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Total Synthesis of the Alkaloids Martinelline and Martinellic Acid via a Hetero Diels–Alder Multicomponent Coupling Reaction†

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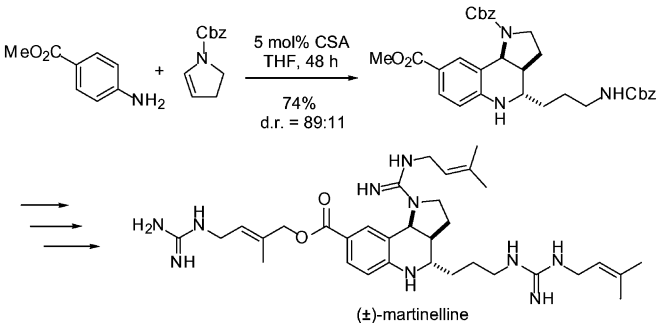
ABSTRACT



A concise synthesis of the guanidine alkaloids, (±)-martinelline and (±)-martinellic acid, using a protic acid catalyzed 2:1 hetero Diels–Alder coupling reaction between *N*-Cbz 2-pyrroline and methyl 4-aminobenzoate, is described. Protic acid catalysis, rather than Lewis acid catalysis, was necessary to achieve the desired sense of diastereocontrol in the coupling reaction.

Root extracts of the *Martinella iquitosensis* vine, found in Amazonian lowland rainforests, are used by indigenous peoples to treat various eye ailments, including inflammation and conjunctivitis.[1] This medicinal use may be attributed, at least in part, to the presence of two novel guanidine alkaloids, martinellic acid **1a** and martinelline **1b**, which have been demonstrated to be modest antibiotics and micromolar binders of several G-protein coupled receptors.[2] Martinelline in particular was identified as the first naturally occurring nonpeptidic bradykinin B2 receptor antagonist. Beyond their intriguing pharmacological profile, the *Martinella* alkaloids have an unprecedented hexahydropyrrolo[3,2-*c*]quinoline core structure with three pendant isoprenyl-derived guanidine moieties (Figure 1).

These features have rendered the heterocyclic core of martinelline an attractive target for synthesis,[3] and there are

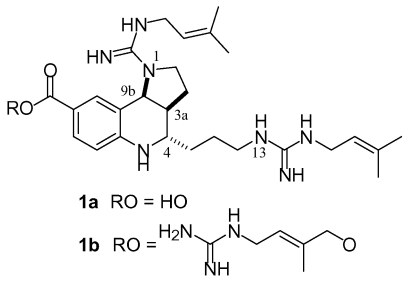


Figure 1. *Martinella* alkaloids (IUPAC numbering).

† Dedicated to the late Professor Richard Evans Schultes (1915−2001), a pioneer in the field of ethnobotany.

(1) Gentry, A.; Cook, K. *J. Ethnopharmacol.* **1984**, *11*, 337−343.

(2) Witherup, K. M.; Ransom, R. W.; Graham, A. C.; Bernard, A. M.; Salvatore, M. J.; Lumma, W. C.; Anderson, P. S.; Pitzenberger, S. M.; Varga, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6682−6685.

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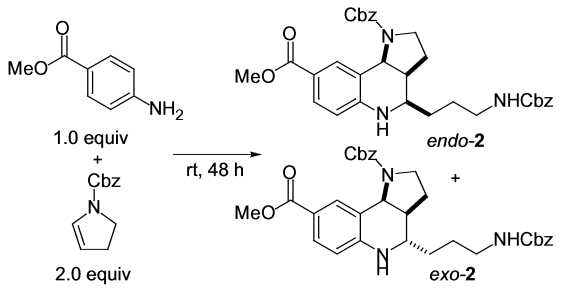
two recently published total syntheses of the less biologically active martinellic acid[4] from the groups of Ma and Snider.[5] We now report the first total synthesis of martinelline, as well as martinellic acid, using a hetero Diels−Alder reaction that we believe is related to that involved in their biosynthesis.

