Synthesis and stereochemical determination of batzelladine C methyl ester†

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Batzelladine C (**3**) is a tricyclic guanidine alkaloid of unknown stereochemistry at one centre as well as unknown absolute stereochemistry. The two possible diastereoisomers of the methyl ester corresponding to this compound have been synthesised, permitting the relative and absolute stereochemistry of this compound to be assigned.

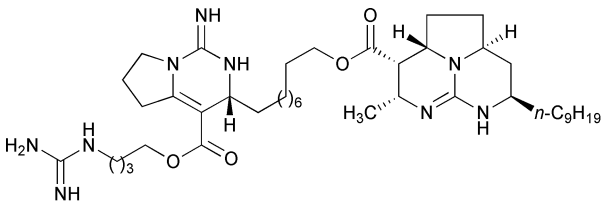
Introduction

The batzelladine alkaloids are a structurally fascinating group of marine natural products containing acyclic, bicyclic and tricyclic guanidines, in some cases all within the same compound. Batzelladines A–E were isolated in 1995,[1] with a further ten compounds isolated later by a number of groups.[2] The structures shown in Fig. 1 are representative of these natural products. These compounds have attracted a great deal of synthetic interest,[3] particularly from the groups of Overman,[4] Nagasawa,[5] Gin,[6] Snider[7] and Murphy[8] and Evans,[9] leading to total syntheses of batzelladines A,[10] D[11] and F,[12] and dehydrobatzelladine C.[13] Our own work in this area focused on the application of a three-component coupling reaction, originally developed by Kishi,[14] to the bicyclic portion of batzelladine A (1).[15,16]

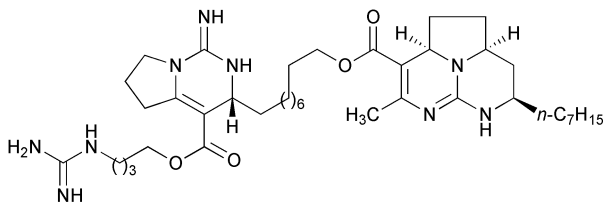
Discussion

Batzelladine C (**3**) is a tricyclic guanidine with unknown stereochemistry at C-4,[17] as well as unknown absolute stereochemistry. Batzelladines J, M (**5**) and N share this stereochemical ambiguity. In fact, the original report on the isolation of batzelladine C states the stereochemistry of the right-hand ring as shown, but does not discuss the basis of this assignment. However, the reports of dehydrobatzelladine C and batzelladines J, M and N all confirm this assignment. Furthermore, g-NOESY NMR spectra of natural batzelladine C obtained in our laboratory show a clear cross-peak between H-7 and H-8a, so we are confident that this stereochemistry is secure.[18]

Our approach to this class of compound (Scheme 1) installs this centre in a diastereoselective three-component coupling of an alkylidenepyrrolidine **6** with an aldehyde and an isothiocyanate. The remaining ring will be formed by iodocyclisation of a bicyclic



1, Batzelladine A



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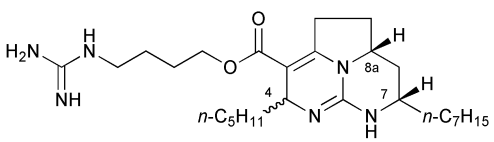
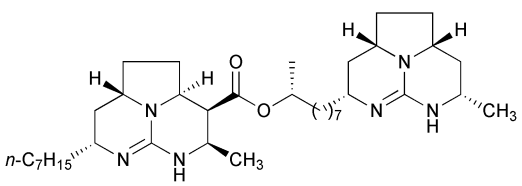
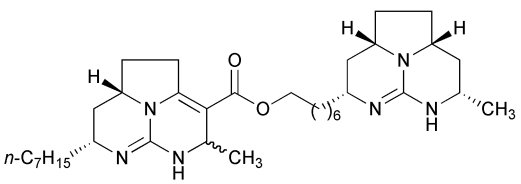


3, Batzelladine C



4, Batzelladine F



5, Batzelladine M

Fig. 1 Selected batzelladine alkaloids.

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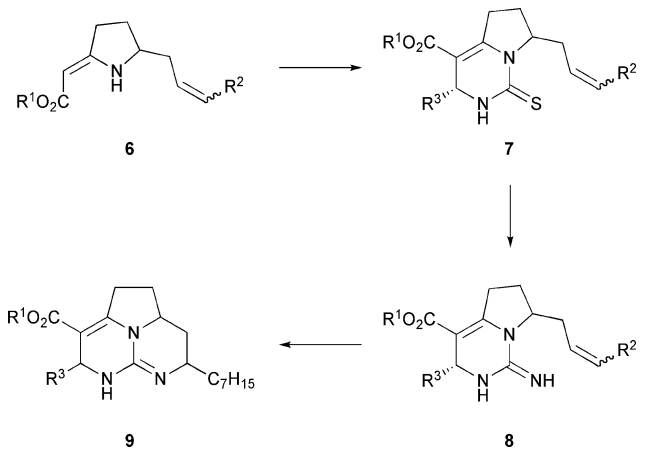
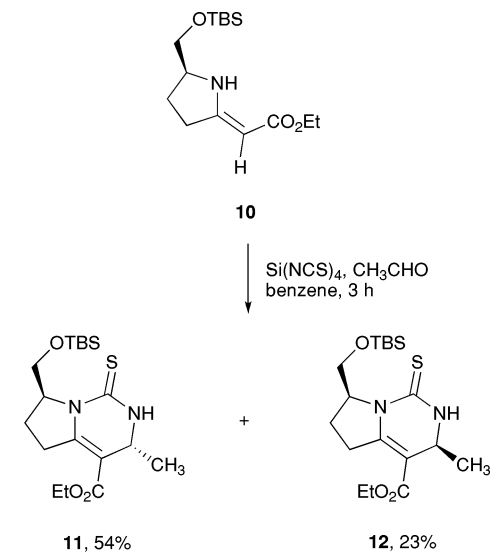
† Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **16**–**31**, ^{1}H–^{1}H COSY and g-NOESY NMR spectra for compound **30** and ^{1}H NMR spectra for batzelladine C (**3**). CCDC reference number 739833. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b914744f



Scheme 1

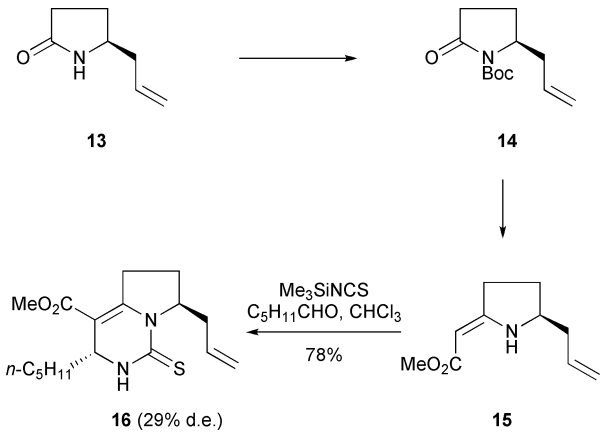
guanidine **8**,[19] a reaction that has been used by Gin in the total synthesis of batzelladine D.[11c] This route has a distinct advantage over some previous studies towards the batzelladine alkaloids, since only a single stereogenic centre is required to produce all of the natural product stereochemistry. We now report the successful realisation of this strategy, in which the methyl esters corresponding to both diastereoisomers of batzelladine C have been synthesised.

We have previously reported the three-component coupling of compound **10** to give a 2 : 1 mixture of compounds **11** and **12** (Scheme 2).[15] The stereochemical assignments were tentative, based on a small nOe in the minor isomer. Clearly, before addressing the stereochemical assignment of batzelladine C, we first needed to confirm the stereochemical outcome of this reaction, and ideally on a substrate more closely related to that which we intended to use in our total synthesis.



Scheme 2

To this effect, compound **15** was prepared from known lactam **13** using a two-step protocol that we reported in 2006.[20] Three-component coupling of this compound with hexanal and trimethylsilyl isothiocyanate gave a 1.8 : 1 mixture favouring compound **16** (Scheme 3). This compound provided crystals suitable



Scheme 3

for X-ray analysis (Fig. 2), so that we were now confident of our previous and subsequent (*vide infra*) stereochemical assignments.

