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Synthesis of the Left Hand Unit of Batzelladine F; Revision of the Reported Relative Stereochemistry

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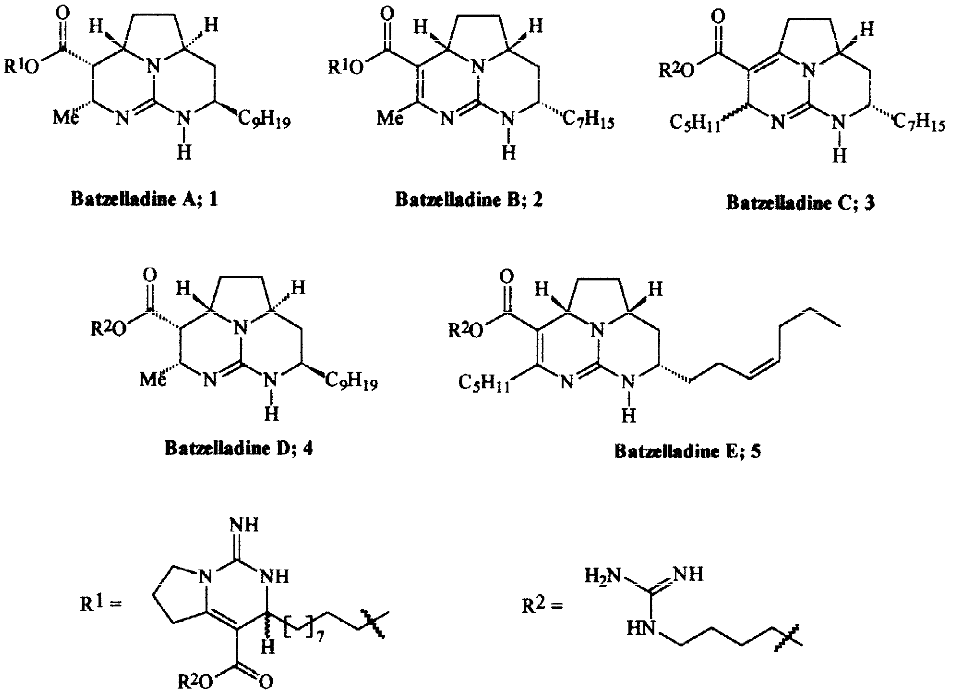
Abstract: The addition of guanidine to the *bis*-α,β-unsaturated ketone **17** is reported, leading to the formation of the tricyclic guanidine **18**, the left hand portion of the naturally occurring alkaloid batzelladine F. Nmr evidence is given which casts doubt upon the assignment of the relative stereochemistry of this metabolite.

Keywords: Batzelladine alkaloids, guanidine, Michael reaction.

There is considerable current biological[1] and synthetic[2] interest in guanidine containing biomolecules. We had previously reported[3] the synthesis of a range of compounds which where models of a series of metabolites isolated from *Batzella Sp.* termed the batzelladine alkaloids A - E **1-5** (Figure 1).[4]



Batzelladine A; 1

Batzelladine B; 2

Batzelladine C; 3

Batzelladine D; 4

Batzelladine E; 5

Figure 1

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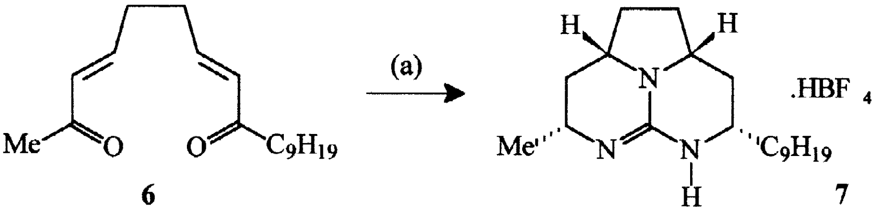
The original stereochemical assignment of the alkaloids **1** and **4** had been presumed to be one in which the methine hydrogens in the pyrrolidine ring and those adjacent to the guanidine were also all *cis*, which was based on a previous literature precedent.[4] Subsequent work by Snider[5] has shown that in the cases of batzelladine A and D the original assignment was incorrect and the relative stereochemistry of these metabolites was in fact *trans*.

Our synthetic approach to these metabolites involved the addition of guanidine to a *bis*-enone such as **6** with subsequent reduction leading to the tricyclic guanidine **7** as a single diastereoisomer in 31% overall yield (Scheme 1), the relative overall *cis*-stereochemistry of these materials being determined by X-ray crystallography.[3]



Scheme 1: (a) (i) Guanidine/DMF/0°C-RT/5hrs, (ii) 3:1:3 DMF/H_2O/MeOH, then $NaBH_4$/16hrs, (iii) HCl, (iv) aq. $NaBF_4$ (sat).

Shortly after the publication of our original communication several further batzelladine metabolites, termed F-I, were isolated.[6] These were interesting in so much as one of them, batzelladine F **8** (figure 2), contained two tricyclic guanidine units, one of which lacked the ester function found in all the metabolites A-E.

