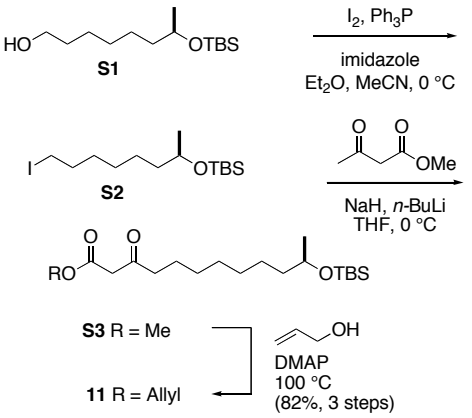
Enantioselective Total Synthesis of Batzelladine F and Definition of Its Structure

*Frederick Cohen and Larry E. Overman**

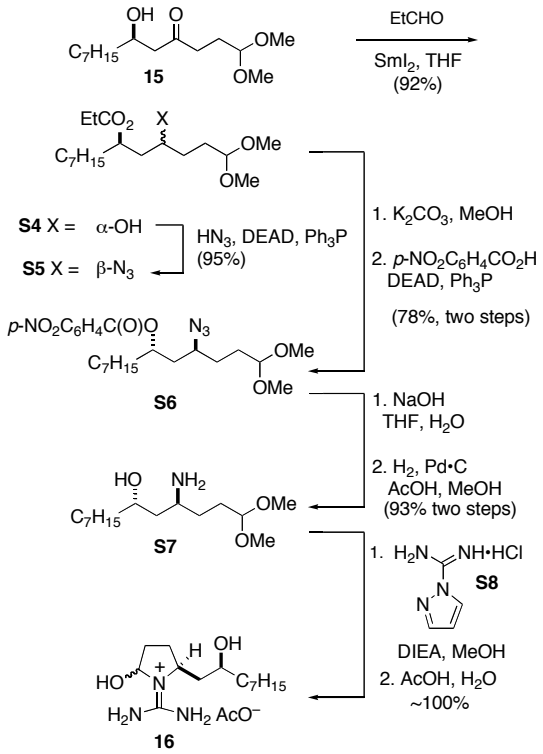
Supporting Information Part 1 (20 Pages)

