1H), 3.98 (q, *J* = 6.1 Hz, 1H), 3.66–3.62 (m, 1H), 3.56–3.51 (m, 1H), 2.35 (ddd, *J* = 12.9, 4.7, 2.5 Hz, 1H), 2.28–2.23 (m, 1H), 2.20–2.08 (m, 2H), 1.74–1.67 (m, 1H), 1.64–1.50 (m, 2H), 1.44–1.25 (m, 22H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.8, 150.5, 63.9, 58.0, 56.2, 53.1, 36.7, 34.0, 33.0, 31.1, 30.6,[17] 30.54, 30.4, 29.3, 26.1, 23.7, 18.1, 14.4; FTIR (film) 3273, 3181, 2926, 2856, 1722, 1633, 1320, 1220 cm^{-1}; $[\alpha]_D^{24} = -12.8$, $[\alpha]_{546}^{24} = -13.3$, $[\alpha]_{435}^{24} = -23.6$, $[\alpha]_{405}^{24} = -25.2$ (*c* 1.55, MeOH); HRMS (ESI) *m/z* 428.1902 (428.1913 Calcd for $C_{20}H_{35}BrN_3O_2$, M).

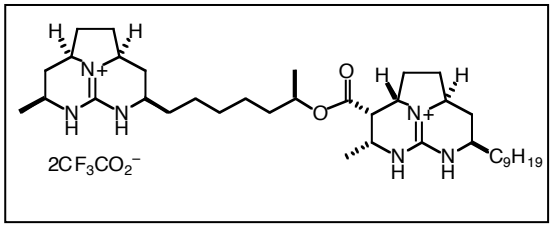
This material was converted to the Cl^- salt in quantitative yield by dissolving in $CHCl_3$ (20 mL), washing with 0.1 N HCl saturated with NaCl (4 × 5 mL), drying (Na_2SO_4), and concentrating.





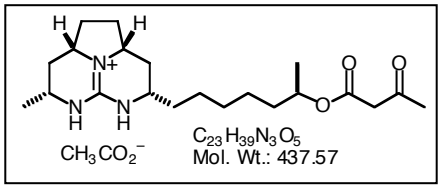
(2a*S*,7*R*,8a*S*,1´*R*,2a´´*S*,4´´*R*,7´´*S*,8a´´*R*)-4-Methyl-7-nonyl-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b,-triazaacenaphthylenium-3-carboxylic acid 1´-methyl-6´-(7´´-methyl-1´´,2´´,2a´´,3´´,4´´,5´´,6´´,7´´,8´´,8a´´-decahydro-5´´,6´´,8b´´-triazaacenaphthylenium-4´´-yl)hexyl ester bis triflouroacetate (76) and (4*R*,7*R*,8a*S*,1´*R*,2a´´*S*,4´´*R*,7´´*S*,8a´´*R*)-4-Methyl-7-nonyl-1,2,4,5,6,7,8,8a-octahydro-5,6,8b,-triazaacenaphthylenium-3-carboxylic acid 1´-methyl-6´-(7´´-methyl-1´´,2´´,2a´´,3´´,4´´,5´´,6´´,7´´,8´´,8a´´-decahydro-5´´,6´´,8b´´-triazaacenaphthylenium-4´´-yl)hexyl ester bis triflouroacetate (75). A mixture of acid **74** (10 mg, 0.02 mmol), alcohol **39** (8 mg, 0.02 mmol) 2-chloro-1-methylpyridinium iodide (28 mg, 0.11 mmol), DMAP (13 mg, 0.11 mmol), and MeCN (0.3 mL) was heated in a sealed tube at 85 °C for 24 h. After cooling to rt, the mixture was filtered through a 0.45 μm filter and concentrated. The residue was purified by HPLC (5 μm C_{18}, gradient elution 50-60% MeCN–H_2O with 0.1% TFA) to provide 6 mg (32%) of **76** and 5 mg (31%) of **75** as a colorless oils. Data for **76** ^{1}H NMR (500 MHz, CD_3OD) δ 5.03–4.95 (m, 1H), 4.28–4.22 (m, 1H), 3.83–3.69 (m, 2H), 3.62–3.49 (m, 3H), 3.44–3.56 (m, 1H), 2.65–2.58 (m, 1H), 2.40–2.29 (m, 2H), 2.29–2.15 (m, 7H), 1.95–1.84 (m, 1H), 1.78–1.49 (m, 10H), 1.44–1.15 (m, 33H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 165.4, 150.7, 149.6, 146.9, 106.4, 72.5, 57.5, 57.4, 56.7, 55.9, 53.5, 51.5, 47.3, 37.0, 36.8, 36.0, 35.8, 34.8, 33.6, 33.1, 33.0, 32.6, 31.14, 31.10, 30.6,[17] 30.5, 30.3, 26.5, 26.4, 26.2, 23.8, 20.8, 20.4, 17.7, 14.5; FTIR (film) 2930, 2860, 1683, 1637, 1324, 1200, 1131 cm^{-1}; $[\alpha]_D^{24}$ = –5.8, $[\alpha]_{546}^{24}$ = –5.8, $[\alpha]_{435}^{24}$ = 4.4, $[\alpha]_{405}^{24}$ = 15.5 (*c* 0.4, MeOH); HRMS (ESI) *m/z* 623.5026 (623.5012 Calcd for $C_{37}H_{63}N_6O_2$, M–H)

Data for **75**: ^{1}H NMR (500 MHz, CD_3OD) δ 5.02–4.98 (m, 1H), 4.49 (q, *J* = 6.3 Hz, 1H), 4.12–4.05 (m, 1H), 3.78–3.68 (m, 2H), 3.69–3.56 (m, 1H), 3.56–3.49 (m, 1H), 3.46–3.40 (m, 1H), 2.92–2.84 (m, 1H), 2.45–2.30 (m, 2H), 2.30–2.14 (m, 5H), 1.76–1.54 (m, 10H), 1.44–1.20 (m, 38H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 165.7, 151.1, 150.6, 149.8, 104.8, 72.7, 58.7, 57.6, 57.5, 52.2, 51.6, 47.7, 47.3, 36.9, 36.8, 35.7, 35.6, 34.8, 34.2, 33.0, 31.1, 31.0, 30.8, 30.6,[17] 30.5, 30.4, 30.3, 26.5, 26.1, 25.9, 23.7, 23.4, 20.7, 20.3, 14.4; FTIR (film) 2930, 2860, 1679, 1633, 1200, 1177, 1131 cm^{-1}; $[\alpha]_D^{24}$ = –0.08, $[\alpha]_{546}^{24}$ = 0.1, $[\alpha]_{435}^{24}$ = 3.0, $[\alpha]_{405}^{24}$ = 6.1 (*c* 1.0, MeOH); HRMS (ESI) *m/z* 623.5024 (623.5012 Calcd for $C_{37}H_{63}N_6O_2$, M–H).

