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Enantioselective Synthesis of the Pyrroloquinoline Core of the Martinellines

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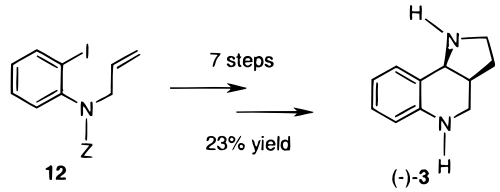
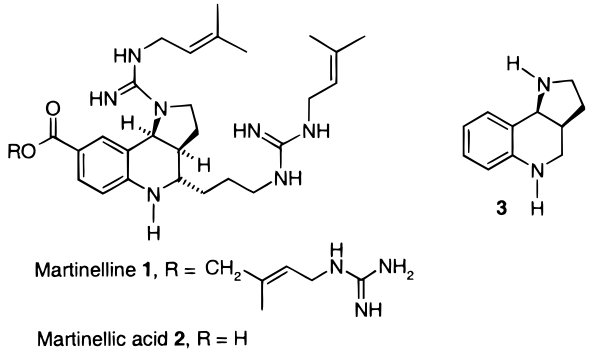
ABSTRACT



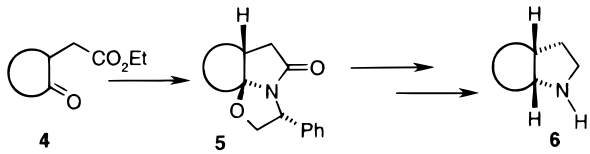
The first enantioselective synthesis of the martinelline core (–)-3 is reported. The synthesis of (–)-3 from *N*-allyl-*N*-(benzyloxycarbonyl)-2-iodoaniline (12) proceeded in seven steps and 23% overall yield. In addition, the preparation of a carbocyclic model system is described.

In 1995, scientists at Merck reported the isolation of two natural products from a family of tropical plants that have long been used by Amazon Indian tribes for medicinal purposes.[1] These new products, martinelline (**1**) and martinellic acid (**2**), were found to possess antibacterial activity as well as affinity for adrenergic, muscarinic, and bradykinin receptors.[1] The relative stereochemical assignments for the martinellines are based entirely on spectral observations, and the absolute configurations are unknown. Although the unusual pyrroloquinoline nucleus of the martinellines has attracted the attention of several research laboratories, only syntheses of the racemic pyrroloquinoline core have been reported to date.[2] Herein we describe our approach to these interesting natural products and the first enantioselective synthesis of **3**, the pyrroloquinoline core of the martinellines.



We have previously described general methodology for the preparation of chiral, *cis*-fused bicyclic pyrrolidines such as **6** (Scheme 1).[3] Condensation of the appropriate γ-ketoester

Scheme 1



(1) 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.

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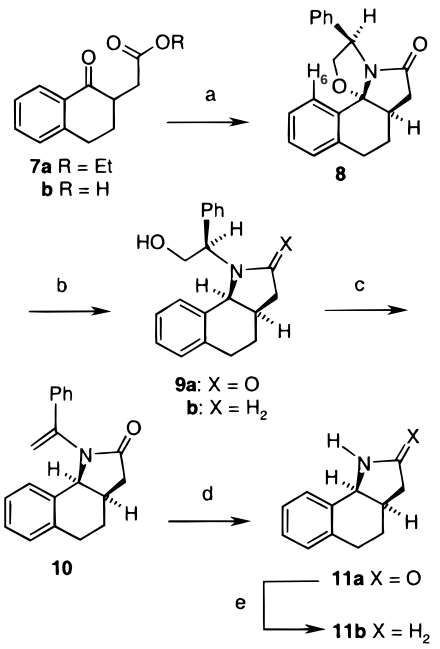
Scheme 2

