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Studies towards the total synthesis of batzelladine A

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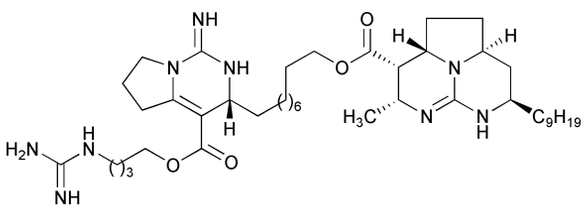
Application of a diastereoselective three-component coupling to the bicyclic core of the batzelladine alkaloids is described. The synthesis features the elaboration of glutamic acid by use of Eschenmoser sulfide contraction. An earlier approach is also included, which shows some limitations of dithiane chemistry when applied to the particular compounds required for this target.

Introduction

The batzelladine alkaloids form part of a structurally and biologically fascinating group of natural products obtained from marine sources. The first of these compounds, batzelladines A–E, were isolated in 1995 and possess a range of interesting and useful biological activity. In particular, batzelladines A (**1**) and B (**2**) inhibit the binding of HIV glycoprotein gp120 to the CD4 receptor and so are of therapeutic interest for the treatment of HIV. Batzelladines C–E, of which batzelladine D (**3**) is structurally representative, are cytotoxic.[1] Subsequent studies led to the isolation of four further alkaloids, named batzelladines F–I, each containing two of the tricyclic units found in batzelladines A–E [*e.g.* batzelladine F (**4**)].[2] These compounds possess structural similarities to a number of other alkaloids, for example, crambescin A (crambine A) (**5**)[3] and ptilomycalin A (**6**).[4]



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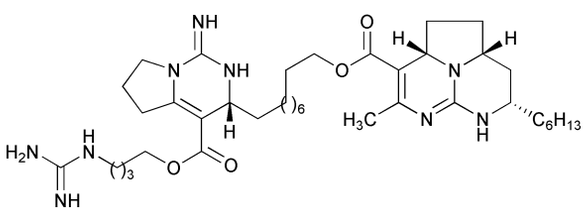

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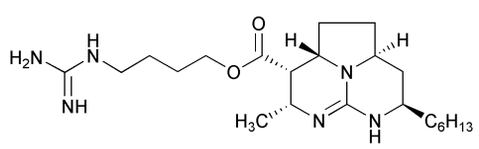
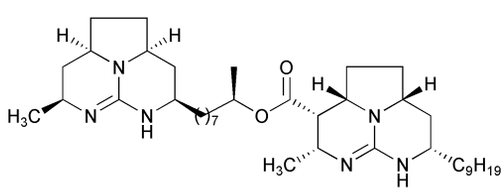
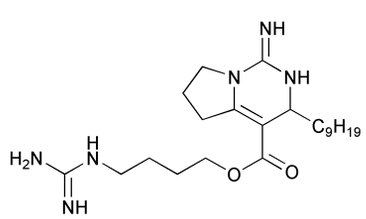


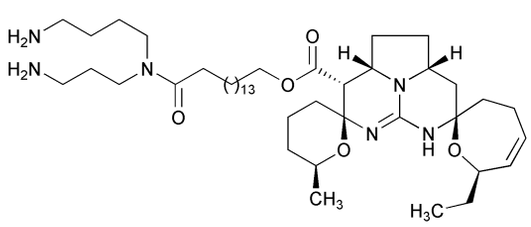
3, Batzelladine D



4, Batzelladine F



5, Crambescin A



6, Ptilomycalin A

These compounds have been the subject of numerous synthetic studies, leading to the development of a wealth of new methodology. The first approach was developed extremely quickly, and features a relatively long linear sequence in the synthesis of the tricyclic cores of batzelladines B and D.[5] Snider and Murphy's groups have independently reported (presumably) biomimetic approaches to the same tricyclic core.[6] This work has led to one total synthesis,[7] and much structural revision.[8] Overman and co-workers have developed tethered Biginelli cyclisations giving bicyclic and tricyclic guanidines,[9,10] culminating in the total syntheses of batzelladines D[11] and F,[12] and also a particularly rapid synthesis of symmetrical analogues.[13] Batzelladine D has also been synthesised by Nagasawa's group.[14] Most of the synthetic work has been directed towards the tricyclic portion of these natural products, one notable exception being a report from the group of Gin in Illinois, who have elucidated the previously unknown stereochemistry of the bicyclic portion of batzelladine A (which is presumably the same as batzelladine B).[15] Very recently, Nagasawa's group have completed the total synthesis of batzelladine A.[16]

In recent years we have developed asymmetric annulation reactions of azolines with heterocumulenes,[17] leading to a stereoselective preparation of fused pyrimidines and piperidines. For example, reaction of oxazoline **7** with phenyl isocyanate gives compound **8** in high yield and with complete diastereocontrol (Scheme 1).[18] Comparison of compound **8** with the batzelladine alkaloids shows considerable similarity in the placement of heteroatoms and stereogenic centres. Our initial disconnection is shown in Scheme 2, in which the core pyrrolo[1,2-*c*]pyrimidine **10** would be derived from a formal hetero-Diels–Alder reaction of alkenylpyrroline **9** with a suitable heterocumulene. In principle, this could then be followed by acylation with a suitable chloroformate, to give **11**.[19] Ideally, 'X' would be nitrogen, but we had previously found that the

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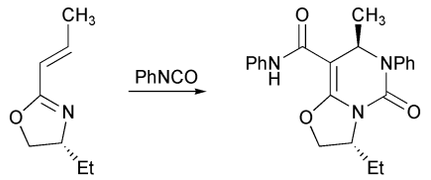
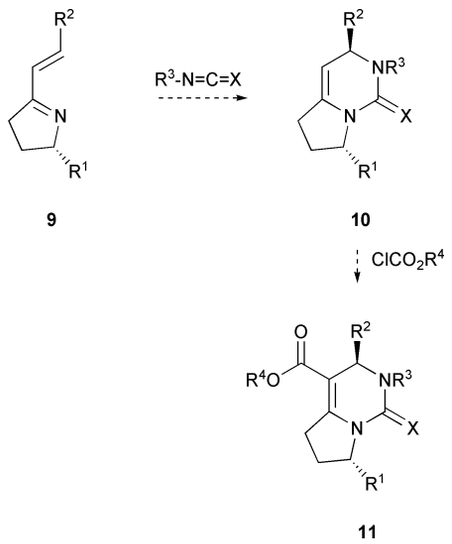


7 8

Scheme 1



9 10 11

Scheme 2

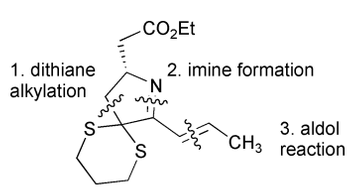
formal aza-Diels–Alder reactions with carbodiimides were sluggish, and so we chose to pursue the case where X = sulfur with a view to converting the thiourea into the corresponding guanidine.[20]

Alkenylpyrrolines are extremely rare, and would be expected to exist in equilibrium with the enamine tautomers. Since the annulation reaction which we are using proceeds in a stepwise manner, it seemed probable that either tautomer would react in a similar manner. However, the safer option was to block the pyrroline at the 3-position. Our choice of a dithiane as blocking group dictated much of our initial approach to the batzelladine alkaloids, as described in the following section.

Results and discussion

Route 1 – the dithiane approach

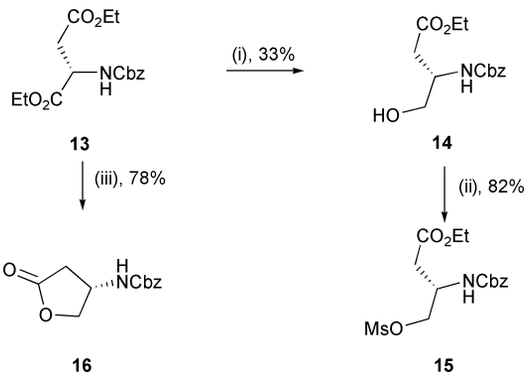
As our initial target for model studies we chose compound **12**, shown below with the relevant disconnections in their intended order of bond formation (Fig. 1). Aspartic acid was chosen as starting material since compound **12** will then contain the latent functionality to allow formation of the third ring in the tricyclic portion of the batzelladine alkaloids.



12

Fig. 1 Retrosynthetic analysis.