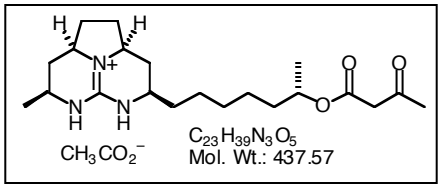


(2a*S*,3*S*,4*R*,7*R*,8a*S*,1´*R*,2a´´*S*,4´´*R*,7´´*S*,8a´´*R*)-4-Methyl-7-nonyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b,-triazaacenaphthylenium-3-carboxylic acid 1´-methyl-6´-(7´´-methyl-1´´,2´´,2a´´,3´´,4´´,5´´,6´´,7´´,8´´,8a´´-decahydro-5´´,6´´,8b´´-triazaacenaphthylenium-4´´-yl)hexyl ester bis triflouroacetate (35). A mixture of unsaturated ester **76** (11 mg 0.013 mmol), 5% Rh·Al_2O_3 (15 mg), 98% formic acid (3 drops), and MeOH (2 mL) was maintained under an atmosphere of H_2 (100 psi) for 48 h. The mixture was filtered through a pad of Celite with MeOH, then filtered through a 0.45 μm filter and concentrated. The residue was purified by HPLC (5 μm C_{18}, gradient elution 50–60% MeCN–H_2O with 0.1% TFA) to provide 1 mg of **35** and 4 mg of **77**. Data for **35**: ^{1}H NMR (500 MHz, CD_3OD) δ 5.05–4.93 (m, 1H), 3.97–3.90 (m, 1H), 3.85–3.80 (m, 1H), 3.77–3.68 (m, 2H), 3.58–3.48 (m, 3H), 3.45–3.37 (m, 1H), 3.08 (dd, *J* = 4.6, 3.3 Hz, 1H), 2.37–2.32 (m, 1H), 2.28–2.15 (m, 6H), 1.72–1.50 (m, 10H), 1.45–1.19 (m, 33H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.8, 151.1, 150.7, 73.3, 58.0, 57.5, 57.4, 57.3,, 53.2, 51.6, 49.9, 47.3, 45.6, 37.1, 36.9, 36.8, 35.9, 34.8, 34.3, 33.1, 31.5, 31.1, 31.0, 30.7,[17] 30.5, 30.4, 29.3, 26.6, 26.3, 23.8, 20.8, 20.5, 18.6, 14.5; HRMS (ESI) *m/z* 625.5182 (625.5169 Calcd for $C_{37}H_{65}N_6O_2$, M–H).

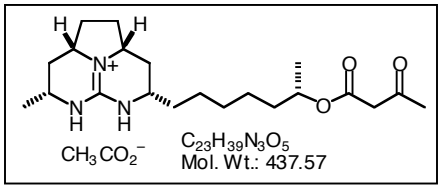
Section IV Experimental



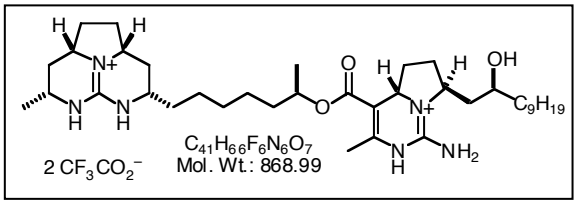
3-Oxobutyric acid (1*R*)-1-methyl-6-((2a*S*,4*S*,7*R*,8a*R*)-7-methyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylenium-4-yl)hexyl ester acetate (82). Following the general procedure of Taber,[19] a solution of alcohol **81** (46 mg, 0.12 mmol), methyl acetoacetate (130 μL, 1.2 mmol), DMAP (15 mg, 0.12 mmol) and toluene (2 mL) was heated at reflux for 18 h. The reaction was allowed to cool, and the residue was chromatographed (SiO_2, gradient elution with 2–5% MeOH–$CHCl_3$ with 1% AcOH) to provide 53 mg (100%) of β-keto ester **82**, as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.15 (br s, 2H), 4.98–4.90 (m, 1H), 3.72–3.61 (m, 2H), 3.58–3.47, (m, 1H), 3.45 (s, 2H), 3.40–3.32 (m, 1H), 2.27 (s, 2H), 2.24–2.15 (m, 4H), 1.86–1.75 (m, 2H), 1.70–1.63 (m, 3H), 1.60–1.55 (m, 1H), 1.52–1.44 (m, 2H), 1.40–1.29 (m, 11H), 1.27–1.19 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 166.5, 149.1, 72.1, 56.1, 56.0, 50.5, 50.4, 46.1, 36.0, 35.6, 34.4, 33.9, 30.4[20], 30.3[21], 29.1, 25.1, 24.9, 20.4, 20.0; IR (film) 3362, 2976, 2937, 1737, 1714, 1621, 1328, 1054 cm^{-1}; $[\alpha]_D^{24}$ = –13.3, $[\alpha]_{546}^{24}$ = –17.6, (*c* 0.85, MeOH); HRMS (ESI) *m/z* 378.2746 (378.2757 Calcd for $C_{21}H_{36}N_3O_3$, M).



3-Oxobutyric acid (1*S*)-1-methyl-6-((2a*R*,4*R*,7*S*,8a*S*)-7-methyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylenium-4-yl)hexyl ester acetate (**V.15**). A solution of **V.13** (44 mg, 0.12 mmol), methyl acetoacetate (62 μL, 0.6 mmol), DMAP (15 mg, 0.12 mmol) and toluene (2 mL) was heated at reflux for 18 h. The reaction was allowed to cool, and the residue was chromatographed (SiO_2, gradient elution with 2–5% MeOH–$CHCl_3$ with 1% AcOH) to provide 38 mg (72%) of β-keto ester **V.15**, as a yellow oil: $[\alpha]_D^{24}$ = 16.3, $[\alpha]_{546}^{24}$ = 19.3, (*c* 0.95, MeOH).

