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An intermolecular 1,3-dipolar cycloaddition approach to the tricyclic core of martinelline and martinellic acid

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Abstract

The tricyclic core of the martinellines has been synthesised stereoselectively in two steps, using 1,3-dipolar cycloaddition of azomethine ylides as a key step.

Keywords: amino acids and derivatives; cycloadditions; pyrrolidines; quinolines.

Martinellic acid (**1**) and martinelline (**2**), isolated from the roots of the tropical plant *Martinella iquitosensis*, are the first alkaloids with the pyrrolo[3,2-*c*]quinoline ring system (Fig. 1).[1] These compounds show unique biological activity, as they are the first naturally occurring nonpeptide bradykinin B_1 and B_2 receptor antagonists. A number of synthetic analogues also have valuable biological properties.[2] It is therefore not surprising that many research groups

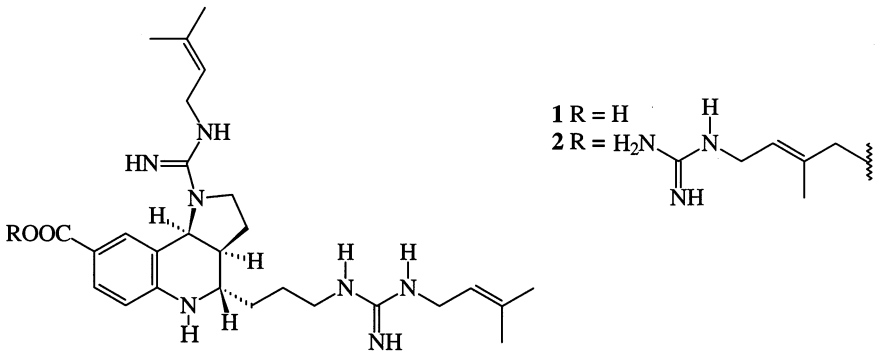

Figure 1.

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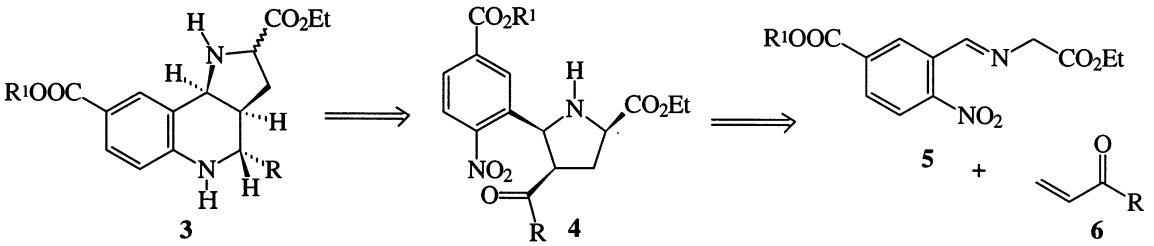
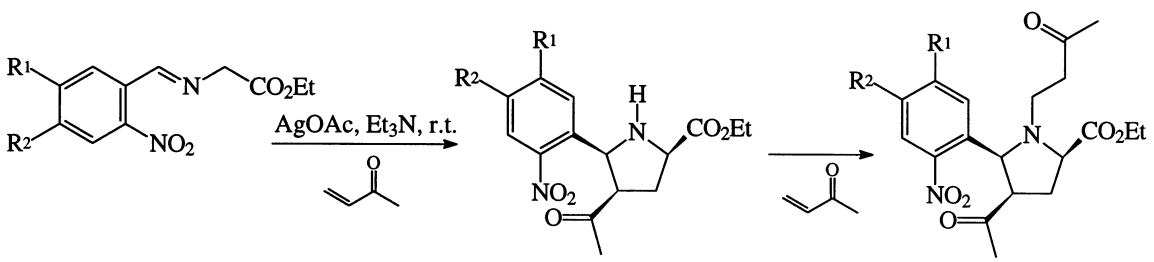
have tried to develop a short and flexible total synthesis of these heterocycles.[3] Amongst other approaches, two independent short communications[4] recently described the synthesis of the pyrrolo[3,2-*c*]quinoline tricyclic core by intramolecular 1,3-dipolar cycloadditions of non-stabilised azomethine ylides using the strategy described by Martin and Cheavens[5] some years earlier. While effective, all of these routes consist of several steps, sometimes with the lack of good yields and/or stereoselectivity.

To overcome these problems we envisioned that useful intermediates, such as **3**, for the synthesis of these alkaloids should be available in one step from keto-pyrrolidine derivative **4** under reductive conditions. This type of compound is easily accessible with the predetermined *cis*-stereochemistry on the five-membered ring from a metal-catalysed intermolecular azomethine ylide cycloaddition[6] of the corresponding imine **5** to an alkyl vinyl ketone **6** (Scheme 1).



Scheme 1.