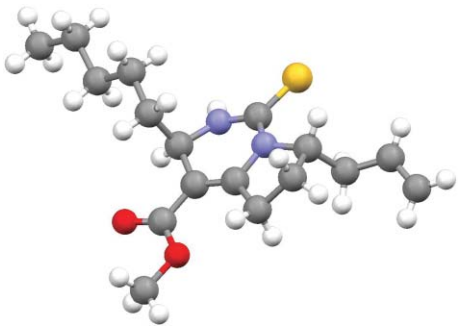
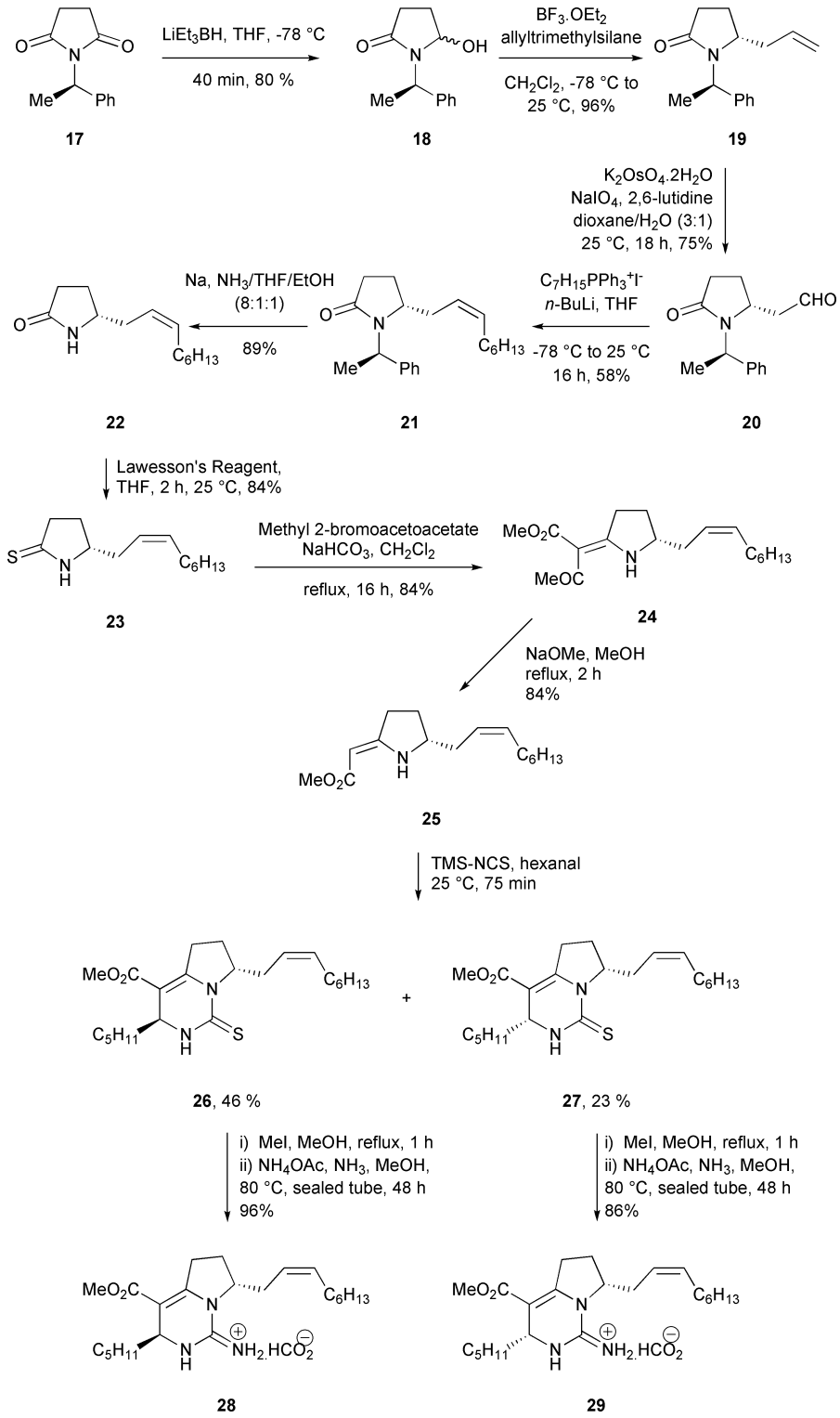


Fig. 2 Structure of compound **16** from X-ray data.

With this stereochemical assignment secured, batzelladine C was approached as follows. Compound **17** was prepared from succinic anhydride and (*R*)-(+)-α-methylbenzylamine[21] according to a known procedure (Scheme 4).[22] Reduction and allylation of this compound, as previously reported for the (*S*)-enantiomer,[23] gave compound **19** as a 4.4 : 1 mixture of diastereoisomers in good overall yield. The terminal double-bond was then cleaved, and the resulting aldehyde **20** subjected to a *cis*-selective Wittig reaction to give alkene **21**, by which time the diastereoselectivity had been enhanced to 6.6 : 1. Deprotection and thionation was followed by Eschenmoser sulfide contraction to give compound **25**. This was carried out in two steps as shown, since in our hands the sulfide contraction is more reliable (particularly on quantities > 200 mg) using the ketoester rather than methyl 2-bromoacetate. From this point, three-component coupling gave a separable mixture of compounds **26** and **27**, which in turn gave bicyclic guanidines **28** and **29**.

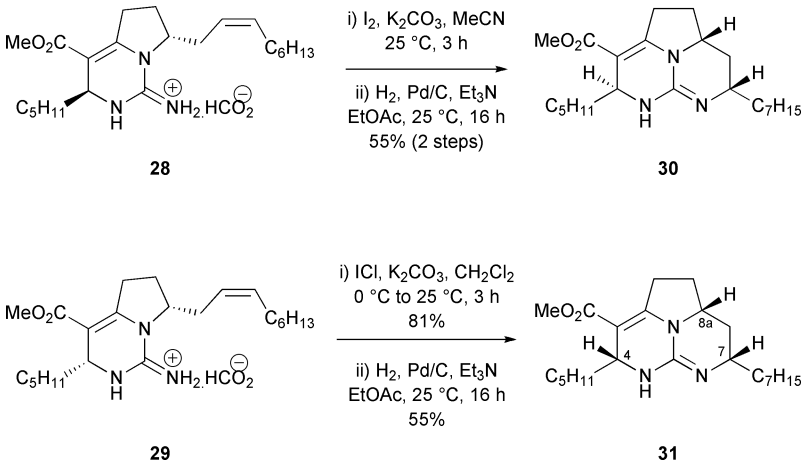
With the two key compounds in hand, iodocyclisation reactions were attempted next. Compound **28** underwent smooth iodocyclisation using iodine/potassium carbonate in acetonitrile (Scheme 5). Immediate hydrogenolysis provided compound **30**. Iodocyclisation of diastereoisomer **29** was more troublesome, but was eventually achieved using iodine monochloride–potassium carbonate in dichloromethane. Hydrogenolysis of the intermediate compound then gave compound **31**. The reason for the more challenging iodocyclisation of compound **29** is unclear.



Scheme 4

Calculations show that there is a significant conformational difference between the bicyclic portions of compound **28** and **29**.[24] However, this does not appear to result in the side-chain double-bond in the latter compound being further from the guanidine nitrogen. When a mixture of these two compounds is subjected to standard iodocyclisation conditions with iodine, only compound **28** undergoes cyclisation. We have observed an identical result with the diastereomeric mixture of guanidines **16** derived from compound **15**.[25]

Not surprisingly, the NMR data for compounds **30** and **31** are extremely similar. However, compound **30** differs in two key area—the ^{1}H chemical shift for H-8a is 4.11 ppm, compared to compound **31** (3.93 ppm), batzelladine C (3.86 ppm) and batzelladine C methyl ester (3.86 ppm).[1] The ^{13}C chemical shift for C-7 is 51.8 ppm

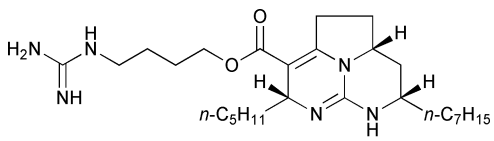


Scheme 5

in compound **30** compared to 53.7 ppm for compound **31** and 53.5 ppm for batzelladine C. The ^{13}C NMR data for batzelladine C methyl ester derived from the natural product were not reported. In other areas of the spectra, both epimers are similar to the natural product. However, particularly in the ^{1}H NMR spectra, compound **31** matches the natural product data whereas compound **30** shows a number of small but significant differences in chemical shift and coupling constants (and peak shapes where coupling constants could not be reliably obtained—see copies of spectra in the ESI†).[26] The optical rotation of compound **31** was –2.4 (c. 0.5, MeOH) compared to –4.2 (c. 0.93, MeOH) for the same compound formed by methanolysis of batzelladine C. Evans has previously noted discrepancies between reported optical rotation data for batzelladine alkaloids,[9] which can most likely be attributed to the presence of impurities. We therefore assign structure **31** as the relative and absolute stereochemistry of batzelladine C methyl ester, from which the stereochemistry of batzelladine C can be readily deduced. A number of attempts were made to transesterify compound **31** with 4-azidobutanol in the presence of Otera's catalyst. Although this protocol was used by Evans in the total synthesis of batzelladine D,[9] it was unsuccessful with compound **31**. Hydrolysis of compound **31** to the corresponding acid gave a very low yield of the corresponding acid. The small amounts of compound **31** available, as a result of it being derived from the minor diastereoisomer from the three-component coupling, precluded evaluation of a broader range of methods.