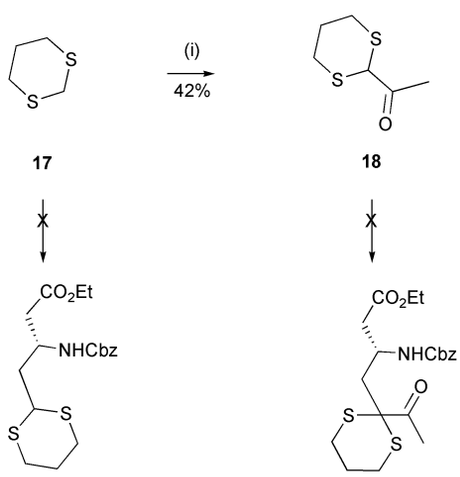
The Cbz-protected diethyl ester of aspartic acid **13** was prepared in routine manner. From this point, regioselective reduction of the α-aminoester gave alcohol **14** which was readily converted into the mesylate ester **15**. If care was not taken to avoid heating during the reduction step and subsequent work-up, variable amounts of lactone **16** were formed. This compound could be prepared as the sole product simply by heating the crude alcohol **14** (Scheme 3).



13 14 16 15

Scheme 3 *Reagents and conditions*: i, $NaBH_4$, EtOH, 0 °C, 18 h; ii, CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C, 3 h; iii, $NaBH_4$, EtOH, 0 °C, 16 h then EtOAc, reflux, 2 h.

1,3-Dithiane **17** underwent ready acylation with ethyl acetate to give **18**. Unfortunately, deprotonation (*n*-BuLi, LiHMDS, NaH) of either **17** or **18** and reaction with mesylate **15** gave none of the desired products (Scheme 4).

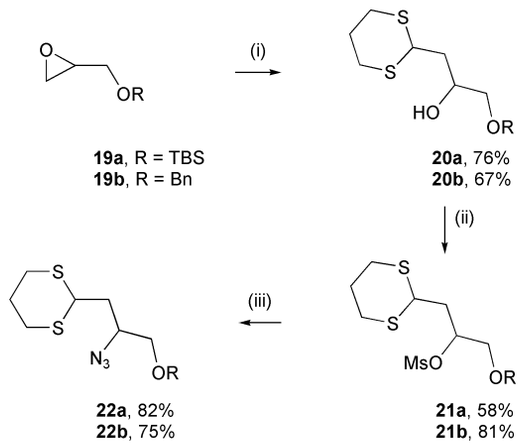


17 18

Scheme 4 *Reagents and conditions*: i, *n*-BuLi, −40 °C, 1 h then EtOAc.

This unfortunate result prompted a change to the synthetic strategy. We had originally envisaged carrying out the aldol reaction after imine formation in order to avoid competing conjugate addition (see structure **12**). As an alternative, if the imine formation was carried out by an aza-Wittig reaction, conjugate addition should not be a problem. In order to realise this scenario, we required a suitable azide which was to be prepared by standard displacement of a mesylate. Ring-opening of glycidol TBS ether **19a** with the anion derived from deprotonation of 1,3-dithiane **17** gave alcohol **20a**. Activation of this secondary alcohol as the mesylate **21a** was followed by displacement with azide to give **22a** (Scheme 5).

Deprotonation of **22a** and reaction with crotonaldehyde gave a somewhat confusing result. Although there was some indication that the required allylic alcohol had been introduced, we were concerned by the lack of azide functionality in the IR spectrum, and also by the clear loss of the TBS protecting group in the proton NMR spectrum. Given the loss of protecting group, the most obvious course of action was to repeat this sequence with an alternative protecting group. This was accomplished starting with benzyl glycidyl ether **19b** (also shown in Scheme 5).

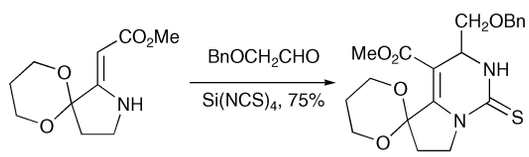


Scheme 5 *Reagents and conditions*: i, 1,3-dithiane, *n*-BuLi, THF −40 °C then **19a** or **19b**, −40 °C, 2 h; ii, CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C, 3 h; iii, NaN_3, DMSO, sealed tube, 80 °C, 72 h.

Unfortunately, once again, deprotonation of **22b** and reaction with crotonaldehyde gave a complex mixture of the products, and we were unable to obtain any evidence that the desired compound had been formed.

Route 2 – three-component coupling[21]

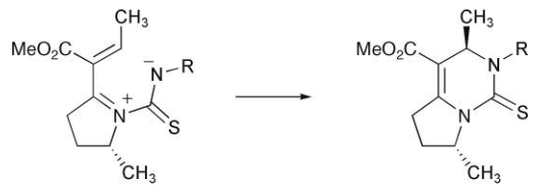
Since the initial route presented us with problems, and the solutions which we considered would render it long-winded, we decided on a substantially modified approach which should still retain the advantages of a formal aza-Diels–Alder reaction. For this purpose, we chose to investigate a diastereoselective version of a reaction used by Kishi and co-workers for the synthesis of saxitoxin.[22] The key step was the three-component coupling of an alkylidenepyrrolidine, an aldehyde and an isothiocyanate to give the key pyrrolo[1,2-*c*]pyrimidine (Scheme 6).

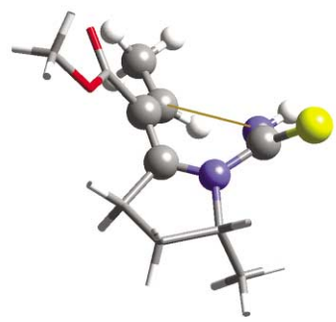


Scheme 6

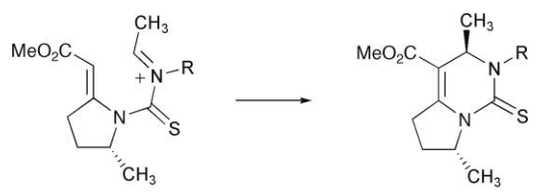
Although the reaction shown features a 1,3-dioxane which functions as a blocking group, subsequent work by Kishi and Hong showed that this is not actually necessary, and in fact diastereoselective annulations were reported using chiral aldehydes.[23] There are two distinct mechanistic possibilities for the final ring-closure step. The first possibility is directly analogous to the ring-closure step in the formal aza-Diels–Alder reaction of alkenylazolines with isocyanates, and would be expected to lead to high diastereoselectivity *via* a transition state shown in Scheme 7.[24] The alternative should also give the same major diastereoisomer, this time *via* the transition state shown in Scheme 8. As in our previous work, the stereochemical outcome is guided by the heterocumulene heteroatom (in this case sulfur) avoiding close contact with the substituent on the azoline ring.

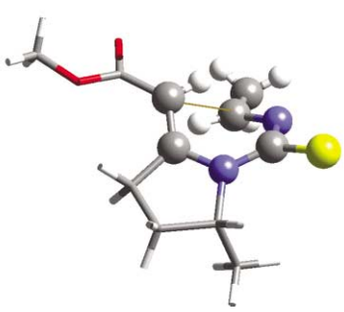
With this in mind, the synthetic strategy simply involved preparation of a suitable alkylidenepyrrolidine and its evaluation in the three-component coupling reaction described above. Our approach begins with ethyl (*S*)-pyroglutamate **23**. Thionation with Lawesson's reagent was followed by Eschenmoser sulfide contraction with **25** to give **26** in good overall yield.[25] Compound **26** was formed as a single double bond isomer, assumed to be that shown,[26] although we were unable to observe any diagnostic NOE enhancements which would confirm this assignment. Chemoselective reduction of the aliphatic ester was followed by protection and de-acylation





Scheme 7



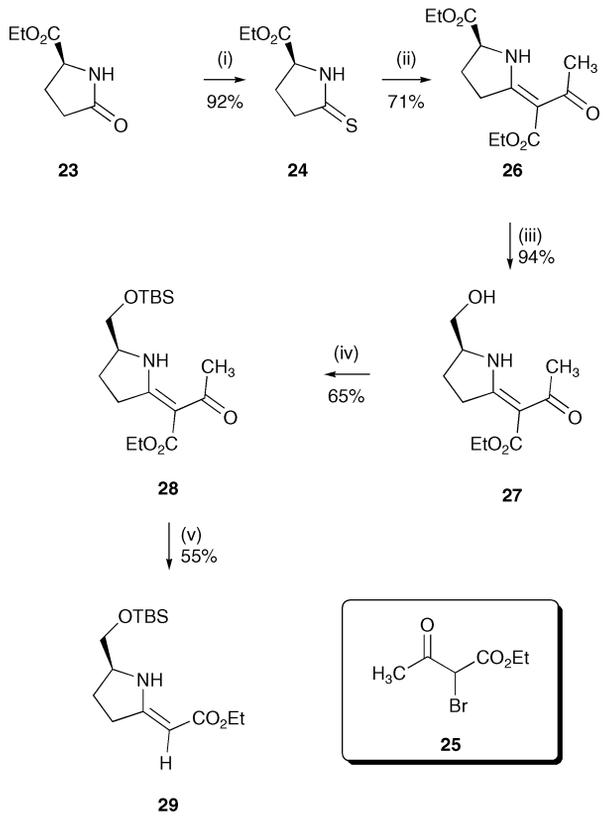


Scheme 8

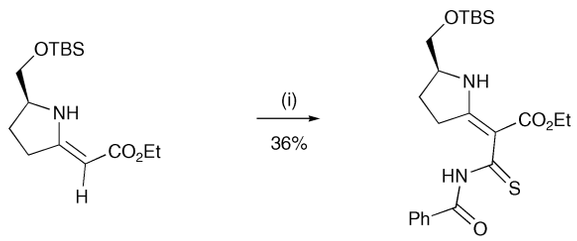
giving the annulation precursor **29**, the double bond geometry of which was confirmed by NOE studies (Scheme 9).

