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A Short Synthetic Route to the Tricyclic Guanidinium Core of the Batzelladine Alkaloids

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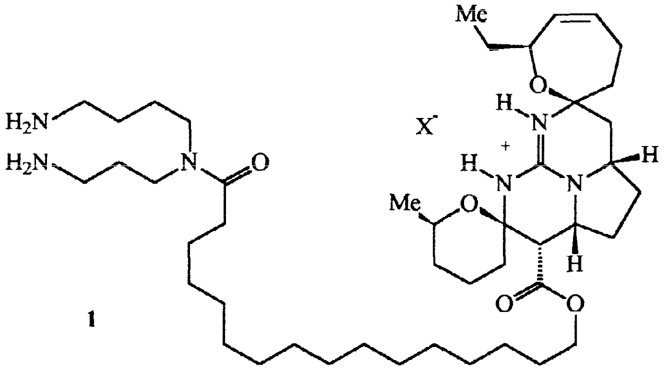
Abstract: The addition of guanidine to a series of *bis*-α,β-unsaturated ketones is reported leading to the formation of tricyclic guanidines, which are models of the naturally occurring batzelladine alkaloids. Nmr evidence is given in support of a new assignment for the relative stereochemistry of batzelladine F.

Keywords: Alkaloids; guanidines; Michael reactions.

There is considerable current biological[1-7] and synthetic[8-19] interest in guanidine containing biomolecules. Much of this interest has been generated by the isolation of the novel bioactive natural product ptilomycalin A **1**, initially from the Caribbean sponge *Ptilocaulis spiculifer* [1] and subsequently from two other sources.[4,7]



1

We recently[20] reported the preparation of a range of compounds which where models of a related series of guanidine alkaloids isolated from the same sponge and termed batzelladine A - E.[7] The structural and relative stereochemical assignment of these metabolites was based on an analogy with ptilomycalin A. However subsequent work by Snider *et al.*[21] has shown that in the cases of batzelladine A and D the original assignment was incorrect and the relative stereochemistry of the metabolites is as illustrated in structures **2-6**.

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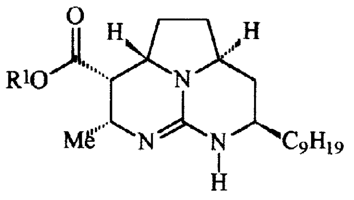
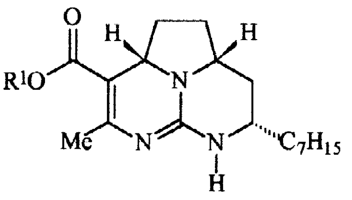
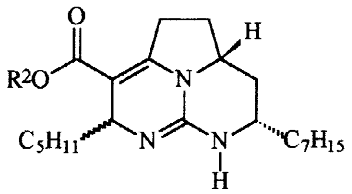