Conclusions

The two possible diastereoisomers of batzelladine C methyl ester **30** and **31** have been synthesised, each in 12 steps from compound **17**, and with 4.3% and 1.6% overall yields respectively. Based on comparison of their spectroscopic data with those of natural material, the stereochemistry of batzelladine C can be assigned as shown in structure **32** (Fig. 3).



32, Batzelladine C

Fig. 3 Stereochemistry of natural batzelladine C.

Experimental

General experimental points

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. Mass spectra were recorded on a Fisons VG Platform II spectrometer and on a Micromass Q-TOF Micro spectrometer. NMR spectra were recorded on a Bruker DPX 400 spectrometer operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C at 25 °C, or on a Bruker Avance 500 spectrometer operating at 500 MHz for 1H and 125 MHz for 13C at 25 °C. All chemical shifts are reported in ppm downfield from TMS. Coupling constants (*J*) are reported in Hz. Multiplicity in ^{1}H NMR spectroscopy is reported as singlet (s), doublet (d), double doublet (dd), double triplet (dt), double quartet (dq), triplet (t), and multiplet (m). Multiplicity in ^{13}C NMR spectroscopy was obtained using the DEPT pulse sequence. Flash chromatography was performed using Matrex silica 60 35–70 micron. Where mixtures of diastereoisomers were not separated, NMR data reported are for the major diastereoisomer. Copies of NMR spectra are provided in the ESI.†

(3*RS*,7*SR*)-Methyl-7-allyl-1,2,3,5,6-hexahydro-3-pentyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate (16)

Trimethylsilyl isothiocyanate (0.22 mL, 1.58 mmol) was added to a solution of hexanal (0.19 mL, 1.58 mmol) in dry CH_2Cl_2 (15 mL) under N_2, and the resulting yellow solution stirred for 30 min at 20 °C. A solution of (2*Z*)-methyl-2-((allylpyrrolidin-2-ylidene)acetate (**15**)[27] (287 mg, 1.58 mmol) in CH_2Cl_2 (3 mL) was then added, and the mixture stirred for a further 2 h at 18 °C. The reaction was then quenched with ~0.1 M aqueous NaOH solution (40 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 × 35 mL). The combined organic washings were then dried over Na_2SO_4, and the solvent removed *in vacuo* to afford the title compound (399 mg, 78%, 29% d.e.) as a yellow gum. The pure major diastereoisomer **11** was isolated by column chromatography (eluting with EtOAc-Hexane, 1 : 6), to

give the title compound (276 mg, 54%) as a yellow solid, m.p. 120–124 °C. Recrystallisation from aqueous ethanol produced crystals suitable for single-crystal X-ray diffraction analysis (found: MH^+, 323.1792. $C_{17}H_{27}N_2O_2S$ requires M, 323.1793); $\nu_{max.}$ 3265, 3212, 2834, 1690, 1647, 1527, 1354 and 1221 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.94 (1 H, broad s, N*H*), 5.73–5.67 (1 H, m, C*H*=CH_2), 5.09–5.03 (2 H, m, CH=CH_2), 4.56–4.52 (1 H, C*H*–allyl), 4.23–4.21 (1 H, m, C*H*–pentyl), 3.65 (3 H, s, CO_2CH_3), 3.32–3.26 (1 H, m, one of pyrrolidine CH_2C=C), 3.04 (1 H, app, dd, *J* 13.3, 4.5, one of pyrrolidine CH_2C=C), 2.90–2.80 (1 H, m, one of CH_2CH=CH_2), 2.15 (1 H, app. dt, *J* 13.5, 9.0, one of CH_2CH=CH_2), 1.94–1.83 (2 H, m, pyrrolidine CH_2CH–N), 1.61–1.44 (2 H, m, CH_2CH–NH), 1.48–1.12 (6 H, m, 3 × CH_2) and 0.81 (3 H, t, *J* 6.8, CH_3CH$_2$); δ_C (125 MHz; $CDCl_3$) 175.2 (*C*=S), 166.1 (*C*=O), 149.8 (C), 134.1 (CH), 118.1 (CH_2), 99.8 (C), 62.5 (CH), 52.1 (CH_3), 51.3 (CH), 37.7 (CH_2), 35.4 (CH_2), 31.4 (CH_2), 30.4 (CH_2), 25.7 (CH_2), 23.5 (CH_2), 22.5 (CH_2) and 14.0 (CH_3); *m*/*z* (ES^+) 323 (MH, 100%). Selected crystallographic data:† $C_{17}H_{26}N_2O_2S$, FW = 322.46, *T* = 150 K, λ = 0.71073 Å, triclinic, $P\bar{1}$, *a* = 8.89400(10) Å, *b* = 15.5730(2) Å, *c* = 26.7230(4) Å, α = 106.7770(10)°, β = 95.5040(10)°, γ = 92.3280(10)°, *V* = 3518.35(8) $Å^3$, *Z* = 8, ρ_c = 1.218 Mg m^{-3}, crystal size = 0.25 × 0.10 × 0.10 mm, μ = 0.193 mm^{-1}, reflections collected = 57716, independent reflections =16123, R_{int} = 0.102, parameters = 905, final R_1 = 0.0805, wR_2 = 0.164 for $I > 2\sigma(I)$ and R_1 = 0.137, wR_2 = 0.187 for all data.

(*R*)-1-(1-Phenylethyl)pyrrolidin-2,5-dione (17)

(*R*)-(+)-α-Methylbenzylamine (13.8 ml, 107 mmol) was added to a suspension of succinic anhydride (10.7 g, 107 mmol) in toluene (250 ml) and the mixture was heated under reflux for 18 h. The solvent was removed *in vacuo* and the residue re-dissolved in acetic anhydride (100 ml). The resulting solution was heated under reflux for 2 h before being poured onto crushed ice with stirring. The mixture was extracted with CH_2Cl_2, the combined extracts being washed thoroughly with saturated aqueous $NaHCO_3$ solution and dried over Na_2SO_4. The solvent was removed *in vacuo* affording the title compound (21.7 g, 100%) as a pure colourless oil. $[\alpha]_D$ +91 (*c* 1, CH_2Cl_2) Lit.[22] $[\alpha]_D$ +91.9 (*c* 4, CH_2Cl_2) (found: MH^+, 204.1018. $C_{12}H_{14}NO_2$ requires M, 204.1025); $\nu_{max.}$ (neat) 2979, 2941, 1679, 1393, 1219, 1188, 1101, 1066, 1023, 953, 821 and 786 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.39 (2 H, d, *J* 8.0, aromatic CH), 7.28–7.19 (3 H, m, aromatic CH), 5.36 (1 H, q, *J* 7.3, CH–Me), 2.57 (4 H, s, 2 × CH_2) and 1.76 (3 H, d, *J* 7.3, Me); δ_C (100 MHz; $CDCl_3$) 177.1 (2 × C=O), 139.7 (C), 128.5 (2 × CH), 127.9 (CH), 127.7 (2 × CH), 50.4 (CH), 28.2 (2 × CH_2) and 16.6 (CH_3); *m*/*z* (TOF AP^+) 204 (MH, 100%), 141 (33) and 105 (6).

5-Hydroxy-1-((*R*)-1-phenylethyl)pyrrolidin-2-one (18)

$LiEt_3BH$ (82.8 ml of 1.0 M solution in THF, 82.8 mmol) was added dropwise to a solution of imide **17** (12.0 g, 59.1 mmol) in THF (150 ml) at −78 °C. The mixture was allowed to stir for 40 min before the THF was removed *in vacuo*. The residue was cooled to 0 °C and the reaction quenched by dropwise addition of saturated aqueous $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2, the combined extracts being treated with 30% H_2O_2 solution (10 ml), washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo* affording the title compound (9.7 g, 80%) as a colourless solid (approx. 2 : 1 mixture of diastereoisomers), m.p. 82–84 °C, $[\alpha]_D$ +60 (*c* 0.5, CH_2Cl_2) (found: MH^+, 206.1177. $C_{12}H_{16}NO_2$ requires M, 206.1181); $\nu_{max.}$ (nujol) 3226, 2922, 2853, 1644, 1426, 1329, 1284, 1248, 1211, 1178, 1059, 1025, 989, 914, 790, 700 and 671 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.37–7.26 (5 H, m, aromatic CH), 5.41–5.34 (1 H, m, C*H*–Me), 4.93 (1 H, t, *J* 6.0, C*H*OH), 2.69–2.58 (1 H, m, one of CH_2C=O), 2.34–2.27 (1 H, m, one of CH_2C=O), 2.24–2.07 (1 H, m, one of pyrrolidine CH_2), 1.90–1.79 (1 H, m, one of pyrrolidine CH_2) and 1.67 (3 H, d, *J* 7.2, Me); δ_C (100 MHz; $CDCl_3$) 174.8 (C), 140.0 (C), 128.9 (2 × CH), 127.9 (CH), 127.8 (2 × CH), 82.4 (CH), 50.4 (CH), 29.2 (CH_2), 29.1 (CH_2) and 19.0 (CH_3); *m*/*z* (TOF ES^+) 247 (MH^+ + MeCN, 100%), 206 (MH, 85), 205 (31), 188 (14), 164 (13) and 155 (2).