The first step of this sequence is well-precedented in other similar cycloaddition reactions.[6] In a model study we have found that azomethine ylides derived from the imines of *o*-nitro-benzaldehydes in the presence of silver acetate and triethylamine in dry toluene react with methyl vinyl ketone to yield the predicted *syn-endo* cycloadducts **8a–c** as single isomers (proven by ^{1}H NOE experiments).[7] In some cases, when we have used the dipolarophile in excess, the cycloadduct reacted further to give **9a–c** in variable yields depending on the amount of the reagent available (Scheme 2).



7a R1 = R2 = H
7b R1 = R2 = OMe
7c R1,R2 = -OCH$_2$O-

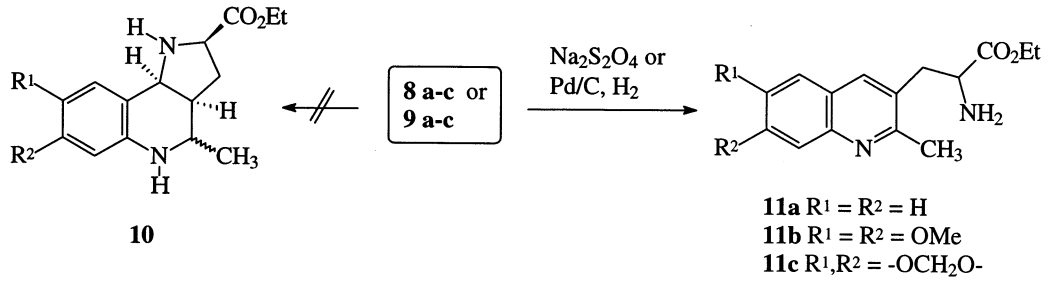
8a R1 = R2 = H (*76 %*)
8b R1 = R2 = OMe (*82 %*)
8c R1,R2 = -OCH$_2$O- (*70 %*)

9a R1 = R2 = H
9b R1 = R2 = OMe
9c R1,R2 = -OCH$_2$O-

Scheme 2.

To our surprise, the reduction of **8a–c** (or even **9**) with sodium hydrosulfite in aqueous ethanolic solution did not give us the expected product **10**, but we could isolate quantitatively the α-amino acid esters **11a–c** (Scheme 3).[8] The same result was obtained by a hydrogenation experiment using 10% Pd/C as a catalyst, while attempts to use Zn/HCl, Fe/HCl or Ni_2B led to a complex mixture of products. These quinoline derivatives are most probably formed by the

reduction of the aromatic nitro group followed by simple condensation of the newly formed aniline with the nearby ketone. This intermediate imine was not further reduced to **10**, but ring opening of the pyrrolidene ring resulted in the formation of **11**. The driving force for this last step is the possibility for aromatisation of the quinoline system.

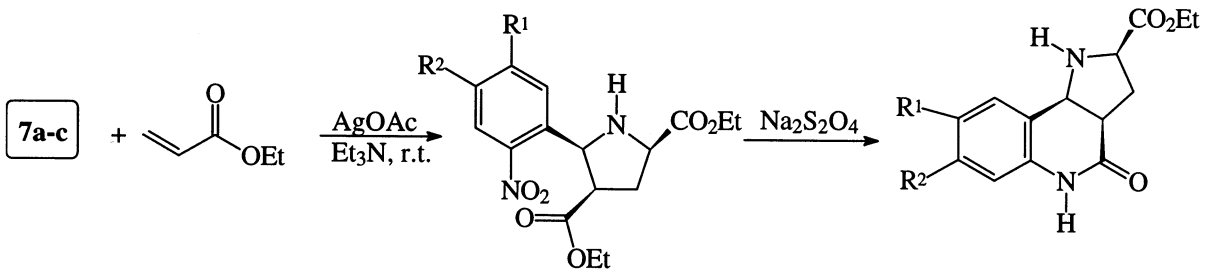


10

11a $R^1 = R^2 = H$
11b $R^1 = R^2 = OMe$
11c $R^1,R^2 = -OCH_2O-$

Scheme 3.

To avoid this interesting, but unwanted reaction we have generated the same azomethine ylides from imines **7a–c** in the presence of ethyl acrylate as a dipolarophile. In accordance with the above experiments we have obtained the *syn-anti* cycloadducts **12a–c** stereoselectively (proven again by ^1H NOE experiments). The reductions of these cycloadducts, again with sodium hydrosulfite, now gave the expected *cis*-fused pyrrolo[3,2-*c*]quinolines in good yield (Scheme 4).



12a $R^1 = R^2 = H$ (*72 %*)
12b $R^1 = R^2 = OMe$ (*80 %*)
12c $R^1,R^2 = -OCH_2O-$ (*71 %*)

13a $R^1 = R^2 = H$ (98 %)
13b $R^1 = R^2 = OMe$ (96 %)
13c $R^1,R^2 = -OCH_2O-$ (92 %)

Scheme 4.

In conclusion, we have developed a two-step, stereoselective route from simple starting materials to the tricyclic core of martinellic acid, which could be a novel building block for combinatorial chemistry applications or a starting material for the synthesis of the natural product itself.

Acknowledgements

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