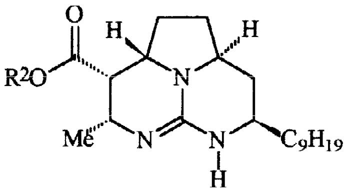
Batzelladine A; 2



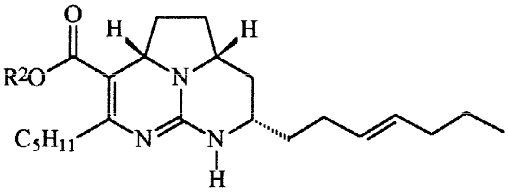
Batzelladine B; 3



Batzelladine C; 4

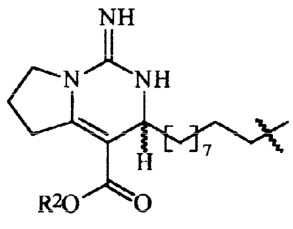


Batzelladine D; 5

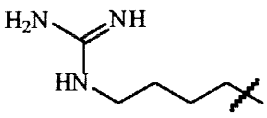


Batzelladine E; 6

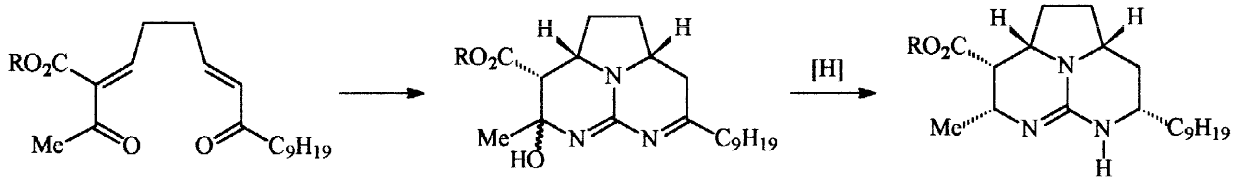
R1 =



R2 =

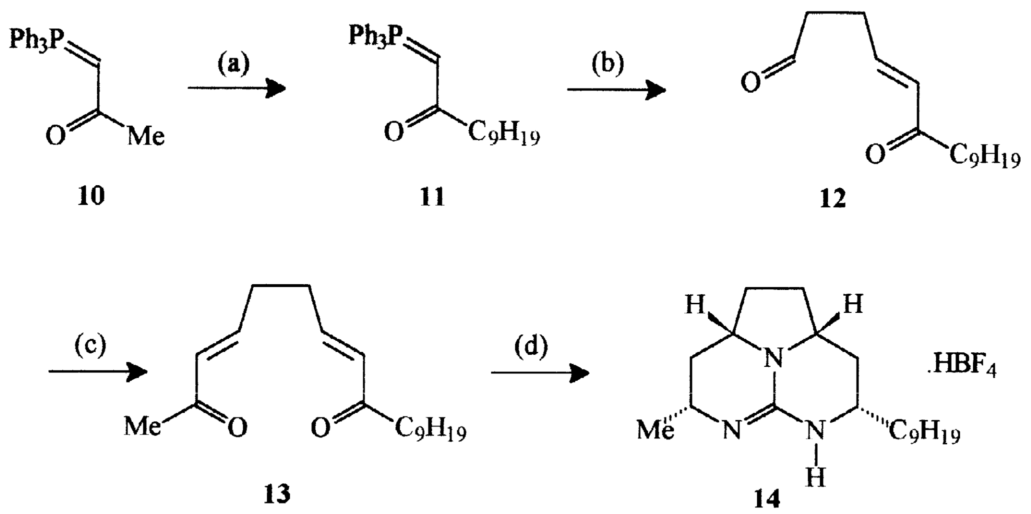


The original stereochemical assignment of the alkaloids A **2** and D **5** had been that illustrated in structure **9**, in which the pyrrolidine ring has a *cis*-arrangement in line with ptilomycalin A **1**. This had led us to propose that, based on our previous work,[19] this system could be prepared *via* a sequential double Michael addition of guanidine to the *bis*-α,β-unsaturated ketone **7**, to give hemi-aminal **8**, which on subsequent stereoselective reduction would give **9**, hopefully, with a high degree of stereocontrol.



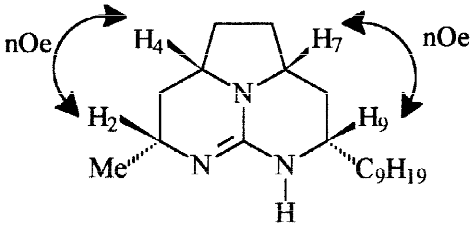
7 **8** **9**

In order to test this hypothesis we prepared the ketone **13** *via* a simple, high yielding three step procedure. Deprotonation of the commercially available phosphorane **10** with *n*-butyl lithium followed by alkylation with *n*-octyl iodide[22] gave the phosphorane **11** in near quantitative yield. Without purification this was reacted further with three equivalents of succinaldehyde[23] to give the aldehyde **12** in 67% overall yield. Reaction of **12** with a further equivalent of phosphorane **10** gave the required ketone **13** in 74% yield. Treatment of **13** with one equivalent of guanidine in DMF for 5 hours, followed by dilution with methanol/water, sodium borohydride reduction, acidification and counterion exchange gave, after purification, the required product **14** as its fluoroborate salt in 31% yield. This material was obtained as a *single diastereoisomer* with no distinct minor isomers detectable by ^{1}H or ^{13}C nmr analysis of the crude reaction products.



(a) nBuLi/-78°C; then $C_8H_{17}I$/RT/16hrs. (b) 3.0 eqv. succinaldehyde/DCM/24hrs. (c) **10**/DCM/24hrs. (d) (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).