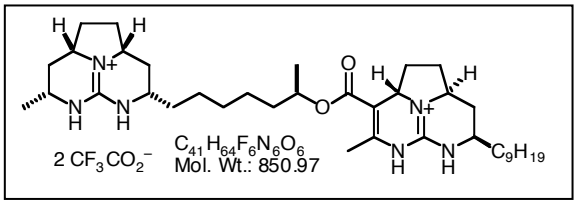


3-Oxobutyric acid (1*S*)-1-methyl-6-((2a*S*,4*S*,7*R*,8a*R*)-7-methyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylenium-4-yl)hexyl ester acetate (**S11**). A solution of alcohol **S8** (31 mg, 0.08 mmol), methyl acetoacetate (87 μL, 0.8 mmol), DMAP (11 mg, 0.08 mmol) and toluene (2 mL) was heated at reflux for 18 h. The reaction was allowed to cool, and the residue was chromatographed (SiO_2, gradient elution with 2–5% MeOH–$CHCl_3$ with 1% AcOH) to provide 30 mg (84%) of β-keto ester **S11** as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.11 (s, 1H), 4.98–4.90 (m, 1H), 3.72–3.61 (m, 2H), 3.58–3.47, (m, 1H), 3.45 (s, 2H), 3.40–3.32 (m, 1H), 2.27 (s, 2H), 2.24–2.15 (m, 4H), 1.86–1.75 (m, 2H), 1.70–1.63 (m, 3H), 1.60–1.55 (m, 1H), 1.52–1.44 (m, 2H), 1.40–1.29 (m, 11H), 1.27–1.19 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 166.5, 149.1, 72.1, 56.1, 56.0, 50.5, 50.4, 46.1, 36.0, 35.6, 34.4, 33.9, 30.4[20], 30.3[21], 29.1, 25.1, 24.9, 20.4, 20.0; IR (film) 3362, 2976, 2937, 1737, 1714, 1621, 1328, 1054 cm^{-1}; $[\alpha]_D^{24}$ = –3.5, $[\alpha]_{546}^{24}$ = –4.5, (*c* 0.6, MeOH); HRMS (FABI) *m*/*z* 378.2752 (378.2757 Calcd for $C_{21}H_{36}N_3O_3$, M).



(4a*S*,7*S*,2′*S*,1′′*R*,2a′′′*R*,4′′′*S*,7′′′*R*,8a′′′*S*)-7-(2′-Hydroxyundecyl)-1-imino-3-methyl-1,2,4a,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidinium-4-carboxylic acid 1′′-methyl-6′′-(7′′′-methyl-1′′′,2′′′,2a′′′,3′′′,4′′′,5′′′,6′′′,7′′′,8′′′,8a′′′-decahydro-5′′′,6′′′,8b′′′,-triazaacenaphthylenium-4′′′-yl)hexyl ester bis triflouroacetate (83). A mixture of β-keto ester **82** (53 mg, 0.12 mmol), guanidine **61** (0.37 mmol), morpholinium acetate (53 mg, 0.37 mmol), Na_2SO_4 (53 mg) and 2,2,2-triflouroethanol (1 mL) was maintained in a sealed tube at 60 °C for 2 d. After cooling to rt, the mixture was filtered through cotton, concentrated, and further filtered through a 0.45 μm filter with MeOH. The filtrate was concentrated, and the residue was purified by HPLC (5 μm C_{18}, 50% MeCN-H_2O with 0.1% TFA) to provide 68 mg (64%) of **83** as a colorless oil: ^{1}H NMR (500 MHz, CD_3OD) δ 5.04–4.98 (m, 1H), 4.50 (dd, *J* = 9.9, 5.3 Hz, 1H),

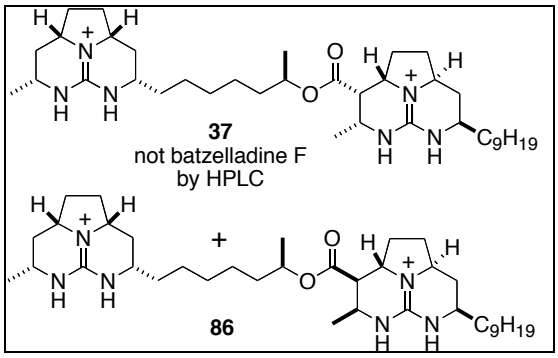
4.41–4.35 (m, 2H), 3.57–3.48 (m, 2H), 3.44–3.38 (m, 1H), 2.58–2.52 (m, 1H), 2.33–2.15 (m, 8H), 1.84 (ddd, J = 14.2, 11.5, 2.9 Hz, 1H), 1.72–1.63 (m, 4H), 1.62–1.55 (m, 5H), 1.51–1.45 (m, 3H), 1.45–1.20 (m, 31H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 151.8, 151.1, 143.1, 104.1, 72.6, 69.0, 58.6, 57.5, 57.4, 51.5, 47.2, 42.6, 38.6, 36.9, 36.8, 35.7, 35.1, 34.8, 33.0, 31.1, 31.0, 30.7, 30.6,[21] 30.4, 30.3, 29.0, 26.5, 26.4, 26.1, 23.7, 20.7, 20.2, 17.5, 14.4; IR (film) 3281, 3200, 2930, 2860, 1675, 1629, 1540, 1177 cm^{-1}; $[\alpha]_D^{24}$ = –22.6, $[\alpha]_{546}^{24}$ = –26.0, $[\alpha]_{435}^{24}$ = –36.2, $[\alpha]_{405}^{24}$ = –36.7 (*c* 0.73, MeOH); HRMS (ESI) *m/z* 641.5106 (641.5118 Calcd for $C_{37}H_{65}N_6O_3$ M-H$^+$).



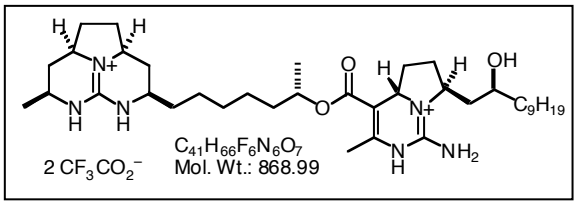
(2a*S*,7*R*,8a*S*,1´*R*,2a´´*R*,4´´*S*,7´´*R*,8a´´*S*)-4-Methyl-7-nonyl-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b,-triazaacenaphthylenium-3-carboxylic acid 1´-methyl-6´-(7´´-methyl-1´´,2´´,2a´´,3´´,4´´,5´´,6´´,7´´,8´´,8a´´-decahydro-5´´,6´´,8b´´-triazaacenaphthylenium-4´´-yl)hexyl ester bis triflouroacetate (85). Bisguanidine **83** (68 mg, 0.078 mmol) was dissolved in $CHCl_3$ (20 mL) and washed with saturated aqueous $NaBF_4$ (3 × 5 mL). The combined aqueous layers were extracted with $CHCl_3$ (1 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered, concentrated, and azeotroped 3 × with C_6H_6 to provide 50 mg (79%) of the bisguanidine as the BF_4^- salt, which was carried on directly.

To a 0 °C solution of the guanidine alcohol BF_4^- salt prepared above (50 mg, 0.061 mmol), Et_3N (245 μL of a 1.0 M solution in CH_2Cl_2, 0.24 mmol) and CH_2Cl_2, (2 mL) was added methanesulphonyl chloride (123 μL of a 1.0 M solution in CH_2Cl_2, 0.12 mmol) over 20 min. After an additional 1 h at 0 °C, ESMS indicated complete consumption of the starting material. The solution was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous $NaBF_4$ (3 × 5 mL). The combined aqueous phases were extracted with $CHCl_3$ (1 × 2 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated, to provide the corresponding mesylate as a yellow oil, which was carried on directly.

