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Total synthesis of (±)-martinelline

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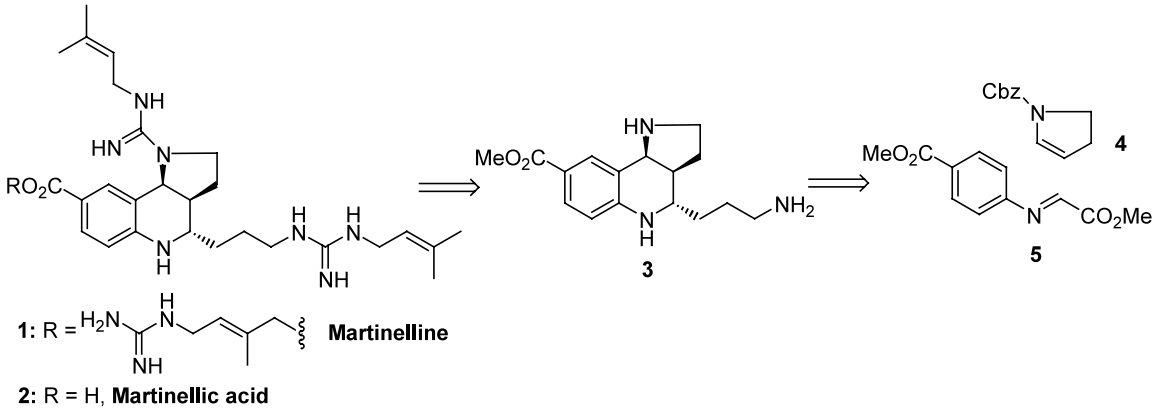
Abstract—The squaric acid-catalyzed imino-Diels–Alder reaction of enamine **4** with the imine **5** provides the pyrroloquinolines **6** and **7**, which were converted to the triamine **3** using regioselective reduction and a Wittig reaction as the key steps. Guanylation of **3** followed by coupling with the alcohol **19** furnished the total synthesis of (±)-martinelline. © 2002 Elsevier Science Ltd. All rights reserved.

The *Martinella* are a family of tropical plants containing two species, *M. iquitosensis* A. Sampaio and *M. obovata* (HBK.) Bur. & K. Schum. Preparations from the root bark of Martinella species have been used as an eye medication in over **13** different ethnolinguistic groups from eight South American countries. In 1995, scientists at Merck reported the isolation of two alkaloids from an organic extract of *M. iquitosensis* roots named as martinelline **1** and martinellic acid **2** (Scheme 1). The presence of alkaloids **1** and **2** in *Martinella* could be used to explain partially its therapeutic properties.[1] Further biological evaluation indicated that martinelline was an effective inhibitor for several G-protein coupled receptor systems including bradykinin (BK), histaminergic, α-adrenergic, and muscarinic receptors. This is the first example of a nonpeptide natural product being identified as a BK receptor antagonist. In addition, both alkaloids contain a pyrroloquinoline skeleton that is unprecedented in nature. Therefore, it is not surprising that synthetic interest in these targets has been considerable. To date, a number of synthetic efforts have been disclosed.[2–6] In a previous report, we described the first total synthesis of martinellic acid using a CuI-catalyzed coupling of an enantiopure β-amino ester as a key step.[4] Herein we wish to report the total synthesis of (±)-martinelline through triamine **3**, a key intermediate obtained this time by a squaric acid-catalyzed Diels–Alder reaction of the enamine **4** with the imine **5**.

Using an imino-Diels–Alder strategy to assemble the core structure of martinellic acid and martinelline was



Scheme 1.