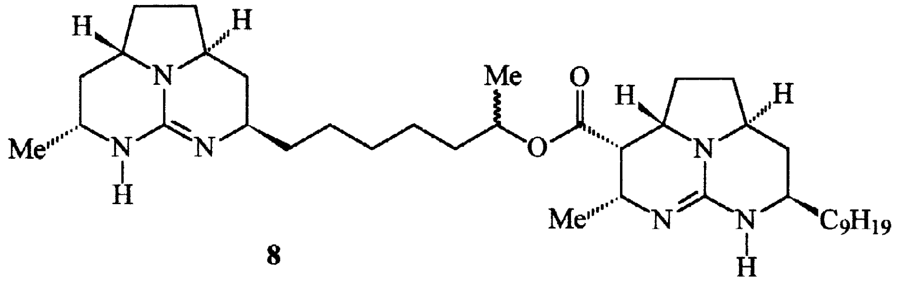
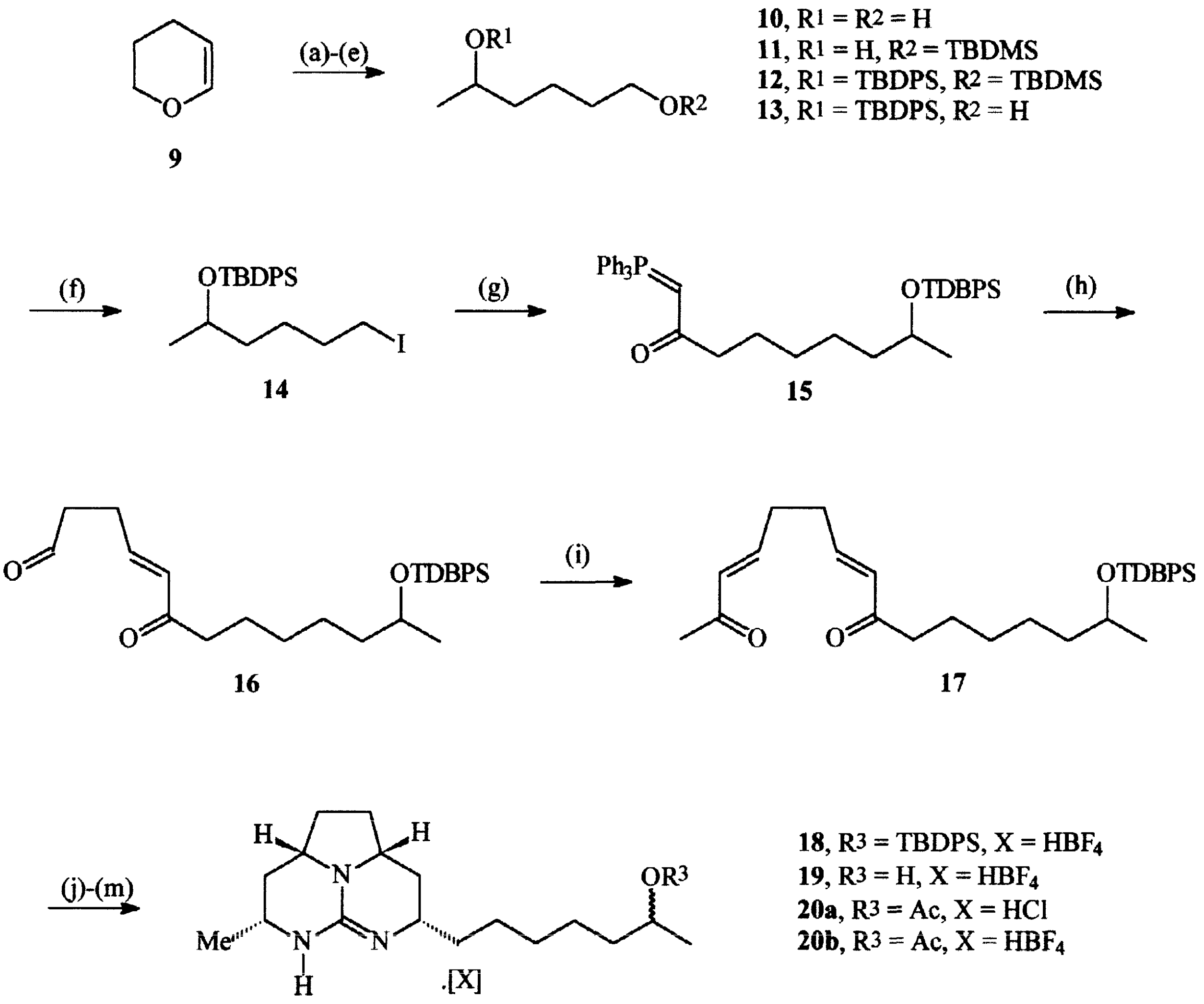


Figure 2: Proposed structure of batzelladine F[6]

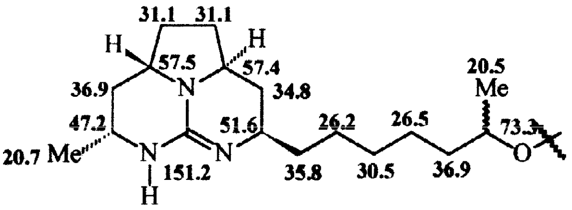
Interestingly batzelladine F, which was similar in structure to our model compound **7** displayed near identical ^1H and ^{13}C nmr spectral data with this model,[7] which suggested that the original assignment[6] of the relative stereochemistry of **8** may be incorrect. This assignment was made by a combination of nOe data[6] and by analogy with the revised[5] stereochemistry of the previously isolated metabolites batzelladine A-E.[4] Indeed the original mis-assignment of these metabolites was due to analogy being drawn from other structurally similar metabolites isolated from the same organism.[1a,b] Because of the confusion over this assignment we wished to prepare the left hand unit of batzelladine F in order that we might make a more direct comparison with the spectral data reported for **8**.