A. Reaction schemes S1–S10

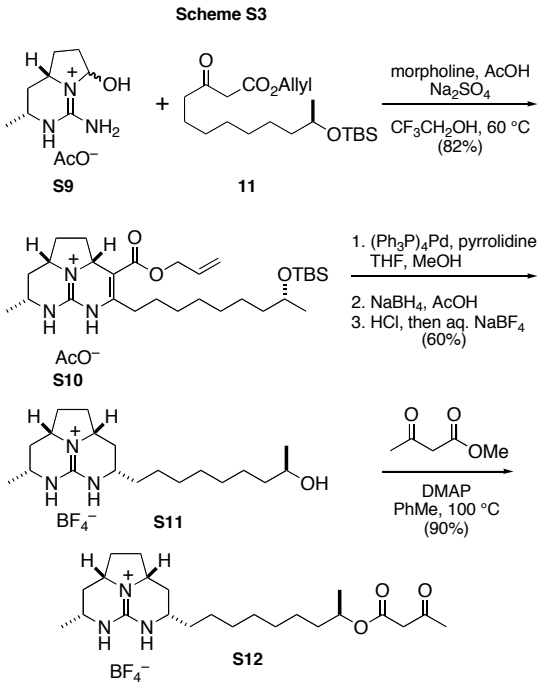
Scheme S1



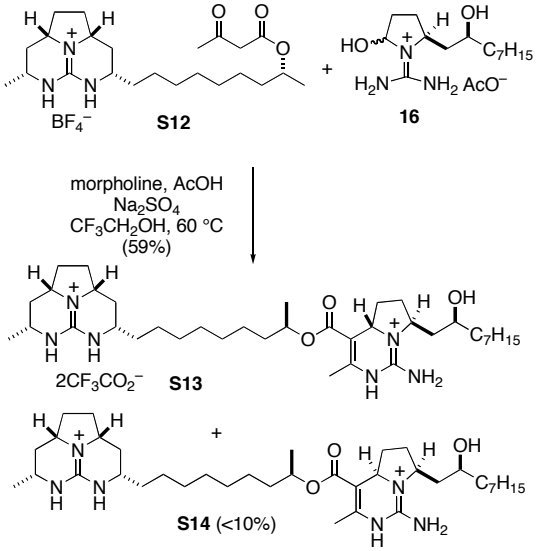
Scheme S2



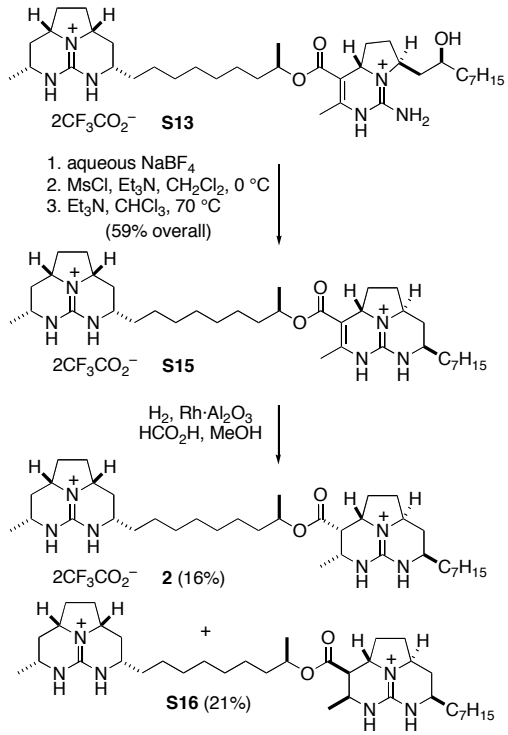
Scheme S3



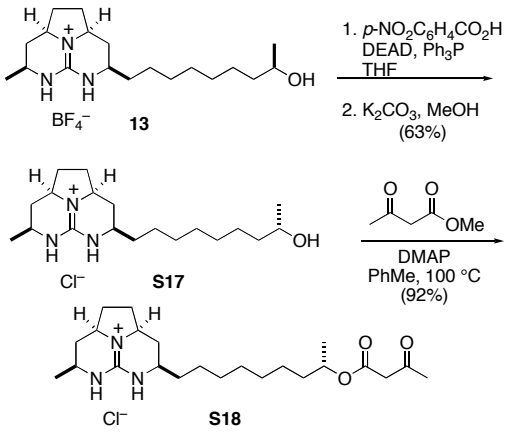
Scheme S4



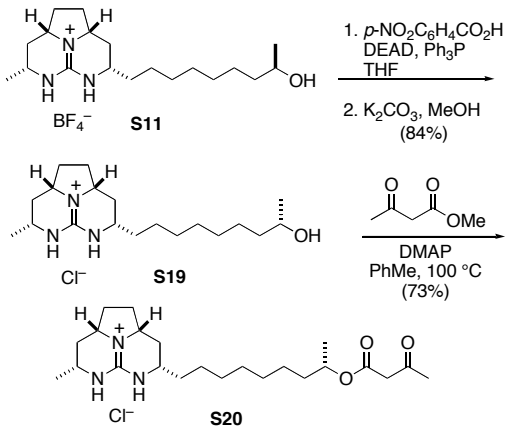
Scheme S5



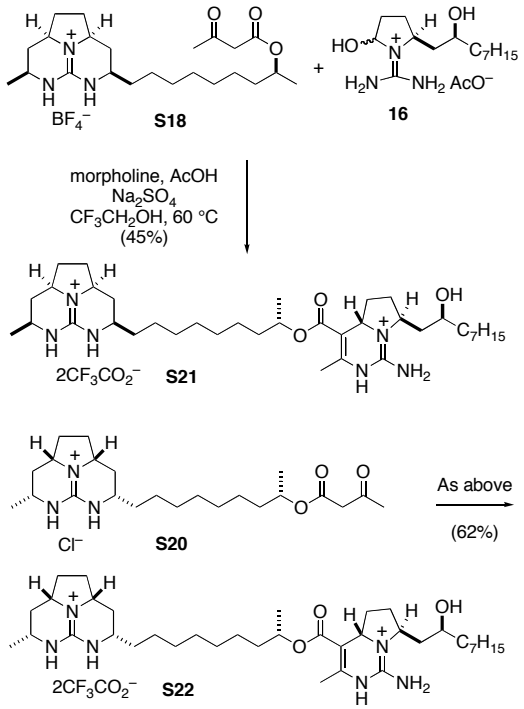
Scheme S6



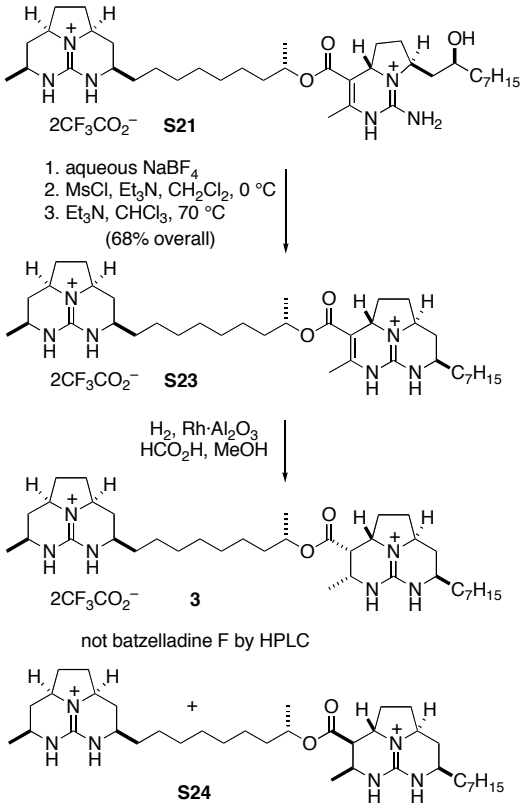
Scheme S7



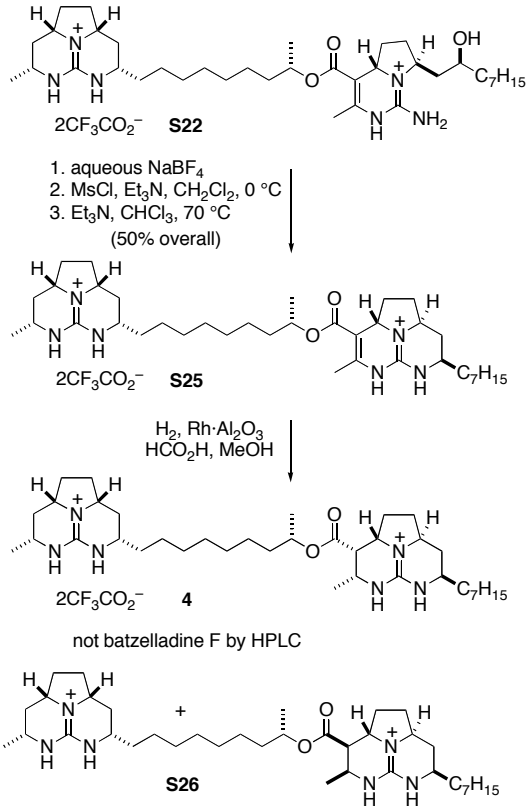
Scheme S8



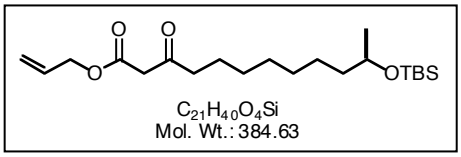
Scheme S9



Scheme S10



B. Experimental details and tabulated characterization data for new compounds not reported in the Experimental Section[1]



(11*R*)-11-(*tert*-Butyldimethylsiloxy)-3-oxododecanoic acid allyl ester (11). Following the general procedure of Corey,[2] solid I_2 (4.01 g, 15.8 mmol) was added in three portions over 30 min to a solution of alcohol **S1**[3] (3.74 g, 14.4 mmol), triphenylphosphine (4.14 g, 15.8 mmol), imidazole (1.95 g, 28.7 mmol), Et_2O (20 mL) and acetonitrile (9 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 was filtered through a plug of SiO_2 topped with a layer of basic Al_2O_3 eluting with 5% Et_2O-hexanes. The solution was concentrated to provide 4.78 g (90%) of iodide **S2**, which was used without further purification. Diagnostic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76–3.72 (m, 1H), 3.19 (t, *J* = 6.8 Hz, 2H), 1.84–1.77 (m, 2H), 1.40–1.28 (m, 9H) 1.11 (d, *J* = 6.0 Hz, 3H) 0.88 (s, 9H), 0.04 (s, 6H).

Following the general procedure of Weiler,[4] methyl acetoacetate (1.5 mL, 14 mmol) was added dropwise to a suspension of NaH (620 mg, 14 mmol, washed with hexanes (1 × 5 mL)), in THF (40 mL) at 0 °C. The resulting solution was maintained at 0 °C for 10 min, then *n*-butyllithium (5.3 mL of 2.5 M in hexanes, 14 mmol) was added dropwise, and the yellow solution was maintained at 0 °C for 10 min. Iodide **S2** was then added dropwise, and the reaction was maintained at 0 °C for 1h. The reaction was poured into cold 1 N HCl (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 3.67 g of β-keto ester **S3**, which was carried on directly. Diagnostic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80–3.72 (m, 4H), 3.45 (s, 2H), 2.52 (t, *J* = 7.5 Hz, 2H), 1.62–1.52 (m, 3H), 1.50–1.15 (m, 10H) 1.10 (d, *J* = 6.1 Hz, 3H) 0.88 (s, 9H), 0.04 (s, 6H).

Ester **S3** (3.67 g, 10.2 mmol), DMAP (1.25 g, 10.2 mmol) and allyl alcohol (11 mL) were heated at 100 °C for 22 h. The solution was partitioned between 0.1 N HCl (200 mL) and 20% EtOAc–hexanes (75 mL). The aqueous layer was extracted with 20% EtOAc–hexanes (3 × 75 mL). The combined organic layers were washed with brine (1 × 100 mL), dried (Na_2SO_4), filtered, concentrated, and the residue was chromatographed (SiO_2, gradient elution with 5–10% EtOAc–hexanes) to provide 3.22 g (82%) of the title compound as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99–5.86 (m, 1H), 5.37–5.22 (m, 2H) 3.71 (dt, *J* = 5.8, 1.4 Hz, 2H), 3.80–3.72

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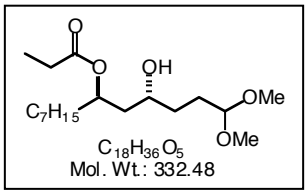
[1] General experimental details have been described: MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc*. **2001**, *123*, 9033–9044.

[2] (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.

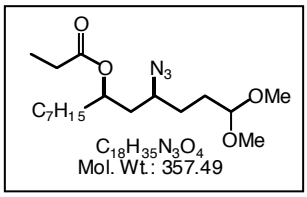
[3] Mori, Kenji; Maemoto, Shunichi. Liebigs Annalen der Chemie (1987), (10), 863-9. or Jones, Graham B.; Huber, Robert S.; Chapman, Brant J. Tetrahedron: Asymmetry (1997), 8(11), 1797-1809.

[4] Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc* **1974**, *96*, 1082–1087.