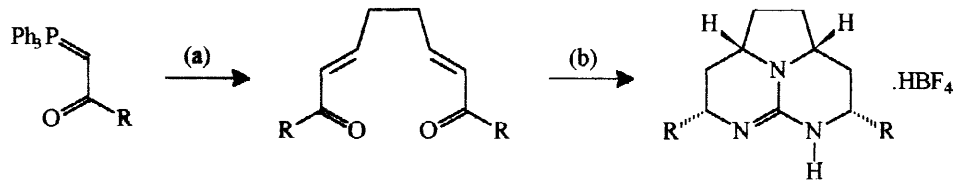
This observation was some what surprising as in previous work we[19] had demonstrated that the double Michael addition of guanidine to bis-α,β-unsaturated ketones leads to the preferential formation of *cis*-substituted pyrrolidines with *ca* 4 : 1 selectivity and were fully expecting this work to parallel these observations. Confirmation of the relative stereochemistry of the product was obtained by selective nOe experiments which confirmed that the protons H_2 and H_4 together with H_7 and H_9 are on the same face of the tricycle.



[14] .HBF4

Confirmation of the relative stereochemistry of the pyrrolidine ring was taken from analogy with our previous work; however we were unable to prepare suitable crystals of **14** for X-ray analysis. In order to overcome this shortfall and to confirm the generality of this methodology we prepared a series of symmetrical tricycles in the hope that these one of these substances would be suitably crystalline. Thus phosphoranes **15a-c** and **11** gave the *bis*-α,β-unsaturated ketones **16a-d** on reaction with succinaldehyde. Treatment of these under the conditions previously outlined gave the tricyclic guanidines **17a-d** in comparable overall yield. (table 1)

With the exception of **15a** (R = Me), which was isolated as a 10 : 1 mixture of diasteromers (the minor isomer being unidentified), all of these molecules were isolated as single diastereoisomers and displayed similar spectroscopic data to **14**. However despite considerable effort they still proved very difficult to crystallise to the standard required for X-ray structure determination. Somewhat fortuitously, we discovered that **13b** (R = Ph) could be isolated as a 1:1 complex with triphenylphosphine oxide[24] and were pleased when crystals of this complex (ethyl acetate/ether) were found to be suitable for X-ray analysis which confirmed the relative stereochemistry as that illustrated in structure **17b** (reported previously[20]).



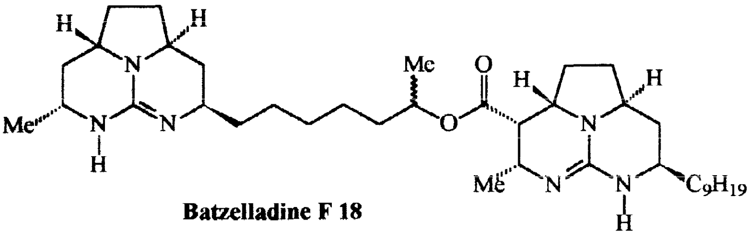
15a-c, 11 **16a-d** **17a-d**

Table 1

	R =	Yield (**16a-d**)	Yield (**17a-d**)
15a	Me	74%	33%
15b	Ph	68%	32%
15c	n-pentyl	70%	27%
11	n-nonyl	36%	22%

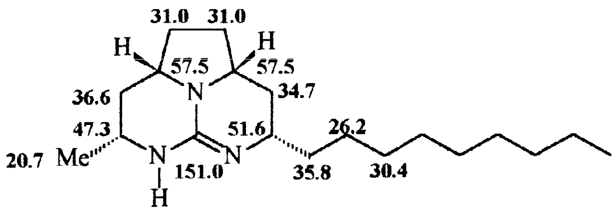
(a) 0.4 eqv. succinaldehyde/THF/24-48hrs. (b) (i) Guanidine/DMF/0°C-RT/5-8hrs, (ii) 3:1:3 DMF/H_2O/MeOH, then $NaBH_4$/16hrs, (iii) HCl, (iv) Saturated aq. $NaBF_4$.

As can be seen, the relative stereochemistry of the products obtained from this reaction is the opposite of that required for the intended targets batzelladine A **2** and D **5**. Shortly after the publication of our original communication several further batzelladine metabolites, termed batzelladine F-I, were isolated;[25] these were interesting in so much as one of them, batzelladine F **18**, contained two tricyclic guanidine units, one of which, lacked the ester function and was very similar in structure to our model compound **14** (the metabolites batzelladine G-I are similar in structure to F, with some variation in degree of unsaturation in the heterocycles and also possess a N-hydroxy function on the left hand guanidine heterocycle).

