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Studies towards the total synthesis of Batzelladine A: synthesis of a model pyrrolo[1,2-*c*]pyrimidine

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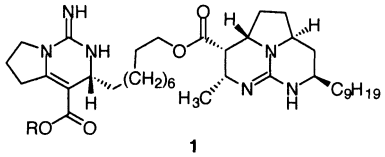
Abstract—A new approach to the synthesis of fragments related to the batzelladine alkaloids has been developed using a formal asymmetric aza-Diels–Alder reaction.

Over the last five years we have investigated the reactions of alkenylazolines with heterocumulenes, leading to a stereoselective preparation of fused pyrimidines and piperidines.[1] It occurred to us that the placement of functionality within our products is very similar to that found in the bi- and tricyclic portions of the batzelladine alkaloids, e.g. Batzelladine A (**1**).[2] These natural products inhibit the binding of HIV envelope glycoprotein gp120 to CD4 receptors, and so are of potential interest for the treatment of HIV. The limited availability of the natural products renders them attractive targets for total synthesis,[3–10] and so we sought to apply our methodology in this area.



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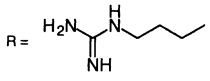
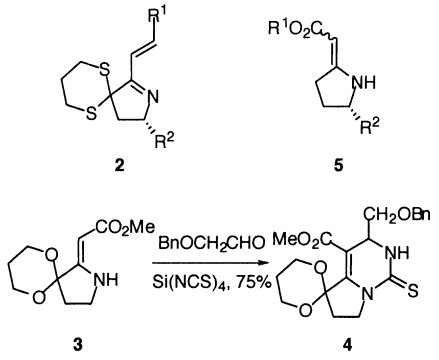


The desired approach would require a 2-alkenylpyrroline as substrate. Since these compounds are expected to be tautomerically unstable with respect to the corresponding enamines, we initially investigated the use of blocked alkenylpyrrolines such as **2**. This has the clear disadvantage that additional steps are required to introduce and remove the blocking group, and various problems with the preparation of such compounds led us to abandon this route. A more efficient approach is highlighted by the total synthesis of saxitoxin from the Kishi group, in which the putative alkenylpyrroline is generated in situ (Scheme 1).[11] While the precise order of steps in the formation of **4** from **3** is unknown, we reasoned that use of a substrate such as **5** would lead to key intermediates suitable for the synthesis of batzelladine A. Herein we report the successful realization of this approach.

There are a number of approaches to compounds such as **5** ($R^2 = CH_2OP$), mostly featuring elaboration of pyroglutamic acid derivatives. Initial studies showed that *O*-methylation and subsequent nucleophilic attack as a method of amide elaboration[12] suffered from reproducibility and protecting group issues. As a result of this we used the route shown in Scheme 2, in which all of the steps are reliable. Our approach begins with the synthesis of ethyl (*S*)-pyroglutamate **7** from glutamic acid **6**. Thionation with Lawesson's reagent was followed by Eschenmoser sulfide contraction with **9** to give **10** in good overall yield. Compound **10** was formed as a single double bond isomer, assumed to be that shown,[13] although we were unable to observe any diagnostic NOE enhancements which would confirm this assignment. Chemoselective reduction of the aliphatic



Scheme 1.

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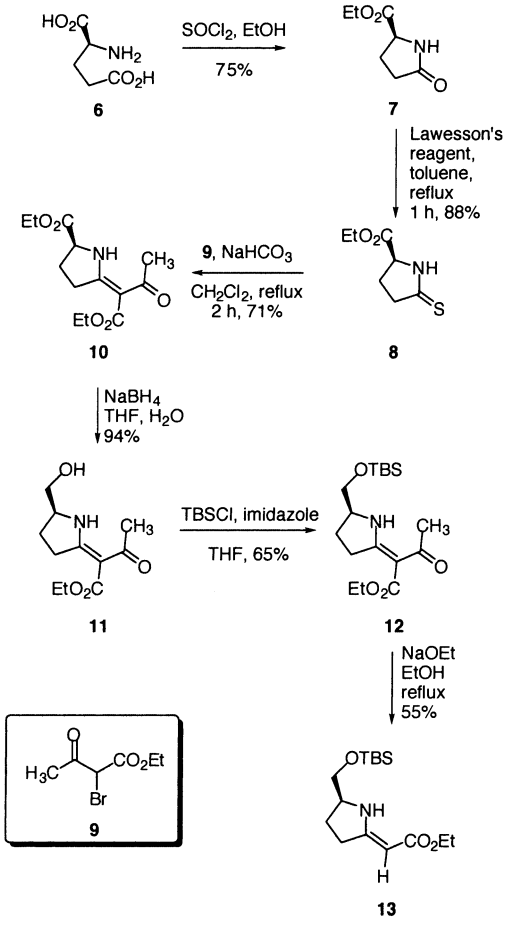


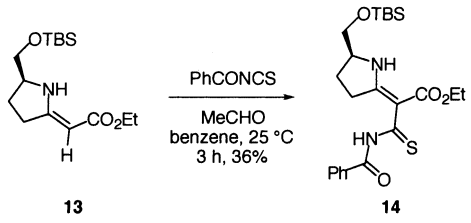
Scheme 2.

ester was followed by protection and de-acylation giving the annulation precursor **13**. All of these steps are amenable to scale-up, so that multigram quantities of **13** are easily accessible. The double bond geometry in **13** was confirmed by NOE studies.