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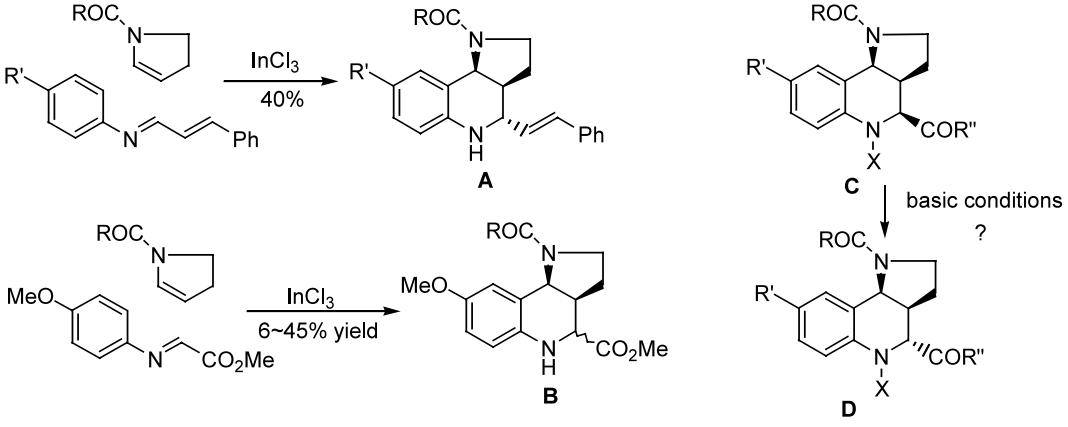
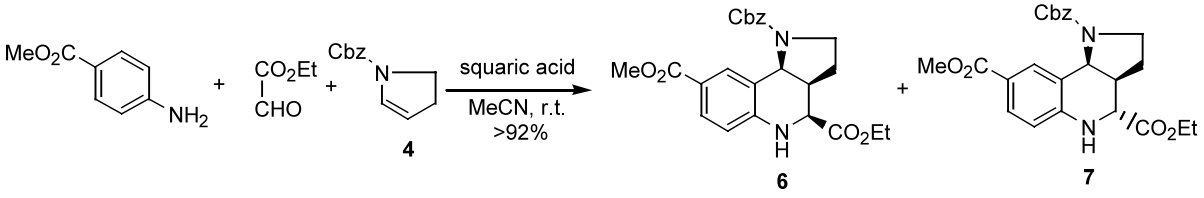
initially studied by Stevenson's and Batey's groups.[2] The advantage of this approach was that all three chiral centers present in the hexahydropyrroloquinone core were generated in one synthetic operation. In fact, the triamine **3** has been successfully obtained utilizing an $InCl_3$-catalyzed cycloaddition (Scheme 2) of a *trans*-cinnamaldehyde derived imine with an electron-rich olefin as the key step.[2b] However, this step gave the desired *exo*-product **A** in 40% yield, together with an almost equal amount of the *endo*-product, which was useless for further transformations. Stevenson and co-workers also found that the Diels–Alder reaction of a methyl glyoxalate derived imine provided **B** as a mixture of *exo*- and *endo*-isomers in rather low yields.[2a,c] After careful analysis of this reaction, we realized that the *endo*-product or its derivative **C** might be converted to the thermodynamically stable *exo*-isomer **D** under basic conditions. If this idea worked, and the reaction yield in the Diels–Alder cycloaddition of glyoxalate-derived imine could be improved, we would be able to develop a very efficient protocol to martinellic acid and martinelline.

With the above idea in mind, we investigated the cycloaddition reaction of the imine with the enamine **4** and found that an unusual catalyst, squaric acid, was an effective catalyst for this transformation. Thus, treatment of a mixture of 4-methoxycarbonylaniline, ethyl glyoxalate and the enamine **4** with **5** mol% of squaric acid in acetonitrile provided the addition products **6** and **7** in a ratio of 2:1 and >92% yield (Scheme 3).[7] Other catalysts we examined such as Lewis acids[2d,e] also worked for this reaction but lower yields were observed. For example, in the case of $Sc(OTf)_3$ as the catalyst, **6** and **7** was obtained in a ratio of 1:2 and 72% yield.

