ORGANIC LETTERS

2005
Vol. 7, No. 12
2437−2440

An Approach to the Tricyclic Core of Madangamines Based upon a Biogenetic Scheme

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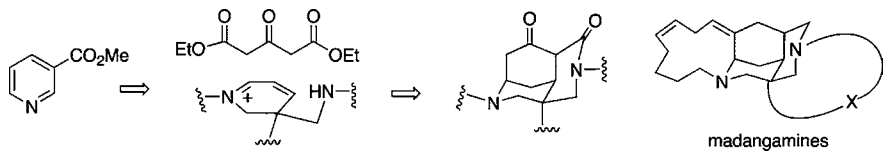
Received April 6, 2005

ABSTRACT



A short synthesis of intermediates possessing the tricyclic core of natural madangamines, bioactive alkaloids found in marine sponges, is described. The key reaction entails the condensation of the sodium salt of diethylacetonedicarboxylate with a dihydropyridinium salt derivative. This new approach is modeled on a biogenetic proposal linking madangamines to ircinals, related alkaloids occurring in sponges of the same order.

Madangamine A (Figure 1) is a cytotoxic alkaloid that exhibits inhibitory activity against a number of tumor cell lines. It was isolated from the marine sponge *Xestospongia ingens* by Andersen in 1994.[1] The discovery of madangamine A was followed by the isolation, from the same sponge, of four analogues, madangamines B−E.[2] These alkaloids belong to a large family of natural products extracted from sponges of the order Haplosclerida.[3] Their tricyclic core is unprecedented, and this original structure has thus encouraged substantial synthetic efforts. As a result two approaches[4] to the tricyclic core of madangamines have been reported to date.

Interestingly, a hypothesis has been proposed to explain the biosynthetic origin of madangamines.[1] This hypothesis, based on the initial proposal of Baldwin and Whitehead concerning the biosynthesis of manzamine alkaloids,[5] suggests that madangamines can be derived from keramaphidin-like derivatives.

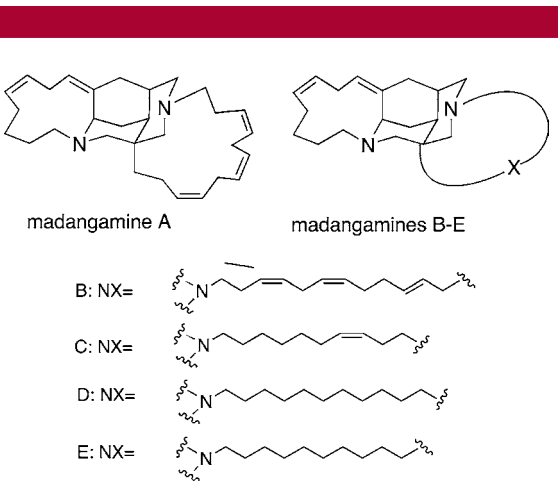


Figure 1. Structures of madangamines A−E.

In this paper we present a related but quite different pathway that links madangamines to ircinal derivatives according to Scheme 1. This proposal is based on our

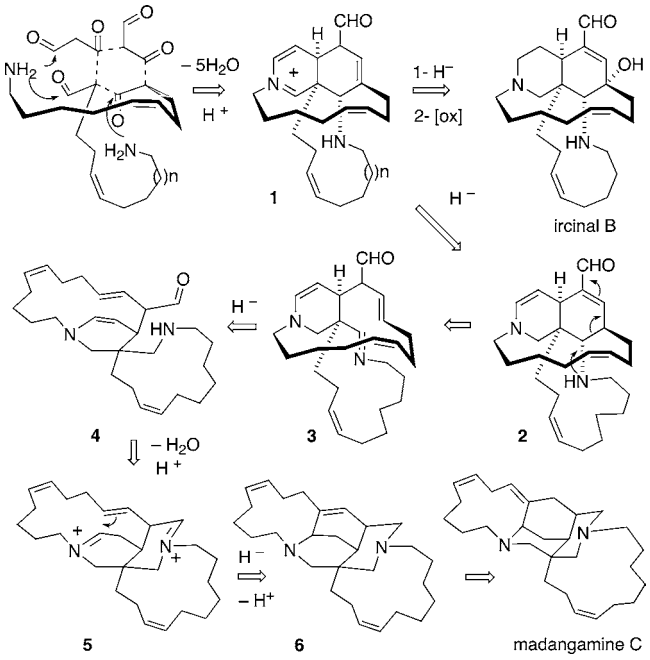
(1) Kong, F.; Andersen, R. J.; Allen, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 6007−6008.