(*R*)-5-Allyl-1-((*R*)-1-phenylethyl)pyrrolidin2-one (19)

Boron trifluoride diethyl etherate (5.79 ml, 47.0 mmol) was added dropwise to a solution of hydroxy lactam **18** (6.43 g, 31.4 mmol) in CH_2Cl_2 at −78 °C. Allyltrimethylsilane (15.0 ml, 94.1 mmol) was then added dropwise and the reaction mixture allowed to warm to room temperature over 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and the aqueous layer extracted with CH_2Cl_2. The combined organic fractions were dried over Na_2SO_4 before the solvent was removed *in vacuo* affording the title compound (6.88 g, 96%) as a pale oil (4.4 : 1 mixture of diastereoisomers), $[\alpha]_D$ +147 (*c* 1, MeOH) (found: MH^+, 230.1547. $C_{15}H_{20}NO$ requires M, 230.1545); $\nu_{max.}$ (neat) 3063, 2976, 2936, 1681, 1368, 1286, 1215, 1183, 1055, 1028, 998, 917 and 788 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.39 (2H, d, *J* 7.5, aromatic CH), 7.33–7.29 (2 H, m, aromatic CH), 7.26–7.24 (1 H, m, aromatic CH), 5.51–5.39 (2 H, m, alkene CH and C*H*–Ph), 4.98–4.95 (1 H, m, one of alkene CH_2), 4.88 (1 H, app. dq, *J* 17.1, 1.4, one of alkene CH_2), 3.76 (1 H, app. ddd, *J* 11.9, 8.4, 3.5, CH-allyl), 2.53–2.44 (1 H, m, one of CH_2C=O), 2.32 (1 H, app. ddd, *J* 17.0, 9.9, 4.7, one of CH_2C=O), 2.06 (1 H, ddt, *J* 12.9, 9.8, 8.2, one of pyrrolidine CH_2), 1.92–1.86 (1 H, m, one of CH_2C=C), 1.78–1.67 (2 H, m, one of pyrrolidine CH_2 and one of CH_2C=C) and 1.65 (3 H, d, *J* 7.3, Me); δ_C (100 MHz; $CDCl_3$) 175.6 (C=O), 142.0 (C), 133.5 (CH), 128.6 (2 × CH), 127.6 (CH), 127.4 (2 × CH), 118.4 (CH_2), 56.5 (CH), 49.7 (CH), 39.0 (CH_2), 30.5 (CH_2), 24.2 (CH_2) and 16.5 (CH_3); *m*/*z* (TOF ES^+) 230 (MH, 100%).

2-(*R*)-5-Oxo-1-((*R*)-1-phenylethyl)pyrrolidin-2-yl)acetaldehyde (20)

Potassium osmate dihydrate (cat.), sodium periodate (24.1 g, 113 mmol) and 2,6-lutidine (6.56 ml, 56.3 mmol) were added to a solution of allyl lactam **19** (6.45 g, 28.2 mmol) in dioxane-H_2O (3 : 1, 520 ml) and the resulting suspension was allowed to stir at room temperature for 18 h. The reaction was quenched with water and the mixture extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 before the solvent was removed *in vacuo*. Flash chromatography on silica gel (EtOAc–acetone 1 : 2) afforded the title compound (4.87 g, 75%) as a colourless oil (6.4 : 1 mixture of diastereoisomers), $[\alpha]_D$ +124 (*c* 1, MeOH) (found: MH^+, 232.1330. $C_{14}H_{18}NO_2$ requires M, 232.1338); $\nu_{max.}$ (neat) 3061, 2975, 1720, 1670, 1417, 1373, 1286, 1215, 1182, 1026, 788 and 758 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 9.33 (1 H, s, aldehyde),

7.34–7.24 (5 H, m, aromatic CH), 5.52 (1 H, q, *J* 7.2, C*H*–Me), 4.20 (1 H, app. ddd, *J* 11.8, 7.9, 3.5, CHN), 2.54–2.45 (1 H, m, one of pyrrolidine $CH_2C{=}O$), 2.36 (1 H, ddd, *J* 16.7, 9.7, 4.2, one of pyrrolidine $CH_2C{=}O$), 2.26 (1 H, ddd, *J* 18.0, 12.7, 8.5, one of pyrrolidine CH_2), 2.15 (1 H, app. dd, *J* 18.0, 8.9, one of CH_2CHO), 2.06 (1 H, dd, *J* 18.1, 3.5, one of CH_2CHO), 1.65–1.61 (1 H, m, one of pyrrolidine CH_2) and 1.58 (3 H, d, *J* 7.3, Me); δ_C (100 MHz; $CDCl_3$) 199.8 (aldehyde CH), 175.2 (lactam C=O), 141.3 (C), 128.8 (2 × CH), 127.9 (CH), 127.4 (2 × CH), 50.8 (CH), 48.9 (CH), 48.6 (CH_2), 30.0 (CH_2), 25.9 (CH_2) and 16.0 (CH_3); *m*/*z* (TOF ES^+) 232 (MH, 100%).

(*R*)-5-((*Z*)-Non-2-enyl)-1-((*R*)-1-phenylethyl)pyrrolidin-2-one (21)

n-Butyllithium (15.3 ml of a 2.5 M solution in hexanes, 38.3 mmol) was added drop-wise to a solution of heptyltriphenylphosphonium iodide (18.7 g, 38.3 mmol) in THF (150 ml) at 0 °C. The solution was allowed to stir at 0 °C for 2 h before a solution of aldehyde **20** (4.42 g, 19.1 mmol) in THF (15 ml) was added at −78 °C. The resulting solution was allowed to warm to room temperature and stirred for 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and the aqueous layer extracted with CH_2Cl_2. The combined organic fractions were dried over Na_2SO_4 before the solvent was removed *in vacuo*. Chromatography on silica gel (EtOAc–hexane 1 : 2) afforded the title compound (3.45 g, 58%) as a yellow oil (6.6 : 1 mixture of diastereoisomers), $[\alpha]_D$ +110 (*c* 1, MeOH) (found: MH^+, 314.2499. $C_{21}H_{32}NO$ requires M, 314.2484); $\nu_{max.}$ (neat) 2928, 2855, 1686, 1416, 1365, 1265, 1216, 1182, 1118 and 787 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.39 (2 H, d, *J* 7.4, aromatic CH), 7.31 (2 H, app. t, *J* 7.4, aromatic CH), 7.25 (1 H, d, *J* 7.0, aromatic CH), 5.49–5.36 (2 H, m, C*H*Me and alkene CH), 5.09–5.02 (1 H, m, alkene CH), 3.76–3.65 (1H, m, CHN), 2.51 (1 H, app. dt, *J* 17.1, 8.8, one of $CH_2C{=}O$), 2.35 (1 H, ddd, *J* 17.1, 9.8, 4.9, one of $CH_2C{=}O$), 2.10–2.00 (2 H, m, $CH_2C{=}C$), 1.94–1.88 (1 H, m, one of pyrrolidine CH_2), 1.81 (2 H, app. q, *J* 6.5, $CH_2C{=}C$), 1.73–1.67 (1 H, m, one of pyrrolidine CH_2), 1.65 (3 H, d, *J* 7.2, Me), 1.30–1.22 (8 H, broad m, 4 × CH_2) and 0.88 (3 H, t, *J* 7.0, CH_3CH_2); δ_C (100 MHz; $CDCl_3$) 175.6 (C=O), 142.1 (C), 133.4 (CH), 128.5 (2 × CH), 127.5 (CH), 127.3 (2 × CH), 124.0 (CH), 57.1 (CH), 49.7 (CH), 32.2 (CH_2), 31.9 (CH_2), 30.5 (CH_2), 29.6 (CH_2), 29.1 (CH_2), 27.6 (CH_2), 24.4 (CH_2), 22.8 (CH_2), 16.5 (CH_3) and 14.3 (CH_3); *m*/*z* (TOF ES^+) 314 (MH, 100%).