The key annulation was initially attempted with benzoyl isothiocyanate and acetaldehyde. However, instead of the desired compound, **30** was formed in low yield as a single double bond isomer. The same compound can be formed in higher yield if the acetaldehyde is omitted (Scheme 10).

This contrasts with an earlier report in which *N*-acylation is observed with similar substrates,[27] although on inspection of the spectroscopic data, we have some concerns about the structural assignments in this work. For instance, for compound **31** the chemical shift of the alkene hydrogen was reported as 7.6 ppm, while that in compound **32** is reported as 6.5 ppm. Additionally, these compounds give peaks assigned to N–H hydrogens at 7.3 and 5.4 ppm respectively. In comparison, the alkene hydrogen in compound **29** resonates at 4.5 ppm. Comparison with other examples in the literature shows that for compound **32** the reported shift is typical, whereas that in **31** seems to us to be too high.[28] The differing reaction conditions for the formation of the two compounds should also be considered. Compound **31** was formed under reflux (benzene) whereas **32** was formed at room temperature. It is reasonable to expect *C*-acylation in the former case and possibly *N*-acylation in the latter.[17] Closer examination of the data lead us to suggest that the compound assigned structure **31** is most probably **33**, with the peaks at 7.3 and 7.6 ppm both being due to N–*H* resonances. Unfortunately the ^{13}C-NMR data, and also



Scheme 9 *Reagents and conditions*: i, Lawesson's reagent, toluene, reflux, 1 h; ii, ethyl 2-bromoacetoacetate **25**, CH_2Cl_2, $NaHCO_3$, reflux, 16 h; iii, $NaBH_4$, THF, reflux, 1 h; iv, TBSCl, imidazole, THF, 72 h; v, NaOEt, EtOH, reflux, 2 h.

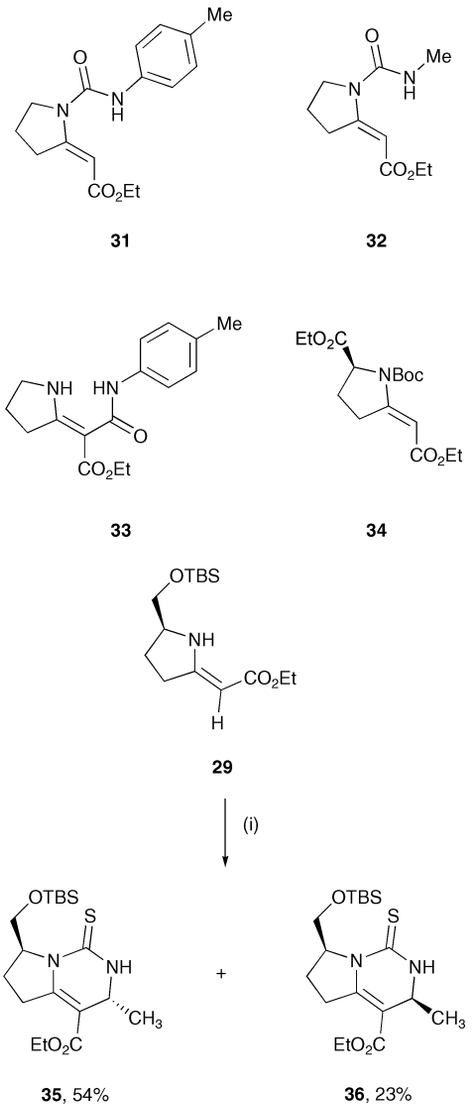


Scheme 10 *Reagents and conditions*: i, PhCONCS, benzene, 2 h.

deuterium exchange ^{1}H-NMR data, which would have allowed unambiguous assignment of structures, were not presented in the original report. In the case of compound **32** the assigned structure should be assumed to be correct. We have recently prepared compound **34**, and it shows a surprisingly broad peak (which is more consistent in appearance with an NH proton) for the alkene hydrogen at 6.45 ppm.[29] The double bond geometry in this compound is presently unknown, and may indeed affect the chemical shifts.

The conditions of Kishi were used next, leading to the high-yielding formation of a mixture of diastereoisomers **35** and **36** in a 2.3:1 ratio (Scheme 11). These isomers were readily separated by flash column chromatography and subjected to extensive NOE NMR studies. The minor isomer **36** shows a 1% NOE as shown in Fig. 2. While this is small, there are no diagnostic enhancements shown by the major isomer **35**, so that on the basis of this, and precedent from our previous work on alkenyloxazolines and alkenylthiazolines,[24] we tentatively assign the stereochemistry of the two isomers as shown.

Based on our previous work we might expect the formation of isomer **35** exclusively under these conditions, since any isomerisation of **35** into **36** would require elevated temperatures. However, this presumes a reaction proceeding *via* an



Scheme 11 *Reagents and conditions*: i, $Si(NCS)_4$, CH_3CHO, benzene, 3 h.

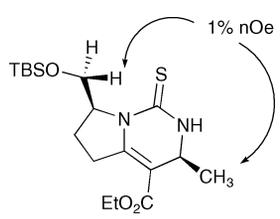
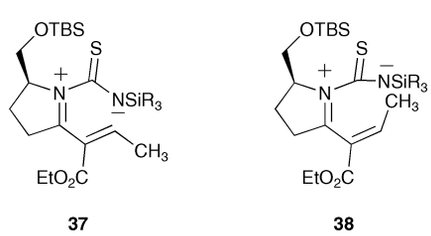


Fig. 2 NOE enchancement for compound **36**.

intermediate related to that shown in Scheme 7. If the intermediate resembles that shown in Scheme 8, as originally proposed by Kishi, the same major isomer would be expected (*vide supra*), although clearly the extent of selectivity would be difficult to predict. There is, however, another distinct possibility for the lower diastereoselectivity. While a *Z* double bond as in **37** would be expected to lead to isomer **35**, the *E* double bond isomer **38** would give, *via* a similar transition state, the isomer **36**.



Finally, conversion of the thiourea into the required guanidine was accomplished as shown in Scheme 12. Serendipitously, the silyl protecting group was removed under these conditions, presumably as a result of anchimeric assistance by the neighbouring guanidine. The product **39** was isolated as the formate salt after chromatography on silica gel, eluting with CH_2Cl_2/MeOH/H_2O/formic acid (85:14:0.5:0.5).[1,15]

35 **39**

Scheme 12 *Reagents and conditions*: i, CH_3I, MeOH, reflux, 1 h then NH_4OAc, NH_3, sealed tube, 80 °C, 48 h.

Conclusion

In summary, we have developed the three-component coupling used by Kishi to prepare a bicyclic guanidine related to the left-hand side of batzelladine A. This compound contains the latent functionality for elaboration to give the tricyclic portion of these natural products. The fully functionalised left-hand side of batzelladine A will require removal of the hydroxymethyl directing group, which we envisage being accomplished by oxidation to the aldehyde and deformylation.[30] This approach, and others, are currently under investigation and will be reported in due course.

Experimental section

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. High-resolution mass spectra were performed at the EPSRC centre for Mass Spectroscopy in Swansea. 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. All chemical shifts are reported in ppm downfield from TMS. Coupling constants (*J*) are reported in Hz. Multiplicity in ^{1}H-NMR 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 was obtained using the DEPT pulse sequence. Flash chromatography was performed using Matrex Silica 60 35–70 micron.