(m, 1H), 3.46 (s, 2H), 2.02 (t, J = 7.3 Hz, 2H),1.62–1.52 (m, 3H), 1.50–1.15 (m, 10H) 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, 131.6, 118.8, 68.6, 65.9, 49.1, 43.1, 39.7, 29.5, 29.3, 29.0, 25.9, 25.7, 23.8, 23.4, 18.1, –4.4, –4.7; IR (film) 2930, 2856, 1747, 1720, 1254 cm^{-1}; $[\alpha]_D^{24}$ = –7.9, $[\alpha]_{546}^{24}$ = –10.2, $[\alpha]_{435}^{24}$ = –16.2, $[\alpha]_{405}^{24}$ = –19.3 (*c* 0.90, $CHCl_3$). Anal. Cacld for $C_{21}H_{40}O_4Si$: C, 65.58; H, 10.48. Found C, 65.49; H, 10.46.



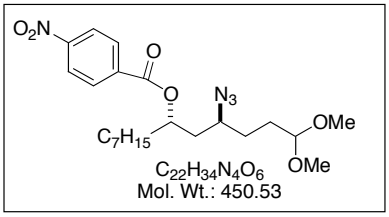
(4*R*,6*R*)-1,1-Dimethoxy-6-propanoyloxytridecane-4-o1 (S4). Following the procedure of Evans,[5] samarium diiodide (74 mL, 0.1 M in THF, 7.4 mmol) was added over 1 h to a solution of freshly distilled propanal (6.9 mL, 96 mmol), ketone **15** and THF (70 mL) at –15 °C (external bath temperature). The 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% ethyl acetate–hexanes (250 mL) and shaken vigorously. The layers were separated and the aqueous layer was extracted with 20% ethyl acetate–hexanes (3 × 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 × 100 mL), brine (1 × 100 mL), dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (SiO_2, elution with 20% ethyl acetate–hexanes containing 1% Et_3N) to give 7.32 g (93%) of hydroxy-ester **S4** as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6) δ 5.29–5.21 (m, 1H), 4.36 (t, J = 5.6 Hz, 1H), 3.62–3.54 (m, 1 H), 3.21 (dd, J = 4.0, 0.8 Hz, 1H), 3.16 (s, 3H), 3.15 (s, 3H), 2.06 (q, J = 7.6 Hz, 2H), 1.84–1.75 (m, 1 H), 1.66–1.45 (m, 5H), 1.35–1.15 (m, 11H), 0.95 (t, J = 7.6 Hz, 3H), 0.89 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 175.5, 105.2, 72.2, 67.6, 52.9, 52.5, 44.0, 35.8, 33.1, 32.5, 30.1, 30.0, 29.7, 28.2, 26.2, 23.4, 14 .7, 9.8; FTIR (film) 3509, 2229, 2857, 1734, 1462, 1194, 1128, 1070 cm^{-1}; $[\alpha]_D^{24}$ = –15.0, $[\alpha]_{546}^{24}$ = –17.4, $[\alpha]_{435}^{24}$ = –29.5, $[\alpha]_{405}^{24}$ = –35.0 (*c* 0.7, C_6H_6). Anal. Calcd for $C_{18}H_{36}O_5$: C, 65.03; H, 10.91. Found: C, 64.92; H 10.91.



(4*S*,6*R*)-4-Azido-1,1-dimethoxy-6-propanoylxytridecane (S5). Diethyl azodicarboxylate (7.0 mL, 44 mmol) was added dropwise over 15 min to a solution of alcohol **S4** (7.31 g, 22.0 mmol), hydrazoic acid (30 mL, 1.5 M in toluene, 44 mmol),[6] triphenylphosphine (11.53 g, 44.0 mmol), and toluene (73 mL) at 0 °C. The reaction was then quenched with saturated aqueous $NaHCO_3$ (2 mL), and concentrated. The residue was adsorbed onto

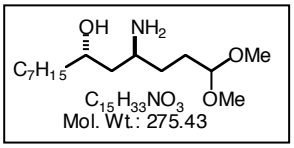
[5] Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1990**, *112*, 6447-6449.
[6] Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem*. **1984**, *49*, 4237-4244.

Celite®, and chromatographed (SiO_2, gradient elution 5% to 10% EtOAc–hexanes containing 1% Et_3N) to yield 7.36 g (94%) of the title compound as a colorless oil: ^{1}H NMR, (500 MHz, C_6D_6) δ 5.18–5.08 (m, 1H), 4.22 (t, *J* = 5.4 Hz, 1H), 3.26–3.19 (m, 1H), 3.11 (s, 6H), 2.17–2.05 (m, 2H), 1.79–1.73 (m, 11H), 1.68–1.56 (m, 2H),1.49–1.39 (m, 3H)1.00 (t, *J* = 7.6 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 173.8, 104.5, 71.5, 60.3, 52.9, 52.7, 39.3, 35.2, 32.5, 30.1, 29.9, 29.8, 29.5, 28.2, 25.9, 23.4, 14.7, 9.7; FTIR (film) 2929, 2857, 2101, 1737, 1462, 1187 cm^{-1}; $[\alpha]_D^{24}$ = 9.4, $[\alpha]_{546}^{24}$ = 10.8, $[\alpha]_{435}^{24}$ = 19.7, $[\alpha]_{405}^{24}$ = 25.0 (*c* 1.20, C_6H_6). Anal. Calcd for $C_{18}H_{35}N_3O_4$: C, 60.48; H, 9.87; N 11.75. Found: C, 60.56; H 9.88; N 11.76.



(4*S*,6*S*)-4-Azido-6-(4-nitrobenzoyloxy)-1,1-dimethoxytridecane (S6). A mixture of azido ester **S6** (6.81 g, 19.0 mmol), K_2CO_3 (5.0 g), and MeOH (100 mL) was heated at reflux for 5 h. The reaction was cooled to rt, and most of the solvent was removed under reduced pressure. The residue was diluted with saturated aqueous $NaHCO_3$ (150 mL) and extracted with 20% EtOAc–hexanes (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was azeotroped from benzene and the resulting alcohol carried on directly.

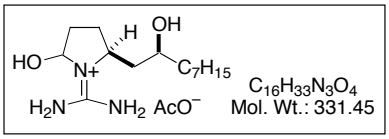
Diethyl azodicarboxylate (5.90 mL, 37.5 mmol) was added dropwise to a 0 °C solution of triphenylphosphine (9.84 g, 37.5 mmol) and toluene (50 mL). The resulting yellow solution was added dropwise over 20 min to a mixture of alcohol prepared above (5.65 g, 18.7 mmol), 4-nitrobenzoic acid (6.26 g, 37.5 mmol) and toluene (50 mL). One hour after addition was complete Celite was added and the mixture was concentrated to a free-flowing powder. This residue was chromatographed (5% then 10% EtOAc-hexanes containing 1% Et_3N) to give 7.55 g (90%) of azido ester **S6** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.9 Hz, 2H), 8.21 (d, *J* = 8.9 Hz, 2H), 5.40–5.30 (m, 1H), 4.35 (t, *J* = 5.3 Hz, 1H), 3.42–3.36 (m, 1H), 3.31 (s, 3H), 3.30 (s, 3H), 1.94–1.86 (m 1H), 1.81–1.73 (m, 3H), 1.70–1.60 (m, 4H) 1.38–1.21 (m, 11H), 0.87 (t, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 150.5, 135.7, 130.7, 123.6, 104.2, 73.4, 59.3, 53.3, 52.9, 39.0, 34.6, 31.7, 29.9, 29.3, 26.1, 29.0, 25.2, 22.6, 14.1 ppm; IR (film) 2929, 2856, 2104, 1724, 1530, 1349, 1274, cm^{-1}; $[\alpha]_D^{24}$ = 28.4, $[\alpha]_{546}^{24}$ = 33.0, $[\alpha]_{435}^{24}$ = 59.8 (*c* 0.8, $CHCl_3$); HRMS (ES+) *m/z* 473.2376 (473.2379 calcd for $C_{22}H_{34}N_4O_6Na$, M+Na).