(*R*)-5-((*Z*)-Non-2-enyl)pyrrolidine-2-one (22)

Sodium metal (1.19 g, 51.6 mmol) was added in portions to a solution of alkenyl lactam **21** (3.23 g, 10.3 mmol) in liquid NH_3–THF–EtOH (8 : 1 : 1, 240 ml) at −78 °C until the blue colour persisted for longer than 3 min. After the solution had turned colourless, solid NH_4Cl was added and the ammonia allowed to evaporate. The reaction mixture was then washed with water and extracted with EtOAc. The combined extracts were dried over Na_2SO_4 before the solvent was removed *in vacuo* affording the title compound (1.93 g, 89%) as a pure yellow oil, $[\alpha]_D$ +15 (*c* 1, MeOH); (found: MH^+, 210.1848. $C_{13}H_{24}NO$ requires M, 210.1858); $\nu_{max.}$ (neat) 3225, 2920, 2860, 1694, 1462, 1379, 1346, 1292, 1262, 1204, 1083 and 734 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.00–5.73 (1 H, broad s, NH), 5.59–5.52 (1 H, m, alkene CH), 5.34–5.27 (1 H, m, alkene CH), 3.71–3.64 (1 H, m, C*H*NH), 2.38–2.32 (2 H, m, $CH_2C{=}O$), 2.30–2.17 (3 H, m, $CH_2C{=}C$ and one of pyrrolidine CH_2), 2.03 (2 H, app. q, *J* 7.1, $CH_2C{=}C$), 1.80–1.71 (1 H, m, one of pyrrolidine CH_2), 1.35–1.22 (8 H, broad m, 4 × CH_2) and 0.88 (3 H, t, *J* 6.8, CH_3); δ_C (100 MHz; $CDCl_3$) 178.2 (C=O), 134.1 (CH), 124.1 (CH), 54.6 (CH), 34.5 (CH_2), 31.9 (CH_2), 30.4 (CH_2), 29.7 (CH_2), 29.2 (CH_2), 27.7 (CH_2), 27.0 (CH_2), 22.8 (CH_2) and 14.3 (CH_3); *m*/*z* (TOF AP^+) 251 (MH + MeCN, 100%), 210 (MH, 43), 124 (4) and 83 (3).

(*R*)-5-((*Z*)-Non-2-enyl)pyrrolidine-2-thione (23)

Lawesson's reagent (1.91 g, 4.71 mmol) was added to a solution of lactam **22** (1.79 g, 8.56 mmol) in THF (80 ml). The resulting solution was allowed to stir at room temperature for 2 h before the solvent was removed *in vacuo*. Chromatography on silica gel (EtOAc–petroleum ether 1 : 9) afforded the title compound (1.62 g, 84%) as a yellow oil, $[\alpha]_D$ +37 (*c* 1, MeOH) (found: MH^+, 226.1621. $C_{13}H_{24}NS$ requires M, 226.1629); $\nu_{max.}$ (neat) 3162, 2925, 2854, 1530, 1456, 1377, 1294, 1119, 1068 and 726 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.87–7.63 (1 H, broad s, NH), 5.60 (1 H, dt, *J* 11.4, 7.5, alkene CH), 5.35–5.27 (1 H, m, alkene CH), 3.94 (1 H, app. quintet, *J* 7.0, C*H*NH), 2.98 (1 H, ddd, *J* 18.2, 9.4, 5.2, one of $CH_2C{=}S$), 2.93–2.84 (1 H, m, one of $CH_2C{=}S$), 2.39–2.24 (3 H, m, $CH_2C{=}C$ and one of pyrrolidine CH_2), 2.06–2.00 (2 H, m, $CH_2C{=}C$), 1.90–1.81 (1 H, m, one of pyrrolidine CH_2), 1.39–1.27 (8 H, broad m, 4 × CH_2) and 0.88 (3 H, t, *J* 6.8, CH_3); δ_C (100 MHz; $CDCl_3$) 205.6 (C=S), 134.7 (CH), 123.4 (CH), 62.5 (CH), 43.2 (CH_2), 33.3 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.2 (2 × CH_2), 27.7 (CH_2), 22.8 (CH_2) and 14.3 (CH_3); *m*/*z* (TOF ES^+) 226 (MH, 100%).

(*E*)-Methyl 2-((*R*)-5-((*Z*)-non-2-enyl)pyrrolidin-2-ylidene)-3-oxobutanoate (24)

Sodium hydrogencarbonate (2.26 g, 26.8 mmol) and methyl 2-bromoacetoacetate[15] (2.62 g, 13.4 mmol) were added to a solution of thiolactam **23** (1.51 g, 6.71 mmol) in CH_2Cl_2 (50 ml), and the mixture was heated under reflux for 16 h. The reaction mixture was then cooled before being filtered through silica and concentrated *in vacuo*. Chromatography on silica gel (Et_2O–petroleum ether 1 : 9) afforded the title compound (1.74 g, 84%) as an orange oil, $[\alpha]_D$ +73 (*c* 1, MeOH) (found: MH^+, 308.2221. $C_{18}H_{30}NO_3$ requires M, 308.2226); $\nu_{max.}$ (neat) 3203, 2928, 2855, 1694, 1600, 1538, 1434, 1359, 1315, 1242, 1189, 1069, 1013, 914 and 784 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 5.61–5.54 (1 H, m, alkene CH), 5.36–5.29 (1 H, m, alkene CH), 3.93 (1 H, app. quintet, *J* 6.6, C*H*NH), 3.73 (3 H, s, OCH_3), 3.22 (1 H, ddd, *J* 18.6, 9.5, 5.4, one of pyrrolidine $CH_2C{=}C$), 3.07 (1 H, app. ddd, *J* 18.6, 9.4, 7.3, one of pyrrolidine $CH_2C{=}C$), 2.40 (3 H, s, CH_3), 2.38–2.22 (2 H, m, $CH_2C{=}C$), 2.18–2.09 (1 H, m, one of pyrrolidine CH_2), 2.01 (2 H, app. q, *J* 6.8, $CH_2C{=}C$), 1.70–1.61 (1 H, m, one of pyrrolidine CH_2), 1.37–1.21 (8 H, broad m, 4 × CH_2) and 0.87 (3 H, t, *J* 6.9, CH_3); δ_C (100 MHz; $CDCl_3$) 197.9 (C=O), 173.8 (C), 169.4 (C), 134.3 (CH), 123.7 (CH), 98.6 (C), 60.9 (CH), 50.7 (CH_3), 35.1 (CH_2), 33.7 (CH_2), 31.9 (CH_2), 31.0 (CH_3), 29.7 (CH_2), 29.1 (CH_2), 27.6 (CH_2), 26.9 (CH_2), 22.8 (CH_2) and 14.3 (CH_3); *m*/*z* (TOF AP^+) 308 (MH, 100%) and 276 (22).

(*Z*)-Methyl 2-(*R*)-5-((*Z*)-non-2-enyl)pyrrolidin-2-ylidene)acetate (25)

Sodium metal (128 mg, 5.57 mmol) was dissolved in dry MeOH (15 ml) under nitrogen and allowed to stir for 30 min. A solution

of β-keto-ester **24** (1.71 g, 5.57 mmol) in dry MeOH (5 ml) was then added and the mixture heated at reflux for 2 h. The solvent was removed *in vacuo* and the resulting residue dissolved in chloroform, washed with saturated aqueous sodium carbonate solution and dried over sodium sulfate. The solvent was removed *in vacuo*. Chromatography on silica gel (Et_2O–petroleum ether 1 : 9) afforded the title compound (1.24 g, 84%) as a yellow oil, $[\alpha]_D$ +149 (*c* 1, MeOH) (found: MH^+, 266.2108. $C_{16}H_{28}NO_2$ requires M, 266.2120); $\nu_{max.}$ (neat) 3362, 2925, 2855, 1667, 1606, 1469, 1430, 1294, 1237, 1147 and 1041 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.08–7.87 (1 H, broad s, NH), 5.57–5.50 (1 H, m, alkene CH), 5.38–5.30 (1 H, m, alkene CH), 4.48 (1 H, s, CHC=O), 3.79 (1 H, app. quintet, *J* 6.5, C*H*NH), 3.63 (3 H, s, OCH_3), 2.68–2.53 (2 H, m, pyrrolidine CH_2C=C), 2.30 (1 H, app. dt, *J* 14.3, 7.2, one of CH_2C=C), 2.24–2.17 (1 H, m, one of CH_2C=C), 2.13–2.06 (1 H, m, one of pyrrolidine CH_2), 2.02 (2 H, app. q, *J* 6.8, CH_2C=C), 1.65–1.56 (1 H, m, one of pyrrolidine CH_2), 1.35–1.20 (8 H, broad m, 4 × CH_2) and 0.87 (3 H, t, *J* 6.9, CH_3); δ_C (100 MHz; $CDCl_3$) 171.1 (C), 166.0 (C), 133.7 (CH), 124.5 (CH), 76.3 (CH), 59.8 (CH), 50.3 (CH_3), 34.1 (CH_2), 32.1 (CH_2), 32.0 (CH_2), 29.7 (CH_2), 29.2 (CH_2), 28.0 (CH_2), 27.7 (CH_2), 22.8 (CH_2) and 14.3 (CH_3); *m*/*z* (TOF ES^+) 266 (MH, 100%).