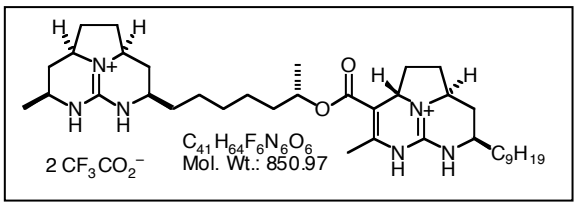
The mesylate prepared above was dried azeotropically with C_6H_6 (3 × 1 mL), and combined with $CHCl_3$ (5 mL, filtered through basic Al_2O_3), and Et_3N (0.5 mL) in a heavy-walled sealable tube. The solution was sparged with N_2 for 15 min, sealed, shielded from light, and heated at 70 °C for 3 d. After cooling to rt, the red solution was concentrated, and the residue was dissolved in MeOH, filtered through a 0.45 μm filter and the filtrate was concentrated. The residue was purified by HPLC (5 μm C_{18}, 50% MeCN-H_2O with 0.1% TFA) to provide 28 mg (55%) of **85** as a colorless oil: ^{1}H NMR (500 MHz, CD_3OD) δ 5.04–4.97 (m, 1H), 4.27–4.23 (m, 1H), 3.64–3.48 (m, 2H), 3.44–3.38 (m, 1H), 2.65–2.59 (m, 1H), 2.40–2.28 (m, 2H), 2.28–2.16 (m, 7H), 1.96–1.86 (m, 1H), 1.80–1.65 (m, 5H), 1.65–1.50 (m, 5H), 1.45–1.20 (m, 32H), 0.89 (t, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 165.8, 151.1, 150.0, 147.3, 106.6, 72.7, 57.5, 57.4, 56.0, 53.5, 51.5, 47.3, 36.9, 36.8, 36.0, 35.7, 34.7, 33.5, 33.1, 33.0, 32.5, 31.14, 31.10, 30.6,[21] 30.47, 30.39, 30.35, 26.6, 26.3, 26.1, 23.7, 20.7, 20.3, 17.7, 14.4; IR (film) 2930, 2860, 1679, 1633, 1324, 1200, 1131 cm^{-1}; $[\alpha]_D^{24}$ = –16.5, $[\alpha]_{546}^{24}$ = –18.0, $[\alpha]_{435}^{24}$ = –15.2, $[\alpha]_{405}^{24}$ = –7.2 (*c* 0.7, MeOH); HRMS (ESI) *m/z* 623.5007 (623.5012 Calcd for $C_{37}H_{63}N_6O_2$, M-H).



Typical hydrogenation experiment to synthesize proposed batzelladine isomer **37**. A mixture of olefin **85** (6 mg, 0.007 mmol), 5% Rh·Al_2O_3 (10 mg), HCO_2H (2 drops) and MeOH (1 mL) was maintained under 100 psi of H_2 with vigorous stirring for 48 h. The mixture was filtered through Celite, then further filtered through a 0.45 μm nylon filter. Analysis of the filtrate by HPLC showed that it contained no batzelladine F. This procedure was repeated for olefins **S13** and **S15**, the synthesis of which is described below.



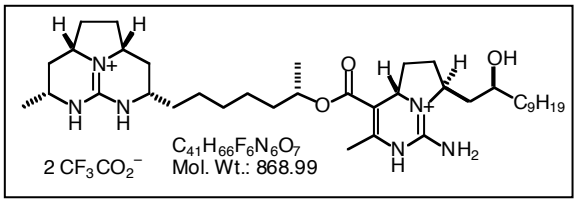
(4a*S*,7*S*,2′*S*,1′′*S*,2a′′′*S*,4′′′*R*,7′′′*S*,8a′′′*R*)-7-(2′-Hydroxyundecyl)-1-imino-3-methyl-1,2,4a,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidinium-4-carboxylic acid 1′′-methyl-6′′-(7′′′-methyl-1′′′,2′′′,2a′′′,3′′′,4′′′,5′′′,6′′′,7′′′,8′′′,8a′′′-decahydro-5′′′,6′′′,8b′′′,-triazaacenaphthylenium-4′′′-yl-hexyl ester bis triflouroacetate (S10). A mixture of ester **S9** (37 mg, 0.085 mmol), guanidine **61** (0.25 mmol), morpholinium acetate (37 mg, 0.25 mmol), Na_2SO_4 (37 mg) and 2,2,2-triflouroethanol (300 μL) was maintained in a sealed tube at 60 °C for 2 d. After cooling to rt, the mixture was filtered through cotton, concentrated, and further filtered through a 0.45 μm filter with MeOH. The solution was concentrated, and the residue was purified by HPLC (5 μm C_{18}, 50% MeCN-H_2O with 0.1% TFA) to provide 49 mg (66%) of **S10** as a colorless oil: ^{1}H NMR (500 MHz, CD_3OD) δ 5.04–4.98 (m, 1H), 4.50 (dd, *J* = 9.9, 5.3 Hz, 1H), 4.41–4.35 (m, 2H), 3.57–3.48 (m, 2H), 3.44–3.38 (m, 1H), 2.58–2.52 (m, 1H), 2.33–2.15 (m, 8H), 1.84 (ddd, *J* = 14.2, 11.5, 2.9 Hz, 1H), 1.72–1.63 (m, 4H), 1.62–1.55 (m, 5H), 1.51–1.45 (m, 3H), 1.45–1.20 (m, 31H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 166.2, 151.8, 151.1, 143.1, 104.1, 72.6, 69.0, 58.6, 57.5, 57.4, 51.5, 47.2, 42.6, 38.6, 36.9, 36.8, 35.7, 35.1, 34.8, 33.0, 31.1, 31.0, 30.7, 30.6,[21] 30.4, 30.3, 29.0, 26.5, 26.4, 26.1, 23.7, 20.7, 20.2, 17.5, 14.4; IR (film) 3281, 3200, 2930, 2860, 1675, 1629, 1540, 1177 cm^{-1}; $[\alpha]_D^{24}$ = 11.7, $[\alpha]_{546}^{24}$ = 15.4, $[\alpha]_{435}^{24}$ = 39.2, $[\alpha]_{405}^{24}$ = 59.8 (*c* 0.95, MeOH); HRMS (ESI) *m/z* 641.5111 (641.5118 Calcd for $C_{37}H_{65}N_6O_3$, M-H).



(2a*S*,7*R*,8a*S*,1´*S*,2a´´*S*,4´´*R*,7´´*S*,8a´´*R*)-4-Methyl-7-nonyl-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b,-triazaacenaphthylenium-3-carboxylic acid 1´-methyl-6´-(7´´-methyl-1´´,2´´,2a´´,3´´,4´´,5´´,6´´,7´´,8´´,8a´´-decahydro-5´´,6´´,8b´´-triazaacenaphthylenium-4´´-yl)-hexyl ester bis triflouroacetate (S13). Bisguanidine **S10** (48 mg, 0.056 mmol) was dissolved in $CHCl_3$ (20 mL) and washed with saturated aqueous $NaBF_4$ (3 × 5 mL). The combined aqueous layers were extracted with $CHCl_3$ (1 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered, concentrated, and azeotroped with C_6H_6 (3 × 1 mL) to provide the bisguanidine as the BF_4^- salt, which was carried on directly.

