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Synthesis of the heterocyclic core of the alkaloids martinelline and martinellic acid

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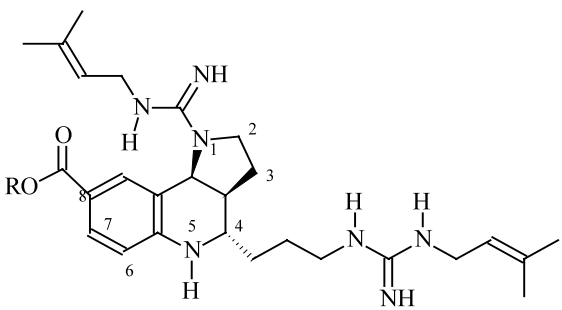
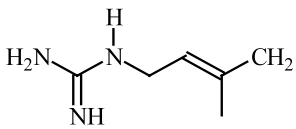
Abstract—The tricyclic core of martinelline and martinellic acid was rapidly assembled utilising an imino Diels–Alder reaction of an imine derived from cinnamaldehyde with a cyclic enamide. The cycloaddition was completely regioselective though the *exo–endo* selectivity was poor. These diastereoisomers were readily separated by flash chromatography and the relative stereochemistry of the *exo*-isomer confirmed by single crystal X-ray crystallography. This intermediate was converted to the central core of the aforementioned alkaloids in five additional synthetic operations.

Martinellic acid and martinelline **1a**,**b** isolated from the medicinal plant *Martinella iquitosensis* by the Merck group,[1] are the first non-peptide natural product bradykinin receptor inhibitors to be identified. The unusual hexahydropyrroloquinoline skeleton, numbering shown based on IUPAC nomenclature, together with the medicinal interest in the development of non-peptide bradykinin inhibitors as therapeutic agents,[2–6] has made these alkaloids attractive synthetic targets.[7–15]



1a R = H

1b R =



To date, two approaches have been successful in assembling the hexahydropyrroloquinoline core of these alkaloids with the important 3′-aminopropyl group at the 4-position. The first employed a *cyclo*-condensation of methyl-4-aminobenzoate with two moles of cyclic enamide **3**.[16] The major drawback with this approach was that the required *exo*-isomer was a minor component in a 5.6:1 mixture of diastereoisomers and it was not clear from the manuscript whether these isomers were separated or not. The second approach employed an intramolecular 1,3-dipolar cycloaddition of an azomethine ylide with an unactivated alkene.[17] This gave the required *exo*-isomer with excellent stereoselectivity, but the particular substrate investigated did not contain the required 8-carboxyl group.

Recently we reported an expedient entry to hexahydropyrroloquinolines utilising an imino Diels–Alder reaction of cyclic enamides with imines derived from aromatic amines.[18] The advantages of this approach were two-fold. Firstly, the symmetry was such that readily available *p*-substituted benzenes ensured the correct regiochemistry of the trisubstituted aromatic ring on cycloaddition, and secondly, the cycloaddition was completely regioselective. The main drawback with this chemistry was that it failed with aliphatic aldehydes making it difficult to introduce the required 4-(3′-aminopropyl) substituent. We now report how this chemistry can be extended to give the tricyclic core of martinelline and martinellic acid (Scheme 1).

Keywords: martinelline; martinellic acid; imino Diels–Alder; alkaloid.