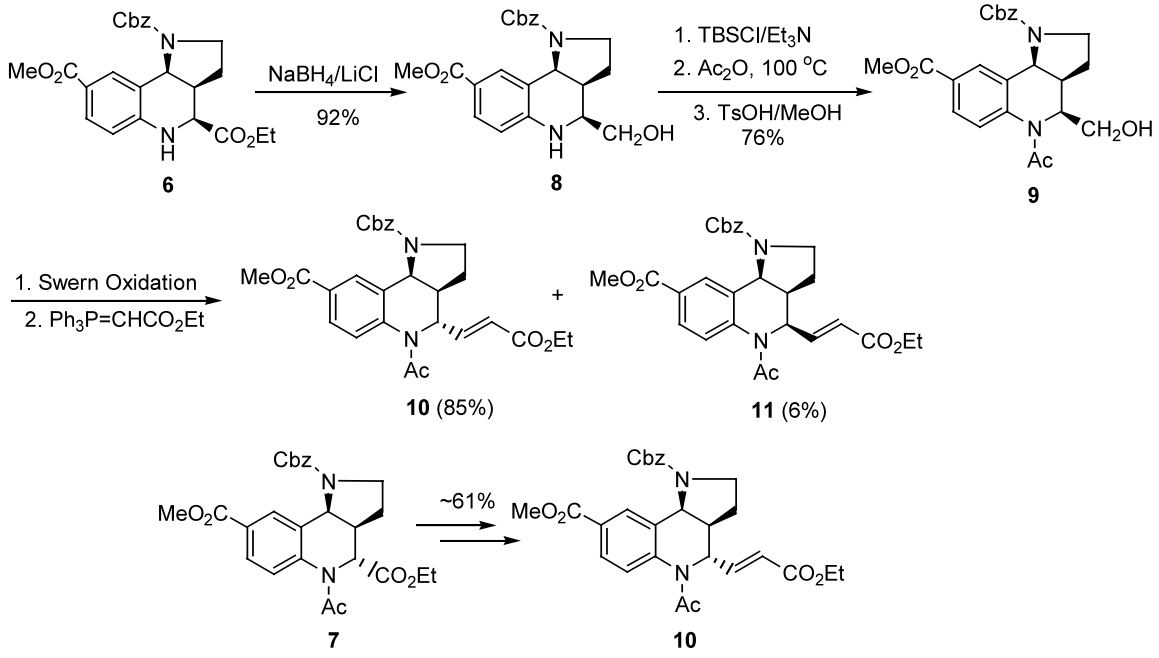
Regioselective reduction of the diester **6** was achieved with $NaBH_4$/LiCl in a mixture of 1/10 methanol–THF at room temperature to afford the alcohol **8** (Scheme 4). In order to attach the side chain by a Wittig reaction, we had to protect the 1-amino group. This was found to be a challenging task because many methods such as direct acylation with acetic anhydride or trifluoroacetic anhydride followed by release of the hydroxyl group under basic conditions were not suitable. This problem resulted from the facile deprotection of the 1-acyl group under basic conditions presumably assisted by the adjacent free hydroxyl group. After many experiments, we found that the following reaction sequence met our requirements: (1) protection of the hydroxyl group as a silyl ether; (2) treatment of the silyl ether with acetic anhydride at 100°C to protect the amino group; (3) removal of the silyl group through the action of TsOH in methanol. Next, a Swern oxidation of **9** gave the corresponding aldehyde as a mixture of *trans*- and *cis*-isomers, which showed that isomerization had occurred at the 2-position as we suspected. Without further purification, this aldehyde mixture was condensed directly with (carbethoxymethylene)-triphenylphosphorane giving diester **10**[8] (85% yield) as the major product, together with a small amount of the 2-epimer **11** (6% yield). This result indicated that during the Swern oxidation and subsequent Wittig reaction the *cis*-aldehyde intermediate was isomerized to its thermodynamically more stable *trans*-isomer. Thus, in this manner we had successfully changed the stereochemistry of the major product from the imino-Diels–Alder reaction to that required for synthesis of martinellic acid and martinelline. Following the same procedure, we transformed the *exo*-isomer **7** to the diester **10** in 61% overall yield. Overall, the



Scheme 2.



Scheme 3.