Diethyl *N*-benzyloxycarbonyl-(*S*)-aspartate (13)

Thionyl chloride (22 g, 282 mmol) was added to absolute ethanol (200 ml) at 0 °C and stirred for 30 min. (*S*)-Aspartic acid (21 g, 158 mmol) was added and the mixture heated under reflux for 16 h. The solvent was removed *in vacuo* and the green oil remaining was dissolved in saturated sodium carbonate solution (200 ml) and cooled to 0 °C. Benzyl chloroformate (28 g, 157 mmol) was added and the mixture stirred at rt for 2 h. The reaction mixture was neutralised with 5 M HCl then extracted with ethyl acetate (5 × 100 ml). The organic portions were dried over $MgSO_4$ and concentrated *in vacuo*. The residual aromatic by-products were removed by vacuum distillation to give a yellow oil, which solidified on standing to give a white solid, recrystallisation of which from ethyl acetate/hexane gave the title compound (48 g, 95%) as a white crystalline solid, mp 63–66 °C (lit.[31] mp 64–66 °C); ν_{max} (neat)/cm^{-1} 1738, 1735 and 1693; δ_H (400 MHz; $CDCl_3$) 7.25 (5H, m, aromatic C*H*), 5.70 (1H, d, *J* 8.3, N*H*), 5.05 (2H, s, PhCH_2O), 4.50 (1H, m, C*H*N), 4.15 (2H, q, *J* 7.1, CH_2O), 4.05 (2H, q, *J* 7.1, CH_2O), 2.95 (1H, dd, *J* 17.0 and 4.6, one of CH_2C=O), 2.75 (1H, dd, *J* 17.0 and 4.6, one of CH_2C=O) and 1.15 (6H, m, 2 × CH_3); δ_C (100 MHz; $CDCl_3$), 171.1 and 171.0 (ester *C*=O), 156.3 (carbamate *C*=O), 136.6 (aromatic *C*), 129.0, 128.6 and 128.5 (aromatic *C*H), 67.5 (Ph–*C*H_2O), 62.3 (O*C*H_2), 61.5 (O*C*H_2), 50.8 (*C*HN), 37.2 (*C*H_2C=O), 14.5 and 14.4 (both OCH$_2$*C*H_3); *m*/*z* (APCI) 324 (MH$^+$, 100%).

Ethyl (3*S*)-3-[(benzyloxycarbonyl)amino]-4-hydroxybutanoate (14)

Diethyl *N*-benzyloxycarbonyl-(*S*)-aspartate **13** (2.0 g, 6.2 mmol) was dissolved in absolute ethanol (20 ml) and cooled to 0 °C. Sodium borohydride (344 mg, 9.5 mmol) was added in portions and the mixture stirred at 0 °C for 18 h. Ethyl acetate (50 ml) was added and the organic layer was separated, washed with brine (5 × 20 ml) and dried over $MgSO_4$. The solvent was removed *in vacuo* to give a pale oil which was purified by column chromatography (eluting with chloroform/ethyl acetate 1:1), late fractions yielding the title compound (575 mg, 33%) as a clear oil which solidified on standing, mp 43–45 °C (lit.[31] mp 44–46 °C); ν_{max} (nujol)/cm^{-1} 3233, 1730 and 1683; δ_H (400 MHz; $CDCl_3$) 7.32–7.11 (5H, m, aromatic C*H*), 5.46 (1H, d, *J* 7.8, N*H*), 5.26 (2H, s, PhCH_2O), 4.16 (2H, q, *J* 7.1, OCH_2), 4.08 (1H, m, C*H*N), 3.67 (2H, m, CH_2OH), 2.56 (2H, m, CH_2CO$_2$Et) and 1.25 (3H, t, *J* 7.1, CH$_2$CH_3); δ_C (100 MHz; $CDCl_3$) 170.7 (ester *C*=O), 156.4 (carbamate *C*=O), 135.2 (aromatic *C*), 127.5, 127.2 and 127.1 (all aromatic *C*H), 65.9 (Ph*C*H_2O), 63.3 (O*C*H_2), 59.9 (*C*H_2OH), 48.7 (*C*HN), 34.9 (*C*H_2CO$_2$Et) and 13.1 (*C*H_3).

Ethyl (3*S*)-3-[(benzyloxycarbonyl)amino]-4-(methylsulfonyloxy)butanoate (15)

Ethyl (3*S*)-3-[(benzyloxycarbonyl)amino]-4-hydroxybutanoate **14** (230 mg, 0.85 mmol) was dissolved in dry CH_2Cl_2 (8 ml) and cooled to 0 °C. Triethylamine (100 mg, 0.1 mmol) was added and the mixture stirred for 10 min. Methanesulfonyl chloride (77 mg, 0.87 mmol) was added and stirring continued at 0 °C for 3 h. Having been washed with brine (20 ml) and dried over $MgSO_4$, the solvent was removed *in vacuo* to give the title compound (250 mg, 82%) as a white solid, mp 50–52 °C; ν_{max} (nujol)/cm^{-1} 3319, 1730, 1683 and 1158; δ_H (400 MHz; $CDCl_3$) 7.32–7.11 (5H, m, aromatic C*H*), 5.39 (1H, br-s, N*H*), 5.04 (2H, s, OCH_2Ph) 4.28 (3H, m, CH_2OMs and C*H*N), 4.15 (2H, q, *J* 7.1, OCH_2), 2.92 (3H, s, CH_3SO$_2$), 2.60 (2H, m, CH_2CO$_2$Et) and 1.21 (3H, t, *J* 7.1, OCH$_2$CH_3); δ_C (100 MHz; $CDCl_3$) 171.0 (ester *C*=O), 156.0 (carbamate *C*=O), 136.5 (aromatic *C*), 129.0, 128.7 and 128.6 (all aromatic *C*H), 70.0 (*C*H_2OMs), 67.5 (PhCH_2O), 61.6 (O*C*H_2), 52.9 (C*H*–N), 37.7 (*C*H_3S), 35.5 (*C*H_2CO$_2$Et) and 14.5 (OCH$_2$*C*H_3); *m*/*z* (APCI) 360.3 (MH$^+$, 70%), 174.3 (50) and 91.1 (100).

(4*S*)-4-[(Benzyloxycarbonyl)amino]-3,4-dihydro-5*H*-furan-2-one (16)

Diethyl *N*-benzyloxycarbonyl-(*S*)-aspartate **13** (9.6 g, 29.7 mmol) was dissolved in absolute ethanol. Sodium borohydride (1.6 g, 43.2 mmol) was added in portions and the mixture stirred at 0 °C for 16 h. 5 M HCl (20 ml) was added slowly followed by ethyl acetate (30 ml). The organic layer was separated, washed with brine (5 × 20ml) and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the yellow oil remaining dissolved in ethyl acetate and heated under reflux for 2 h. The solution remaining was concentrated *in vacuo* to give a white solid, recrystallisation (ethyl acetate/chloroform/hexane) of which yielded the title compound (5.46 g, 78%) as colourless crystals, mp 100–104 °C (lit.[32] mp 101–103 °C); ν_{max} (nujol)/cm^{-1} 1778 and 1693; δ_H (400 MHz; $CDCl_3$) 7.31–7.10 (5H, m, aromatic C*H*), 5.10 (1H, br-s, N*H*), 5.04 (2H, s, PhCH_2O),

4.55–4.43 (2H, m, CH_2O), 4.17 (1H, m, CHN), 2.78 (1H, dd, J 17.8 and 7.3, CH_2C=O) and 2.40 (1H, dd, J 17.8 and 3.0, one of CH_2C=O); δ_C (100 MHz; $CDCl_3$) 176.0 (lactone C=O), 156.3 (carbamate C=O), 136.4 (aromatic C), 129.0, 128.8 and 128.6 (aromatic CH), 74.1 (OCH$_2$), 67.6 (PhCH_2O), 48.4 (CHN) and 35.1 (CH$_2$C=O); m/z (APCI) 236 (MH^+, 10%) and 91 (100).

1-(1,3-Dithian-2-yl)-1-ethanone (18) [33]

1,3-Dithiane **17** (3 g, 27 mmol) was dissolved in dry THF (50 ml) and cooled to −40 °C under N_2. *n*-Butyllithium (14 ml of a 2.5 M solution in hexanes, 35.1 mmol) was added and the miture stirred at −40 °C under N_2 for 1 h. Dry ethyl acetate (5.16 ml, 54 mmol) was added and the reaction mixture stirred at −40 °C for 1 h, and allowed to warm to rt. Saturated ammonium chloride solution (30 ml) and diethyl ether (30 ml) were added. The organic layer was separated, washed with brine (20 ml) dried over $MgSO_4$, and concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography (eluting with diethyl ether/petroleum ether 1:4), late fractions yielding the title compound (2.0 g, 42%) as a clear oil; ν_{max} (neat)/cm^{-1} 1708, 1422 and 1358; δ_H (400 MHz; $CDCl_3$) 4.16 (1H, s, SCHS), 3.20 (2H, m, CH_2S), 2.55 (2H, m, CH_2S), 2.24 (3H, s, CH_3C=O) and 2.02–1.89 (2H, m, CH_2CH$_2$S); δ_C (100 MHz; $CDCl_3$) 201.2 (C=O), 49.1 (SCHS), 28.0 (CH$_2$S), 27.0 (CH$_3$C=O) and 26.7 (CH$_2$CH$_2$S).