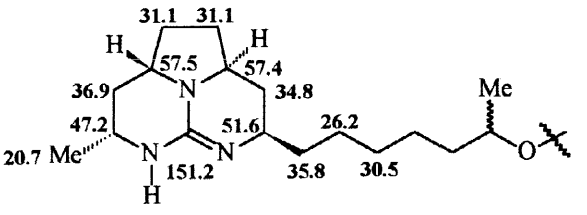


Batzelladine F 18

The stereochemical assignment of these metabolites was taken by analogy with the revised stereochemistry of the previously isolated metabolites batzelladine A-E. Interestingly on comparison of the spectral data for batzelladine F **18** and **14**, it is apparent that there is a strong correlation between the data of these compounds. For example the following scheme illustrates the reported ^{13}C data for **18** together with the recorded data for **14** (both in CD_3OD).



14



Batzelladine F 18

The strong agreement in the data for these two molecules may cast some doubt upon the assignment of the stereochemistry of the left hand ring of batzelladine F, indicating that the arrangement of the substituients on the pyrrolidine ring is indeed *cis*. This is not surprising as a similar observation has been made with the metabolite 13,14,15-isocrambescidine 800[3] which is a *trans*-pyrrolidine analogue of ptilomycalin A **1**, which in itself is a co-metabolite of the batzelladines.

We are currently endeavouring to modify our methodology to effect a synthesis of the left hand portion of batzelladine F, in order that a more direct comparison with natural material will be possible.

Acknowledgements

Thanks are given to Dr Ian Parsons (Pfizer) for the nOe studies and to Pfizer Central Research and the EPSRC for a CASE studentship to GPB. The Support of the EPSRC Mass spectrometry centre at Swansea is also acknowledged.

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 (PE) refers to the 40-60 fraction. Dichloromethane, diethyl ether (E), 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. ^1H nmr spectra were run at 250MHz on a Bruker AC250 spectrometer unless otherwise stated. ^{13}C 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.

(*4E*)-6-Oxopentadec-enal; 12

n-Butyllithium (13.3ml, 1.29M in hexane, 17.2mmol), was added to a cooled (-78°C) solution of **10** (5.00g, 15.7mmol) in THF (200ml), causing a deep red colour to develop. The mixture was stirred for 30 minutes, whereupon n-octyl iodide (4.57g, 19.0mmol) was added dropwise; the mixture was then allowed to stir at room temperature for 18 hours. After evaporation of the THF the resulting red oil was dissolved in ethyl acetate (100ml) and washed with water (2 x 50ml), dried ($MgSO_4$) and evaporated to give the crude phosphorane **11** as a viscous oil in essentially quantitative yield (6.75g). Succinaldehyde (2.7g, 31.4mmol) was added to a solution of **11** (6.75g, 15.7mmol) in dichloromethane (30ml) and the mixture stirred at RT for 48 hours. The solution was then washed with water (2 x 50ml) to remove excess succinaldehyde, separated, evaporated and most of the triphenylphosphine oxide removed by trituration using E/PE (1 : 1). Evaporation and purification by column chromatography (15-30% E in PE) afforded the title compound **12** as an oil (2.50g, 67%, Rf = 0.26 in 40% E in PE). The ketone **16d** was also isolated in 14% yield (0.86g, Rf = 0.45 in 40% E in PE).

^{1}H nmr: δ = 0.88 (t, 3H, J = 6.5Hz), 1.27 (m, 12H), 1.60 (m, 2H), 2.52 (m, 4H), 2.65 (m, 2H), 6.12 (d, 1H, J = 15.9Hz), 6.81 (dt, 1H, J = 6.6, 15.9Hz), 9.81 (s, 1H). **^{13}C nmr**: δ = 14.01, 22.58, 24.09, 24.55, 29.20, 29.36, 31.79, 40.31, 41.87, 130.99, 143.95, 200.25, 200.34. **IR**: ν_{max} = 2926, 2856 (C-H), 2718 (aldehyde C-H) 1727, 1675 (C=O), 1631 (C=C). **MS(CI)**: m/z = 256 (100% $[M+NH_4]^+$), 239 (60% $[M+H]^+$), 238 (20% $[M]^+$), 221 (42% $[M-OH]^+$). **HRMS(CI)**: $C_{15}H_{27}O_2$ ($[M+H]^+$) requires 239.2012, found 239.2011.