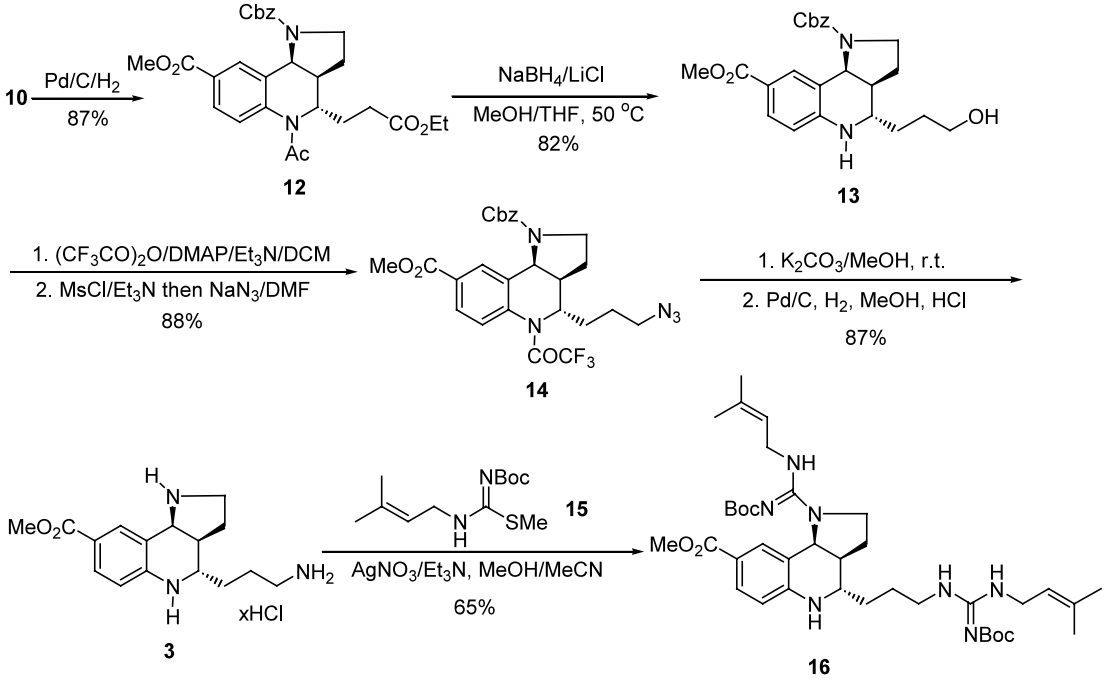


Scheme 4.

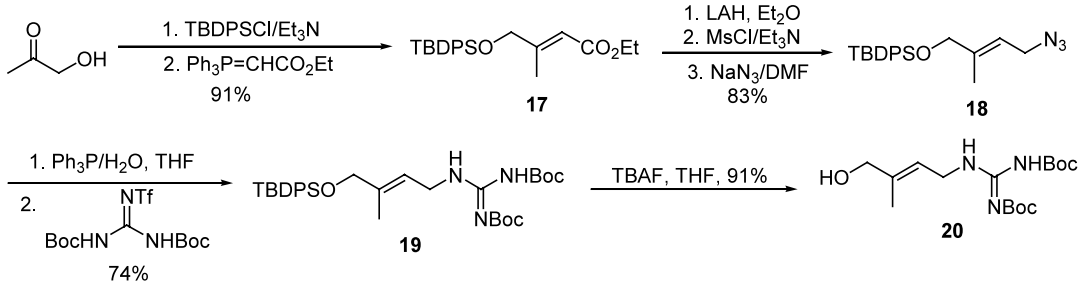
yield of intermediate **10** from the imino-Diels–Alder reaction was 54%.

Hydrogenation of **10** afforded the diester **12**, which was reduced with $NaBH_4/LiCl$ in a mixture of 1/10 methanol–THF at 50°C to give the alcohol **13** (Scheme 5). Reprotection of the amino group with $(CF_3CO)_2O$ followed by conversion of the hydroxyl to the azido group provided the azide **14**. After hydrolysis of **14** with K_2CO_3 in methanol, Pd/C catalyzed hydrogenation was carried out to remove the Cbz group and reduce the azide moiety to provide **3** as its hydrochloride salt. Condensation of the triamine **3** with *S*-methylisothiourea **15** gave the guanylation product **16** in 68% yield.[4]