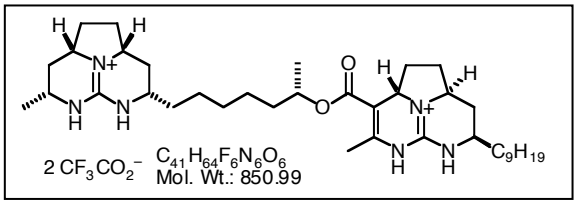
To a 0 °C solution of the guanidine alcohol BF_4^- salt prepared above (43 mg, 0.053 mmol), Et_3N (212 μL of a 1.0 M in CH_2Cl_2, 0.21 mmol) and CH_2Cl_2, (2 mL) was added methanesulphonyl chloride (106 μL of a 1.0 M solution in CH_2Cl_2, 0.12 mmol) over 20 min. After an additional h at 0 °C, ESMS indicated complete consumption of the starting material. The solution was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous $NaBF_4$ (3 × 5 mL). The combined aqueous phases were extracted with $CHCl_3$ (1 × 2 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated, to provide the corresponding mesylate as a yellow oil, which was carried on directly.

The mesylate prepared above was dried azeotropically with C_6H_6 (3 × 1mL), and combined with $CHCl_3$ (3 mL, filtered through basic Al_2O_3) and Et_3N (0.3 mL) in heavy-walled sealable tube. The solution was sparged with N_2 for 15 min, sealed, shielded from light, and heated at 70 °C for 3 d. The red solution was concentrated, and the residue dissolved in MeOH, filtered through a 0.45 μm filter, and the filtrate was concentrated. The residue was purified by HPLC (5 μm C_{18}, 50% MeCN-H_2O with 0.1% TFA) to provide 24 mg (53%) of **S13** as a colorless oil: ^{1}H NMR (500 MHz, CD_3OD) δ 5.04–4.97 (m, 1H), 4.27–4.23 (m, 1H), 3.64–3.48 (m, 2H), 3.44–3.38 (m, 1H), 2.65–2.59 (m, 1H), 2.40–2.28 (m, 2H), 2.28–2.16 (m, 7H), 1.96–1.86 (m, 1H), 1.80–1.65 (m, 5H), 1.65–1.50 (m, 5H), 1.45–1.20 (m, 32H), 0.89 (t, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 165.8, 151.1, 150.0, 147.3, 106.6, 72.7, 57.5, 57.4, 56.0, 53.5, 51.5, 47.3, 36.9, 36.8, 36.0, 35.7, 34.7, 33.5, 33.1, 33.0, 32.5, 31.1, 31.0, 30.6,[21] 30.56, 30.42, 30.37, 30.31, 26.6, 26.3, 26.1, 23.7, 20.7, 20.3, 17.7, 14.4; IR (film) 2930, 2860, 1679, 1633, 1324, 1200, 1131 cm^{-1}; $[\alpha]_D^{24}$ = 25.7, $[\alpha]_{546}^{24}$ = 32.7, $[\alpha]_{435}^{24}$ = 79.8, $[\alpha]_{405}^{24}$ = 113.7 (*c* 0.66, MeOH); HRMS (ESI) *m/z* 623.5027 (623.5012 Calcd for $C_{37}H_{63}N_6O_2$, M-H).



(4a*S*,7*S*,2´*S*,1´´*S*,2a´´´*R*,4´´´*S*,7´´´*R*,8a´´´*S*)-7-(2´-Hydroxy-undecyl)-1-imino-3-methyl-1,2,4a,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidinium-4-carboxylic acid 1´´-methyl-6´´-(7´´´-methyl-1´´´,2´´´,2a´´´,3´´´,4´´´,5´´´,6´´´,7´´´,8´´´,8a´´´-decahydro-5´´´,6´´´,8b´´´,-triazaacenaphthylenium-4´´´-yl-hexyl ester bis triflouroacetate (S10). A mixture of β-keto ester **S11** (29 mg, 0.07 mmol), guanidine **61** (0.20 mmol), morpholinium acetate (30 mg, 0.20 mmol), Na_2SO_4 (30 mg) and 2,2,2-triflouroethanol (0.5 mL) was maintained in a sealed tube at 60 °C for 2 d. The mixture was filtered through cotton, concentrated, and further filtered through a 0.45 μm filter with MeOH. The solution was concentrated, and the residue was purified by HPLC (5 μm C_{18}, 50% MeCN-H_2O with 0.1% TFA) to provide 27 mg (47%) of **S12** as a colorless oil: ^{1}H NMR (500 MHz, CD_3OD) δ 5.04–4.98 (m, 1H), 4.50 (dd, J = 9.9, 5.3 Hz, 1H),

4.41–4.35 (m, 2H), 3.57–3.48 (m, 2H), 3.44–3.38 (m, 1H), 2.58–2.52 (m, 1H), 2.33–2.15 (m, 8H), 1.84 (ddd, J = 14.2, 11.5, 2.9 Hz, 1H), 1.72–1.63 (m, 4H), 1.62–1.55 (m, 5H), 1.51–1.45 (m, 3H), 1.45–1.20 (m, 31H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 166.2, 151.8, 151.1, 143.1, 104.1, 72.6, 69.0, 58.6, 57.5, 57.4, 51.5, 47.2, 42.6, 38.6, 36.9, 36.8, 35.7, 35.1, 34.8, 33.0, 31.1, 31.0, 30.7, 30.6,[21] 30.4, 30.3, 29.0, 26.5, 26.4, 26.1, 23.7, 20.7, 20.2, 17.5, 14.4; IR (film) 3281, 3200, 2930, 2860, 1675, 1629, 1540, 1177 cm^{-1}; $[\alpha]_D^{24}$ = 6.3, $[\alpha]_{546}^{24}$ = 9.2, $[\alpha]_{435}^{24}$ = 34.6, $[\alpha]_{405}^{24}$ = 57.5 (*c* 0.9, MeOH); HRMS (ESI) m/z 641.5106 (641.5118 Calcd for $C_{37}H_{65}N_6O_3$, M-H).



(2a*S*,7*R*,8a*S*,1´*S*,2a´´*R*,4´´*S*,7´´*R*,8a´´*S*)-4-Methyl-7-nonyl-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b,-triazaacenaphthylenium-3-carboxylic acid 1´-methyl-6´-(7´´-methyl-1´´,2´´,2a´´,3´´,4´´,5´´,6´´,7´´,8´´,8a´´-decahydro-5´´,6´´,8b´´-triazaacenaphthylenium-4´´-yl)-hexyl ester bis triflouroacetate (S15). Bisguanidine **S10** (26 mg, 0.03 mmol) was dissolved in $CHCl_3$ (20 mL) and washed with saturated aqueous $NaBF_4$ (3 × 5 mL). The combined aqueous layers were extracted with $CHCl_3$ (1 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered, concentrated, and azeotroped with C_6H_6 (3 × 1 mL) to provide the bisguanidine as the BF_4^- salt, which was carried on directly.