(2) Kong, F.; Graziani, E. I.; Andersen, R. J. *J. Nat. Prod.* **1998**, *61*, 267−271.

(3) For reviews, see: (a) Matzanke, N.; Gregg, R. J.; Weinreb, S. M. *Org. Prep. Proc. Int.* **1998**, *30*, 3−51. (b) Tsuda, M.; Kobayashi, J. *Heterocycles* **1997**, *46*, 765−794. (c) Andersen, R. J.; Van Soest, R. W. M.; Kong, F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Elsevier Science: New York, 1996; Vol. 10, pp 301−355. (d) Crews, P.; Cheng, X.-C.; Adamczeski, M.; Rodriguez, J.; Jaspar, M.; Schmitz, F. J.; Traeger, S. C.; Pordesimo, E. O. *Tetrahedron* **1994**, *50*, 13567−13574.

10.1021/ol050740i CCC: $30.25
Published on Web 05/14/2005

Scheme 1. Possible Biogenetic Scenario Linking Madangamines to Ircinal Derivatives

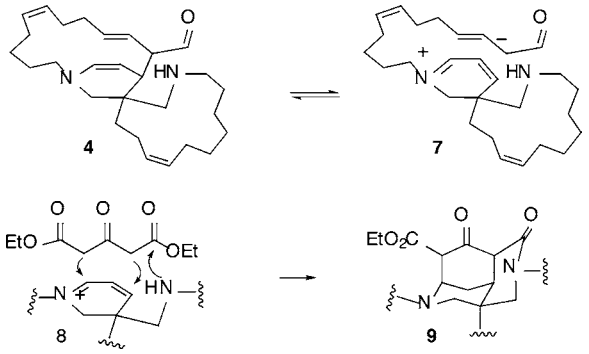


suggested modification[6] of the Baldwin and Whitehead hypothesis in which manzamine alkaloids can alternatively be viewed as derived from malondialdehyde and long chain aminoaldehyde derivatives to give intermediates such as **1** (Scheme 1). Reduction of these intermediates followed by oxidation can give access to ircinal derivatives such as ircinal B ($n = 1$), precursors of manzamines.

As an alternate pathway, intermediate **1** ($n = 3$) was reduced to give, after double-bond migration, amino aldehyde **2**. Ring opening could then occur, leading to the imine derivative **3** whose reduction would afford secondary amine **4**. Cyclization to the corresponding double-iminium salt derivative **5** could then produce produce pentacyclic intermediate **6**, a final double-bond migration affording madangamine C.

Interestingly, intermediate **4** can be considered as being in equilibrium with dihydropyridinium intermediate **7** via a retro-vinylogous Mannich reaction (Scheme 2). This observation is at the origin of our retrosynthetic analysis of the madangamine core skeleton. Accordingly, we decided to target the dihydropyridinium salts of general structure **8** and to study their reaction with acetone dicarboxylate as a bisnucleophilic reagent in order to access to the tricyclic

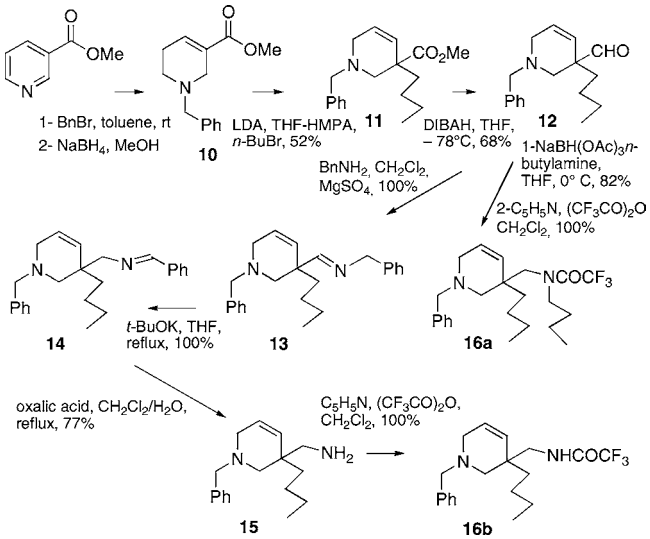
Scheme 2. From the Biogenetic Scenario to a Synthetic Strategy



derivatives **9**. In this paper we report, as a result of model experiments, the success of this approach for the construction of the tricyclic core of madangamines.