2-Hydroxy-3-(1,3-dithian-2-yl)propyl *tert*-butyl(dimethyl)silyl ether (20a) [34]

1,3-Dithiane **17** (4.26 g, 34.6 mmol) was dissolved in dry THF (40 ml), cooled to −40 °C, and stirred under N_2 for 1 h. *n*-Butyllithium (17.2 ml of a 2.5 M solution in hexane, 43 mmol) was added and the mixture stirred for 1 h at −40 °C. *tert*-Butyldimethylsilyloxy-2,3-epoxypropane **19a** [35] (6.5 g, 33 mmol) in dry THF (5 ml) was added with stirring under N_2. The mixture was stirred at −40 °C for 2 h and allowed to warm to rt. Water (15 ml) and diethyl ether (20 ml) were added and the organic layer separated, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to yield the title compound (7.7 g, 76%) as a clear oil; δ_H (400 MHz; $CDCl_3$) 4.22 (1H, dd, J 9.7 and 4.8, SCHS), 3.95 (1H, m, CHOH), 3.55 (1H, dd, J 9.7 and 3.7, one of CH_2OSi), 3.35 (1H, J 9.7 and 6.4, one of CH_2OSi), 2.90–2.75 (4H, m, 2 × CH_2S), 2.00 (1H, m, one of CH_2CHOH), 1.90–1.70 (3H, m, CH_2CH$_2$S and one of CH_2CHOH), 0.82 [9H, s, (CH_3)$_3$Si] and −0.02 [6H, s, (CH_3)$_2$Si].

2-Methanesulfonyloxy-3-(1,3-dithian-2-yl)propyl *tert*-butyl-(dimethyl)silyl ether (21a)

2-Hydroxy-3-(1,3-dithian-2-yl)propyl *tert*-butyl(dimethyl)silyl ether **20a** (4.6 g, 15 mmol) was dissolved in dry CH_2Cl_2 (20 ml) and cooled to 0 °C. Triethylamine (2.16 ml, 16.5 mmol) and methanesulfonyl chloride (1.28 ml, 16.5 mmol) were added and the reaction mixture was stirred at 0 °C for 3 h. Water (40 ml) was added and the organic layer was separated, washed with brine (20ml), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting brown oil was purified by column chromatography (eluting with CH_2Cl_2), early fractions yielding the title compound (3.4 g, 58%) as a yellow oil; ν_{max} (neat)/cm^{-1} 2930, 1360 and 1173; δ_H (400 MHz; $CDCl_3$) 4.83 (1H, m, CHOMs), 4.04 (1H, dd, J 9.3 and 5.3, SCHS), 3.71 (1H, dd, J 11.0 and 5.3, one of CH_2OSi), 3.65 (1H, dd, J 11.0 and 4.6, one of CH_2OSi), 3.05 (3H, s, CH_3SO$_2$), 2.89–2.70 (4H, m, 2 × CH_2S), 2.18–2.02 (3H, m, CH_2CHOMs, and one of CH_2CH$_2$S), 1.81–1.66 (1H, m, one of CH_2CH$_2$S), 0.80 [9H, s, (CH_3)$_3$CSi] and 0.02 [6H, s, 2 × (CH_3)$_2$Si]; δ_C (100 MHz; $CDCl_3$) 80.3 (CHOMs), 65.2 (CH_2OSi), 53.6 (CH_3S), 43.2 (SCHS), 37.4 (CH$_2$CHOMs), 30.4 and 30.0 (CH$_2$S), 26.2 [(CH$_3$)$_3$CSi], 26.0 (CH$_2$CH$_2$S) and 18.5 [(CH$_3$)$_3$$C$Si] and −4.6 [($CH_3$)$_2$Si].

2-Azido-3-(1,3-dithian-2-yl)propyl *tert*-butyl(dimethyl)silyl ether (22a)

2-Methanesulfonyloxy-3-(1,3-dithian-2-yl)propyl *tert*-butyl-(dimethyl)silyl ether **21a** (1 g, 2.6 mmol) was dissolved in dry DMSO (5 ml). Sodium azide (400 mg, 6.1 mmol) was added and the mixture heated in a sealed tube at 80 °C for 72 h. Dichloromethane (20 ml) and water (20 ml) were added, the organic layer was separated, washed with brine (10ml) and water (10ml), dried over $MgSO_4$, and concentrated *in vacuo*. The brown oil remaining was purified by column chromatography (eluting with CH_2Cl_2), early fractions providing the title compound (760 mg, 82%) as a yellow oil (Found: MNH_4^+, 351.1696. $C_{13}H_{31}N_4OS_2Si$ requires M, 351.1709); ν_{max} (neat)/cm^{-1} 2928, 2125, 1253 and 1113; δ_H (400 MHz; $CDCl_3$) 4.09 (1H, dd, J 9.2 and 5.4, SCHS), 3.67 (2H, m, one of CH_2OSi and CHN$_3$), 3.56 (1H, dd, J 11.3 and 3.5, one of CH_2OSi), 2.95–2.75 (4H, m, 2 × CH_2S), 2.15 (1H, m, one of CH_2CHN$_3$), 1.85–1.68 (3H, m, one of CH_2CHN$_3$ and CH_2CH$_2$S), 0.80 [9H, s, (CH_3)$_3$CSi], 0.00 (3H, s, CH_3Si) and −0.03 (3H, s, CH_3Si); δ_C (100 MHz; $CDCl_3$) 65.4 (CH_2OSi), 59.8 (CHN$_3$), 42.9 (SCHS), 35.3 (CH_2CHN$_3$), 29.3 (one of CH_2S), 28.9 (one of CH_2S), 26.3 [(CH_3)$_3$CSi], 26.2 (CH_2CH$_2$S), 18.3 [(CH$_3$)$_3$$C$Si] and 0.0 [(C$H_3$)$_2$Si]; m/z (CI) 351 (MNH_4^+, 20%), 308 (79), 133 (100) and 119 (54).

2-Hydroxy-3-(1,3-dithian-2-yl)propyl benzyl ether (20b) [36]

1,3-Dithiane **17** (1.48 g, 12 mmol) was dissolved in dry THF (30 ml) and cooled to −40 °C. *n*-Butyllithium (6.4 ml of a 2.5 M solution in hexane, 16 mmol) was added and the mixture stirred under N_2 for 1 h. Benzyl glycidyl ether **19b** [37] (2 g, 12 mmol) was added and the reaction mixture stirred for 1 h at −40 °C, then allowed to warm to rt over 1 h. The solution was quenched with saturated ammonium chloride solution (20 ml). Diethyl ether (20 ml) was added and the organic layer was separated, washed with brine (20 ml), dried over $MgSO_4$, and concentrated *in vacuo*. The yellow oil resulting was dissolved in CH_2Cl_2 and filtered through a pad of silica. The filtrate was concentrated *in vacuo* to give the title compound (2.3 g, 67%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3434, 2899 and 1115; δ_H (400 MHz; $CDCl_3$) 7.32–7.11 (5H, m, aromatic CH), 4.46 (1H, d, J 11.8, OCH_2Ph), 4.42 (1H, d, J 11.8, OCH_2Ph), 4.24 (1H, dd, J 9.6 and 4.9, SCHS), 4.04 (1H, m, CHOH), 3.55 (1H, dd, J 10.0 and 3.8, one of CH_2OBn), 3.30 (1H, dd, J 10.0 and 6.6, one of CH_2OBn), 2.89–2.72 (4H, m, 2 × CH_2S), 2.05 (1H, m, one of CH_2CHOH) and 1.93–1.73 (3H, m, CH_2CH$_2$S and one of CH_2CHOH); δ_C (100 MHz; $CDCl_3$) 138.2 (aromatic C), 128.9, 128.3 and 128.2 (aromatic CH), 74.4 (PhCH_2O), 73.8 (CH_2OBn), 67.6 (CHOH), 44.1 (SCHS), 39.3 (CH_2CHOH), 30.8 and 30.4 (CH_2S) and 26.3 (CH_2CH$_2$S); m/z (APCI) 285 (MH^+, 100%), 177 (100) and 87 (75).

2-Methanesulfonyloxy-3-(1,3-dithian-2-yl)propyl benzyl ether (21b)

2-Hydroxy-3-(1,3-dithian-2-yl)propyl benzyl ether **20b** (1.56 g, 5.3 mmol) was dissolved in dry CH_2Cl_2 (20 ml). Triethylamine (0.76 ml, 5.3 mmol) was added and the mixture stirred at 0 °C for 10 min. Methanesulfonyl chloride (0.43 ml, 4.3 mmol) was then added and the mixture stirred for 0 °C for 3 h. Water (10 ml) was added and the organic layer was separated, washed with brine (20ml), dried over $MgSO_4$ and concentrated *in vacuo*. The brown oil resulting was purified by column chromatography (eluting with CH_2Cl_2), early fractions yielding the title compound (1.55 g, 81%) as a clear oil (Found: MH^+, 363.5416. $C_{15}H_{23}O_4S_3$ requires M, 363.5413); ν_{max} (neat)/cm^{-1} 2819, 1354 and 1172; δ_C (400 MHz; $CDCl_3$) 7.32–7.11 (5H, m, aromatic CH), 5.03 (1H, m, CHOMs), 4.50 (1H, d, J 11.9, one of PhCH_2O), 4.47 (1H, d, J 11.9, one of PhCH_2O), 4.03 (1H, dd, J 10.4 and 4.9, SCHS), 3.47 (2H, m, CH_2OBn), 2.98 (3H, s,

CH_3SO_2), 2.80 (4H, m, 2 × CH_2S), 2.22–2.10 (1H, ddd, *J* 14.2, 8.3 and 4.9, one of CH_2CHOMs), 2.00 (2H, m, one of CH_2-CHOMs and one of CH_2CH_2S) and 1.90 (1H, m, CH_2CH_2S); δ_C (100 MHz; $CDCl_3$) 135.8 (aromatic *C*), 127.1, 126.5 and 126.4 (aromatic *C*H), 76.9 (*C*HOMs), 71.9 (Ph*C*H_2O), 69.8 (*C*H_2OBn), 41.1 (S*C*HS), 37.2 (*C*H_3SO_2), 35.8 (*C*H_2CHOMs), 28.5 and 28.2 (*C*H_2S) and 24.2 (*C*H_2CH_2S); *m*/*z* (APCI) 363 (MH^+, 100%) and 69 (70).