The *bis*-enone **17** required for the guanidine addition was prepared in 9 steps from tetrahydropyran **9** (Scheme 2). Hydrolysis of **9** followed by treatment with excess methyl magnesium chloride gave the diol **10** in good yield which was converted into the mono-protected alcohol **13** in three high yielding steps. Mesylation of **13** followed by reaction with NaI gave **14** in 67% yield, which after treatment with the anion generated from phosphorane **21**,[8] gave ylide **15**. Reaction of **15** with succinaldehyde led to **16** in 54% yield which, on reaction with a further equivalent of **21**, gave the bis-enone **17** in 91% yield.

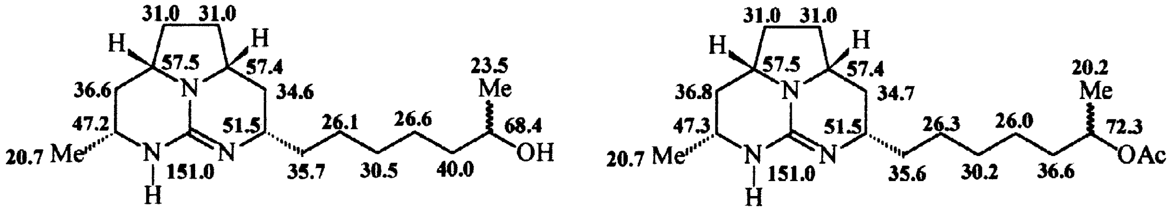


Scheme 2: (a) HCl/H_2O/reflux, 92%. (b) MeMgCl/THF/Reflux, 95%. (c) TBDMSCl/Imid./DCM/24hrs, 92%. (d) TBDPSCl/Imid./DCM, 89%. (e) PyHTos/DCM, 91%. (f) (i) MsCl/NEt_3/DCM/24hrs. (ii) NaI/Acetone/ 24 hrs, 67% (89% based on recovered mesylate) (g) $CH_3COCHPPh_3$ (**21**)/BuLi/THF/-78°C - RT. (h) succinaldehyde/DCM/24hrs, 54% for 2 steps. (i) $CH_3COCHPPh_3$/DCM/24hrs, 91%. (j) (i) Guanidine/ DMF/0°C/5hrs, (ii) 3:1:3 DMF/H_2O/MeOH, then $NaBH_4$/16hrs, (iii) HCl (aq), (iv) Saturated aq. $NaBF_4$; **18**, 29% overall. (k) (i) MeOH/HCl, (ii) Saturated aq. $NaBF_4$; **19**, 91%, (l) Ac_2O/Py, then HCl (2N); **20a**, 41%. (m) Saturated aq. $NaBF_4$; **20b**, quantitative.

The addition of guanidine to **17** followed by reduction of the intermediate and counter-ion exchange led to the formation of the silylated guanidine **18** in 29% overall yield. This was deprotected in 91% yield to give the alcohol **19** which in turn was acetylated to give **20** in 41% yield. The acetate **20** is analogous to Batzelladine F **8** and comparison of the ^{13}C nmr spectra (.HBF_4 salts) of **19** and **20b** with that reported for **8**[6] indicates a strong correlation between these compounds (Figure 3).



Proposed structure of batzelladine F **8**



19 **20**

Figure 3

Whilst these assignments are not absolute proof of the structure of **8**, the spectroscopic evidence presented does suggests that the original assignment of batzelladine F is possibly incorrect and that the stereochemistry is as illustrated in structure **19** and **20** i.e. an all *cis*-arrangement of the hydrogens around the tricycle.

Acknowledgements

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Experimental

Column chromatography was carried out on Kieselgel (230-400 mesh) with the eluant specified in each case and tlc was conducted on precoated Kieselgel 60 F254 (Art. 5554; Merck) glass plates. All non-aqueous reactions were conducted in oven-dried apparatus under a static atmosphere of argon. Petrol refers to the 40-60 fraction. Dichloromethane, diethyl ether, DMF and THF were dried and distilled before use using standard methods. Chemical ionisation (CI) mass spectra were recorded on a VG Masslab Model 12/253 spectrometer and high resolution mass spectra (HRMS) on a VG Analytical ZAB-E spectrometer at the EPSRC Mass Spectrometry Service Centre at Swansea. Proton nmr spectra were run at 250MHz on a Bruker AC250 spectrometer unless otherwise stated. Carbon-13 nmr spectra were run at 62.5MHz on a Bruker AC250 spectrometer unless otherwise stated and were gate decoupled. All spectra were obtained from solutions in deuterated chloroform unless otherwise specified. Chemical shifts are reported as δ values (ppm) relative to tetramethylsilane as an internal standard. All non-aqueous reactions were performed using oven-dried glassware which was cooled under a stream of argon or nitrogen gas. All experiments were conducted under a positive pressure of the inert gas. All compounds were homogeneous by thin-layer chromatography. E refers to diethyl ether, PE to petroleum ether (40/60), DCM to dichloromethane and EA to ethyl acetate.