The key annulation was initially attempted with benzoyl isothiocyanate and acetaldehyde. However, instead of the desired compound, **14** was formed as a single double bond isomer (Scheme 3). The same compound can be formed in higher yield if the acetaldehyde is omitted. This contrasts with an earlier report in which *N*-acylation is observed with similar substrates.[14,15]

The conditions of Kishi were used next, leading to the high-yielding formation of a mixture of diastereoisomers **15** and **16** in a 2:1 ratio.[16] These isomers were readily separated by flash column chromatography and subjected to extensive NOE NMR studies. The minor isomer **16** shows a 1% NOE as shown in Fig. 1. While this is small, there are no diagnostic enhancements shown by the major isomer **15**, so that on the basis of this, and precedent from our previous work on alkenyloxazolines and alkenylthiazolines,[1] we tentatively assign the stereochemistry of the two isomers as shown (Scheme 4).

Based on our previous work we might expect the formation of isomer **15** exclusively under these condi-



Scheme 3.

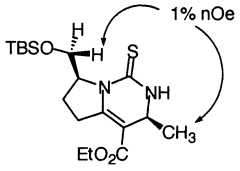
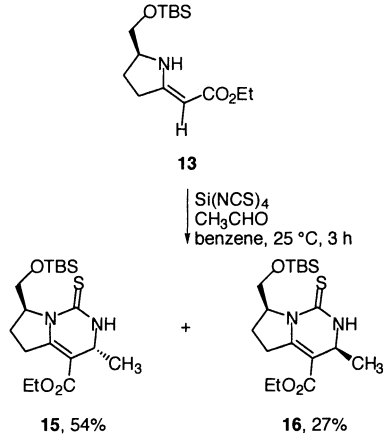


Figure 1.

tions, since any isomerisation of **15** into **16** would require elevated temperatures. However, this presumes a reaction proceeding via an intermediate such as **17** (Fig. 2). If the intermediate resembles **18**, as originally proposed by Kishi, the same major isomer would be expected, although clearly the extent of selectivity would be difficult to predict. However, in this case we have another distinct possibility for the lower diastereoselectivity. While a *Z* double bond, as in **17** would be expected to lead to isomer **15**, the *E* double bond isomer **19** would give, via a similar transition state, the isomer **16**. We believe that this is a far more likely explanation for the erosion of stereochemical control, and are currently investigating these possibilities.



Scheme 4.

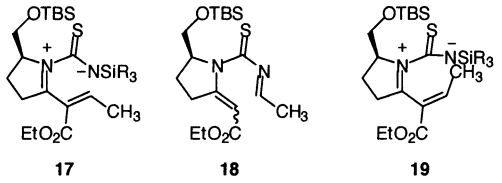
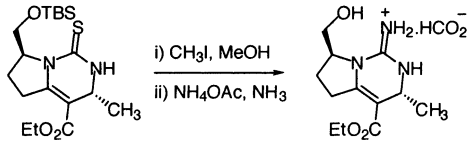


Figure 2.



15 20

Scheme 5.

Finally, conversion of the thiourea into the required guanidine was accomplished as shown in Scheme 5. Serendipitously the silyl protecting group was removed under these conditions, presumably as a result of anchimeric assistance by the neighbouring guanidine. The product **20** 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).[7]

Completion of the left hand side of Batzelladine A will require removal of the hydroxymethyl group, which we envisage will be accomplished by oxidation and either deformylation or decarboxylation. Homologation of this group and ring-closure will allow entry into the tricyclic portion of the title natural products. These studies are underway and will be reported in due course.

Acknowledgements

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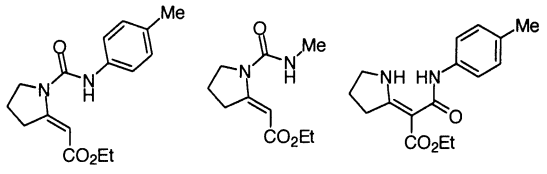
15. We have some concerns about the structural assignments as given in Ref. 14. For instance, for compound **21** the chemical shift of the alkene hydrogen was reported as 7.6 ppm, while that in compound **22** is reported as 6.5 ppm. Additionally these compounds give peaks assigned to N–H hydrogens at 7.3 and 5.4 ppm respectively. In comparison, the alkene hydrogen in compound **13** resonates at 4.5 ppm.



21 22 23

Comparison with other examples in the literature show that for compound **22** the reported shift is typical, while that in **21** seems to us to be too high.[17] The differing reaction conditions for the formation of the two compounds should also be considered. Compound **21** was formed under reflux (benzene) while **22** was formed at room temperature. It is reasonable to expect *C*-acylation

in the former case and possibly *N*-acylation in the latter.[18] Closer examination of the data lead us to suggest that the compound assigned structure **21** is most probably **23**, 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 deuterium exchange ^{1}H NMR data, which would have allowed unambiguous assignment of structures was not presented in the original report. In the case of compound **22** the assigned structure should be assumed to be correct.

16. In one instance a ratio of 4:1 was obtained. However, while we are confident that improvements will be made, the 2:1 ratio reported herein is presently the reproducible stereoselectivity.
17. For representative examples, see: Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223; (b) Brunerie, P.; Célérier, J.-P.; Petit, H.; Lhommet, G. *J. Heterocyclic Chem.* **1986**, *23*, 1183; (c) Lee, H. K.; Kim, J.; Pak, C. S. *Tetrahedron Lett.* **1999**, *40*, 2173.
18. For a detailed review of such reactions, see: Elliott, M. C.; Kruiswijk, E.; Long, M. S. *Tetrahedron* **2001**, *57*, 6651.