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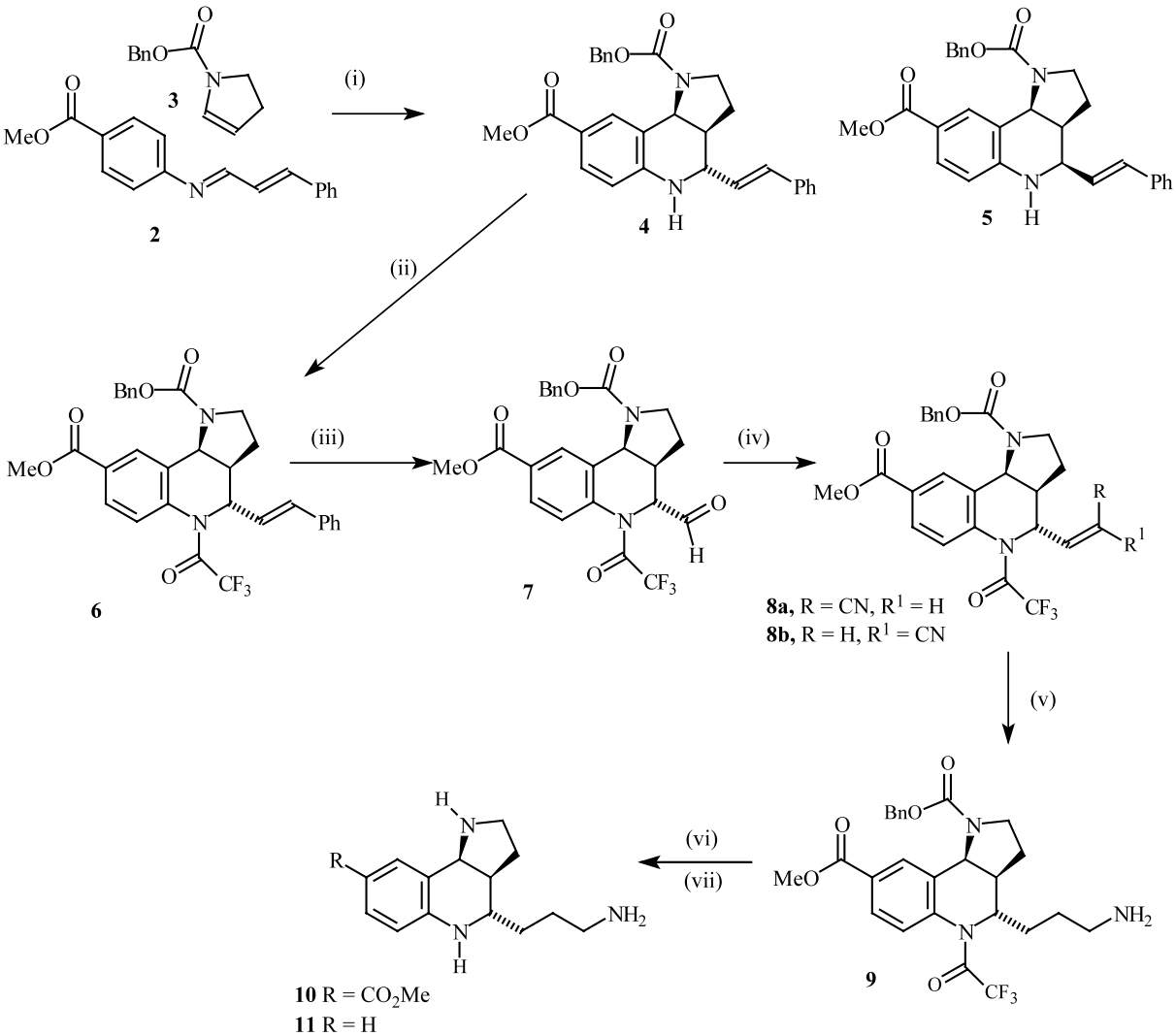

Scheme 1. *Reagents and conditions*: (i) 12 mol% $InCl_3$, CH_3CN, 25°C, 12 h; (ii) trifluoroacetic anhydride, DMAP, toluene 108°C, 30 h; (iii) CH_2Cl, O_3 −78°C then Me_2S; (iv) Ph_3P=CHCN; (v) PtO_2, EtOH, $CHCl_3$, 70°C, 45 psi, 144 h; (vi) MeOH, NH_3, 25°C, 24 h; (vii) $Pd(OH)_2$, CH_3OH, 60°C, 45 psi, 24 h.