To a 0 °C solution of the guanidine alcohol BF_4^- salt prepared above (23 mg, 0.03 mmol), Et_3N (113 μL of a 1.0 M solution in CH_2Cl_2, 0.113 mmol) and CH_2Cl_2, (1 mL) was added methanesulphonyl chloride (57 μL of a 1.0 M solution in CH_2Cl_2, 0.57 mmol) over 20 min. After an additional h at 0 °C, ESMS indicated complete consumption of the starting material. The solution was diluted with CH_2Cl_2, (20 mL) and washed with saturated aqueous $NaBF_4$ (3 × 5 mL). The combined aqueous phases were extracted with $CHCl_3$ (1 × 2 mL). The combined organic phases were dried (Na_2SO_4), filtered, concentrated, to provide the corresponding mesylate as a yellow oil, which was carried on directly.

The mesylate prepared above was dried azeotropically with C_6H_6 (3 × 1 mL), and combined with $CHCl_3$ (3 mL, filtered through basic Al_2O_3) and Et_3N (0.3 mL) in heavy-walled sealable tube. The solution was sparged with N_2 for 15 min, sealed, shielded from light, and heated at 70 °C for 3 d. The red solution was concentrated, and the residue was dissolved in MeOH, filtered through a 0.45 μm filter, and the filtrate was concentrated. The residue purified by HPLC (5 μm C_{18}, 50% MeCN-H_2O with 0.1% TFA) to provide 17 mg (60%) of **S15** as a colorless oil: ^{1}H NMR (500 MHz, CD_3OD) δ 5.04–4.97 (m, 1H), 4.27–4.23 (m, 1H), 3.64–3.48 (m, 2H), 3.44–3.38 (m, 1H), 2.65–2.59 (m, 1H), 2.40–2.28 (m, 2H), 2.28–2.16 (m, 7H), 1.96–1.86 (m, 1H), 1.80–1.65 (m, 5H), 1.65–1.50 (m, 5H), 1.45–1.20 (m, 32H), 0.89 (t, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 165.8, 151.1, 150.0, 147.3, 106.6, 72.7, 57.5, 57.4, 56.0, 53.5, 51.5, 47.3, 36.9, 36.8, 36.0, 35.7, 34.7, 33.5, 33.1, 33.0, 32.5, 31.1, 31.0, 30.6,[21] 30.42, 30.37, 30.31, 26.6, 26.3, 26.1, 23.7, 20.7, 20.3, 17.7, 14.4; IR (film) 2930, 2860, 1679, 1633, 1324, 1200, 1131 cm^{-1}; $[\alpha]_D^{24}$ = 16.4, $[\alpha]_{546}^{24}$ = 22.5, $[\alpha]_{435}^{24}$ = 63.3, $[\alpha]_{405}^{24}$ = 95.4 (*c* 1.1, MeOH); HRMS (ESI) *m/z* 623.5007 (623.5012 Calcd for $C_{37}H_{63}N_6O_2$, M-H$^+$).

D. HPLC chromatograms of repuified natural batzelladine F, and synthetic batzelladine analogs 36, 37, 38, 86, S14 and S16.

Figure S1. HPLC chromatogram of re-purified Batzelladine F.

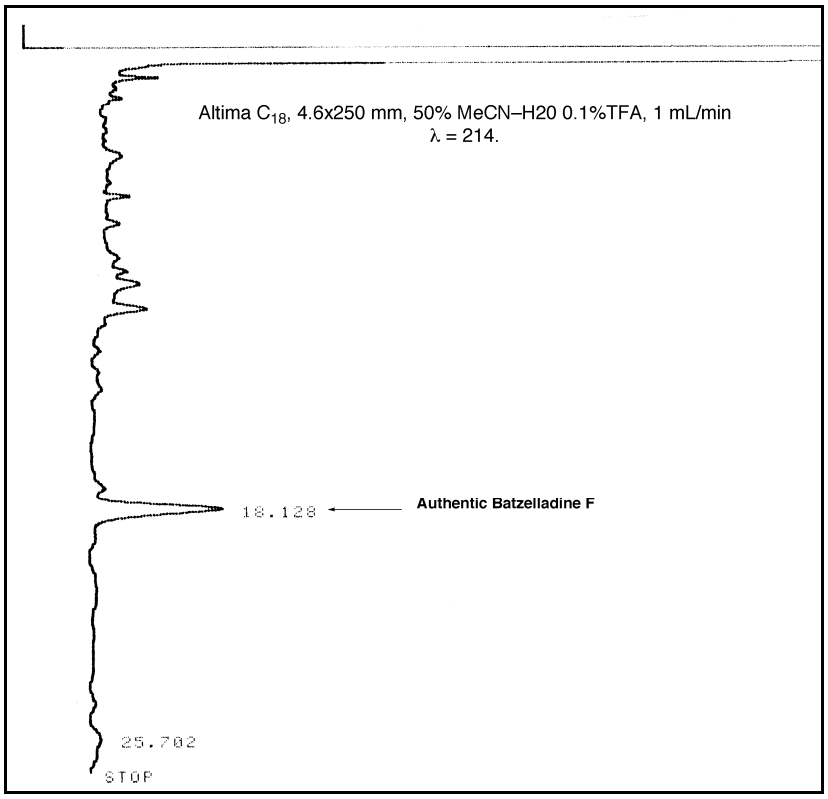


Figure S2. HPLC chromatograms of synthetic batzelladine analogs **37**, **38**, **86**, and **S16.**