Martinelline is a demanding target; its deceptively simple heterocyclic structure belies the challenges posed by the presence of three differentiated and polar guanidine functionalities. Our initial interest in martinelline stemmed from the use of the heterocyclic core structure as a novel combinatorial scaffold[6] and the recognition that it could be constructed through a multicomponent "Povarov" reaction.[7] This reaction couples an electron-rich alkene with an *N*-arylimine (derived from an aniline and an aldehyde), a process that may occur through a concerted inverse electron demand hetero Diels−Alder mechanism or via a stepwise "Mannich-like" pathway. Furthermore, we have proposed that the *Martinella* alkaloids are conceivably biosynthesized through an unprecedented enzyme-catalyzed Povarov reaction.[6] Thus, the N-1 and N-13 isoprenylated guanidine groups would originate from a common intermediate, a guanidine-substituted 2-pyrroline derivative or hydrated equivalent. Supporting this hypothesis is the observation of lanthanide(III)-catalyzed 2:1 couplings of substituted anilines with 2 equiv of electron-rich alkenes such as N-protected 2-pyrrolines and dihydrofuran to give highly functionalized tetrahydroquinolines.[6,8] Methyl 4-aminobenzoate reacts with 2 equiv of *N*-Cbz-2-pyrroline, for example, to provide the hexahydropyrrolo[3,2-*c*]quinoline core **2** of martinelline as an 85:15 mixture of diastereomers in favor of the undesired *endo*[9] product (Scheme 1). The 2-pyrroline derivative serves

Scheme 1



a dual role in this multicomponent Povarov reaction, acting as an electron-rich dienophile and as the aldehyde component in the formation of the Schiff base (*N*-arylimine). We have categorized this as an "*ABB*"-type multicomponent coupling reaction,[8a] in which one component serves quite different roles in the reaction.[10]

While the lanthanide(III)-promoted reactions provide some support for the biogenetic hypothesis, the wrong "*endo*" diastereomer is preferentially formed. To achieve a synthesis of the martinelline alkaloids, a catalyst that would favor formation of the *exo* diastereomer was required, and our attention turned to protic acids, which have also been utilized in Povarov reactions.[11] After much experimentation, we find that reaction of methyl 4-aminobenzoate with 2 equiv of *N*-Cbz 2-pyrroline in the presence of 5 mol % camphorsulfonic acid (CSA) in anhydrous THF yields the corresponding tricyclic triamine core **2** in 74% yield and as an 11:89 mixture of diastereomers in favor of the desired *exo* product (Scheme 1). A variety of protic acids were surveyed in the 2:1 coupling reaction as outlined in Table 1. The

Table 1. Protic Acid Catalyzed Formation of **2**

protic acid (mol %)	solvent	yield[a] (%)	endo/exo[b]
DL-tartaric acid (50)	MeCN	61	82:18
AcOH (50)	MeCN	62	84:16
TFA (50)	MeCN	93	74:26
PPTS (50)	MeCN	69	57:43
citric acid (50)	MeCN	67	39:61
p-TsOH·H_2O (50)	MeCN	65	35:65
CSA (50)	MeCN	62	30:70
CSA (10)	MeCN	92	32:68
CSA (10)	toluene	(52)	52:48
CSA (10)	Et_2O	(40)	49:51
CSA (5)	THF	74	11:89
CSA (10)	DMF	(52)	39:61
CSA (10)	THF/H_2O (4:1)	(58)	82:18

[a] Isolated yield. Number in parentheses represents percent conversion as determined by ^{1}H NMR of the crude reaction mixture. [b] Determined by HPLC of the crude reaction mixture. TFA = trifluoroacetic acid, PPTS = pyridinium *p*-toluenesulfononic acid, *p*-TsOH = *p*-toluenesulfonic acid.

remarkable switchover in diastereoselection from the lanthanide-catalyzed reaction is not general for all protic acids and appears to be related, at least in part, to the pK_a of the

(3) (a) Gurjar, M. K.; Pal, S.; Rao, A. V. R. *Heterocycles* **1997**, *45*, 231−234. (b) Ho, T. C. T.; Jones, K. *Tetrahedron* **1997**, *53*, 8287−8294. (c) Hadden, M.; Stevenson, P. J. *Tetrahedron Lett.* **1999**, *40*, 1215−1218. (d) Lovely, C. J.; Mahmud, H. *Tetrahedron Lett.* **1999**, *40*, 2079−2082. (e) Snider, B. B.; Ahn, Y.; Foxman, B. M. *Tetrahedron Lett.* **1999**, *40*, 3339−3342. (f) Kang, S. K.; Park, S. S.; Kim, S. S.; Choi, J.-K.; Yum, E. K. *Tetrahedron Lett.* **1999**, *40*, 4379−4382. (g) Frank, K. E.; Aubé, J. *J. Org. Chem.* **2000**, *65*, 655−666. (h) Nyerges, M.; Fejes, I.; Töke, L. *Tetrahedron Lett.* **2000**, *41*, 7951−7954. (i) Escolano, C.; Jones, K. *Tetrahedron Lett.* **2000**, *41*, 8951−8955. (j) Nieman, J. A.; Ennis, M. D. *Org. Lett.* **2000**, *2*, 1395−1397. (k) Snider, B. B.; O'Hare, S. M. *Tetrahedron Lett.* **2001**, *42*, 2455−2458. (l) Hadden, M.; Nieuwenhuyzen, M.; Osborne, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron Lett.* **2001**, *42*, 6417. (m) Batey, R. A.; Powell, D. A. *Chem. Commun.* **2001**, 2362−2363. (n) Hamada, Y.; Kunimune, I.; Hara, O. *Heterocycles* **2002**, *56*, 97−100. (o) He, Y.; Mahmud, H.; Wayland, B. R.; Dias, H. V. R.; Lovely, C. J. *Tetrahedron Lett.* **2002**, *43*, 1171−1174.