(*3E, 7E*)-2,7-Dioxooctadeca-3,7-diene; 13

Phosphorane **10** (2.67g, 8.40mmol) was added to a solution of aldehyde **12** (1.66g, 6.97mmol) in dichloromethane (20ml) and the mixture stirred at RT for 24 hours. The solvent was then evaporated and triphenylphosphine oxide removed by trituration with E/PE (1 : 1). Purification by column chromatography (30-40% E in PE) gave the title compound **13** as an oil (1.43g, 74%, Rf = 0.24 in 40% E in PE).

^{1}H nmr: δ = 0.88 (t, 3H, J = 6.5Hz), 1.27 (bm, 12H), 1.62 (m, 2H), 2.26 (s, 3H), 2.41 (m, 4H), 2.53 (t, 2H, J = 7.3Hz), 6.10 (d, 1H, J = 15.9Hz), 6.16 (d, 1H, J = 15.9Hz), 6.74-6.83 (m, 2H). **^{13}C nmr**: δ = 14.01, 22.58, 24.14, 26.97, 29.21, 29.35, 29.90, 30.01, 31.79, 40.37, 130.95, 131.86, 144.33, 145.72, 198.07, 200.35. **IR**: ν_{max} = 2928, 2852 (C-H), 1690, 1672 (C=O), 1631 (C=C). **MS(CI)**: m/z = 296 (90% $[M+NH_4]^+$), 279 (20% $[M+H]^+$), 240 (100%). **HRMS(CI)**: $C_{18}H_{31}O_2$ ($[M+H]^+$) requires 279.2324, found 279.2324

rac-(*4S,3aS,8aR,7R*)-4-Nonyl-7-methyl-(1,2,3,4,7,8-hexahydro-5H-5,6,8b-triazaacenaphthalene)-6-ium tetrafluoroborate; 14

General method: Guanidine (117mg, 1.98mmol), in DMF (3ml) was added to a cooled (0°C) and stirred solution of **13** (550mg, 1.98mmol) in DMF (10ml) and the mixture was allowed to warm to room temperature over 5 hours. The reaction was cooled (0°C) and water (5ml) and methanol (15ml) were added, followed by $NaBH_4$ (451mg, 11.87mmol); this mixture was allowed to warm to room temperature and was stirred for 16 hours. The methanol was evaporated in vacuo and the reaction diluted with dichloromethane (50ml). The solution was then treated with aqueous HCl (20ml, 1M), separated and washed with water (2 x 50ml) and brine (2 x 50ml) and the combined aqueous layers back extracted with dichloromethane (20ml); the combined organic layers were then washed with saturated LiBr (2 x 20ml). The organic phase was dried over magnesium sulphate and evaporated in vacuo to give a brown oil (550mg), which was dissolved in dichloromethane (25ml); an aliquot (ca 5ml) of saturated aqueous sodium tetrafluoroborate was added and the mixture stirred briskly for 2 hours. The aqueous layer was then separated, extracted with dichloromethane (2 x 25ml) and the combined organic extracts dried ($MgSO_4$) and evaporated giving a brown oil (570mg). Purification by column chromatography (0-4% methanol in chloroform) was followed by precipitation of **14** from a dichloromethane solution using a mixture of E and PE (250mg, 31%, amorphous solid M. pt. = 80-82°C, Rf = 0.22, 4% methanol in chloroform).

^{1}H nmr (500MHz, CD_3OD): δ = 0.89 (3H, t, J = 6.6 Hz, CH_3) 1.25 (2H, m, $H_{3\alpha}$, $H_{8\alpha}$), 1.26 (3H, d, J = 6.4 Hz, CH_3) 1.28-1.45 (14H, m, $H_{12\text{-}18}$), 1.55 (2H, m, H_{11}), 1.68 (2H, m, $H_{5\beta}$, $H_{6\beta}$), 2.20-2.30 (4H, m, $H_{3\beta}$, $H_{5\alpha}$, $H_{6\beta}$ and $H_{8\beta}$), 3.42 (1H, ddt, J = 3.2, 11.3, 6.6 Hz, H_9), 3.54 (1H, ddq, J = 3.2, 11.1, 6.4 Hz, H_2), 3.74 (2H, m, H_4 and H_7). **^{13}C nmr**: δ = 14.14, 20.26 (2 x CH_3), 22.65, 25.03, 29.23, 29.29, 29.39, 29.48, 29.63, 30.22, 31.85, 34.45, 35.80 (12 x CH_2), 46.10, 50.47, 56.00, 56.06 (4 x CH) 149.31 (C). Spectrum in CD_3OD: 14.41, 20.70 (2 x CH_2), 23.68, 26.18, 30.39, 30.54, 30.57, 30.99, 33.00, 34.69, 35.82, 36.63 (12 x CH_2), 47.26, 51.58, 57.45, 57.50, (4 x CH) 151.20 (C). **IR**: ν_{max} = 3385 (N-H), 2924 (C-H), 1627 (C=N). **MS(CI)**; 306 (100%, $[M+H]^+$). **HRMS(CI)**; $C_{19}H_{36}N_3$ ($[M+H]^+$) requires 306.2909, found 306.2909.