(3*S*,7*R*)-Methyl 1,2,3,5,6,7-hexahydro-7-((*Z*)-non-2-enyl)-3-pentyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate (26) and (3*R*,7*R*)-methyl 1,2,3,5,6,7-hexahydro-7-((*Z*)-non-2-enyl)-3-pentyl-1-thioxopyrrolo[1,2-*c*]pyrimidine-4-carboxylate (27)

Hexanal (1.10 ml, 8.98 mmol) was added to a solution of trimethylsilyl isothiocyanate (1.27 ml, 8.98 mmol) in CH_2Cl_2 (40 ml) and the solution was stirred at room temperature for 30 min. A solution of alkylidenepyrrolidine **25** (1.19 g, 4.49 mmol) in CH_2Cl_2 (10 ml) was then added and the resulting solution allowed to stir for 45 min. The reaction was quenched with ~0.1 M NaOH solution and the aqueous layer extracted with CH_2Cl_2. The combined extracts were dried over sodium sulfate before the solvent was removed *in vacuo*. Chromatography on silica gel (Et_2O–petroleum ether 1 : 9) gave, in order of elution, compound **26** (833 mg, 46%) and compound **27** (425 mg, 23%), both as yellow oils.

Data for compound 26. $[\alpha]_D$ −36 (*c* 1, MeOH); found: MH^+, 407.2728. $C_{23}H_{39}N_2O_2S$ requires M, 407.2732; $\nu_{max.}$ (neat) 3198, 2914, 2860, 1699, 1660, 1432, 1386, 1222, 1162, 1098, 971, 933, 893, 827 and 776 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.72 (1 H, broad s, NH), 5.53 (1 H, dt, *J* 10.8, 7.4, alkene CH), 5.34–5.27 (1 H, m, alkene CH), 4.56 (1 H, app. ddt, *J* 8.5, 6.4, 3.2, CHNC=S), 4.28–4.26 (1 H, m, CH–pentyl), 3.72 (3 H, s, OCH_3), 3.39–3.32 (1 H, ddd, *J* 18.2, 5.4, 3.7, one of pyrrolidine CH_2C=C), 3.06 (1 H, app. broad dd, *J* 13.4, 6.2, one of side-chain CH_2C=C), 2.92 (1 H, app. dt, *J* 18.2, 10.4 one of pyrrolidine CH_2C=C), 2.21 (1 H, dt, *J* 13.7, 9.3, one of side-chain CH_2C=C), 2.08 (2 H, app. broad q, *J* 7.3, CH_2C=C), 1.95–1.90 (2 H, m, pyrrolidine CH_2), 1.63–1.50 (2 H, broad m, CH_2), 1.43–1.21 (14 H, broad m, 7 × CH_2) and 0.89–0.86 (6 H, m, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 175.5 (C=S), 166.3 (C=O), 150.0 (C), 134.0 (CH), 124.4 (CH), 99.9 (C), 63.4 (CH), 52.3 (CH), 51.5 (CH_3), 38.0 (CH_2), 32.0 (CH_2), 31.6 (CH_2), 30.7 (CH_2), 29.9 (CH_2), 29.2 (CH_2), 28.8 (CH_2), 27.9 (CH_2), 26.0 (CH_2), 23.7 (CH_2), 22.9 (CH_2), 22.8 (CH_2) and 14.3 (2 × CH_3); *m*/*z* (TOF ES^+) 407 (MH, 100%).

Data for compound 27. $[\alpha]_D$ +99 (*c* 1, MeOH); found: MH^+, 407.2734. $C_{23}H_{39}N_2O_2S$ requires M, 407.2732; $\nu_{max.}$ (neat) 3198, 2980, 1693, 1644, 1427, 1381, 1223, 1155, 1105, 976, 933, 889 and 778 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.98 (1 H, app. broad d, *J* 3.4, NH), 5.54 (1 H, dt, *J* 10.8, 7.3, alkene CH), 5.35–5.28 (1 H, m, alkene CH), 4.91 (1 H, tt, *J* 8.6, 2.9, CHNC=S), 4.28 (1 H, app. dt, *J* 7.5, 3.8, CH-pentyl), 3.73 (3 H, s, OCH_3), 3.29 (1 H, ddd, *J* 18.9, 9.9, 2.9, one of pyrrolidine CH_2C=C), 3.01 (1 H, app. dt, *J* 18.9, 9.4, one of pyrrolidine CH_2C=C), 2.69–2.63 (1 H, m, one of CH_2C=C), 2.39 (1 H, app. dt, *J* 14.0, 8.3, one of CH_2C=C), 2.13–1.95 (3 H, broad m, CH_2C=C and one of pyrrolidine CH_2), 1.86–1.79 (1 H, m, one of pyrrolidine CH_2), 1.57–1.42 (2 H, broad m, CH_2), 1.39–1.20 (14 H, broad m, 7 × CH_2) and 0.89–0.85 (6 H, m, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 176.0 (C=S), 166.2 (C=O), 150.7 (C), 134.2 (CH), 123.8 (CH), 100.5 (C), 63.1 (CH), 52.0 (CH), 51.6 (CH_3), 37.0 (CH_2), 32.0 (CH_2), 31.6 (CH_2), 31.2 (CH_2), 30.6 (CH_2), 29.8 (CH_2), 29.2 (CH_2), 27.8 (CH_2), 24.9 (CH_2), 23.9 (CH_2), 22.8 (2 × CH_2), 14.3 (CH_3) and 14.2 (CH_3); *m*/*z* (TOF ES^+) 407 (MH, 100%).

(3*S*,7*R*)-7-((*Z*)-Non-2-enyl)-4-(methoxycarbonyl)-3-pentyl-2,3,6,7-tetrahydropyrrolo[1,2-*c*]pyrimidine-1(5*H*)-iminium formate (28)

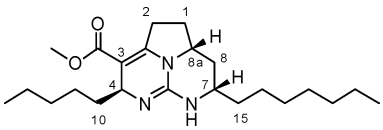
Iodomethane (0.02 ml, 0.291 mmol) was added to a solution of bicyclic thiourea **26** (118 mg, 0.291 mmol) in dry MeOH (3 ml) and the mixture was heated at reflux for 1 h. The volatiles were removed *in vacuo* and the resulting residue re-dissolved in dry MeOH (3 ml). The solution was transferred to a mixture of NH_4OAc (112 mg, 1.45 mmol) in dry MeOH (2 ml) and liquid ammonia bubbled through the reaction for 10 min. The resulting suspension was heated in a sealed tube at 80 °C for 48 h. The solvent was removed *in vacuo* before chromatography on silica gel (CH_2Cl_2–MeOH–HCO_2H–H_2O 84 : 14 : 0.5 : 0.5) gave the title compound (121 mg, 96%) as an orange oil, $[\alpha]_D$ +7 (*c* 1, MeOH) (found: MH^+, 390.3134. $C_{23}H_{40}N_3O_2$ requires M, 390.3121); $\nu_{max.}$ (CH_2Cl_2) 3229, 3155, 2927, 2856, 1699, 1649, 1599, 1548, 1438, 1379, 1346, 1212, 1177, 1104, 912 and 646 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.18 (1 H, s, NH), 8.08–7.77 (2 H, broad s, NH_2), 5.57 (1 H, dt, *J* 11.0, 7.2, alkene CH), 5.52–5.43 (1 H, m, alkene CH), 4.73–4.69 (1 H, m, CHNC=N), 4.46–4.42 (1 H, m, CH–pentyl), 3.74 (3 H, s, OCH_3), 3.32 (1 H, dd, *J* 18.7, 7.9, one of pyrrolidine CH_2C=C), 2.93–2.83 (1 H, m, one of pyrrolidine CH_2C=C), 2.49–2.45 (1 H, m, one of CH_2C=C), 2.34 (1 H, dt, *J* 14.3, 9.1, one of CH_2C=C), 2.11–1.95 (4 H, broad m, CH_2C=C and pyrrolidine CH_2), 1.71–1.50 (3 H, broad m, methylene protons), 1.43–1.24 (13 H, broad m, methylene protons) and 0.89–0.85 (6 H, m, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 165.1 (C=O), 150.9 (C=N), 149.7 (C), 134.7 (CH), 123.0 (CH), 102.0 (C), 60.3 (CH), 51.9 (CH_3), 50.9 (CH), 37.5 (CH_2), 31.9 (CH_2), 31.4 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 27.7 (CH_2), 26.6 (CH_2), 24.1 (CH_2), 22.8 (CH_2), 22.6 (CH_2) and 14.3 (2 × CH_3); *m*/*z* (TOF AP^+) 390 (MH, 100%).