2-Azido-3-(1,3-dithian-2-yl)propyl benzyl ether (22b)

2-Methanesulfonyloxy-3-(1,3-dithian-2-yl)propyl benzyl ether **21b** (500 mg, 1.38 mmol) was dissolved in DMSO (3 ml). Sodium azide (449 mg, 7.0 mmol) was added and the solution heated in a sealed tube at 80 °C for 72 h. Water (10 ml) and CH_2Cl_2 (10 ml) were added and the organic layer was separated, washed with water (5 × 10ml), dried over $MgSO_4$, and concentrated *in vacuo*. The brown oil resulting was purified by column chromatography (eluting with CH_2Cl_2) early fractions yielding the title compound (310 mg, 75%) as a clear oil (Found: MH^+, 310.1048. $C_{14}H_{20}N_3OS_3$ requires M, 310.1052); ν_{max} (neat)/cm^{-1} 2901, 2101, 1257 and 1112; δ_H (400 MHz; $CDCl_3$) 7.32–7.10 (5H, m, aromatic C*H*), 4.53 (1H, d, *J* 12.0, one of PhCH_2O), 4.49 (1H, d, *J* 12.0, one of PhCH_2O), 4.09 (1H, dd, *J* 7.9 and 6.4, SC*H*S), 3.86 (1H, m, C*H*N_3), 3.55 (1H, dd, *J* 10.0 and 3.9, one of CH_2OBn), 3.45 (1H, dd, *J* 10.0 and 7.0, one of CH_2OBn), 2.92–2.71 (4H, m, 2 × CH_2S), 2.10 (1H, m one of CH_2CH_2S) and 1.92–1.78 (3H, m, one of CH_2CH_2S and CH_2CHN_3); δ_C (100 MHz; $CDCl_3$) 138.0 (aromatic *C*), 128.9, 128.2 and 128.0 (aromatic *C*H), 73.7 (Ph*C*H_2O), 73.0 (*C*H_2OBn), 58.7 (S*C*HS), 44.2 (*C*HN_3), 36.9 (*C*H_2CHN_3), 30.7 and 30.3 (2 × *C*H_2S) and 26.2 (*C*H_2CH_2S); *m*/*z* (APCI) 310 (MH^+, 100%).

Ethyl (*S*)-pyroglutamate (23)

(*S*)-Glutamic acid (10 g, 68 mmol) was dissolved in absolute ethanol (100 ml), and cooled to 0 °C. Thionyl chloride (10 ml, 136 mmol) was added dropwise, the mixture stirred for 30 min at rt, and heated under reflux for 90 min. The clear solution resulting was concentrated *in vacuo* to give a thick oil, which was heated under aspirator vacuum at 130 °C for 1 h. The viscous oil remaining solidified on standing to give a waxy white solid which was distilled twice under reduced pressure (Kugelrohr oven temp. 180 °C, 0.1 torr) to give the title compound (7.0 g, 75%) as a clear oil that solidified on standing, mp 49–50 °C (lit.[38] mp 50–51 °C); ν_{max} (neat)/cm^{-1} 1735 and 1634; δ_H (400 MHz; $CDCl_3$) 6.80 (1H, br-s, N*H*), 4.25 (3H, m, CH_2O and C*H*N), 2.56–2.34 (3H, m, CH_2CO, and one of CH_2), 2.28–2.19 (1H, m, one of CH_2) and 1.25 (3H, t, *J* 7.1, OCH_2CH_3); δ_C (100 MHz; $CDCl_3$), 178.6 (ester *C*=O), 172.4 (lactam *C*=O), 62.1 (*C*H_2–O), 55.9 (*C*H-N), 29.7 (*C*H_2–CO), 25.6 (*C*H_2) and 14.5 (*C*H_3); *m*/*z* (APCI) 158 (MH^+, 100%).

Ethyl (2*S*)-5-thioxo-3,4-dihydro-5*H*-pyrrole-2-carboxylate (24)

Ethyl (*S*)-pyroglutamate **23** (1.14 g, 7.3 mmol) was dissolved in dry toluene (15 ml). To the stirred solution, Lawesson's reagent (1.6 g, 4.0 mmol) was added in one portion and the mixture heated under reflux under N_2 for 1 h. The dark mixture resulting was concentrated under reduced pressure to give a dark residue which was purified by column chromatography (eluting with hexane/ethyl acetate 5:1), late fractions affording the title compound (1.15g, 92%) as a yellow oil that crystallised on standing, mp 67–69 °C (lit.[26] mp 67–68 °C); ν_{max} (neat)/cm^{-1} 3307, 2980, 1737, 1505 and 1212; δ_H (400 MHz; $CDCl_3$) 7.85 (1H br-s, N*H*), 4.45 (1H, dd, *J* 8.5 and 6.5, C*H*N), 4.15 (2H, q, *J* 7.1, OCH_2), 2.99–2.82 (2H, m, CH_2C=S), 2.58–2.45 (1H, m, one of CH_2CHN), 2.35–2.20 (1H, m, one of CH_2CHN) and 1.25 (3H, t, *J* 7.1, CH_3); δ_C (100 MHz; $CDCl_3$) 207.4 (*C*=S), 170.6 (*C*=O), 63.1 (*C*HN), 62.5 (O*C*H_2), 43.1 (*C*H_2C=S), 27.4 (*C*H_2CHN) and 14.5 (*C*H_3).

Ethyl 2-bromoacetoacetate (25)[39]

Ethyl acetoacetate (15 g, 0.11 mol) was dissolved in dry acetone and cooled to 0 °C under N_2. *N*-Bromosuccinimide (20 g, 0.11 mol) was added and the yellow solution stirred for 1 h. After filtration, the mixture was concentrated *in vacuo* to give a white residue which was washed with hexane (5 × 30 ml). The combined hexane washings were washed with water (30 ml) and dried over $MgSO_4$. Concentration *in vacuo* gave the title compound (15.9 g, 69%) a clear oil which was used without further purification; ν_{max} (neat)/cm^{-1} 1728; δ_H (400 MHz; $CDCl_3$) 4.81 (1H, s, C*H*Br), 4.23 (2H, q, *J* 7.1, OCH_2), 2.42 (3H, s, CH_3C=O) and 1.26 (3H, t, *J* 7.1, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 191.0 (ketone *C*=O), 174.4 (ester *C*=O), 63.9 (O*C*H_2), 49.6 (*C*HBr), 26.8 (*C*H_3C=O) and 14.2 (OCH_2CH_3).

Ethyl (2*S*)-5-[(*E*)-1-(ethoxycarbonyl)-2-oxopropylidene]-3,4-dihydro-2*H*-pyrrole-2-carboxylate (26)[26]

Ethyl (2*S*)-5-thioxo-3,4-dihydro-5*H*-pyrrole-2-carboxylate **24** (1 g, 5.9 mmol) was dissolved in dry CH_2Cl_2 (30 ml). To the stirred solution, sodium hydrogencarbonate (2.0 g, 24 mmol) and ethyl 2-bromoacetoacetate **25** (2.45 g, 12 mmol) were added and the mixture heated under reflux for 16 h under N_2. The green reaction mixture was filtered through Celite® and concentrated *in vacuo*. The resulting green oil was purified by column chromatography (eluting with hexane/ethyl acetate 4:1), late fractions yielding the title compound (1.19 g, 71%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3219, 1745, 1690, 1642 and 1547; δ_H (400 MHz; $CDCl_3$) 11.72 (1H, br-s, N*H*), 4.45 (1H, dd, *J* 9.0 and 5.5, C*H*–N), 4.20–4.10 (4H, m, 2 × OCH_2), 3.20–3.05 (2H, m, CH_2C=C), 2.35 (3H, s, CH_3C=O), 2.27 (1H, m, one of CH_2CHN), 2.10 (1H, m, one of CH_2CHN) and 1.24 (6H, m, 2 × OCH_2CH_3); δ_C (100 MHz; $CDCl_3$) 197.4 (ketone *C*=O), 172.8 (one of ester *C*=O), 169.8 (one of ester *C*=O), 167.4 (C=*C*N), 98.7 (*C*=CN), 68.9 (one of O*C*H_2), 60.4 (*C*HN), 58.7 (one of O*C*H_2), 33.3 (*C*H_2C=C), 29.9 (*C*H_3C=O), 24.3 (*C*H_2CHN), 13.4 (one of OCH_2CH_3) and 13.1 (OCH_3CH_3); *m*/*z* (APCI) 270 (MH^+, 100%).