Hexane-1,5-diol 10

Aqueous HCl (0.2M, 30 ml) was added to a cooled (0°C) solution of 2,3-dihydropyran (9.22g, 0.1096 mol). The resultant solution was stirred to room temperature for 19 hrs, whereupon the solution was extracted with ethyl acetate (3 x 50 ml), the combined organic layers were washed with saturated sodium hydrogen carbonate (50ml), dried ($MgSO_4$) and evaporated to yield crude 5-hydroxypentanal (8.92g, 79%) as a clear oil.

^{1}H nmr: δ = 1.45-1.60 (m, 4H), 1.80 (m, 2H), 3.3 (m, 1H, OH), 3.6 (m, 1H, CH), 4.0 (m, 1H, CH), 4.9 (br m, 1H, CH(2)). **IR**: ν_{max} = 3399 (br, s, OH), 2918 (s, C-H), 1723 (s, C=O). **^{13}C nmr**: δ = d 20.34 (CH_2), 25.32 (CH_2), 31.97 (CH_2), 63.85 (CH_2), 94.43 (CH).

Methylmagnesium chloride (3.0M in THF, 56 ml, 168 mmol) was added dropwise over 20 min to a cooled (0°C) and stirred solution of the crude 5-hydroxypentanal (8.5g, 83.3 mmol) in THF (80 ml). The resulting solution was allowed to warm to room temperature over 30 minutes and then heated at reflux for 16 hrs. The resulting mixture was then cooled (0°C) and quenched by careful addition of saturated ammonium chloride solution (20 ml). The resulting mixture was dried ($MgSO_4$) and filtered through a sinter (packed with further $MgSO_4$) and the pad eluted with ethyl acetate (5 x 50 ml). The solvent was removed by vacuo yielding the product **10** (9.29g, 95%) as an oil which could be purified by passing through a short plug of silica (eluting with E) if required (Rf = 0.10 in E). Spectral data was consistent with commercially available material.

^{1}H nmr: δ = 1.16 (d, 3H, J = 6.2Hz), 1.43 (m, 4H), 1.52 (m, 2H), 2.91 (s, 2H, 2 x OH), 3.60 (t, 1H, J = 6.1Hz), 3.8 (m, 1H). **^{13}C nmr**: δ = 21.84 (CH_3), 23.42 (CH_2), 32.34 (CH_2), 38.67 (CH_2), 62.26 (CH_2), 67.70 (CH). **IR**: ν_{max} = 3334 (br, O-H), 2935, 2864 (C-H).

1-*tert*-Butyldimethylsilyloxyhexan-5-ol 11

To a stirred (0°C) solution of **10** (2.00g, 16.94 mmol) in DMF (40 ml) was added imidazole (2.30g, 33.88 mmol) and tert-butyldimethylsilyl chloride (2.56g, 16.94 mmol) and the mixture stirred for 1 hr at room temperature. The mixture was diluted with ether (100 ml) and washed with water (3 x 50 ml). The aqueous phase was extracted with ether (50 ml) and the combined organic layers dried ($MgSO_4$) and evaporated. Chromatography (10-20% EA in PE) gave **11** as an oil (3.6g, 92%, Rf = 0.17 in 10% EA in PE).

^{1}H nmr: δ = 0.01 (s, 6H, 2 x Me), 0.82 (s, 9H, tBu), 1.13 (d, 3H, J = 6.1 Hz), 1.35-1.52 (m, 6H), 3.61 (t, 2H, J = 6.2 Hz), 3.76 (m, 1H). **^{13}C nmr**: δ = -4.89 (2 x CH_3), 18.29 (3 x CH_3), 21.96 (CH_2), 23.34 (CH_3), 25.91 (C), 32.66 (CH_2), 38.95 (CH_2), 63.06 (CH_2), 67.82 (CH). **IR**: ν_{max} = 3412 (O-H), 2929, 2899 (C-H). **MS(CI)**: m/z = 250 (8%, $[M+NH_4]^+$), 233 (100%, $[M+H]^+$). **HRMS(CI)**: $C_{12}H_{29}O_2Si$ ($[M+H]^+$) requires 233.1937, found 233.1937.

1-(tert-Butyldimethylsilyloxy)-5-(tert-Butyldiphenylsilyloxy)hexane 12

Alcohol **11** (9.8g, 0.042 mol) was dissolved in dry DCM (200 ml) and TBDPSCl (12.73g, 0.046 mol) was added followed by imidazole (4.3g, 0.063 mol) and a catalytic amount of DMAP (100mg). A white suspension formed which was stirred overnight. Evaporation and column chromatography (3% EA in PE) gave **12** as an oil (16.61g, 84%).