(3*R*,7*R*)-7-((*Z*)-Non-2-enyl)-4-(methoxycarbonyl)-3-pentyl-2,3,6,7-tetrahydropyrrolo[1,2-*c*]pyrimidine-1(5*H*)-iminium formate (29)

Iodomethane (0.04 ml, 0.0.621 mmol) was added to a solution of bicyclic thiourea **27** (252 mg, 0.621 mmol) in dry MeOH (5 ml) and the mixture was heated at reflux for 1 h. The volatiles were removed *in vacuo* and the resulting residue re-dissolved in dry

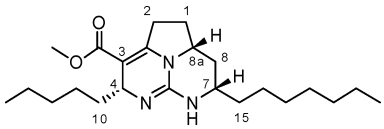
MeOH (5 ml). The solution was transferred to a mixture of NH_4OAc (239 mg, 3.10 mmol) in dry MeOH (3 ml) and liquid ammonia bubbled through the reaction for 10 min. The resulting suspension was heated in a sealed tube at 80 °C for 48 h. The solvent was removed *in vacuo* before chromatography on silica gel (CH_2Cl_2–MeOH–HCO_2H–H_2O 84 : 14 : 0.5 : 0.5) gave the title compound (233 mg, 86%) as an orange oil, $[\alpha]_D$ +19 (*c* 1, MeOH) (found: MH^+, 390.3113. $C_{23}H_{40}N_3O_2$ requires M, 390.3121); $\nu_{max.}$ (CH_2Cl_2) 3241, 3148, 2957, 2927, 2856, 1696, 1681, 1655, 1548, 1436, 1385, 1349, 1184 and 1106 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.99–8.65 (1 H, broad s, NH), 8.16–7.60 (2 H, broad s, NH_2), 5.58 (1 H, dt, *J* 10.6, 7.4, alkene CH), 5.39–5.32 (1 H, m, alkene), 4.96–4.88 (1 H, m, CHNC=N), 4.43 (1 H, app. dd, *J* 7.0, 3.8, CH–pentyl), 3.74 (3 H, s, OCH_3), 3.20 (1 H, ddd, *J* 19.0, 10.0, 3.8, one of pyrrolidine CH_2C=C), 3.07–2.98 (1 H, m, one of pyrrolidine CH_2C=C), 2.52–2.36 (2 H, m, CH_2C=C), 2.21 (1 H, app. dq, *J* 12.7, 9.1, one of pyrrolidine CH_2), 2.00 (2 H, app. q, 6.6, CH_2C=C), 1.93–1.86 (1 H, m, one of pyrrolidine CH_2), 1.58–1.40 (3 H, m, methylene protons), 1.36–1.24 (13 H, broad m, methylene protons) and 0.87 (6 H, app. t, *J* 6.4, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 165.2 (C=O), 151.4 (C=N), 150.6 (C), 135.1 (CH), 122.2 (CH), 102.8 (C), 60.1 (CH), 51.9 (CH_3), 50.3 (CH), 36.7 (CH_2), 31.9 (CH_2), 31.5 (CH_2), 30.9 (CH_3), 29.7 (CH_2), 29.2 (2 × CH_2), 27.8 (CH_2), 26.4 (CH_2), 24.1 (CH_2), 22.8 (CH_2), 22.7 (CH_2), 14.3 (CH_3) and 14.2 (CH_3); *m*/*z* (TOF AP^+) 390 (MH, 100%) and 376 (1).

(4*S*,7*S*,8a*R*)-Methyl 7-heptyl-4-pentyl-1,2,4,5,7,8-hexahydro-11a*H*-2a^1,5,6-triaza-acenaphthylene-3-carboxylate (30)



Iodine (350 mg, 1.38 mmol) and potassium carbonate (95 mg, 0.690 mmol) were added to a solution of bicyclic guanidine **28** (100 mg, 0.230 mmol) in MeCN (3 ml), and the resulting mixture was allowed to stir at room temperature for 3 h. The reaction mixture was filtered through silica and concentrated *in vacuo*. The crude iodinated tricyclic guanidine was immediately re-dissolved in EtOAc (6 ml), and triethylamine (0.16 ml, 1.15 mmol) and 10% Pd/C (cat.) added. The black suspension was degassed and stirred under an atmosphere of H_2 for 16 h. The reaction mixture was then filtered through celite and the solvent removed *in vacuo*. Chromatography on silica gel (EtOAc–CH_2Cl_2 1 : 2) afforded the title compound (49 mg, 55%) as a yellow oil, $[\alpha]_D$ −13 (*c* 0.5, MeOH) (found: MH^+, 390.3111. $C_{23}H_{40}N_3O_2$ requires M, 390.3121); $\nu_{max.}$ (CH_2Cl_2) 3180, 2931, 2856, 1704, 1679, 1644, 1573, 1493, 1437, 1373, 1335, 1227, 1195, 1115, 1080, 917 and 702 cm^{-1}; δ_H (400 MHz; MeOD) 4.40 (1 H, app. dd, *J* 7.4, 4.2, H-4), 4.11 (1 H, app. tdd, *J* 10.3, 6.5, 3.8, H-8a), 3.74 (3 H, s, OCH_3), 3.67–3.60 (1 H, m, H-7), 3.41 (1 H, app. dd, *J* 18.7, 9.0, H-2β), 2.89 (1 H, ddd, *J* 18.7, 11.4, 8.9, H-2α), 2.46–2.39 (2 H, m, H-1β and H-8β), 1.77–1.62 (2 H, m, H–1α and H-8α), 1.60–1.48 (3 H, m, three of H-10/H-15), 1.41–1.27 (17 H, m, one of H-10/H15 and 8 × CH_2) and 0.90–0.87 (6 H, m, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 165.0 (C), 149.1 (C), 148.5 (C), 103.3 (C), 57.4 (CH), 52.0 (CH_3), 51.3 (CH), 50.9 (CH), 37.1 (CH_2), 34.7 (CH_2), 33.9 (CH_2), 31.9 (CH_2), 31.4 (CH_2), 30.0 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 25.5 (CH_2), 24.3 (CH_2), 22.8 (CH_2), 22.6 (CH_2) and 14.3 (2 × CH_3); *m*/*z* (TOF ES^+) 390 (MH, 100%), 146(2) and 130 (4).

(4*R*,7*S*,8a*R*)-Methyl 7-heptyl-4-pentyl-1,2,4,5,7,8-hexahydro-11a*H*-2a^1,5,6-triaza-acenaphthylene-3-carboxylate (batzelladine C methyl ester) (31)



Potassium carbonate (51 mg, 0.366 mmol) was added to a solution of bicyclic guanidine **29** (53 mg, 0.122 mmol) in dry CH_2Cl_2 (2 ml) at 0 °C. Iodine monochloride (0.18 ml of a 1 M solution in CH_2Cl_2, 0.183 mmol) was added dropwise and the resulting suspension was allowed to warm to room temperature and stirred for ~3 h (TLC). The solvent was removed *in vacuo* before chromatography on silica gel (EtOAc–CH_2Cl_2 1 : 2) afforded the iodinated tricyclic guanidine (51 mg, 81%) as a brown oil. The tricyclic guanidine (41 mg, 0.0796 mmol) was immediately re-dissolved in EtOAc (3 ml), and triethylamine (0.05 ml, 0.398 mmol) and 10% Pd/C (cat.) added. The black suspension was de-gassed and stirred under an atmosphere of H_2 for 16 h. The reaction mixture was filtered before chromatography on silica gel (MeOH–EtOAc 1 : 19) afforded the title compound (17 mg, 55%) as a colourless oil, $[\alpha]_D$ −2.4 (*c* 0.5, MeOH); lit. $[\alpha]_D$ −4.2 (*c* 0.93, MeOH)1 (found: MH^+, 390.3113. $C_{23}H_{40}N_3O_2$ requires M, 390.3121); $\nu_{max.}$ (CH_2Cl_2) 3177, 2926, 2856, 1682, 1644, 1574, 1435, 1372, 1336, 1199, 1097 and 736 cm^{-1}; δ_H (400 MHz; MeOD); 4.46–4.44 (1 H, m, H–4), 3.93 (1 H, tdd, *J* 11.4, 5.4, 2.7, H-8a), 3.70 (3 H, s, OCH_3), 3.60 (1 H, app. td, *J* 11.1, 6.4, H-7), 3.32 (1 H, dd, *J* 18.2, 7.8, H-2β), 2.79 (1 H, dddd, *J* 18.2, 12.0, 7.5, 1.4, H–2α), 2.38 (1 H, ddd, *J* 13.1, 3.9, 2.9, H–8β), 2.33–2.27 (1 H, m, H-1β), 1.72–1.52 (5 H, m, H-1α, H-10 and H-15), 1.35–1.24 (17 H, m, H-8α and 8 × CH_2) and 0.88–0.85 (6 H, m, 2 × CH_3); δ_C (125 MHz; MeOD) 58.9 (CH), 53.8 (CH), 52.5 (CH), 52.2 (CH_3), 38.2 (CH_2), 36.0 (CH_2), 33.3 (CH_2), 33.1 (CH_2), 32.7 (CH_2), 31.1 (CH_2), 30.6 (CH_2), 30.5 (CH_2), 30.4 (CH_2), 26.1 (CH_2), 24.5 (CH_2), 23.8 (CH_2), 23.7 (CH_2), 14.5 (CH_3) and 14.4 (CH_3); *m*/*z* (TOF ES^+) 390 (MH, 100%), 361 (8) and 342 (1).