Ethyl 2-[(5*S*)-5-(hydroxymethyl)-3,4-dihydro-2*H*-pyrrole-2-ylidene]-3-oxobutanoate (27)[26]

Ethyl (2*S*)-5-[(*E*)-1-(ethoxycarbonyl)-2-oxopropylidene]-3,4-dihydro-2*H*-pyrrole-2-carboxylate **26** (1.35 g, 5.1 mmol) was dissolved in THF (12 ml) and water (3 ml). Sodium borohydride (1.87 g, 5.1 mmol) was added and the mixture heated under reflux for 1 h. The THF was removed *in vacuo* and the remaining aqueous residue was saturated with sodium chloride and extracted with CH_2Cl_2 (4 × 10ml). The organic portions were combined, dried over $MgSO_4$, and concentrated *in vacuo* to yield the title compound (1.08 g, 94%) as a yellow oil that was used without further purification; ν_{max}/cm^{-1} (neat) 3397, 1685 and 1595; δ_H (400 MHz; $CDCl_3$) 11.60 (1H, br-s, N*H*), 4.12 (2H, q, *J* 7.1, OCH_2), 4.00 (1H, m, C*H*–N), 3.70 (1H, dd, *J* 11.4 and 4.5, one of CH_2OH), 3.48 (1H, dd, *J* 11.4 and 7.1, one of CH_2OH), 3.13 (1H, ddd, *J* 15.6, 9.4 and 5.9, one of CH_2C=C), 3.06 (1H, ddd, *J* 15.6, 9.5 and 6.1, one of CH_2C=C), 2.25 (3H, s, CH_3C=O), 2.03 (1H, m, one of CH_2CHN) and 1.73 (1H, m, one of CH_2CHN) and 1.35 (3H, t, *J* 7.1, OCH_2CH_3); δ_C (100 MHz; $CDCl_3$) 188.8 (ketone *C*=O), 174.9 (ester *C*=O), 169.2 (C=*C*N), 99.4 (*C*=CN), 65.3 (O*C*H_2), 62.9 (*C*HN), 60.0 (*C*H_2OH), 35.5 (*C*H_2C=C), 31.0 (*C*H_3C=O), 23.3 (*C*H_2CHN) and 14.8 (CH_2CH_3); *m*/*z* (APCI) 228 (MH^+, 100%).

Ethyl 2-[(5*S*)-5-(*tert*-butyl(dimethyl)siloxymethyl)-3,4-dihydro-2*H*-pyrrole-2-ylidene]-3-oxobutanoate (28)

Ethyl 2-[(5*S*)-5-(hydroxymethyl)-3,4-dihydro-2*H*-pyrrole-2-ylidene]-3-oxobutanoate **27** (1.35 g, 3.96 mmol) in dry THF (10 ml) was added to a stirred solution of chloro-*t*-butyldimethylsilane (595 mg, 3.96 mmol) and imidazole (280 mg,

4.05 mmol) in dry THF (10 ml). The reaction mixture was stirred at room temperature for 72 h. Water (10 ml) and diethyl ether (10 ml) were added, and the organic layer was separated, dried over $MgSO_4$, and concentrated *in vacuo* to yield the title compound (1.05g, 65%) as a clear oil that was used without further purification; ν_{max} (neat)/cm^{-1} 1689, 1601 and 1544; δ_H (400 MHz; $CDCl_3$) 12.45 (1H, br-s, NH), 4.15 (2H, q, *J* 7.1, OCH_2), 3.94 (1H, m, CHN), 3.61 (1H, dd, *J* 10.3 and 4.1, one of CH_2OSi), 3.44 (1H, dd, *J* 10.3 and 6.4, one of CH_2OSi), 3.17 (1H, ddd, *J* 15.9, 9.6 and 6.3, one of $CH_2C{=}C$), 3.05 (1H, ddd, *J* 15.9, 9.6 and 6.2, one of $CH_2C{=}C$), 2.30 (3H, s, $CH_3C{=}O$), 2.00 (1H, m, one of CH_2CHN), 1.72 (1H, m, CH_2CHN), 1.21 (3H, t, *J* 7.1, OCH_2CH_3), 0.80 [9H, s, $(CH_3)_3CSi$], 0.06 (3H, s, one of $SiCH_3$) and 0.01 (3H, s, one of $SiCH_3$); δ_C (100 MHz; $CDCl_3$) 196.7 (ketone C=O), 173.0 (ester C=O), 167.8 (C=CN), 97.7 (C=CN), 65.0 (OCH_2), 61.9 (CHN), 58.6 (CH_2OSi), 37.6 ($CH_2C{=}C$), 33.5 ($CH_3C{=}O$), 28.4 (CH_2CHN), 25.8 [$(CH_3)_3CSi$], 20.8 (OCH_2CH_3), 17.1 [$(CH_3)_3CSi$], −2.8 and −2.9 (both CH_3Si); *m*/*z* (APCI) 342 (MH$^+$, 100%).

Ethyl 2-[(5*S*)-5-(*tert*-butyl(dimethyl)siloxymethyl)-3,4-dihydro-2*H*-pyrrole-2-ylidene]acetate (29)

Sodium metal (98 mg, 4.3 mmol) was added to absolute ethanol (10ml) and allowed to dissolve over 30 min. Ethyl 2-[(5*S*)-5-(*tert*-butyl(dimethyl)siloxymethyl)-3,4-dihydro-2*H*-pyrrole-2-ylidene]-3-oxobutanoate **28** (1.42 g, 4.3 mmol) in absolute ethanol (5 ml) was added and the mixture heated under reflux for 2 h. The ethanol was removed *in vacuo*, and the resulting residue was dissolved in chloroform (20 ml), washed with saturated sodium carbonate solution (10 ml), dried over $MgSO_4$, and the solvent removed *in vacuo*. The brown oil remaining was purified by column chromatography (eluting with hexane/ethyl acetate 3:1), early fractions affording the title compound (680 mg, 55%) as a yellow oil (Found: MH$^+$, 299.2346. $C_{15}H_{29}NO_3Si$ requires M, 299.2342); ν_{max} (neat)/cm^{-1} 3396 and 1715; δ_H (400 MHz; $CDCl_3$) 7.95 (1H, br-s, NH), 4.47 (1H, s, alkene CH), 4.05 (2H, q, *J* 7.1, OCH_2), 3.85 (1H, m, CHN), 3.55 (1H, dd, *J* 10.1 and 3.8, one of CH_2OSi), 3.49 (1H, dd, *J* 10.1 and 6.5, one of CH_2OSi), 2.65–2.48 (2H, m, $CH_2C{=}CH$), 1.95 (1H, m, one of CH_2CHN), 1.75 (1H, m, one of CH_2CHN), 1.24 (3H, t, *J* 7.1, CH_3), 0.85 [9H, s, $(CH_3)_3CSi$], 0.05 (3H, s, one of CH_3Si) and 0.00 (3H, s, one of CH_3Si); δ_C (100 MHz; $CDCl_3$) 170.9 (C=O), 166.2 (C=CN), 77.1 (alkene CH), 66.9 (OCH_2CH_3), 61.5 (CHN), 58.8 (CH_2OSi), 32.0 ($CH_2C{=}CH$), 26.1 [$(CH_3)_3CSi$], 24.6 (CH_2CHN), 18.7 [$(CH)_3CSi$], 15.1 (OCH_2CH_3), −4.4 and −4.5 (both CH_3Si); *m*/*z* (APCI) 300 (MH$^+$, 100%).