^{1}H nmr: δ = 0.0 (s, 6H, 2 x Me), 0.85 (s, 9H, tBu), 1.0 (m, 12H, tBu + Me), 1.2-1.5 (m, 6H)), 3.5 (t, 2H, J = 5.9 Hz), 3.8 (m, 1H, CH), 7.3-7.7 (m, 10H, 2 x Ph). **^{13}C nmr**: δ = -5.01 (2 x CH_3) 18.37 (C), 19.28 (C), 21.5 (CH_2), 23.18 (2 x CH_3), 26.00 (3 x CH_3), 27.05 (3 x CH_3), 32.91 (CH_2), 39.25 (CH_2), 63.20 (CH_2), 69.56 (CH), 127.38, 127.47, 129.37, 129.44 (8 x CH), 134.58, 134.96, (2 x C), 135.88 (2 x CH). **IR**: ν_{max} = 3070, 2929 (C-H). **MS(CI)**: m/z = 488 (5% $[M+NH_4]^+$), 357 (100% $[M+NH_4\text{-TBDMS}]^+$). **HRMS(CI)**: $C_{28}H_{50}O_2NSi_2$ ($[M+NH_4]^+$) requires 488.3380, found 488.3380.

5-(tert-Butyldiphenylsilyloxy)-hexan-1-ol 13

Silyl ether **12** (5.95g, 0.013 mol) was dissolved in absolute ethanol (55 ml), and PPTS (1.05g, 4.2 mmol) was added. After stirring for 48 hrs. at room temperature, the reaction mixture was evaporated and the resulting oil was purified by column chromatography (4% EA in hexane) to give **13** as an oil (4.00g, 91%).

^{1}H nmr: δ = 1.0 (m, 12H, tBu + Me), 1.3-1.45 (m, 6H), 1.90 (br s, 1H, OH), 3.45 (t, 2H, J = 6.3Hz), 3.8 (m, 1H, CH), 7.3-7.6 (m, 10H, 2 x Ph). **^{13}C nmr**: 19.33 (C), 21.42 (CH_2), 23.26 (CH_3), 27.12 (3 x CH_2), 32.71 (CH_2), 39.17 (CH_2), 62.76 (CH_2), 69.50 (CH), 127.48, 127.56, 129.49, 129.55 (8 x CH), 134.60, 134.87 (2 x C), 135.38 (2 x CH). **IR**: ν_{max} = 3386 (O-H), 2971 (C-H). **MS(CI)**: m/z = 374 (30% $[M+NH_4]^+$), 357 (100% $[M+H]^+$). **HRMS(CI)**: $C_{22}H_{33}O_2NSi$ ($[M+H]^+$) requires 357.2250, found 357.2250

5-(*t*-Butyldiphenylsilyloxy)-1-iodohexane 14

To a stirred and cooled (0°C) solution of **13** (4.51g, 12.67 mmol) in dry DCM (40 ml) was added triethylamine (2.4 ml, 17.2 mmol) and methanesulphonyl chloride (1.33 ml, 17.2 mmol). After stirring for one hr at room temperature, water (100 ml) was added and the reaction extracted with DCM (2 x 50 ml). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo, yielding the crude mesylate (5.68g, 100%). This was dissolved in acetone (20 ml) and a solution of sodium iodide (3.8g, 25.5mmol) dissolved in acetone (20 ml) was added. After stirring for 24 hrs at room temperature, ether (100 ml) was added and the reaction was washed with water (2 x 50 ml), sodium thiosulphate solution (2 x 30 ml) and brine (2 x 50 ml). The organic phase was dried ($MgSO_4$), evaporated in vacuo and purified by column chromatography (2% E in PE and then 25% EA in PE) to give **14** (3.93g, 67% (89% based on recovered mesylate) Rf = 0.53; 2% E in PE) and unreacted intermediate mesylate (1.38g, 25%, Rf = 0.33 in 25% EA in P).

^{1}H nmr: δ = 1.08 (m, 12H, tBu + Me), 1.4 (m, 4H), 1.7 (m, 2H) 3.1 (t, 2H, J = 7Hz), 3.9 (m, 1H, CH), 7.2-7.7 (m, 10H, 2 x Ph). **^{13}C nmr**: δ = 7.10 (CH_2), 19.31 (C), 23.27 (CH_3), 26.20 (CH_2), 27.11 (3 x CH_3), 33.51 (CH_2), 38.20 (CH_2), 69.20 (CH), 127.48, 127.58, 129.50, 129.58 (8 x CH), 134.47, 134.77 (C), 135.91 (2 x CH). **IR**: ν_{max} = 3069, 2930 (C-H). **MS(CI)**: 484 (100% $[M+NH_4]^+$), 467 (40% $[M+H]^+$). **HRMS(CI)**: $C_{22}H_{32}OSiI$ ($[M+H]^+$) requires 467.1267, found 467.1267.

12-(*t*-Butyldiphenylsilyloxy)-6-oxotridec-4-enal 15

To a cooled (-78°C) solution of acetylmethylenetriphenylphosphorane (1.19g, 3.73 mmol) in THF (20 ml) was added n-butyllithium (1.68 ml, 2.44M, 4.09 mmol) dropwise. The resulting red solution was stirred between -50 and -60°C for 1 hour and then iodide **14** (1.91g, 4.09 mmol) was added as a solution in THF (10 ml) at -78°C. The mixture was allowed to warm (20°C) with stirring over 3 hours. Water (100 ml) was added and reaction extracted with ethyl acetate (2 x 20 ml) which was washed with water (2 x 50 ml), dried ($MgSO_4$) and evaporated. The resulting phosphorane was dissolved in DCM (10 ml) and succinaldehyde (2.7g) in dry DCM (10 ml) was added, this was then left to stand overnight in the freezer. The reaction mixture was diluted with DCM (50 ml), washed with water (3 x 250 ml) to remove excess succinaldehyde and the organic phase dried ($MgSO_4$) and evaporated. The resultant oil was purified by column chromatography (15% EA in P and 25% EA in P) to give **15** (0.93g, 54%, Rf = 0.21, 15% EA in PE) as an oil together with recovered **14** (0.43g).