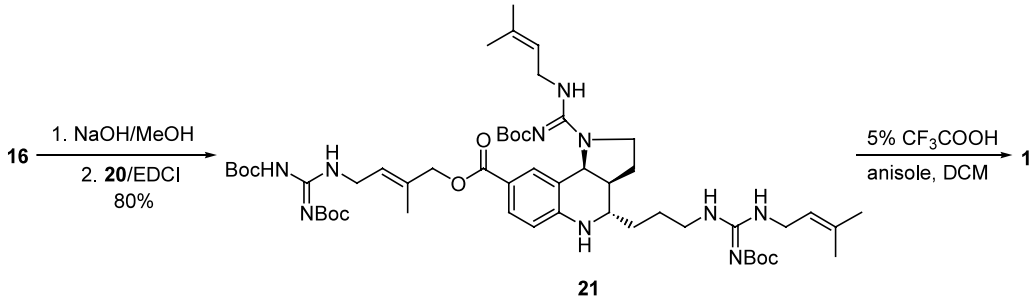
In order to introduce the ester moiety of martinelline, we required a functionalized alcohol **20**, which was synthesized as outlined in Scheme 6. This synthesis started from 1-hydroxyacetone and utilized a Wittig



Scheme 5.



Scheme 6.



Scheme 7.

reaction and a guanylation[9] with *N*,*N*-di-Boc-triflylguanidine as the key steps.

After hydrolysis of **16** with NaOH in methanol, the resultant acid was coupled with **19** mediated with EDCI to provide the ester **21**[10] in 80% yield (Scheme 6). Finally, treatment of **21** with 5% TFA under the assistance of anisole afforded martinelline **1**, which showed identical analytical data with those reported. Thus, the total synthesis of (±)-martinelline was achieved in **17** linear steps and 8% overall yield (Scheme 7).

Acknowledgements

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7. Typical procedure: A mixture of 4-methoxycarbonylaniline (1 mmol), ethyl glyoxalate (1 mmol) and the enamine **4** (1.05 mmol) in 5 mL of acetonitrile was stirred for 40 min at rt. After squaric acid (0.05 mmol) was added, the solution was stirred for 2 h at rt. The mixture was concentrated and chromatographed to afford **6** and **7**.

8. Selected data for **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 0.6H), 8.31 (s, 0.4H), 7.94 (d, $J=8.2$ Hz, 1H), 7.37–7.25 (m, 6H), 6.72 (d, $J=14.8$ Hz, 1H), 5.78 (d, $J=15.7$ Hz, 1H), 5.61 (m, 1H), 5.20 (m, 3H), 4.10 (q, $J=7.1$ Hz, 2H), 3.90 (s, 3H), 3.64 (m, 1H), 3.43 (m, 1H), 2.82 (m, 1H), 2.30 (s, 3H), 2.19 (m, 1H), 1.85 (m, 1H), 1.22 (t, $J=7.1$ Hz, 3H); HRMS calcd for $C_{28}H_{30}N_2O_7$ (M^+) 506.2053. Found: 506.2082.
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10. Selected data for **21**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.49 (br s, 1H), 9.00 (br s, 1H), 8.25 (m, 1H), 7.94 (s, 1H), 7.67 (d, $J=8.1$ Hz, 1H), 6.59 (d, $J=8.4$ Hz, 1H), 6.08 (br s, 1H), 5.75 (d, $J=7.2$ Hz, 1H), 5.56 (t, $J=7.0$ Hz, 1H), 5.28 (t, $J=6.8$ Hz, 1H), 5.20 (t, $J=6.7$ Hz, 1H), 4.87 (m, 2H), 4.65 (q, $J=3.6$ Hz, 2H), 4.09 (m, 2H), 3.87 (m, 1H), 3.75 (m, 2H), 3.46–3.29 (m, 3H), 3.15 (m, 1H), 2.36 (m, 2H), 2.13–2.05 (m, 4H), 1.75 (s, 3H), 1.73 (s, 3H), 1.70 (s, 3H), 1.67 (s, 3H), 1.63 (s, 3H), 1.49 (s, 36H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 166.3, 163.5, 155.9, 153.2, 146.7, 137.8, 137.5, 135.4, 131.4, 130.3, 122.4, 119.7, 119.1, 117.8, 113.9, 83.1, 79.3, 68.6, 50.5, 47.3, 44.6, 40.0, 38.9, 38.6, 32.5, 31.9, 31.2, 29.7, 29.6, 28.3, 28.2, 28.1, 27.4, 26.2, 25.6, 22.7, 22.5, 22.4, 18.1, 18.0, 14.2, 14.1; ESI-MS m/z 1021 ($M+H^+$); HRMS calcd for $C_{53}H_{84}N_{10}O_{10}$: 1021.6372 ($M+H^+$). Found: 1021.6407.