(4) **1a** and **1b** have binding affinities toward guinea pig bradykinin B2 of >25 and 10 mg/mL, respectively.

(5) (a) Ma, D.; Xia, C.; Jiang, J.; Zhang, J. *Org. Lett.* **2001**, *3*, 2189−2191. (b) Snider, B. B.; Ahn, Y.; O'Hare, S. M. *Org. Lett.* **2001**, *3*, 4217−4220.

(6) Batey, R. A.; Simoncic, P. D.; Lin, D.; Smyj, R. P.; Lough, A. J. *Chem. Commun.* **1999**, 651−652.

(7) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656−670 and references cited therein.

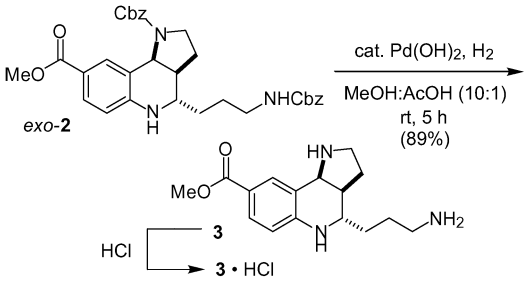
(8) (a) Batey, R. A.; Powell, D. A.; Acton, A.; Lough, A. J. *Tetrahedron Lett.* **2001**, *42*, 7935−7939. Subsequent to this report, two other groups have reported similar reactions. (b) Chang, J.; Li, C.-J. *J. Org. Chem.* **2002**, *67*, 3969−3971. (c) Yadav, J. S.; Reddy, B. V. S.; Sadasiv, K.; Reddy, P. S. R. *Tetrahedron Lett.* **2002**, *43*, 3853−3856.

(9) The *endo*- and *exo*-diastereomers are defined based on the Diels−Alder reaction where H-4 and H-3a have a *cis* and *trans* relationship, respectively.

acid. With 50 mol % AcOH, TFA, or DL-tartaric acid, the *endo* diastereomer is formed predominately, whereas with the sulfonic or citric acids, the *exo* diastereomer is favored. Pronounced solvent effects were also observed, with notably THF/H_2O preferentially giving the *endo* adduct. However, conducting the reaction in dry THF and reducing the amount of CSA to 5 mol % gives the optimal yield and selectivity for *exo*-**2**.

Separation of the diastereomers by flash chromatography through silica gel gave *exo* adduct **2** in 65% yield and >98% d.r. as determined by ^{1}H NMR. Deprotection of *exo*-**2** with Pearlman's catalyst followed by acidification with HCl yielded the triamine salt **3**, which displayed ^{1}H and ^{13}C NMR spectra identical to the same compound synthesized independently by Ma and Snider[5] (Scheme 2). This 2:1 coupling