(4*S*,6*S*)-4-Amino-1,1-dimethoxytridecane-6-o1 (S7). A mixture of ester **S6** (7.50 g, 16.7 mmol), 1 N NaOH (80 mL) and THF (80 mL) was heated at reflux for 12 h. The reaction was allowed to cool to rt, and the THF removed under reduced pressure. The aqueous phase was extracted with 20% EtOAc–hexanes (3 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 × 50 mL), brine (1 × 50 mL), dried (Na_2SO_4), filtered, and concentrated to yield 4.87 g (97%) of the hydroxy–azide as a colorless oil: ^{1}H NMR (500 MHz,

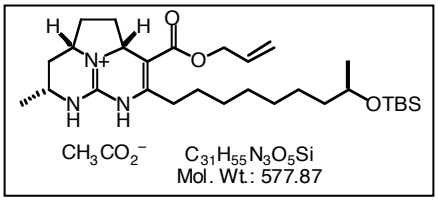
$CDCl_3$) δ 4.38 (t, *J* = 5.4 Hz, 1H), 3.85–3.78 (m, 1H), 3.66–3.60 (m, 1H), 3.30 (s, 6H), 1.81–1.65 (m, 2H), 1.65–1.51 (m, 5H), 1.48–1.39 (m, 3H), 1.36–1.23 (m, 9H), 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 104.1, 68.6, 59.6, 53.0, 52.8, 41.8, 38.2, 31.8, 29.9, 29.5, 29.2, 29.1, 25.6, 22.6, 14.1; FTIR (film) 3423, 2927, 2856, 2102, 1129 cm^{-1}; $[\alpha]_D^{24}$ = 26.3, $[\alpha]_{546}^{24}$ = 30.9, $[\alpha]_{435}^{24}$ = 52.3, $[\alpha]_{405}^{24}$ = 63.1 (*c* 0.95, $CHCl_3$). Anal. Calcd for $C_{15}H_{31}N_3O_3$: C, 59.77; H, 10.37; N 13.94. Found: C, 59.91; H 10.28; N 14.13.

A mixture of the azide prepared above (4.74 g, 15.7 mmol), 10% Pd·C (400 mg), and MeOH (50 mL) was maintained under 50 psi of H_2 for 24 h. The mixture was filtered through Celite©, and the pad was washed with MeOH (50 mL). The filtrate was concentrated to provide 4.15 g (96%) of the title compound as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 (t, *J* = 5.5 Hz, 1H), 3.90–3.83 (m, 1H), 3.33 (s, 6H), 3.15–3.10 (m, 1H), 2.75–2.35 (br s, 3H), 1.69–1.59 (m, 2H), 1.58–1.35 (m, 7H), 1.33–1.23 (m, 9H), 0.87 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 104.5, 69.3, 53.0, 52.9, 49.0, 41.0, 37.8, 32.5, 31.8, 29.7, 29.5, 29.3, 25.9, 22.6, 14.1; FTIR (film) 3356, 2927, 2855, 1458, 1126, 1054 cm^{-1}; $[\alpha]_D^{24}$ = 1.6, $[\alpha]_{546}^{24}$ = 2.4, $[\alpha]_{435}^{24}$ = 4.8, $[\alpha]_{405}^{24}$ = 6.4 (*c* 0.90, $CHCl_3$); HRMS (CI) *m/z* 276.2537 (276.2538 calcd for $C_{15}H_{33}NO_3$, M+H).



Guanidine hemiaminal 16. Following the general procedure of Bernatowitz,[7] a solution of amine **S7** (1.00 g, 3.63 mmol), 1*H*-pyrazole-1-carboxamidine hydrochloride (560 mg 3.81 mmol), *i*-Pr_2NEt (670 μL, 3.81 mmol), and MeOH (1.8 mL) was maintained at rt for 24 h, then concentrated at 0.5 mm for 12 h to yield the guanidine as a colorless oil, which was used without further purification. Diagnostic data: ^{1}H NMR (400 MHz, CD_3OD) δ 4.37 (t, *J* = 5.1 Hz, 1H), 3.75–3.66 (m, 1H), 3.58–3.50 (m, 1H), 3.32 (s, 6H), 1.72–1.66 (m, 1H), 1.65–1.59 (m, 3H), 1.59–1.52 (m, 3H), 1.50–1.40 (m, 4H) 1.36–1.25 (m, 11H), 0.91–0.86 (m, 3H). MS (ESI) *m/z* 318.2.

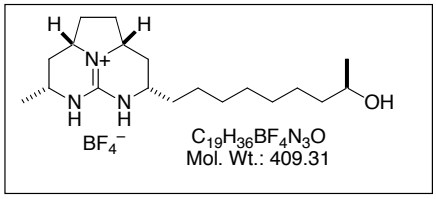
A solution of guanidine (0.48 mmol) and 50% aqueous acetic acid (5 mL) was maintained at rt for 24 h, then concentrated at 0.5 mm for 24 h to yield guanidine **16** as a colorless oil, which was used immediately. Diagnostic data ^{1}H NMR (400 MHz, CD_3OD) δ 5.40–5.36 (m). MS (ESI) *m/z*= 272.2.



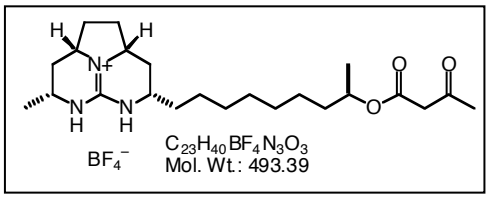
(2a*R*,7*R*,8a*S*)-3-Allyloxycarbonyl-4-[6*R*-(*tert*-butyldimethylsiloxy)nonyl]-7-methyl-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b-triazaacenaphthylenium acetate (**S10**). A mixture of guanidine **S9**[8] (1.53 mmol), β-keto ester **11** (1.77 g, 4.6 mmol), morpholinium acetate (250 mg, 1.7 mmol), Na_2SO_4 (500 mg), and trifluoroethanol (3.0 mL) was heated at 60 °C for 2 d. After cooling to rt, the mixture was filtered, concentrated. The residue was chromatographed (SiO_2,

[7] Bernatowitz, M. S.; Wu, Y.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, *34*, 3389–3392.
[8] Cohen, F; Overman, L. E. preceeding contribution in this issure.

gradient elution with 2–5% MeOH–$CHCl_3$ with 1% AcOH) to provide 670 mg (78%) of tricyclic guanidine **S10** as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99–5.86 (m, 1H), 5.34–5.23 (m, 2H), 4.66–4.58 (m, 2H), 4.42 (dd, *J* = 9.8, 6.0 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, 15H), 1.09 (d, *J* = 6.1 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 165.0, 150.5, 147.0, 132.2, 118.4, 99.0, 68.7, 64.9, 57.0, 55.6, 55.3, 54.3, 47.4, 45.4, 39.7, 35.7, 33.2, 30.7, 29.6, 29.4, 28.7, 27.0, 25.9, 25.8, 23.8, 22.9, 19.4, 18.1, –4.5, –4.7; IR (film) 2930, 2857, 1688, 1626, 1538, 1258 cm^{-1}; $[\alpha]_D^{24}$ = 62.0, $[\alpha]_{546}^{24}$ = 74.6, $[\alpha]_{435}^{24}$ = 146.1, $[\alpha]_{405}^{24}$ = 191.5 (*c* 0.50, MeOH); HRMS (ESI) *m/z* 518.3765 (518.3778 calcd for $C_{29}H_{52}N_3O_3Si$, M).