General method for the preparation of *bis*-α,β-unsaturated ketones 16.

Succinaldehyde (0.4 eqv.) dissolved in dichloromethane (2ml per mmol of phosphorane) was added to a solution of the phosphorane (**15a-c**, **11**) in dichloromethane (2ml per mmol of phosphorane) and the mixture stirred at room temperature for 24-48 hours. After washing with water (generally 2 x 100ml) to remove excess succinaldehyde, the solvent was evaporated and the resulting oil purified by column chromatography (E in PE).

(*3E, 7E*)-2,9-Dioxodeca-3,7-diene; 16a.

15.7 mmol scale, 74% yield, Rf = 0.11 (40% E in PE). **^{1}H nmr**: δ = 1.94 (s, 6H), 2.14 (m, 4H), 5.80 (d, 2H, J= 15.9Hz), 6.51 (dt, 2H, J = 6.2, 15.9Hz). **^{13}C nmr**: δ = 27.25, 30.54, 131.81, 145.79, 198.12. **IR**: ν_{max} = 2925 (C-H), 1670 (C=O), 1625 (C=C). **MS(CI)**: m/z = 184 (100% $[M+NH_4]^+$), 167 (60% $[M+H]^+$). **HRMS(CI)**: $C_{10}H_{18}NO_2$ ($[M+NH_4]^+$) requires 184.1338, found 184.1338.

(*2E, 6E*)-1,8-Dioxo-1,8-diphenylocta-2,6-diene; 16b.

13.2 mmol scale, 68% yield, **Rf** = 0.24 (40% E in PE).^{1}**H nmr**: δ = 2.60 (m, 4H), 6.97 (m, 2H), 7.40-7.93 (m, 12H). ^{13}**C nmr**: δ = 31.16, 126.68, 128.42, 128.55, 132.60, 137.65, 147.40, 190.38. **IR**: ν_{max} = 3063, 2952, 2928 (C-H), 1667 (C=O), 1624 (C=C). **MS(CI)**: m/z = 308 (100% $[M+NH_4]^+$), 291 (50% $[M+H]^+$). **HRMS(CI)**: $C_{20}H_{22}NO_2$ ($[M+NH_4]^+$) requires 308.1651, found 308.1651.

(*7E, 11E*)-6,13-dioxooctadeca-7,11-diene 16c

Phosphorane **15c** was prepared from **10** (5.00g, 15.7mmol) and *n*-BuI using the method described for the preparation of **11**. This was then employed in the preparation of **16c** as described above; 70% yield, Rf = 0.25 (40% E in PE). ^{1}**H nmr**: δ = 0.86 (t, 6H, J = 6.8Hz), 1.29 (m, 8H), 1.60 (m, 4H), 2.39 (m, 4H), 2.51 (t, 4H, J = 7.4Hz), 6.12 (d, 2H, J = 15.8Hz), 6.80 (m, 2H). ^{13}**C nmr**: δ = 13.83, 22.38, 23.79, 30.65, 31.36, 40.23, 130.89, 144.52, 200.37. **IR**: ν_{max} = 2940, 2930 (C-H), 1697 (C=O), 1623 (C=C). **MS(CI)**: m/z = 296 (100% $[M+NH_4]^+$), 279 (25% $[M+H]^+$). **HRMS(CI)**: $C_{18}H_{31}O_2$ ($[M+H]^+$) requires 279.2324, found 279.2330