Scheme 2

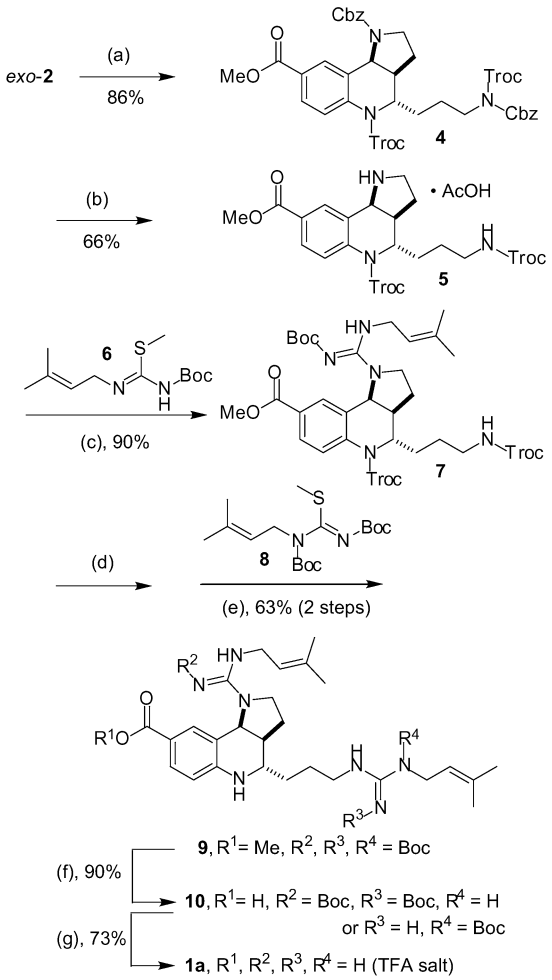


reaction allows for the rapid synthesis of the vital tricyclic triamine core of the martinelline alkaloids in only two synthetic steps and 58% overall yield. In addition, the reaction has been carried out on relatively large scales (20 mmol) with no significant change in the yield or diastereomeric ratio of product.

Having established a route for the tricyclic triamine core of the *Martinella* alkaloids, we turned our attention to the challenging task of installing the guanidine moieties. Initial attempts to install both the N-1 and N-13 isoprenylguanidines directly onto **3** were met with limited success, and we decided to introduce each guanidine group sequentially, beginning with the more substituted guanidine at the pyrrolidine nitrogen. Protection of *exo*-**2** at both the aniline and carbamate nitrogens by deprotonation with 3.0 equiv KHMDS and treatment with TrocCl yielded the fully protected triamine **4** (Scheme 3).

The Cbz groups were then removed by hydrogenation with Pearlman's catalyst in 20:1 MeOH/AcOH to give the free

Scheme 3[a]



[a] Reagents and conditions: (a) (i) KHMDS (3.0 equiv), THF/dioxane (20:1), −78 °C, 1 h, (ii) TrocCl (3.5 equiv), −78 °C, 4 h; (b) $Pd(OH)_2$ on C (12 mol %), H_2, MeOH/AcOH (20:1), rt, 4 h; (c) **6** (1.2 equiv), $HgCl_2$ (1.2 equiv), Et_3N (3.0 equiv), DMF, rt, 4 h; (d) Zn dust (15 equiv), THF/1.0 M aq pH = 4 buffer (20:1), rt, 2 h; (e) **8** (2.0 equiv), MeCN, 75 °C, 16 h; (f) MeOH/0.2 M aq NaOH (3:1), 85 °C, 16 h; (g) CH_2Cl_2/TFA (100:1), rt, 24 h.

amine **5** as the acetic acid salt.[12] The trisubstituted guanidine moiety at N-1 was installed through a $HgCl_2$-promoted guanidinylation[13] with isothiourea **6** to afford guanidine **7**. The installation of the N-13 guanidine was accomplished first by deprotection of both Troc groups using Zn dust in THF in the presence of a pH = 4.0 buffer. The crude primary amine was then refluxed in the presence of isothiourea **8** to afford the bisguanidine compound **9** in 63% yield for the two-step procedure. Conversion to the free carboxylic acid **10** was attained by refluxing methyl ester **9** in a 3:1 mixture

(10) This notation makes a distinction between "*AB*^{2}" reactions, for instance, in which one component reacts in a similar manner (e.g., diacylation of a diamine). Further discussions on the classification of these types of reactions will be the subject of a future paper.

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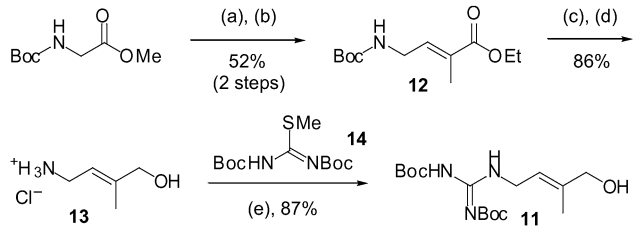
(12) In accord with earlier observations, we have found that the Troc group in not stable to hydrogenation; however, deprotection of the Cbz groups occurs faster than the Troc group, and if the reaction is carefully monitored, adequate yields of **5** can be obtained. Hancock, G.; Galpin, I. J.; Morgan, B. A. *Tetrahedron Lett.* **1982**, *23*, 249−252.