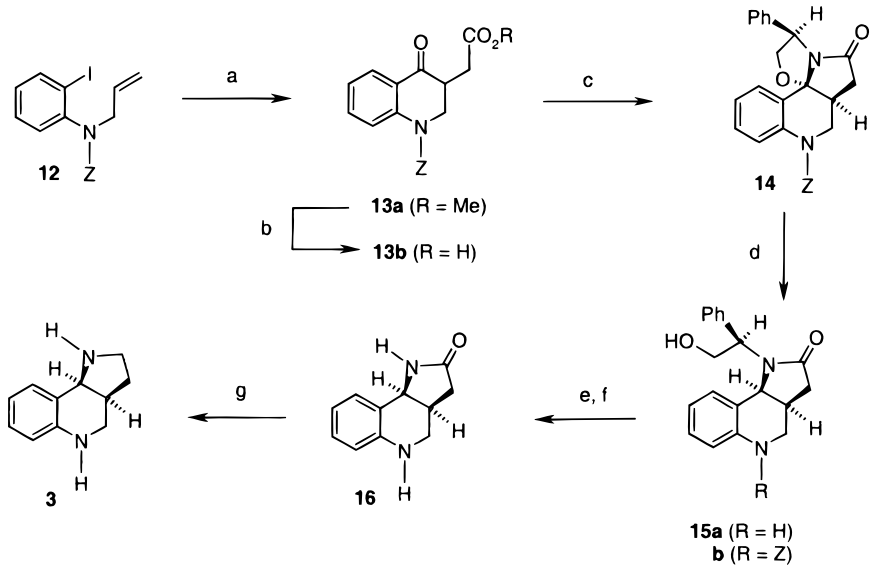


Reaction Conditions: a) (*R*)-(-)-phenylglycinol, toluene, reflux, 76%; b) Et_3SiH, $TiCl_4$, -78 °C to rt, 92% for **9a**; c) $LiOH{\cdot}H_2O$, DMSO, 140 °C; d) HCl, THF, H_2O, reflux, 76%; e) $LiAlH_4$, THF, reflux, 85%.

4 with phenylglycinol generates the lactam **5**, in which the absolute stereochemistry of the ring-junction carbons is established. To test the viability of this approach toward the synthesis of the martinellines, we examined this chemistry on the readily accessible tetralone **7a** (Scheme 2).[4] Unlike our earlier studies, ester **7a** failed to react with phenylglycinol even under forcing conditions. Fortunately, the derived carboxylic acid **7b** participated nicely in the desired chemistry. Condensation of **7b** with (*R*)-(−)-phenylglycinol in refluxing toluene generated the lactam **8** in a 76% isolated yield as a single stereoisomer. Analysis of a series of differential NOE experiments supported the stereochemical assignment depicted.[5] Although **8** could be stereoselectively reduced to the pyrrolidine **9b** with a variety of reducing agents ($LiAlH_4$, BH_3•THF, and DIBAL-H), the presence of two benzylic carbon−nitrogen bonds in **9b** complicated efforts to selectively cleave the pendant 2-hydroxy-1-phenethyl moiety. However, successful removal was realized through tricyclic-lactam **9a**, readily obtained by stereoselective reduction of **8** with triethylsilane in the presence of titanium tetrachloride.[3] Treatment of **9a** as a solution in DMSO with lithium hydroxide at elevated temperatures generates **10**, which upon acid-catalyzed hydrolysis provides the known lactam **11a** in 76% overall yield from **8**.[6] The coupling constant observed for the ring-fusion protons (J = 6.5 Hz) was consistent with the reported values for the *cis*-isomer (lit.,[7,8] J = 6.4 and 6.5 Hz). Finally, reduction of **11a** with lithium aluminum hydride generated the pyrrolidine **11b** in 85% yield.

Encouraged by the successful outcome of these model reactions, we turned our attention to the pyrroloquinoline core of the martinellines (**3**). Toward this end, we required the carboxylic acid **13b** (Scheme 3). We prepared this material via a modification of the palladium-catalyzed carbonylative cyclization procedure reported by Negishi et al.[9] Treatment of the Z-protected *N*-allyl-2-iodoaniline **12**

Scheme 3



Reaction Conditions: a) $Pd(PPh_3)_2Cl_2$, Et_3N, MeOH, PhH, MeCN, 65 °C, CO (1600 psi), 60%; b) LiOH, dioxane, H_2O, 0 °C, 95%; c) (*R*)-(-)-phenylglycinol, toluene, reflux (-H_2O), 77%; d) $TiCl_4$, Et_3SiH, CH_2Cl_2, -78 °C to rt, 85% (**15a** and **15b**); e) $LiOH{\cdot}H_2O$, DMSO, 140 °C, 84%; f) HCl, THF, H_2O, reflux, 80%; g) $LiAlH_4$, THF, reflux, 92%.