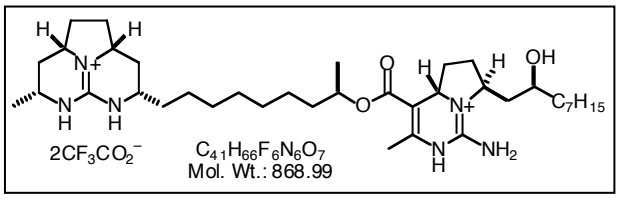


(2a*R*4*S*,7*S*,8a*S*)-4-[6*R*-Hydroxynonly]-7-methyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylenium tetrafluoroborate (S11). A solution of ester **S10** (200 mg, 0.35 mmol), $(PPh_3)_4Pd$ (10 mg, 0.009 mmol), pyrrolidine (140 μL, 1.7 mmol), THF (2 mL), and MeOH (2 mL) was maintained at rt and monitored by ESMS. After 6 h, the reaction was concentrated and acetic acid (5 mL) was added. Solid $NaBH_4$ (64 mg, 1.7 mmol) was added in portions over 20 min and the mixture was stirred overnight. The solvent was removed by azeotroping with heptane (2 × 5 mL) under reduced pressure, 1 N HCl (5 mL) was and the resulting solution was maintained at rt for 1 d. This solution was diluted with 1 N HCl (10 mL) and extracted with $CHCl_3$ (6 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. This residue was chromatographed (SiO_2, gradient elution with 2–5–10% MeOH–$CHCl_3$); the fractions containing the product were combined, concentrated, and azeotroped with heptane. The residue was dissolved in $CHCl_3$ (20 mL), washed with saturated aqueous $NaBF_4$ (3 × 5 mL), dried (Na_2SO_4), filtered, and concentrated to provide 80 mg (56%) of tricyclic guanidine **S11** 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), 2.26–2.17 (m, 4H), 1.72–1.64 (m, 2H), 1.61–1.53 (m, 2H), 1.46–1.33 (m, 13H), 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, 57.52, 57.46, 51.6, 47.3, 40.2, 36.7, 35.8, 34.7, 31.02, 30.99, 30.7, 30.51, 30.47, 26.8, 26.2, 23.5, 20.8; IR (film) 2929, 2856, 1621, 1062 cm^{-1}; $[\alpha]_D^{24}$ = –13.3, $[\alpha]_{546}^{24}$ = –16.0, $[\alpha]_{435}^{24}$ = –26.8, $[\alpha]_{405}^{24}$ = –32.3 (*c* 0.80, MeOH); HRMS (FAB) *m/z* 322.2847 (322.2858 calcd for $C_{19}H_{36}N_3O$).

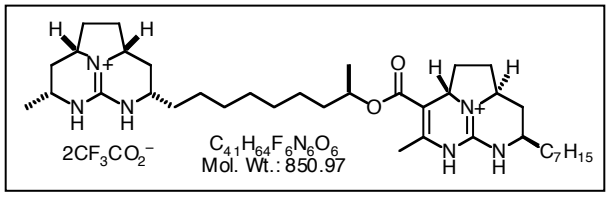


3-Oxo-butyric acid (1*R*)-1-methyl-8-((2a*S*,4*S*,7*R*,8a*R*)-7-methyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylenium-4-yl)octyl ester acetate (**S12**). A solution of alcohol **S11** (64 mg, 0.16 mmol), methyl acetoacetate (170 μL, 1.2 mmol), DMAP (20 mg, 0.16

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 64 mg (81%) of β-keto ester **S12**, as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (br s, 1H), 6.75 (br 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), 2.27–2.15 (m, 6H), 1.86–1.75 (m, 2H), 1.70–1.63 (m, 3H), 1.60–1.55 (m, 1H), 1.52–1.44 (m, 2H), 1.40–1.19 (m, 16H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8, 166.8, 149.2, 72.3, 56.0, 55.9, 50.5, 50.4, 46.0, 36.0, 35.8, 35.7, 34.4, 33.6, 33.0, 30.2, 30.1, 29.1, 25.1, 24.8, 20.1, 19.8; IR (film) 3356, 2933, 2858, 1713, 1622, 1326, 1060 cm^{-1}; $[\alpha]_D^{24}$ = –13.3, $[\alpha]_{546}^{24}$ = –16.1, (*c* 0.60, MeOH); HRMS (ESI) *m/z* 406.3069 (406.3070 calcd for $C_{23}H_{40}N_3O_3$, M).



(4a*S*,7*S*,2´*S*,1´´*R*,2a´´´*R*,4´´´*S*,7´´´*R*,8a´´´*S*)-7-(2´-Hydroxynonyl)-1-imino-3-methyl-1,2,4a,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidinium-4-carboxylic acid 1´´-methyl-9´´-(7´´´-methyl-1´´´,2´´´,2a´´´,3´´´,4´´´,5´´´,6´´´,7´´´,8´´´,8a´´´-decahydro-5´´´,6´´´,8b´´´,-triazaacenaphthylenium-4´´´-yl)nonyl ester bis trifluoroacetate (S13). A mixture of β-keto ester **S12** (52 mg, 0.11 mmol), guanidine **16** (0.33 mmol), morpholinium acetate (50 mg, 0.33 mmol), Na_2SO_4 (50 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 48 mg (50%) of **S13** 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, 30.4, 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}; $[\alpha]_D^{24}$ = –27.0, $[\alpha]_{546}^{24}$ = –31.3, $[\alpha]_{435}^{24}$ = –44.0, $[\alpha]_{405}^{24}$ = –45.3 (*c* 0.96, MeOH); HRMS (ESI) *m/z* 641.5112 (641.5118 calcd for $C_{37}H_{65}N_6O_3$ M-H$^+$).

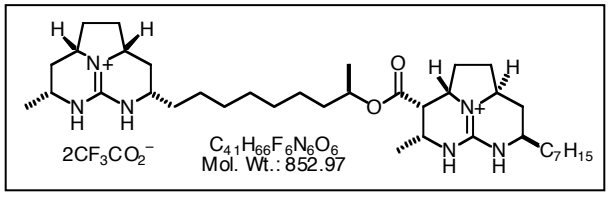


(2a*S*,7*R*,8a*S*,1´*R*,2a´´*R*,4´´*S*,7´´*R*,8a´´*S*)-4-Methyl-7-heptyl-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b,-triazaacenaphthylenium-3-carboxylic acid 1´-methyl-9´-(7´´-methyl-1´´,2´´,2a´´,3´´,4´´,5´´,6´´,7´´,8´´,8a´´-decahydro-5´´,6´´,8b´´-triazaacenaphthylenium-4´´-yl)nonyl ester bis triflouroacetate (S15). Bisguanidine **S13** (46 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

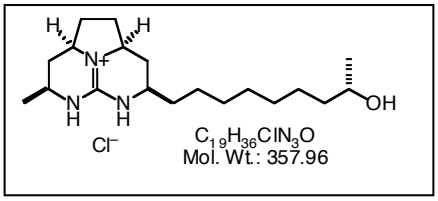
(Na_2SO_4), filtered, concentrated, and azeotroped with C_6H_6 (3 × 1 mL) to provide bisguanidine **S13** as the BF_4^- salt, which was carried on directly.

To a 0 °C solution of the guanidine alcohol BF_4^- salt prepared above (38 mg, 0.047 mmol), Et_3N (190 μL, 1.0 M in CH_2Cl_2, 0.19 mmol) and CH_2Cl_2, (2 mL) was added methanesulphonyl chloride (93 μL, 1.0 M in CH_2Cl_2, 0.093 mmol) over 10 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 concentrated. The residue was purified by HPLC (5 μm C_{18}, 50% MeCN-H_2O with 0.1% TFA) to provide 27 mg (58%) 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, 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}; $[\alpha]_D^{24}$ = –15.7, $[\alpha]_{546}^{24}$ = –17.4, $[\alpha]_{435}^{24}$ = –15.8, $[\alpha]_{405}^{24}$ = –8.5 (*c* 0.7, MeOH); HRMS (ESI) *m/z* 623.5019 (623.5012 calcd for $C_{37}H_{63}N_6O_2$, M-H$^+$).