(*11E, 15E*)-10,17-Dioxohexacosa-11,15-diene: 16d

Phosphorane **11** was prepared from **10** (5.00g, 15.7mmol) and n-octyl iodide using the procedure described for the preparation of aldehyde **12**. This was then used in the preparation of **16d** as described above; 36% yield, Rf = 0.45 (40% E in PE). ^{1}**H nmr**: δ = 0.89 (t, 6H, J = 6.5Hz), 1.28 (bm, 22H), 1.61 (bm, 6H), 2.41 (m, 4H), 2.53 (t, 4H, J = 7.4Hz), 6.15 (d, 2H, J = 15.8Hz), 6.81 (m, 2H). ^{13}**C nmr**: δ = 13.13, 21.70, 23.27, 28.34, 28.48, 29.80, 30.91, 39.52, 130.03, 143.56, 199.50. **IR**: ν_{max} = 3023, 2926 (C-H), 1688 (C=O), 1658 (C=O). **MS(CI)**: m/z = 408 (100% $[M+NH_4]^+$), 391 (20% $[M+H]^+$). **HRMS(CI)**: $C_{26}H_{50}NO_2$ ($[M+NH_4]^+$) requires 408.3841, found 408.3841

General method for the preparation of guanidines 17a-d.

The method described for the preparation of **14** was followed.

meso-4,7-Dimethyl-(1,2,3,4,7,8-hexahydro-5H-5,6,8b-triazaacenaphthalene)-6-ium tetrafluoroborate: 17a

3.66 mmol scale, 33% yield, M.pt. = 111-113°C, (Rf = 0.20, 6% $MeOH/CHCl_3$). ^{1}**H nmr**: δ = 1.23 (d, 6H, J = 6.2Hz), 1.60 (m, 4H), 2.10-2.32 (m, 4H), 3.51 (m, 2H), 3.65 (m, 2H), 6.01 (s, 2H, NH). ^{13}**C nmr**: δ = 20.24, 30.11, 35.63, 46.05, 56.00, 149.10. **IR**: ν_{max} = 3371 (N-H) 2975, 2927 (C-H), 1626 (C=N). **MS(CI)**: m/z = 194 (3% $[M+H]^+$), 193 (6% $[M]^+$). **HRMS(CI)**: $C_{11}H_{19}N_3$ ($[M]^+$) requires 193.1580, found 193.1579.

meso-4,7-Diphenyl-(1,2,3,4,7,8-hexahydro-5H-5,6,8b-triazaacenaphthalene)-6-ium tetrafluoroborate: 17b

0.862 mmol scale, 32% yield, M.pt. = 90-92°C Rf = 0.23 (5% $MeOH/CHCl_3$). ^{1}**H nmr**: δ = 1.62-1.80 (m, 4H), 2.25-2.46 (m, 4H), 3.97 (m, 2H), 4.59 (dd, 2H, J = 12.3, 3.9Hz), 7.29 (s, 2H), 7.30-7.60 (m, 10H). ^{13}**C nmr**: δ = 29.73, 36.90, 54.42, 55.99, 126.20, 128.59, 129.04, 138.66, 149.90. **IR**: ν_{max} = 3371 (N-H) 3060, 2977, 2929 (C-H), 1616 (C=N). **MS(CI)**: m/z = 318 (15% $[M+H]^+$), 317 (5% $[M]^+$). **HRMS(CI)**: $C_{21}H_{24}N_3$ ($[M+H]^+$) requires 318.1970, found 318.1970.

meso-4,7-Dipentyl-(1,2,3,4,7,8-hexahydro-5H-5,6,8b-triazaacenaphthalene)-6-ium tetrafluoroborate: 17c

1.55 mmol scale, 27% yield, M.pt = 84-88°C, Rf = 0.20 (4% $MeOH/CHCl_3$). ^{1}**H nmr**: δ = 0.86 (t, 6H, J = 6.5Hz), 1.28-1.40 (m, 16H), 1.63 (m, 4H), 2.24 (m, 4H), 3.37 (m, 2H), 3.68 (m, 2H), 6.58 (br s, 2H). ^{13}**C nmr**: δ = 13.91, 22.37, 24.59, 30.22, 31.44, 33.56, 34.34, 50.49, 56.04, 149.32. **IR**: ν_{max} = 3370 (N-H), 2982, 2928 (C-H), 1635 (C=N). **MS(CI)**: m/z = 306 (100% $[M+H]^+$). **HRMS(CI)**: $C_{19}H_{36}N_3$ ($[M+H]^+$) requires 306.2909, found 306.2909.