with catalytic dichlorobis(triphenylphosphine)palladium(II) under 1600 psi carbon monoxide at 60 °C in the presence of methanol provided the quinolone ester **13a** in 60% isolated yield.[10] Hydrolysis of **13a** provided the acid **13b**,[11] which upon condensation with (*R*)-(−)-phenylglycinol generated tetracyclic lactam **14** in 77% isolated yield as a single isomer. Treatment of **14** with triethylsilane in the presence of titanium tetrachloride gave a 3:1 ratio of the *cis*-fused pyrrolidinones **15a** and **15b** in 85% yield. An X-ray crystal structure of **15a** confirmed the indicated absolute stereochemistry of the pyrroloquinoline ring-fusion. Removal of the 2-hydroxy-1-phenethyl moiety from **15a** and **15b** was readily accomplished using the two-step elimination/hydrolysis protocol described above to give the lactam **16** in 67% yield.[12] Finally, reduction of **16** with lithium aluminum hydride afforded the tricyclic diamine **3** in 92% yield.[13]

The preparation of the pyrroloquinolone **3** represents the first enantioselective synthesis of the heterocyclic core of the martinellines. We are currently applying the methodology described herein toward the full construction of these interesting natural products.

Acknowledgment. We thank Randy M. Jensen for performing the NOE difference experiments on compound **8**. We also thank Fusen Han for solving the X-ray crystal structure of compound **15a**.

Supporting Information Available: Experimental procedures and full characterization of compounds **3**, **8**, **9a**, **9b**, **11a**, **11b**, **13a**, **13b**, and **14**−**16** are included.

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(3) Ennis, M. D.; Hoffman, R. L.; Ghazal, N. B.; Old, D. W.; Mooney, P. A. *J. Org. Chem.* **1996**, *61*, 5813. For pioneering work in this area see the A. I. Meyers references cited within.

(4) For the synthesis of **7a** and **7b**, see: Ravina, E.; Fueyo, J.; Teran, C.; Cid, J.; Garcia Mera, G.; Orallo, F.; Bardan, B. *Pharmazie* **1992**, *47*, 574. Barlocco, D.; Pinna, G. A.; Carboni, L.; Cipolla, P. *Farmaco* **1989**, *44*, 967. Fontenla, J. A.; Osuna, J.; Rosa, E.; Castro, M. E.; G-Ferreiro, T.; Loza-García, I.; Calleja, J. M.; Sanz, F.; Rodríquez, J.; Raviña, E.; Fueyo, J.; F-Masaguer, C.; Vidal, A.; de Ceballos, M. L. *J. Med. Chem.* **1994**, *37*, 2564.

(5) The key finding in support of structure **8** was an observed NOE between the phenylglycinol-derived aromatic ring and the indicated H_6 proton.

(6) For a related, three-step procedure for the removal of a 2-hydroxy-1-phenethyl side-chain, see Fains, O.; Vernon, J. M. *Tetrahedron Lett.* **1997**, *38*, 8265.

(7) Oppolzer, W. *J. Am. Chem. Soc.* **1971**, *93*, 3834.

(8) Koot, W.-J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1992**, *33*, 7969.

(9) Tour, J. M.; Negishi, E. *J. Am. Chem. Soc.* **1985**, *107*, 8289. Negishi, E.; Copéret, C.; Ma, S.; Mita, T.; Sugihara, T.; Tour, J. M. *J. Am. Chem. Soc.* **1996**, *118*, 5904.

(10) We have applied this palladium-catalyzed carbonylative cyclization chemistry to the synthesis of related heterocycles. Further details of this interesting transformation will be reported shortly.

(11) Although the application of H_2O as the nucleophile instead of methanol in the carbonylative cyclization reaction with **12** generated **13b** directly, purification from other carboxylic acid byproducts proved to be problematic.

(12) Compounds **15a** and **15b** can be subjected separately or as a crude mixture to the elimination protocol. When the crude mixture was used, an improved three-step yield of 67% for **16** was realized.

(13) As with compounds **11a** and **11b**, compounds **16** and **3** displayed the ring-fusion proton coupling constant typical for a *cis*-fused product (J = 6.8 and 6.3 Hz, respectively). See also ref 1.