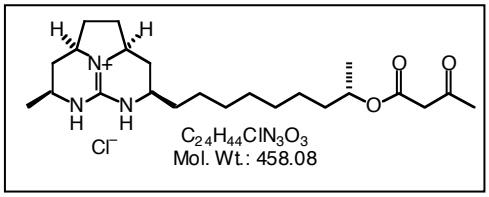
Batzelladine F isomer 2. A mixture of olefin **S15** (12 mg, 0.014 mmol), 5% Rh·Al_2O_3 (25 mg), HCO_2H (5 drops) and MeOH (2 mL) was maintained under 90 psi of H_2 for 48 h. Celite was added and the mixture was filtered through Celite, then further filtered through a 0.45 μm nylon filter, rinsing with MeOH. The filtrate was concentrated, and the residue was purified by HPLC (5 μm C_{18}, 40–50% MeCN-H_2O with 0.1% TFA) to provide 3.6 mg (30%) of **2** as a colorless oil. See Tables S1 and S2 for ^{1}H and ^{13}C NMR; IR (film) 3196, 3119, 2930, 2860, 1725, 1679, 1637, 1328, 1200 cm^{-1}; $[\alpha]_D^{24}$ = –7.7, $[\alpha]_{546}^{24}$ = –9.5, $[\alpha]_{435}^{24}$ = –16.5, $[\alpha]_{405}^{24}$ = –20.1 (*c* 0.25, MeOH); HRMS (ESI) *m/z* 625.5169 (625.5182 calcd for $C_{37}H_{65}N_6O_2$, M-H$^+$).



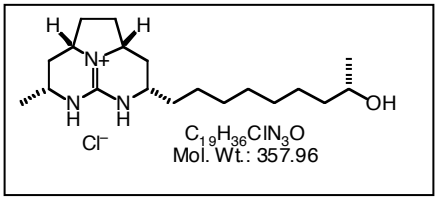
(2a*S*,4*R*,7*R*,8a*R*)-4-[6*S*-Hydroxynonyl]-7-methyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylenium chloride (S17, *ent*-S11). Diethyl azodicarboxylate (160 μL, 1.0

mmol) was added dropwise to a solution of alcohol **13** (200 mg, 0.50 mmol, azeotroped 3 × with C_6H_6), *p*-nitrobenzoic acid (170 mg, 1.0 mmol), triphenylphosphine (260 mg, 1.0 mmol), and THF (3 mL) over 10 min. The mixture was adsorbed onto Celite, and chromatographed (SiO_2, gradient elution with 2–5% MeOH–$CHCl_3$, 1% AcOH) to provide the corresponding 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* 471.

The ester prepared above was combined with K_2CO_3 (700 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 × 5 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 110 mg (63%) of tricyclic guanidine **S17** (*ent*–**S11**) as a colorless oil: $[\alpha]_D^{24}$ = 17.9, $[\alpha]_{546}^{24}$ = 20.9, $[\alpha]_{435}^{24}$ = 36.2, $[\alpha]_{405}^{24}$ = 43.6 (*c* 1.0, MeOH).

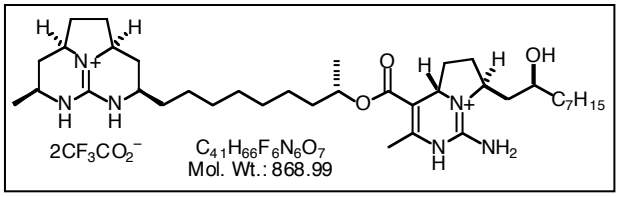


3-Oxobutyric acid (1*S*)-1-methyl-8-((2a*R*,4*R*,7*S*,8a*S*)-7-methyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylenium-4-yl)octyl ester tetrafluoroborate (S18, *ent*-S12). A solution of alcohol **S17** (57 mg, 0.16 mmol), methyl acetoacetate (170 μL, 1.2 mmol), DMAP (20 mg, 0.16 mmol), and 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 64 mg (92%) of β-keto ester **S12**, as a yellow oil.

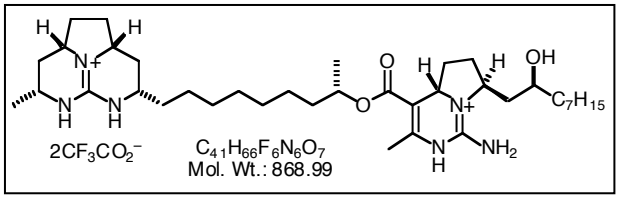


(2a*R*4*S*,7*S*,8a*S*)-4-[6*S*-Hydroxynonly]-7-methyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylenium chloride (S19, *ent*–13). Diethyl azodicarboxylate (160 μL, 1.0 mmol) was added dropwise to a solution of alcohol **S11** (210 mg, 0.50 mmol, azeotroped 3 × with C_6H_6), *p*-nitrobenzoic acid (170 mg, 1.0 mmol), triphenylphosphine (260 mg, 1.0 mmol), and THF (3 mL) over 10 min. The mixture was adsorbed onto Celite, and chromatographed (SiO_2, gradient elution with 2–5% MeOH–$CHCl_3$, 1% AcOH) to provide the corresponding 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* 471.

The ester prepared above was combined with K_2CO_3 (700 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 × 5 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 155 mg (84%) of tricyclic guanidine **S19** (*ent*–**13**) as a colorless oil: $[\alpha]_D^{24}$ = –9.3, $[\alpha]_{546}^{24}$ = –11.6, $[\alpha]_{435}^{24}$ = –20.3, $[\alpha]_{405}^{24}$ = –24.8 (*c* 1.0, MeOH).

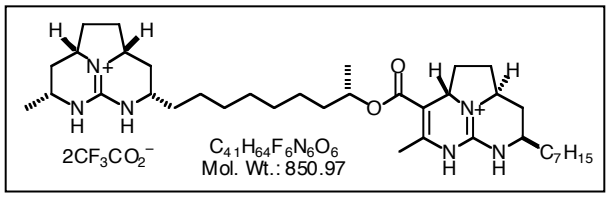


(4a*S*,7*S*,2´*S*,1´´*S*,2a´´´*S*,4´´´*R*,7´´´*S*,8a´´´*R*)-7-(2´-Hydroxynonyl)-1-imino-3-methyl-1,2,4a,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidinium-4-carboxylic acid 1´´-methyl-9´´-(7´´´-methyl-1´´´,2´´´,2a´´´,3´´´,4´´´,5´´´,6´´´,7´´´,8´´´,8a´´´-decahydro-5´´´,6´´´,8b´´´,-triazaacenaphthylenium-4´´´-yl)nonyl ester bis trifluoroacetate (S21). A mixture of β-keto ester **S18** (70 mg, 0.15 mmol), guanidine **16** (0.48 mmol), morpholinium acetate (70 mg, 0.48 mmol), Na_2SO_4 (70 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}, gradient 40–55% MeCN-H_2O with 0.1% TFA) to provide 62 mg (45%) of **S21** 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, 30.4, 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}; $[\alpha]_D^{24}$ = 15.5, $[\alpha]_{546}^{24}$ = 19.8, $[\alpha]_{435}^{24}$ = 53.6, $[\alpha]_{405}^{24}$ = 80.4 (*c* 1.2, MeOH); HRMS (ESI) *m/z* 641.5107 (641.5118 calcd for $C_{37}H_{65}N_6O_3$ M-H$^+$).