meso-4,7-Dinonyl-(1,2,3,4,7,8-hexahydro-5H-5,6,8b-triazaacenaphthalene)-6-ium tetrafluoroborate: 17d

0.513 mmol scale, 22% yield, M.pt = 68-70°C, Rf = 0.25 (3% MeOH/$CHCl_3$). **^{1}H nmr**: δ = 0.87 (t, 6H, J = 6.4Hz), 1.18-1.33 (br s, 32H), 2.13 (m, 4H), 2.20 (m, 4H), 3.63 (m, 2H), 4.03 (m, 2H) 6.15 (s, 2H). **^{13}C nmr**: δ = 14.03, 22.61, 25.46, 29.10, 29.28, 29.29, 29.55 (3 x CH_2), 31.84, 37.23, 50.44, 55.98, 149.34. **IR**: ν_{max} = 3367 (N-H), 2988, 2924 (C-H), 1632 (C=N). **MS(CI)**: m/z = 418 (100% $[M+H]^+$). **HRMS(CI)**: $C_{27}H_{52}N_3$ ($[M+H]^+$) requires 418.4161, found 418.4161.

References

1 Kashman, Y.; Hirsh, S.; McConnell, O. J.; Ohtini, I.; Kusumi, T.; Kakisawa, H.; *J. Am. Chem. Soc.*, 1989, **111**, 892.

2 Ohtini, I.; Kusumi, T.; Kakisawa, H.; Kashman, Y.; Hirsh., S.; *J. Am. Chem. Soc.*, 1992, **114**, 8472.

3 Jares-Erijman, E. A.; Sakai, R.; Rinehart, K. L.; *J. Org. Chem.*, 1991, **56**, 5712.

4 Berlinck, R. G. S.; Braekman, J.C.; Dalose, D.; Hallenga, E.; Ottinger, R.; Bruno, I.; Riccio, R.; *Tetrahedron Lett.*, 1990, **31**, 6531.

5 Ohtani, I.; Kusumi, T.; Kakisawa, H.; Kashman, Y.; Hirsh, S.; *J. Am. Chem. Soc.*, 1992, **14**, 8472.

6 Ohtani, I.; Kusumi, T.; Kakisawa, H.; *Tetrahedron Lett.*, 1992, **33**, 2525.

7 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.

8 Snider, B.; Shi, Z.; *Tetrahedron Lett.*, 1993, **34**, 2099.

9 Snider, B.; Shi, Z.; *J. Am. Chem. Soc.*, 1994, **116**, 547.

10 Overman, L. E.; Rabinowitz, M. H.; *J. Org. Chem.*, 1993, **58**, 3235.

11 Snider, B.; Shi, Z.; *J. Org. Chem.*, 1993, **58**, 3828.

12 Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A.; *J. Am. Chem. Soc.*, 1995, **117**, 2657.

13 Rama Rao, A. V; Gurjar, M. K.; Vasudevan, J.; *J. Chem. Soc. Chem. Commun.*, 1995, 1369.

14 Louwrier, S.; Ostendorf, M.; Tuynman, A.; Hiemstra, H.; *Tetrahedron Lett.*, 1996, **37**, 905.

15 Grillot, A-L.; Hart, D. J.; *Tetrahedron*, 1995, **42**, 11377.

16 Murphy, P. J.; Williams, H. L.; Hursthouse, M. B.; Abdul Malik, K. M.; *J. Chem. Soc. Chem. Commun.*, 1993, 119.

17 Murphy, P. J.; Williams, H. L.; *J. Chem. Soc. Chem. Commun.*, 1993, 819.

18 Murphy, P. J.; Williams, H. L.; Hibbs, D. E.; Hursthouse, M. B; Abdul Malik, K. M.; *J. Chem. Soc. Chem. Commun.*, 1996, 445.

19 Murphy, P. J.; Williams, H. L.; Hibbs, D. E.; Hursthouse, M. B; Abdul Malik, K. M.; *Tetrahedron*, 1996, **52**, 8315.

20 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.

21 Snider, B. B.; Chen, J.: Patil, A. D.; Freyer, A. J.; *Tetrahedron Lett.*, 1996, **37**, 6977.

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

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

24 Etter, M.C.; Baures, P. W.; *J. Am. Chem. Soc.*, 1988, **110**, 639.

25 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.