The synthesis of dihydropyridinium species corresponding to **8** started from tetrahydropyridine **10** (Scheme 3), available

Scheme 3. Synthesis of Tetrahydropyridines **16a**,**b**



in two steps from nicotinic acid methyl ester. Alkylation[7] with *n*-butyl bromide afforded derivative **11**, which was reduced to aldehyde **12**. Formation of imine **13** followed by isomerization to **14**[8] and hydrolysis gave primary amine **15**. Additionaly, reductive amination of aldehyde **12** with *n*-butylamine followed by trifluoroacetylation afforded tetrahydropyridine **16a**. Trifluoroacetylation of amine **15** finally gave tetrahydropyridine **16b**. Treatment of **16a** or **16b** (Scheme 4) with *m*-CPBA afforded *N*-oxide derivatives **17a** and **17b**, respectively, as a mixture of diastereoisomers that can be separated by chromatography on silica gel (undefined

(4) (a) Matzanke, N.; Gregg, R. J.; Weinreb, S. M.; Parvez, M. *J. Org. Chem.* **1997**, *62*, 1920−1921. (b) Yamazaki, N.; Kusanagi, T.; Kibayashi, C. *Tetrahedron Lett.* **2004**, *45*, 6509−6512. For other synthetic efforts, see: Vila, X.; Quirante, J.; Paloma, L.; Bonjoch, J. *Tetrahedron Lett.* **2004**, *45*, 4661−4664.

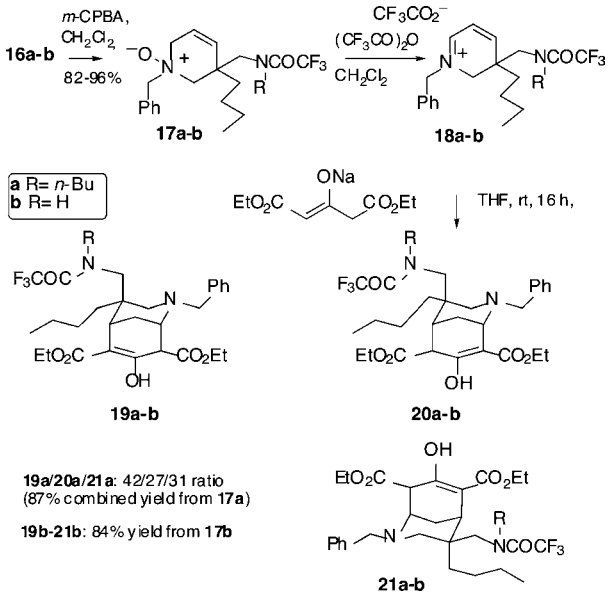
(5) Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, *33*, 2059−2062. Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C. *Chem. Eur. J.* **1999**, *5*, 3154−3161 and references therein.

(6) Kaiser, A.; Billot, X.; Gateau-Olesker, A.; Marazano, C.; Das, B. C. *J. Am. Chem. Soc.* **1998**, *120*, 8026−8034. Sanchez-Salvatori, M. d. R.; Marazano, C. *J. Org. Chem.* **2003**, *68*, 8883−8889 and references therein.

(7) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, *14*, 2433−2436.

(8) De Kimpe, N.; De Smaele, D.; Hofkens, A.; Dejaegher, Y.; Kesteleyn, B. *Tetrahedron* **1997**, *53*, 10803−10816.

Scheme 4. Synthesis of Salts **18**, Analogues of Salts **8**, and Their Reactions with Acetone Dicarboxylate Diethylester as a Bisnucleophilic Reagent



stereochemistry). The desired dihydropyridinium salts **18a** and **18b** were, however, obtained using the conditions of the Polonovski−Potier reaction[9] on the corresponding crude *N*-oxide diastereoisomeric mixtures.

In a preliminary study, salt **18a** was treated with the sodium salt of acetone dicarboxylate diethyl ester at ambient temperature, and the adducts were purified by chromatography on silica gel. Three adducts **19a**, **20a**, and **21a** were isolated under these conditions in a 42/27/31 ratio, and their structure was resolved by NMR spectroscopy.[10] This structural attribution was further secured by an X-ray analysis of adduct **19a**, depicted in Figure 2. The results clearly showed that the stereoselectivity of addition was rather low and in favor of the undesired isomers **19a** and **20a**, which cannot, in principle, form an amide bond with the masked secondary amine to give the madangamine core.

However, this problem was shown to be easily overcome on the basis of a study of the reaction starting from dihydropyridinium salt **18b**.

Thus, treatment of salt **18b** with the sodium salt of acetone dicarboxylate diethyl ester resulted in the formation of a mixture of adducts. Adducts **19b** and **21b** were detected in this mixture, but due to a difficult separation, only adduct **19b** could be isolated and characterized.