(4a*S*,7*S*,2´*S*,1´´*S*,2a´´´*R*,4´´´*S*,7´´´*R*,8a´´´*S*)-7-(2´-Hydroxynonyl)-1-imino-3-methyl-1,2,4a,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidinium-4-carboxylic acid 1´´-methyl-9´´-(7´´´-methyl-1´´´,2´´´,2a´´´,3´´´,4´´´,5´´´,6´´´,7´´´,8´´´,8a´´´-decahydro-5´´´,6´´´,8b´´´,-triazaacenaphthylenium-4´´´-yl)nonyl ester bis trifluoroacetate (S22). A mixture of β-keto ester **S20** (35 mg, 0.08 mmol), guanidine **16** (0.24 mmol), morpholinium acetate (35 mg, 0.24 mmol), Na_2SO_4 (35 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}, gradient 40–55% MeCN-H_2O with 0.1% TFA) to provide 43 mg (62%) of **S22** 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, 30.4, 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}; $[\alpha]_D^{24}$ = 3.9,

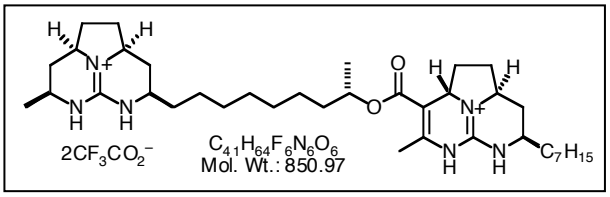
$[\alpha]_{546}^{24}$ = 6.1, $[\alpha]_{435}^{24}$ = 29.3, $[\alpha]_{405}^{24}$ = 50.7 (*c* 0.86, MeOH); HRMS (ESI) *m/z* 641.5120 (641.5118 calcd for $C_{37}H_{65}N_6O_3$ M-H^+).



(2a*S*,7*R*,8a*S*,1´*S*,2a´´*R*,4´´*S*,7´´*R*,8a´´*S*)-4-Methyl-7-heptyl-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b,-triazaacenaphthylenium-3-carboxylic acid 1´-methyl-9´-(7´´-methyl-1´´,2´´,2a´´,3´´,4´´,5´´,6´´,7´´,8´´,8a´´-decahydro-5´´,6´´,8b´´-triazaacenaphthylenium-4´´-yl)nonyl ester bis triflouroacetate (S25). Bisguanidine **S22** (41 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 bisguanidine **S22** as the BF_4^- salt, which was carried on directly.

To a 0 °C solution of the guanidine alcohol BF_4^- salt prepared above (33 mg, 0.041 mmol), Et_3N (160 μL, 1.0 M in CH_2Cl_2, 0.16 mmol) and CH_2Cl_2, (3 mL) was added methanesulphonyl chloride (80 μL, 1.0 M in CH_2Cl_2, 0.080 mmol) over 10 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 dissolvedin MeOH, filtered through a 0.45 μm filter, and concentrated The residue was purified by HPLC (5 μm C_{18}, 50% MeCN-H_2O with 0.1% TFA) to provide 20 mg (50%) of **S25** 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, 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}; $[\alpha]_D^{24}$ = 16.6, $[\alpha]_{546}^{24}$ = 20.2, $[\alpha]_{435}^{24}$ = 61.2, $[\alpha]_{405}^{24}$ = 93.7 (*c* 0.4, MeOH); HRMS (ESI) *m/z* 623.5025 (623.5012 calcd for $C_{37}H_{63}N_6O_2$, M-H^+).



(2a*S*,7*R*,8a*S*,1´*S*,2a´´*S*,4´´*R*,7´´*S*,8a´´*R*)-4-Methyl-7-heptyl-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b,-triazaacenaphthylenium-3-carboxylic acid 1´-methyl-9´-(7´´-methyl-

1´´,2´´,2a´´,3´´,4´´,5´´,6´´,7´´,8´´,8a´´-decahydro-5´´,6´´,8b´´-triazaacenaphthylenium-4´´-yl)nonyl ester bis triflouroacetate (S23). Bisguanidine **S21** (62 mg, 0.07 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 bisguanidine **S21** as the BF_4^- salt, which was carried on directly.

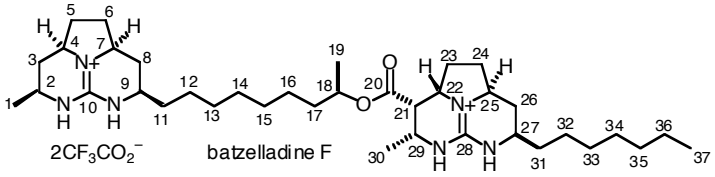
To a 0 °C solution of the guanidine alcohol BF_4^- salt prepared above (48 mg, 0.06 mmol), Et_3N (240 μL, 1.0 M in CH_2Cl_2, 0.0.24 mmol), and CH_2Cl_2, (5 mL) was added methanesulphonyl chloride (120 μL, 1.0 M in CH_2Cl_2, 0.12 mmol) over 10 min. After an additional h at 0 °C, ESMS indicated complete 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 $CHCl_3$ (6 mL, filtered through basic Al_2O_3) and Et_3N (0.6 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 concentrated. The residue was purified by HPLC (5 μm C_{18}, 50% MeCN-H_2O with 0.1% TFA) to provide 39 mg (78%) of **S23** 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, 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}; $[\alpha]_D^{24}$ = 27.6, $[\alpha]_{546}^{24}$ = 34.3, $[\alpha]_{435}^{24}$ = 85.2, $[\alpha]_{405}^{24}$ = 122.2 (*c* 0.8, MeOH); HRMS (ESI) *m/z* 623.4993 (623.5012 calcd for $C_{37}H_{63}N_6O_2$, M-H$^+$).

Batzelladine F isomers 3 and 4. A mixture of olefin **S23** (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 this mixture contained no batzelladine F.

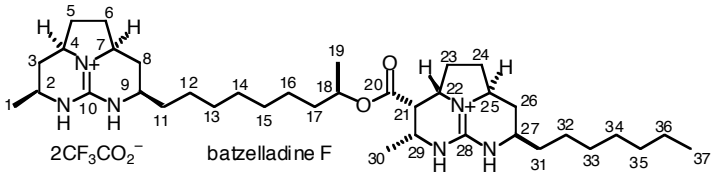
C. Table S1: ^{1}H NMR Data (CD_3OD) for natural batzelladine F and synthetic isomer 2. Table S2: ^{13}C NMR Data (CD_3OD) for natural and synthetic batzelladine F and synthetic isomer 2.

Table S1: ^{1}H NMR Data (CD_3OD) for natural batzelladine F and synthetic isomer **2**.



Position	Natural (400 MHz)	Synthetic (500 MHz) and 2
18	4.97 (m, 1H)	5.00–4.94 (m, 1H)
22	3.94 (m, 1H)	3.97–3.91 (m, 1H)
29	3.82 (m, 1H)	3.83–3.80 (m, 1H)
4, 7	3.72 (m, 2H)	3.76–3.69 (m, 2H)
2, 25, 27	3.52 (m, 3H)	3.57–3.49 (m, 3H)
9	3.40 (m, 1H)	3.43–3.48 (m, 1H)
21	3.06 (dd, *J* = 4.7, 3.4 Hz, 1H)	3.08 (dd, *J* = 4.7, 3.4 Hz, 1H)
26	2.34 (m, 1H)	2.35 (ddd, *J* = 12.7, 5.1, 2.2 Hz, 1H)
3, 5, 6, 8, 23, 26	2.30–2.18 (m, 6H)	2.30–2.18 (m, 6H)
5, 6, 11, 15, 23, 24, 31	1.70–1.50 (m, 10H)	1.70–1.50 (m, 10H)
1, 3, 8, 12–17, 19, 26, 30–36	1.45–1.20 (m, 32H)	1.45–1.20 (m, 32H)
37	0.90 (t, *J* = 7 Hz, 3H)	0.90 (t, *J* = 6.8 Hz, 3H)

Table S2: ^{13}C NMR Data (CD_3OD) for natural and synthetic batzelladine F and synthetic isomer 2.