^{1}H nmr: δ = 1.05 (m, 12H, tBu + Me), 1.1-1.5 (m, 8H), 2.45 (t, 2H, J = 7.4Hz), 2.56 (t, 2H, J = 6.4Hz), 2.6 (m, 2H), 3.8 (m, 1H, CH), 6.1 (br d, 1H, CH, J = 15.8 Hz), 6.8 (dt, 1H, J = 15.8, 7.0 Hz, CH), 7.35-7.80, (m, 10H, 2 x Ph) 9.8 (s, 1H, CHO). **^{13}C nmr**: δ = 19.27 (C), 23.26 (CH_3), 24.03, 24.66, 25.01 (3 x CH_2), 27.05 (3 x CH_3), 29.25, 39.23, 40.28, 41.92 (4 x CH_2), 69.49 (CH), 127.39, 127.46, 129.38, 129.44 (8 x CH), 130.97 (CH), 134.57, 134.89 (2 x C), 135.87 (2 x CH), 144.04 (CH), 200.36 (CHO). **IR**: ν_{max} = 3069, 3047, 2931, 2857 (C-H), 1725 (C=O), 1697 (C=O), 1672, 1630 (C=C). **MS(CI)**: 482 (20% $[M+NH_4]^+$), **HRMS(CI)**: $C_{29}H_{44}O_3SiN$ ($[M+NH_4]^+$) requires 482.3091, found 482.3090.

15-(*t*-Butyldiphenylsilyloxy)-2,9-dioxohexadeca-3,7-diene 17

Acetylmethylene triphenylphosphorane (3.45, 10.8 mmol) was added to a solution of **29** (2.6g, 5.44 mmol) in dry DCM (15 ml) and the mixture stirred at room temperature. After 24 hours further phosphorane (2g 6.3 mmol) was added and stirring continued for a further 24 hours. After evaporation of the solvent, chromatography (15-20% EA in PE) gave **17** (2.46g, 91%, Rf = 0.16, 15% EA in PE) as an oil.

^{1}H nmr: δ = 1.05 (m, 12H, tBu + Me), 1.15-1.65 (m, 8H), 2.26 (s, 3H, Me), 2.4 (m, 4H), 2.56 (t, 2H, J = 7.4Hz), 3.8 (m, 1H, CH), 6.1 (br d, 2H, 2 x CH, J = 17 Hz), 6.8 (m, 2H, 2 x CH), 7.35-7.65, (m, 10H, 2 x Ph). **^{13}C nmr**: δ = 19.27 (C), 23.25 (CH_3), 24.05, 24.99 (2 x CH_2), 26.90 (3 x CH_3), 27.04 (CH_3), 29.27, 30.67, 30.73, 39.23, 40.35 (5 x CH_2), 69.48, (CH), 127.37, 127.45, 129.37, 129.43 (8 x CH), 130.97, 131.46 (2 x CH), 134.57, 134.88 (2 x C), 135.86 (2 x CH), 144.38, 145.79 (2 x CH), 198.22, 200.34 (2 x C=O). **IR**:

ν_{max} = 3070, 3047, 2931, 2857 (C-H), 1698 (C=O), 1676, 1628 (C=C). **MS(CI)**: 522 (100% $[M+NH_4]^+$), **HRMS(CI)**: $C_{32}H_{48}O_3SiN$ ($[M+NH_4]^+$) requires 522.3403, found 522.3368.

rac-(*3aS,4S,8aR,7R*)-4-[(*6'R/S*)-6'-(*t*-Butyldiphenylsilyloxy)heptyl]-7-methyl-(1,2,3,4,7,8-hexahydro-5H-5,6,8b-triazaacenapthylene)-6-ium tetrafluoroborate 18

Guanidine (117.mg, 1.99 mmol) as a solution in DMF (2.2 ml) was added in a dropwise fashion to a stirred, cooled (0°C) solution of **17** (1.0g, 1.99 mmol) in DMF (4.3 ml). This was then left to stir and warm to room temperature over 4 hours at which point the reaction was cooled (0°C) and methanol (6 ml) and water (2 ml) were added followed by sodium borohydride (451 mg, 11.9 mmol). After stirring to RT. overnight, the reaction mixture was diluted with DCM (20 ml) and acidified with HCl (2N, 3.5 ml). After extraction with DCM (4 x 40 ml), the combined extracts were washed with water (2 x 40 ml), brine (2 x 40 ml) and LiBr solution (2 x 40 ml) then dried ($MgSO_4$) and the solvent was removed to give a brown oil. This was then dissolved in DCM and saturated sodium tetrafluoroborate solution (20 ml) was added; after vigorous stirring overnight the organic layer was separated and the aqueous phase extracted with further DCM (3 x 30 ml). Drying ($MgSO_4$) and evaporation followed by chromatography with a graduated solvent system, (DCM-5% MeOH in $CHCl_3$) gave **18** (353.1 mg, 29%, Rf = 0.15 in 5% MeOH in $CHCl_3$ double eluted) as an oil.