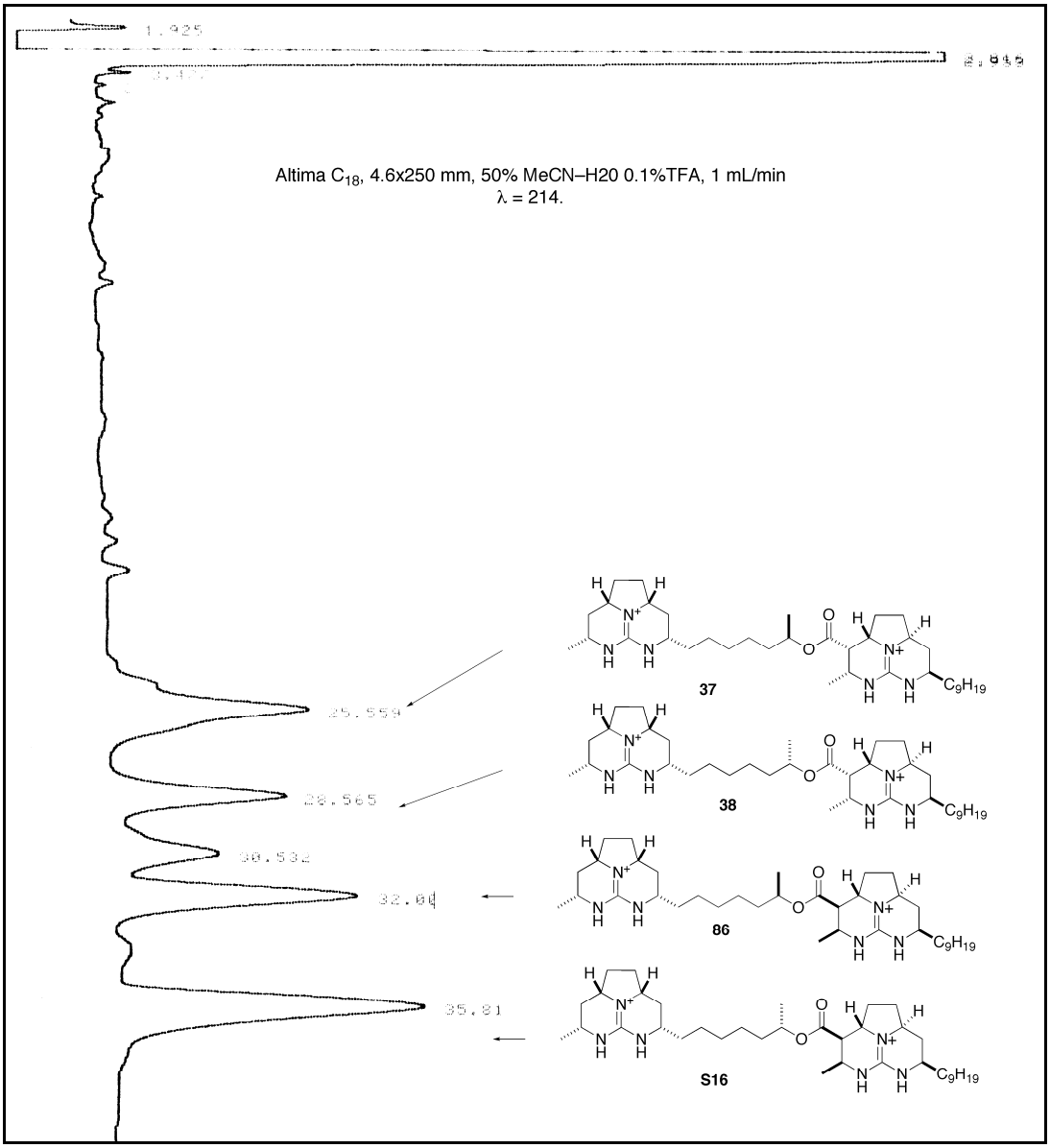
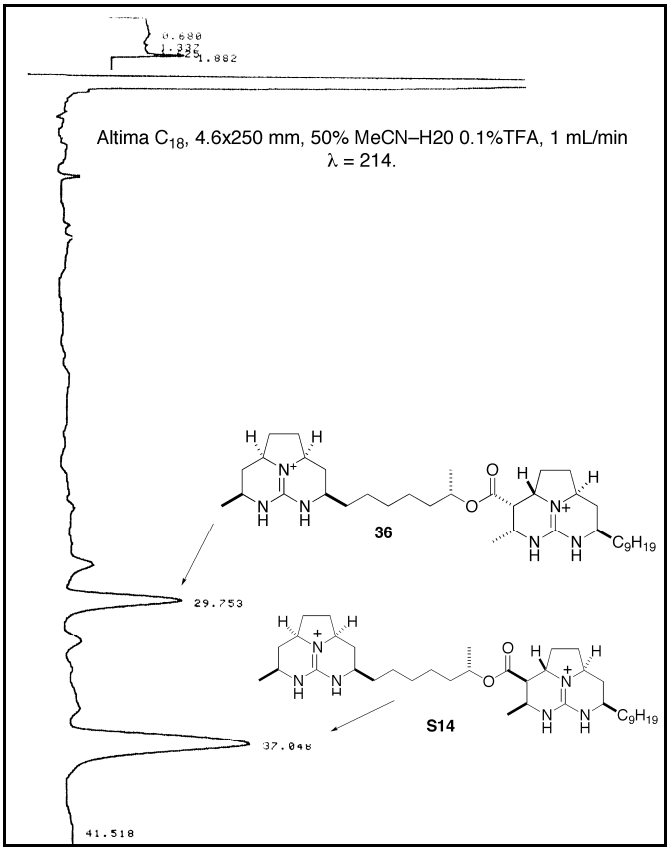


Figure S3. HPLC chromatogram of synthetic batzelladine analogs **36**, and **S14.**



E. ESI analysis of synthetic batzelladine analog 37 and authentic batzelladine F.

Figure S4. ESI analysis of synthetic batzelladine analog **37**.