Position	Natural (100 MHz)	Synthetic (125 MHz)	2
1	20.7	20.74	20.73
2	47.2	47.28	47.28
3	36.9	37.01	37.00
4	57.5	57.55	57.55
5,6	31.1	31.08, 31.04	31.07, 31.03
7	57.4	57.48	57.48
8	34.8	34.77	34.77
9	51.6	51.60	51.60
10	151.2	151.11	151.11
11	35.8	35.87	35.86
12	26.2	26.23	26.21
13–15	30.5	30.5	30.5
16	26.5	26.57	26.54
17	36.7	37.01	37.00
18	73.3	73.40	73.40
19	20.5	20.45	20.43
20	170.3	170.28	170.28
21	45.6	45.59	45.59
22	57.9	57.98	57.98
23	29.2	29.22	29.21
24	31.4	31.41	31.40
25	57.3	57.35	57.35
26	34.2	34.23	34.23
27	53.2	53.23	53.23
28	151.6	151.55	151.55
29	49.9	49.93	49.93
30	18.5	18.50	18.48
31	36.9	36.90	36.89
32–34	30.5	30.5	30.5
35	33.0	32.94	32.92
36	23.7	23.71	23.68
37	14.5	14.41	14.38

D. Figure S1: HPLC Co-injection of 2 and 4. Figure S2: HPLC Co-injection of 4 and authentic batzelladine F. Figure S3: HPLC Co-injection of 3 and 4

Figure S1 HPLC Co-injection of 2 and 4.

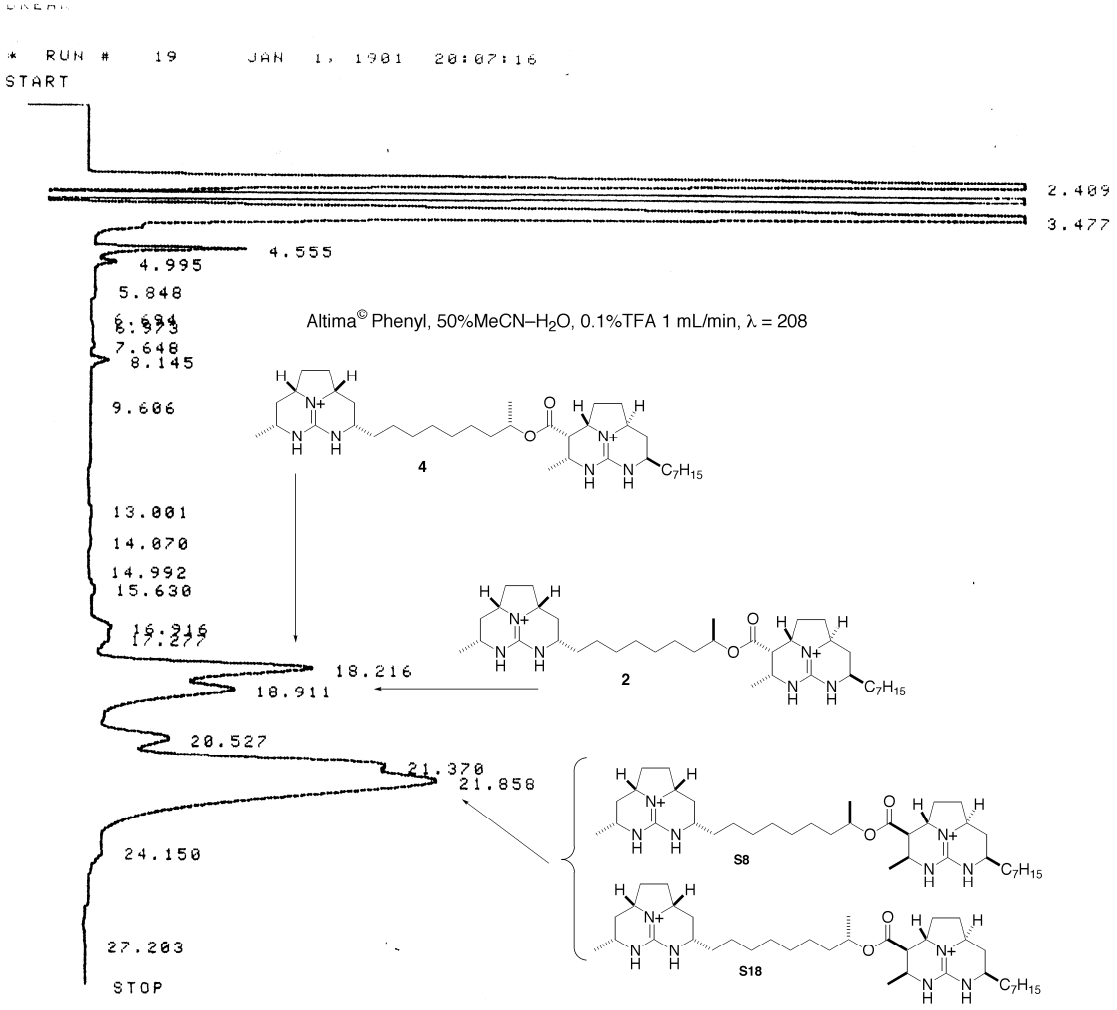


Figure S2 HPLC Co-injection of 4 and authentic batzelladine F.

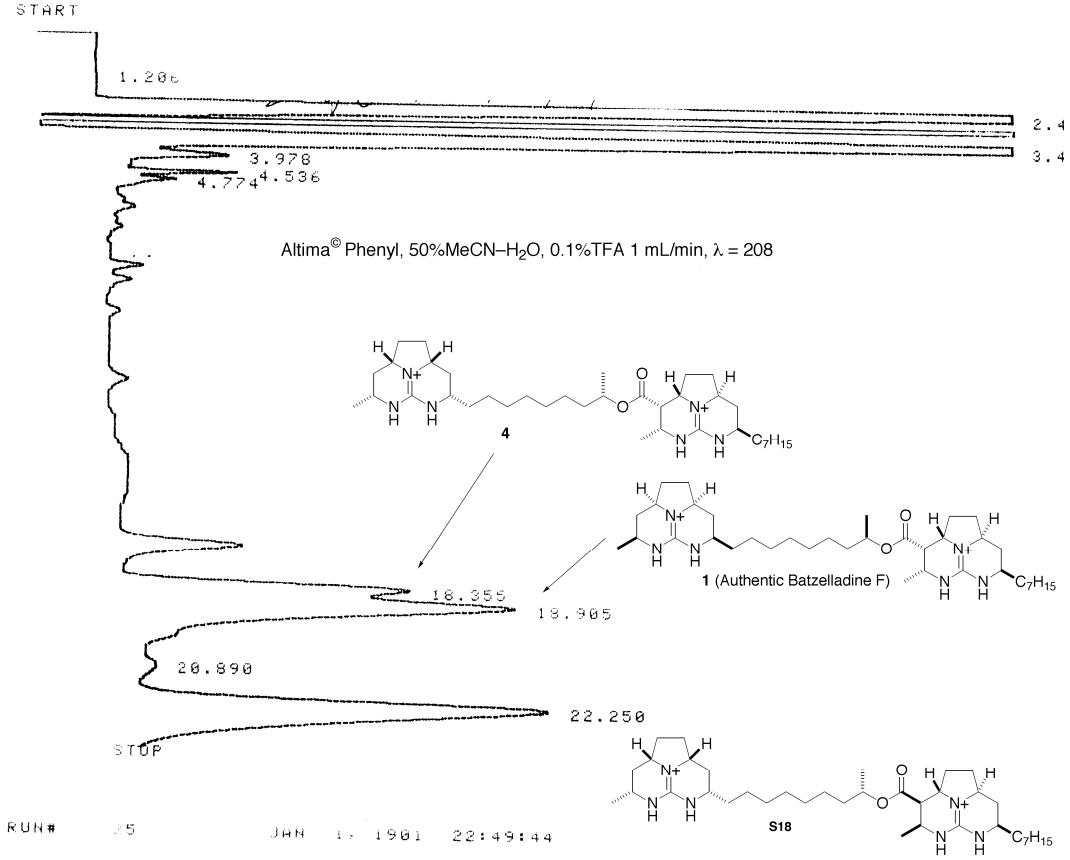


Figure S3. HPLC Co-injection of 3 and 4.