Reaction of imine **2** with enamide **3** using indium trichloride as catalyst gave a 1.1:1 mixture of *exo–endo* stereoisomers **4** and **5**, respectively, from which the desired *exo*-isomer **4** could be isolated in 40% yield. The de for this reaction could not be improved further by varying either the temperature or solvent. The presence of the carbamate protecting group made the proton NMR spectra of compounds **4** and **5** broad and difficult to interpret. The relative stereochemistry of the major *exo*-isomer **4** was established by single crystal X-ray crystallography, and this is shown in Fig. 1. Of particular note is that the molecule adopts a conformation which puts the groups at C3a and C4 *trans*-diaxial, when one would have intuitively expected these groups to be *trans*-diequatorial. This effect has been previously noted in a series of 4-substituted hexahyropyrroloquinolines and indicates that the desired *exo*-diasteroisomer may be thermodynamically less stable than the *endo* isomer.[19]

It proved necessary to protect the aromatic amine prior to oxidative alkene cleavage. The presence of the *p*-carbomethoxy group had a dramatic deactivating effect on the nucleophilicity of the aromatic amine. However, reaction with trifluoroacetic anhydride in refluxing toluene containing a catalytic quantity of 4-dimethylaminopyridine gave amide **6** in 83% yield. Ozonolysis of adduct **6** gave an unstable aldehyde **7** which could

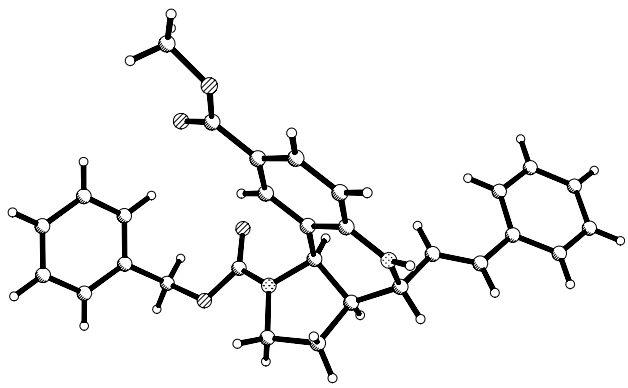

Figure 1. X-Ray structure of *exo*-cycloadduct depicting relative configuration and conformation.

not be isolated. Fortunately, it was possible to intercept this compound by trapping with the nitrile stabilised ylide (triphenylphosphoranylidene)acetonitrile at −78°C prior to work up. This gave a 2:1 mixture of *Z*–*E* α,β-unsaturated nitriles **8a** and **8b**, respectively, in 74% overall yield from **6**. Although the *Z*:*E*-selectivity for this reaction was poor it was of no consequence as the alkene double bond was removed in the next step. A potentially more elegant convergent approach to **8b** based on cycloaddition of the corresponding imine derived from 3-cyanoacrolein,[20] with cyclic enamide **3** was abandoned due to the highly unfavourable *exo*–*endo* selectivity of 1:3 with the indium catalyst.

Introduction of the 4-(3′-aminopropyl) substituent was completed by chemoselective reduction of the α,β-unsaturated nitrile using hydrogen and Adam's catalyst, and this gave primary amine **9** in 78% yield after a basic work up. Finally, sequential removal of the two orthogonal nitrogen protecting groups gave the central heterocyclic core of martinellic acid **10** in 71% overall yield for the two steps. The ^{13}C NMR spectrum of compound **10**,[21] was in good agreement in the aliphatic region with that of compound **11** previously reported by Professor Snider.[17]

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21. Carbon spectrum for compound **10**: $\delta_{C\text{-}13}$ (125 MHz, $CDCl_3$), 167.3, 148.8, 132.6, 129.9, 121.0, 118.6, 113.6, 57.7, 52.2, 51.5, 44.7, 42.0, 41.0, 31.0, 29.7, 29.5.