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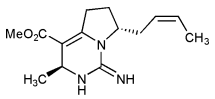
Notes and references

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

2 (*a*) A. D. Patil, A. J. Freyer, P. B. Taylor, B. Carté, G. Zuber, R. K. Johnson and D. J. Faulkner, *J. Org. Chem.*, 1997, **62**, 1814; (*b*) J. C. Braekman, D. Daloze, R. Tavares, E. Hajdu and R. W. M. Van Soest, *J. Nat. Prod.*, 2000, **63**, 193; (*c*) W. A. Gallimore, M. Kelly and P. J. Scheuer, *J. Nat. Prod.*, 2005, **68**, 1420; (*d*) H.-M. Hua, J. Peng, D. C.

Dunbar, R. F. Schinazi, A. G. de Castro Andrews, C. Cuevas, L. F. Garcia-Fernandez, M. Kelly and M. T. Hamann, *Tetrahedron*, 2007, **63**, 11179.
3 For a review see L. Heys, C. G. Moore and P. J. Murphy, *Chem. Soc. Rev.*, 2000, **29**, 57.
4 (*a*) A. S. Franklin, S. K. Ly, G. H. Mackin, L. E. Overman and A. J. Shaka, *J. Org. Chem.*, 1999, **64**, 1512; (*b*) A. I. McDonald and L. E. Overman, *J. Org. Chem.*, 1999, **64**, 1520; (*c*) F. Cohen, S. K. Collins and L. E. Overman, *Org. Lett.*, 2003, **5**, 4485; (*d*) Z. D. Aron and L. E. Overman, *Chem. Commun.*, 2004, 253.
5 (*a*) K. Nagasawa, H. Koshino and T. Nakata, *Tetrahedron Lett.*, 2001, **42**, 4155; (*b*) K. Nagasawa, T. Ishiwata, Y. Hashimoto and T. Nakata, *Tetrahedron Lett.*, 2002, **43**, 6383.
6 S. G. Duron and D. Y. Gin, *Org. Lett.*, 2001, **3**, 1551.
7 (*a*) B. B. Snider, J. Chen, A. D. Patil and A. J. Freyer, *Tetrahedron Lett.*, 1996, **37**, 6977; (*b*) B. B. Snider and J. Chen, *Tetrahedron Lett.*, 1998, **39**, 5697; (*c*) B. B. Snider and N. V. Busuyek, *J. Nat. Prod.*, 1999, **62**, 1707.
8 (*a*) P. J. Murphy, H. L. Williams, M. B. Hursthouse and K. M. A. Malik, *J. Chem. Soc., Chem. Commun.*, 1994, 119; (*b*) P. J. Murphy and H. L. Williams, *J. Chem. Soc., Chem. Commun.*, 1994, 819; (*c*) P. J. Murphy, H. L. Williams, M. B. Hursthouse and K. M. A. Malik, *Tetrahedron*, 1996, **52**, 8315; (*d*) G. P. Black, P. J. Murphy, N. D. A. Walshe, D. E. Hibbs, M. B. Hursthouse and K. M. A. Malik, *Tetrahedron Lett.*, 1996, **37**, 6943; (*e*) G. P. Black, P. J. Murphy and N. D. A. Walshe, *Tetrahedron*, 1998, **54**, 9481; (*f*) G. P. Black, P. J. Murphy, A. J. Thornhill, N. D. A. Walshe and C. Zanetti, *Tetrahedron*, 1999, **55**, 6547.
9 P. A. Evans, J. Qin, J. E. Robinson and B. Bazin, *Angew. Chem., Int. Ed.*, 2007, **46**, 7417.
10 J. Shimokawa, K. Shirai, A. Tanatani, Y. Hashimoto and K. Nagasawa, *Angew. Chem., Int. Ed.*, 2004, **43**, 1559.
11 (*a*) F. Cohen, L. E. Overman and S. K. Ly Sakata, *Org. Lett.*, 1999, **1**, 2169; (*b*) T. Ishiwata, T. Hino, H. Koshino, Y. Hashimoto, T. Nakata and K. Nagasawa, *Org. Lett.*, 2002, **4**, 2921; (*c*) M. A. Arnold, S. G. Durón and D. Y. Gin, *J. Am. Chem. Soc.*, 2005, **127**, 6924; (*d*) Reference 9.
12 (*a*) F. Cohen and L. E. Overman, *J. Am. Chem. Soc.*, 2001, **123**, 10782; (*b*) F. Cohen and L. E. Overman, *J. Am. Chem. Soc.*, 2006, **128**, 2594; (*c*) F. Cohen and L. E. Overman, *J. Am. Chem. Soc.*, 2006, **128**, 2604.
13 S. K. Collins, A. I. McDonald, L. E. Overman and Y. H. Rhee, *Org. Lett.*, 2004, **6**, 1253.
14 (*a*) H. Tanino, T. Nakata, T. Kaneko and Y. Kishi, *J. Am. Chem. Soc.*, 1977, **99**, 2818; (*b*) Y. Kishi, *Heterocycles*, 1980, **14**, 1477; (*c*) C. Y. Hong and Y. Kishi, *J. Am. Chem. Soc.*, 1992, **114**, 7001.
15 M. C. Elliott and M. S. Long, *Tetrahedron Lett.*, 2002, **43**, 9191; M. C. Elliott and M. S. Long, *Org. Biomol. Chem.*, 2004, **2**, 2003.
16 C. D. Davies, M. C. Elliott, J. Hill-Cousins, M. A. Khan, T. Maqbool and J. L. Wood, *Synlett*, 2008, 2028.
17 Throughout this manuscript, we are using systematic numbering based on the triaza-acenaphthylene ring system rather than the natural product numbering used in reference 1.
18 Sample of batzelladine C kindly provided by Professor Mark Hamann (University of Mississippi).
19 M. Dennis, L. M. Hall, P. J. Murphy, A. J. Thornhill, R. Nash, A. L. Winters, M. B. Hursthouse, M. E. Light and P. Horton, *Tetrahedron Lett.*, 2003, **44**, 3075.
20 M. C. Elliott and S. V. Wordingham, *Synthesis*, 2006, 1162.
21 The (*R*) enantiomer was chosen arbitrarily.
22 P. D. Bailey, K. M. Morgan, D. I. Smith and J. M. Vernon, *Tetrahedron*, 2003, **59**, 3369.
23 R. P. Polniaszek, S. E. Belmont and R. Alvarez, *J. Org. Chem.*, 1990, **55**, 215; R. P. Polniaszek and S. E. Belmont, *J. Org. Chem.*, 1990, **55**, 4688.
24 Calculations were carried out using MacSpartan 1.2.1. The conformations of compounds **28** and **29** were carried out at the PM3 semieprirical level. Calculations were carried out at the 3-21G(*) level on the simplified compounds **33** and **34**, with identical results obtained at both levels of theory.



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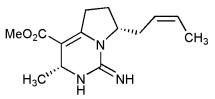

34

25 S. V. Wordingham, PhD Thesis, Cardiff University, 2006.
26 In the reported data for batzelladine C, the ^{1}H chemical shifts for H-1β and H-8β appear to have been transposed. This has been confirmed by examination of the ^{1}H-^{1}H COSY NMR spectra in reference 1. Our own data for compound **31** are identical in this region to those of the natural product.
27 J. L. Wood, PhD Thesis, Cardiff University, 2008.