However, when the crude mixture of adducts was treated with an alkaline solution of EtOH/H_2O at reflux, two tricyclic derivatives **22** and **23** were obtained in 50% overall yield

(9) (a) Grierson, D. S.; Harris, M.; Husson, H.-P. *J. Am. Chem. Soc.* **1980**, *102*, 1064−1082. (b) For a review, see: Grierson, D. S. *Org. React.* **1990**, *39*, 85−295.

(10) All complex structures were resolved by intensive NMR spectroscopic studies, including one- and two-dimensional NMR experiments (COSY 90, NOESY, HMQC, HMBC).

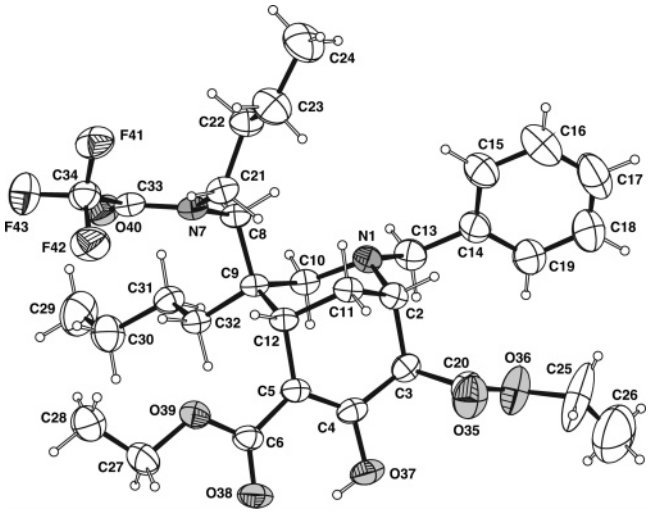
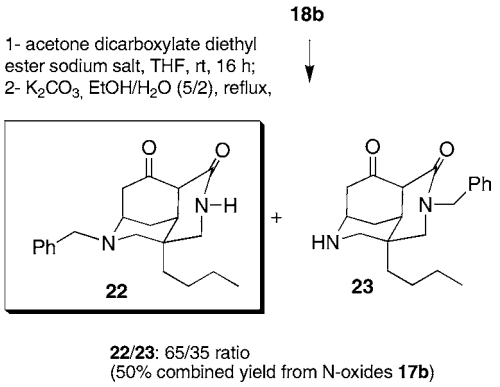


Figure 2. ORTEP drawing of adduct **19a**. Displacement ellipsoids are shown at the 30% probability level.

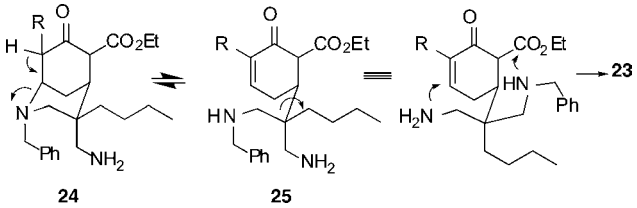
from *N*-oxides **17b** and in a 65/35 ratio (Scheme 5). These products were separated by chromatography on silicagel.

Scheme 5. Madangamine Tricyclic Core Models



This result demonstrates that the "wrong" isomers **19** and **20** can in fact also give access to the desired tricyclic core of madangamines via an interesting rearrangement. A simple mechanism for this rearrangement, explaining the formation of the tricyclic derivative **23**, is depicted in Scheme 6. The

Scheme 6. Proposed Mechanism for the Formation of Tricyclic Derivative **23**



initial adduct **24** (equivalent to **19b** and **20b** if R = CO_2Et, but R = H is also to be considered) is likely to be in equilibrium with enone **25** by a retro Michael process. Rotation of the C−C bond adjacent to the quaternary center then allows amide formation with the benzylic amino group followed by Michael addition of the primary amine and decarboxylation to give tricyclic derivative **23**.

In conclusion, the successful synthesis of madangamine models **22** and **23** is encouraging for future work concerning the total synthesis of madangamines based upon our biogenetically inspired strategy. The approach is stereoselective and also offers some flexibility. In addition, this access to the core skeleton of madangamines competes favorably with other reported strategies with regard to the number of steps (10 steps from the readily accessible tetrahydropyridine **11**). Finally, it should be emphasized that the novel "3 + 3" nucleophilic addition of acetone dicarboxylate esters to dihydropyridinium salts described here, which gives adducts such as **19**−**21**, offers a practical access to the 2-azabicyclo-[3.3.1]nonane framework.

Supporting Information Available: Experimental procedures and copies of NMR spectra for compounds **11**−**15**, **16a**,**b**, **17a**,**b**, **18a**,**b**, **19a**,**b**, **20a**, **21a**, **22**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050740I