Ethyl 3-(benzoylamino)-2-{(5*S*)-5-(*tert*-butyl(dimethyl)siloxymethyl)-3,4-dihydro-2*H*-pyrrole-2-ylidene}-3-thioxopropanoate (30)

Ethyl 2-[(5*S*)-5-(*tert*-butyl(dimethyl)siloxymethyl)-3,4-dihydro-2*H*-pyrrole-2-ylidene]acetate **29** (100 mg, 0.34 mmol) was dissolved in dry benzene (7 ml). Benzoylisothiocyanate (55 mg, 0.34 mmol) was added and the yellow mixture stirred under N_2 at rt for 2 h. The yellow solution resulting was concentrated *in vacuo* and purified by column chromatography (eluting with CH_2Cl_2/diethyl ether 5:1). Early fractions yielded the title compound (56 mg, 36%) as a yellow solid, mp 128–130 °C; ν_{max} (neat)/cm^{-1} 3432, 2927, 1702, 1603, 1517 and 1214; δ_H (400 MHz; $CDCl_3$), 13.85 (1H, br-s, S=CNHC=O), 12.71 (1H, br-s, NH), 7.94 (2H, d, *J* 7.1, aromatic CH), 7.59 (1H, t, *J* 7.1, aromatic CH), 7.44 (2H, t, *J* 7.1, aromatic CH), 4.16 (3H, m, OCH_2 and CHN), 3.73 (1H, dd, *J* 11.3 and 4.0, one of CH_2OSi), 3.51 (1H, dd, *J* 11.3 and 7.0, one of CH_2OSi), 3.30 (1H, m, one of $CH_2C{=}C$), 3.14 (1H, m, one of $CH_2C{=}C$), 2.10 (1H, m, one of CH_2CHN), 1.72 (1H, m, one of CH_2CHN), 1.20 (3H, t, *J* 7.1, OCH_2CH_3), 0.84 [9H, s, $(CH_3)_3CSi$], 0.02 (3H, s, one of CH_3Si) and 0.00 (3H, s, one of CH_3Si); δ_C (100 MHz; $CDCl_3$) 174.5 (ester C=O), 164.8 (C=CN), 134.8 (aromatic C), 132.3, 128.8 and 127.8 (all aromatic CH), 101.5 (C=CN), 63.7 (OCH_2), 63.2 (CHN), 60.8 (CH_2OSi), 33.7 ($CH_2C{=}C$), 25.8 [$(CH_3)_3CSi$], 23.6 (CH_2CHN), 18.2 [$(CH_3)_3CSi$], 14.3 (OCH_2CH_3), −5.3 and −5.4 (both CH_3Si); *m*/*z* (APCI) 463 (MH$^+$, 100%).

Ethyl 7-(*tert*-butyl(dimethyl)siloxymethyl)-3-methyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylate (35 and 36)

Silicon tetraisothiocyanate (700 mg, 2.7 mmol) was suspended in dry benzene (10 ml). Acetaldehyde (110 mg, 2.7 mmol) was added and the mixture stirred for 20 min at rt under N_2. Ethyl 2-[(5*S*)-5-(*tert*-butyl(dimethyl)siloxymethyl)-3,4-dihydro-2*H*-pyrrole-2-ylidene]acetate **29** (800 mg, 2.7 mmol) in dry benzene (5 ml) was added and the mixture stirred at rt under N_2 for a further 3 h, then concentrated *in vacuo* to give the title compound as a 2:1 mixture of diastereoisomers which were separated by column chromatography (eluting with hexane/ethyl acetate 9:1).

Major isomer (35)

Clear gum (556 mg, 54%) (Found: MH$^+$, 385.1978. $C_{18}H_{33}N_2O_3SSi$ requires M, 385.1981); ν_{max} (neat)/cm^{-1} 3390, 1686, 1649 and 1264; δ_H (400 MHz; $CDCl_3$) 6.91 (1H, br-s, NH), 4.59 (1H, m, CHN), 4.30 (1H, q, *J* 6.0, $CHCH_3$), 4.15 (1H, dd, *J* 10.5 and 4.5, one of CH_2OSi), 4.00 (2H, m, OCH_2), 3.75 (1H, dd, *J* 10.5 and 3.3, one of CH_2OSi), 3.15 (1H, apparent dd, *J* 9.1 and 8.4, one of $CH_2C{=}C$), 3.05 (1H, m, one of $CH_2C{=}C$), 2.10–1.89 (2H, m, CH_2CHN), 1.24 (3H, d, *J* 6.0, $CHCH_3$), 1.19 (3H, t, *J* 7.1, OCH_2CH_3), 0.77 [9H, s, $(CH_3)_3CSi$], 0.07 (3H, s, one of CH_3Si) and 0.00 (3H, s, one of CH_3Si); δ_C (100 MHz; $CDCl_3$) 173.6 (C=S), 164.6 (C=O), 149.4 (C=CN), 99.6 (C=CN), 62.9 (CHN), 61.9 (OCH_2), 59.0 (CH_2OSi), 47.2 ($CHCH_3$), 30.8 ($CH_2C{=}C$), 24.7 [$(CH_3)_3CSi$], 24.2 (CH_2CHN), 24.1 ($CHCH_3$), 16.1 [$(CH_3)_3CSi$], 13.4 (OCH_2CH_3), 0.0 (CH_3Si) and −4.6 (CH_3Si); *m*/*z* (APCI) 385 (MH$^+$, 100%).

Minor isomer (36)

Clear gum (240 mg, 23%) (Found: MH$^+$, 385.1982. $C_{18}H_{33}N_2O_3SSi$ requires M, 385.1981); ν_{max} (neat)/cm^{-1} 3390, 1686, 1649 and 1264; δ_H (400 MHz; $CDCl_3$) 7.01 (1H, br-s, NH), 4.93 (1H, m, CHN), 4.35 (1H, m, $CHCH_3$), 4.15 (2H, q, *J* 7.1, OCH_2), 4.06 (1H, dd, *J* 10.4 and 3.6, one of CH_2OSi), 3.67 (1H, dd, *J* 10.4 and 2.3, one of CH_2OSi), 3.20 (1H, m, one of $CH_2C{=}C$), 3.05 (1H, m, one of $CH_2C{=}C$), 2.01 (2H, m, CH_2CHN), 1.20 (3H, t, *J* 7.1, OCH_2CH_3), 1.18 (3H, d, *J* 6.3, CH_3CH), 0.85 [9H, s, $(CH_3)_3CSi$], 0.06 (3H, s, one of CH_3Si) and 0.00 (3H, s, one of CH_3Si); δ_C (100 MHz; $CDCl_3$) 174.2 (C=S), 164.5 (C=O), 149.9 (C=CN), 100.1 (C=CN), 63.3 (OCH_2), 63.0 (CHN), 59.9 (CH_2OSi), 46.7 ($CHCH_3$), 30.6 ($CH_2C{=}C$), 24.8 [$(CH_3)_3CSi$], 22.7 (CH_2CHN), 22.2 (CH_3CH), 17.0 [$(CH_3)_3CSi$], 13.4 (OCH_2CH_3) and 0.00 [$(CH_3)_2Si$]; *m*/*z* (APCI) 385 (MH$^+$, 100%).

Ethyl (3*R*,7*S*)-7-(hydroxymethyl)-3-methyl-1-imino-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylate formic acid salt (39)

Ethyl (3*R*,7*S*)-7-(*tert*-butyl(dimethyl)siloxymethyl)-3-methyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylate **35** (130 mg, 0.34 mmol) was dissolved in dry methanol (5 ml). Iodomethane (23 µl, 0.35 mmol) was added and the solution heated under reflux for 1 h. The volatiles were removed *in vacuo* and the residue redissolved in dry methanol (2 ml). Ammonium acetate (140 mg, 1.8 mmol) was added, and gaseous ammonia bubbled through the solution for 10 min. The solution was then heated in a sealed tube at 80 °C for 48 h. The solution was loaded directly onto a silica column and eluted

with CH_2Cl_2/MeOH/HCO_2H/H_2O (85:14:0.5:0.5), late fractions yielding the title compound (74 mg, 73%) as a clear gum; δ_H (400 MHz; $CDCl_3$) 8.40 (1H, br-s, N*H*), 8.00–7.70 (2H, br-s, NH_2), 4.45 (1H, q, *J* 6.1, C*H*CH_3), 4.38 (1H, m, C*H*N), 4.15 (2H, m, OCH_2), 3.81 (1H, dd, *J* 11.8 and 3.1, one of OCH_2), 3.75 (1H, dd, *J* 11.8 and 2.6, one of CH_2OH), 3.31 (1H, apparent dd, *J* 17.9 and 8.2, one of CH_2C=C), 2.80 (1H, m, one of CH_2C=C), 2.19–2.01 (1H, m, one of CH_2CHN), 2.04–1.94 (1H, m, one of CH_2CHN), 1.37 (3H, d, *J* 6.1, CHCH_3) and 1.19 (3H, t, *J* 7.1, OCH$_2$CH_3); δ_C (100 MHz; $CDCl_3$) 165.0 (ester C=O), 151.1 (*C*=NH), 150.9 (N*C*=C), 102.5 (*C*=CN), 62.8 (*C*HN), 61.8 (OCH_2), 59.0 (OCH_2), 46.3 (*C*HCH$_3$), 29.9 (*C*H$_2$C=C), 20.5 (*C*H$_3$CH), 23.2 (*C*H$_2$CHN) and 13.9 (OCH$_2$*C*H$_3$); *m*/*z* (APCI) 254 (cation M^+, 100 %).

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