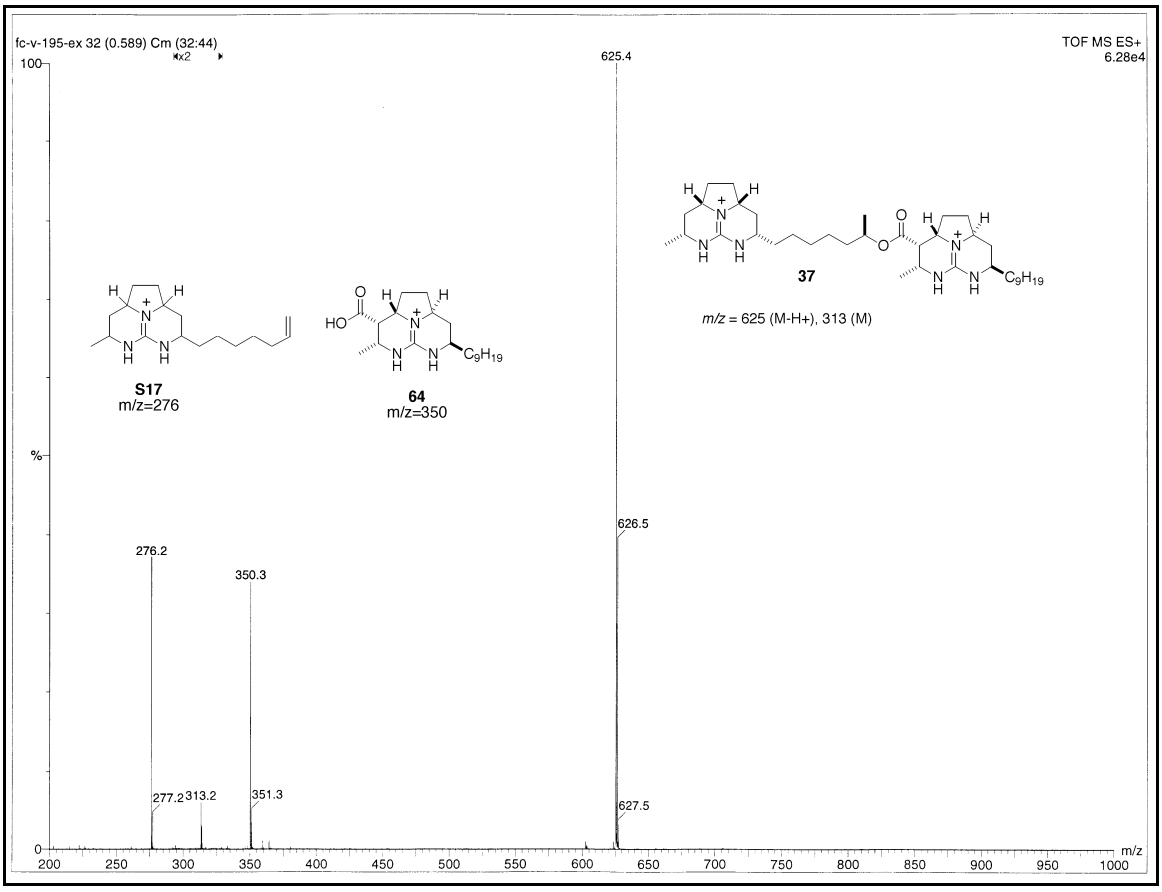
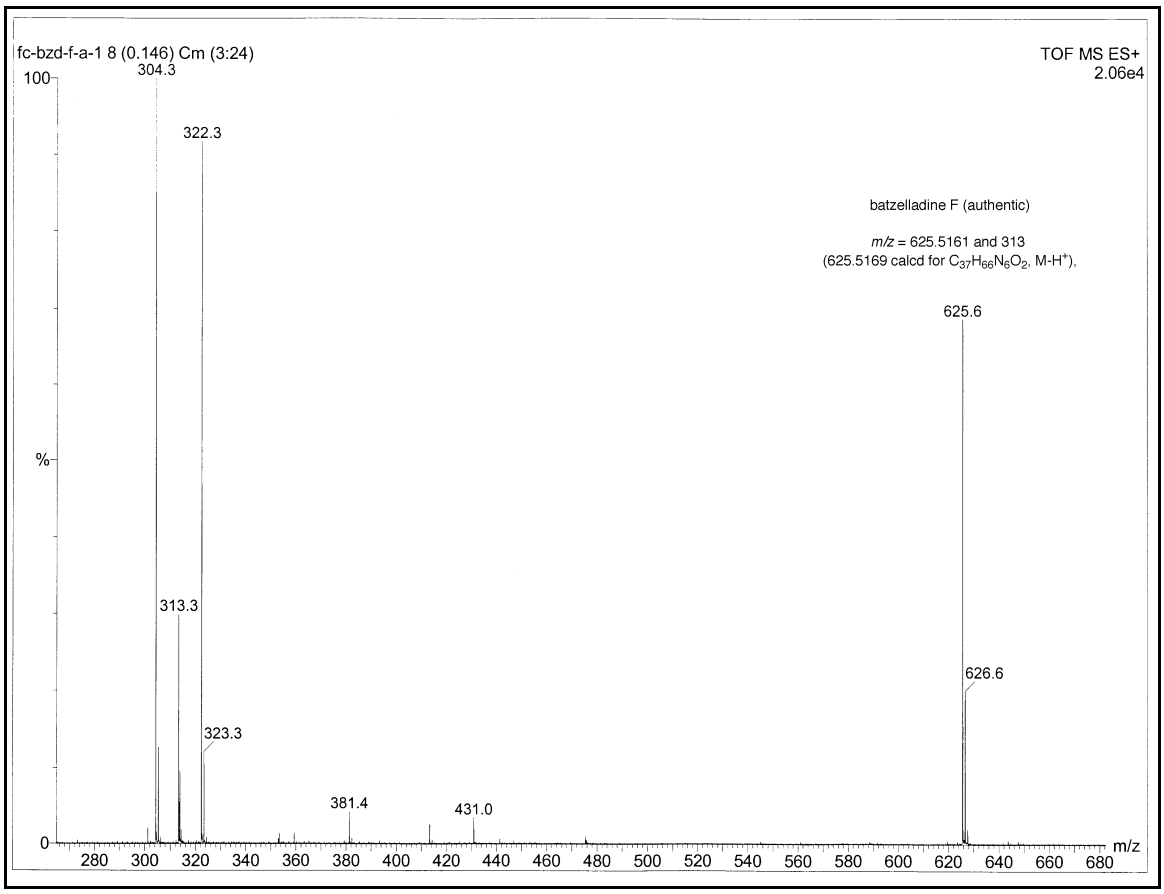


Figure S5. ESI analysis of authentic batzelladine F **37**.



References

[1] General experimental details have been described: MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc*. **2001**, *123*, 9033.
[2] Lee, T. V.; Porter, J. R. *Org. Synth*. **1995**, *72*, 189.
[3] Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1990**, *112*, 6447.
[4] Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.*, **1984**, *49*, 4237.
[5] Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.
[6] Sjiki, H.; Hattori, K.; Hirota, K. *J. Org. Chem.* **1998**, *63*, 7990.
[7] Three overlapping resonances.
[8] Williams, M. J.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.–H.; Grabowski, E. J. J. *Tetrahedron Lett*. **1995**, *36*, 5461.
[9] Seebach, D.; Beck, A. K.; Breitschuh, R.; Job, K. *Org. Synth*. **1993**, *71*, 39.
[10] Lee, T. V.; Porter, J. R. *Org. Synth*. **1995**, *72*, 189.
[11] Chen, K. M.; Hardmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett*. **1987**, *28*, 155.
[12] Atkins, P. R.; Glue, S. E.; Kay, I. T. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2644.
[13] (a) Maemoto, S.; Mori, K. *Chem. Lett*. **1987**, 109. (b) Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem*. **1993**, *58*, 2335.
[14] Several lengthier syntheses of this compound are reported: (a) Nokami, J.; Taniguchi, T.; Ogawa, Y. *Chem. Lett*. **1995**, 43. (b) Solladie, G.; Lohse, O. *J. Org. Chem*. **1993**, *58*, 4555. (c) Ernst, B.; Wagner, B. *Helv. Chim. Acta*. **1989**, *72*, 165.
[15] (a) Singh, S. N.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc*. **1987**, *109*, 6187. (b) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1,* **1980**, 2866.
[16] Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc* **1974**, *96*, 1082.
[17] Three overlapping resonances.
[18] Five overlapping resonances.
[19] Taber, D. F.; Amedio, J. C.; Patel, Y. K. *J. Org. Chem*. **1985**, *50*, 3618.
[20] Two overlapping resonances.
[21] Three overlapping resonances.