^{1}H nmr: δ = 1.05 (s, 12H, tBu + Me), 1.15-1.45 (m, 13H), 1.55-1.70 (m, 4H), 2.10 (s, 4H), 3.3 (m, 1H), 3.55 (br m, 1H, CH), 3.70 (m, 2H, 2 x CH), 3.9 (m, 1H, CH), 6.74 (br s, 1H, NH), 6.88 (br s, 1H, NH), 7.37-7.70 (m, 10H, Ph). **^{13}C nmr**: δ = 19.28 (C), 20.27, 23.23 (2 x CH_3), 25.01 (CH_2), 27.06 (3 x CH_3), 29.29, 29.69, 30.21, 30.26, 33.63, 34.45, 35.75, 39.27 (8 x CH_2), 46.10, 50.41, 55.97, 56.05, 69.49 (5 x CH), 127.39, 127.47, 129.39, 129.44 (8 x CH), 134.60, 134.90 (2 x C), 135.86 (2 x CH), 149.28 (C). **IR**: ν_{max} = 3361 (N-H) 2931 (C-H), 1624 (C=N). **MS(CI)**: 532 (80% $[M]^+$), **HRMS(CI)**: $C_{33}H_{50}OSiN_3$ ($[M]^+$) requires 532.3723, found 532.3719.

rac-(*3aS,4S,8aR,7R*)-4-[(*6'R/S*)-6'-hydroxyheptyl]-7-methyl-(1,2,3,4,7,8-hexahydro-5H-5,6,8b-triazaacenapthylene)-6-ium tetrafluoroborate 19

Compound **18** (212.6 mg, 0.34 mmol) was dissolved in methanol (7 ml) and cooled (0°C) and a solution of methanolic HCl (prepared from AcCl (0.5 ml) and methanol (10 ml) was added. After standing to RT. overnight the reaction was evaporated, re-dissolved in DCM (10 ml), washed with saturated sodium tetrafluoroborate solution (2 x 20 ml), dried ($MgSO_4$) and the solvent removed by vacuo, producing a crude brown oil (224.7mg). This oil was purified by column chromatography (gradient elution DCM to 10% MeOH in $CHCl_3$) to give **19** (93.8 mg, 91%, Rf = 0.03 in 5% MeOH in $CHCl_3$ double eluted) as an oil.

^{1}H nmr: δ = 1.15 (d, 3H, J = 6.2 Hz, Me), 1.28 (d, 3H, J = 6.4 Hz, Me), 1.30-1.59 (m, 10H), 1.62 (m, 4H), 2.00 (br s, 1H, OH), 2.30 (m, 4H) 3.36 (m, 1H, CH), 3.53 (br m, 1H, CH), 3.76 (m, 3H, 3 x CH), 6.78 (br s, 1H, NH), 6.88 (br s, 1H, NH). **^{13}C nmr** (CD_3OD): δ = 20.70 (CH_3), 23.52 (CH_3) 26.12, 26.64, 30.51, 30.98, 34.64, 35.71, 36.60, 39.96 (9 x CH_2), 47.21, 51.51, 57.40, 57.46, 68.44 (5 x CH), 150.99. **IR**: ν_{max} = 3370 (O-H) 2929 (C-H), 1621 (C=N). **MS(CI)**: 294 (30% $[M]^+$), **HRMS(CI)**: $C_{17}H_{32}ON_3$ ($[M]^+$) requires 294.2545, found 294.2545.

rac-(*3aS,4S,8aR,7R*)-4-[(*6'R/S*)-6'-acetoxyheptyl]-7-methyl-(1,2,3,4,7,8-hexahydro-5H-5,6,8b-triazaacenapthylene)-6-ium chloride 20a and tetrafluoroborate 20b

Alcohol **19** (86.5 mg, 0.29 mmol) was dissolved in dry pyridine (35 mg, 0.44 mmol, 0.04 ml) and acetic anhydride (148 mg, 1.45 mmol) was added. After stirring for 48hrs at RT., the reaction was diluted with chloroform (10 ml) and washed with HCl (2N, 2 x 20 ml), dried ($MgSO_4$) and the solvent removed by vacuo. Purification by column chromatography (gradient elution; $CHCl_3$ to 30% MeOH in $CHCl_3$) gave **20a** (39.3mg, 41%, Rf = 0.05 in 2% MeOH in $CHCl_3$ eluted twice). Washing of a DCM solution of **20a** with saturated sodium tetrafluoroborate solution (2 x 20 ml) followed by drying ($MgSO_4$) and evaporation gave **20b**.