(13) (a) Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677−7680. (b) Guo, Z.-X.; Cammidge, A. N.; Horwell, D. C. *Synth. Commun.* **2000**, *30*, 2933−2943. (c) Levallet, C.; Lerpiniere, J.; Ko, Y. S. *Tetrahedron* **1997**, *53*, 5291−5304.

of MeOH/aqueous NaOH (0.2 M) for 16 h. Hydrolysis under these conditions resulted in the removal of one of the Boc groups. Deprotection of the remaining two Boc groups with TFA/CH_2Cl_2 followed by HPLC purification afforded (±)-martinellic acid **1a** in eight steps and 14% overall yield.

The synthesis of the allylic alcohol side chain **11** required for martinelline synthesis was accomplished through a five-step sequence[14] beginning with *N*-Boc glycine methyl ester (Scheme 4). The ester was reduced to the aldehyde with

Scheme 4[a]



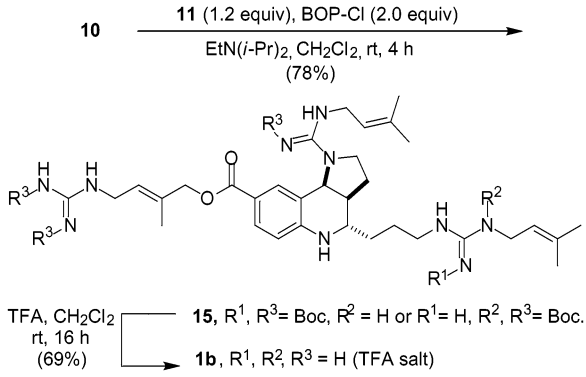
[a] Reagents and conditions: (a) DIBAL (1.5 equiv), CH_2Cl_2, −78 °C, 1 h; (b) $Ph_3P{=}C(CH_3)CO_2Et$ (1.0 equiv), CH_2Cl_2, rt, 4 h; (c) DIBAL (3 equiv), CH_2Cl_2, −78 °C, 2 h; (d) 1 M aq HCl, rt, 2 h; (e) **14** (1.2 equiv), $HgCl_2$ (1.2 equiv), Et_3N, DMF, rt, 4 h.

DIBAL and immediately reacted with the commercially available Wittig reagent to give a greater than 10:1 mixture of diastereomers in favor of the desired *E*-α,*β*-unsaturated ester **12**. Reduction of the ester to the alcohol and deprotection of the Boc group, under acidic conditions, gave the ammonium salt **13**, which was guanidinylated with di-Boc-protected methyl isothiourea **14**[13b] to afford the protected side chain **11** in 39% overall yield.

Coupling of fragments **10** and **11** was more difficult than originally anticipated possibly due to the reduced nucleophilicity of the allylic alcohol **11** and/or steric hindrance at the aromatic carboxylic acid. Many commonly employed ester coupling reagents, including EDCI/HOBt/DMAP, $SOCl_2$, CDI, CH_3SO_2Cl, DEAD/PPh_3, BOP reagent, and Mukaiyama's reagent, gave only starting material or a complex mixture of products. This reaction was finally achieved using BOP-Cl and Hünig's base, providing protected martinelline **15** in 78% yield (Scheme 5). Global deprotection of the Boc groups with TFA in CH_2Cl_2 followed by reversed-phase preparative HPLC gave (±)-martinelline **1b**, which displayed identical ^1H and ^{13}C spectra to the original compound.[2]

(14) Evidente, A.; Piccialli, G.; Sisto, A.; Ohba, M.; Honda, K.; Fujii, T. *Chem. Pharm. Bull.* **1992**, *40*, 1937−1939.

Scheme 5



In conclusion, the total synthesis of guanidine-containing alkaloids (±)-martinelline and (±)-martinellic acid has been achieved, with the heterocyclic core synthesized using a 2:1 multicomponent coupling of a substituted aniline with 2 equiv of an endocyclic enamine. We propose that this process is the first example of a biomimetic Povarov reaction. Selectivity in favor of the *exo*-diastereomer could only be achieved using protic acid catalysis under clearly defined conditions, with Lewis acid catalysis favoring the *endo*-diastereomer. Other key steps in the synthesis include a Hg(II)-promoted guanidinylation to install the sterically hindered N-1 pyrrolidine guanidine and a BOP-Cl-mediated coupling to install the ester side chain. This approach allows for the rapid synthesis of (±)-martinellic acid and the biologically more significant (±)-martinelline in nine steps (from the longest linear sequence) and 10% overall yield.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds as well as spectroscopic information for **1a** and **1b**. This information is available free of charge via the Internet at http://pubs.acs.org.

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