^{1}H nmr (20a): δ = 1.17 (d, 3H, J = 6.2 Hz, Me), 1.32 (d, 3H, J = 6.4 Hz, Me), 1.47-1.63 (m, 14H), 2.00 (s, 3H, COMe), 2.19 (m, 4H) 3.32 (m, 1H, CH), 3.49 (m, 1H, CH), 3.62 (m, 2H, 2 x CH), 3.62 (app sextet, 1H, J = 6.4 Hz, CH), 8.58 (br s, 1H, NH), 8.73 (br s, 1H, NH). **^{13}C nmr (20a)**: δ = 20.13, 20.70, 21.61 (3 x CH_3) 25.32, 25.39, 29.36, 29.85, 30.54, 34.29, 34.88, 35.97, 36.22 (9 x CH_2), 45.88, 50.27, 55.95, 56.06, 71.13 (5 x CH), 150.19, (C), 171.02 (C=O). **^{1}H nmr (20a, CD_3OD)**: δ = 1.19 (d, 3H, J = 6.2 Hz, Me), 1.27 (d, 3H, J = 6.4 Hz, Me), 1.31-1.70 (m, 14H), 1.99 (s, 3H, COMe), 2.22 (m, 4H) 3.44 (m, 1H, CH), 3.54 (m, 1H, CH), 3.73 (m, 2H, 2 x CH), 4.85 (1H, app sextet, J = 6.4 Hz, CH) (2 x NH exchanged). **^{13}C nmr (20b, CD_3OD)**: δ = 20.21, 20.72, 21.23 (3 x CH_3) 26.04, 26.32, 30.23, 31.00, 34.65, 35.69, 36.64, 36.78 (9 x CH_2), 47.25, 51.51, 57.43, 57.51, 72.26 (5 x CH), 151.02, (C), 172.68 (C=O). **IR**: ν_{max} = 3388 (N-H) 2928 (C-H), 1726 (C=O), 1630 (C=N). **MS(CI)**: 336 (100%, $[M]^+$). **HRMS(CI)**: $C_{19}H_{34}O_2N_3$ ($[M]^+$); requires 336.2651, found 336.2645.

References

1. a) Kashman, Y.; Hirsh, S.; McConnell, O. J.; Ohtini, I.; Kusumi, T.; Kakisawa, H., *J. Am. Chem. Soc.*, 1989, **111**, 892.
   (b) Ohtini, I.; Kusumi, T.; Kakisawa, H.; Kashman, Y.; Hirsh., S.; *J. Am. Chem. Soc.*, 1992, **114**, 8472.
   (c) Jares-Erijman, E. A.; Sakai, R.; Rinehart, K. L., *J. Org. Chem.*, 1991, **56**, 5712.
   (d) Berlinck, R. G. S.; Braekman, J. C.; Dalose, D.; Hallenga, E.; Ottinger, R.; Bruno, I.; Riccio, R., *Tetrahedron Lett.*, 1990, **31**, 6531.
   (e) Ohtani, I.; Kusumi, T.; Kakisawa, H., *Tetrahedron Lett.*, 1992, **33**, 2525.

2 (a) Snider, B.; Shi, Z., *Tetrahedron Lett.*, 1993, **34**, 2099.
   (b) Snider, B.; Shi, Z., *J. Am. Chem. Soc.*, 1994, **116**, 547.
   (c) Overman, L. E.; Rabinowitz, M. H., *J. Org. Chem.*, 1993, **58**, 3235.
   (d) Snider, B.; Shi, Z., *J. Org. Chem.*, 1993, **58**, 3828.
   (e) Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A., *J. Am. Chem. Soc.*, 1995, **117**, 2657.
   (f) Rama Rao, A. V; Gurjar, M. K.; Vasudevan, J., *J. Chem. Soc. Chem. Commun.*, 1995, 1369.
   (g) Louwrier, S.; Ostendorf, M.; Tuynman, A.; Hiemstra, H., *Tetrahedron Lett.*, 1996, **37**, 905.
   (h) Grillot, A-L.; Hart, D. J., *Tetrahedron,* 1995, **42**, 11377.
   (i) Murphy, P. J.; Williams, H. L.; Hibbs, D. E.; Hursthouse, M. B; Abdul Malik, K. M., *Tetrahedron*, 1996, **52**, 8315.

3. Black, G.P.; Murphy, P. J.; Walshe, N. D. A.; Hibbs, D. E.; Hursthouse, M. B; Abdul Malik, K. M., *Tetrahedron Lett.*, 1996, **37**, 6493.

4 Patil, A. D.; Kumar, A. V.; Kokke W. C.; Bean, M. F.; Freyer, A. J.; De Brosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson R. K.;Westley, J. W.; Potts, B. C. M., *J. Org. Chem.*, 1995, **60**, 1182.

5 (a) Snider, B. B.; Chen, J.: Patil, A. D.; Freyer, A. J., *Tetrahedron Lett.*, 1996, **37**, 6977.
   (b) The alkene stereochemistry in Batzelladine E has also been recently reassigned see: Snider, B. B.; Chen, J. S., *Tetrahedron Lett.*, 1998, **39**, 5697.

6 Patil, A. D.; Freyer, A. J.; Taylor, P. B.; Carte, B.; Zuber, G.; Johnson R. K.; Faulkner, D. J., *J. Org. Chem.*, 1997, **62**, 1814.

7 Black, G. P.; Murphy, P. J.; Walshe, N. D. A., *Tetrahedron*, 1998, **54**, 9481.

8 Taylor; J. D.; Wolf; J. F., *J. Chem. Soc. Chem. Commun.*, 1972, 876.

9 Fakstorp, J.; Raleigh, D.; Schniepp, L. E., *J. Am. Chem. Soc.*, 1950, **72**, 869.