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Synthesis of (+)-Madindoline A and (+)-Madindoline B

Lifeng Wan and Marcus A. Tius*

Department of Chemistry, 2545 The Mall, University of Hawaii, Honolulu, Hawaii 96822, and The Cancer Research Center of Hawaii, 1236 Lauhala Street, Honolulu, Hawaii 96813

tius@gold.chem.hawaii.edu

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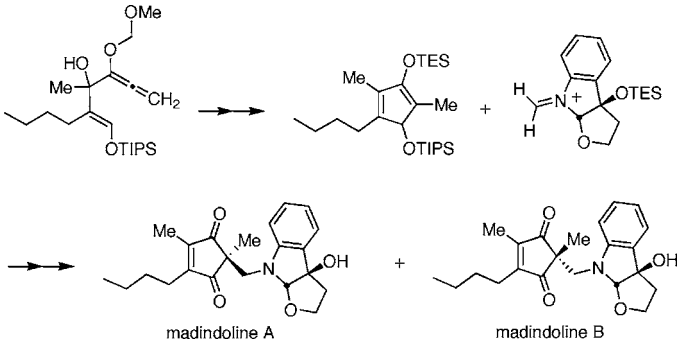
ABSTRACT



The allene ether version of the Nazarov cyclization was used to construct the cyclopentane dione portion of madindolines A and B. The racemic cyclopentane dione from the Nazarov cyclization was converted to an enol ether that was combined with the chiral, nonracemic hydroxyfuroindoline in a Mannich reaction. Deprotection and oxidation led to (+)-madindoline A and (+)-madindoline B.

In 1996, Ōmura and co-workers isolated two small molecules, madindolines A and B, of unique structure from the fermentation broth of *Streptomyces nitrosporeus* K93-0711.[1,2] Both compounds have extraordinary activity and are selective inhibitors of interleukin-6 (IL-6).[3,4] Because the overproduction of IL-6 is associated with, inter alia, cancer cachexia,[5] multiple myeloma,[6] and rheumatoid arthritis,[7] the madindolines could serve as pharmaceutical lead compounds. As sometimes happens, the microorganism stopped producing these two metabolites. Because these compounds have become unavailable from their original source, chemical synthesis provides the only means of acquiring material for biological study.

A number of syntheses have been developed. A summary of the successful synthetic strategies that have been employed appears in Scheme 1. The first synthesis by Ōmura, Smith, and co-workers[8,9] formed the cyclopentene through the RCM reaction of diene **1**. Kobayashi's synthesis made use of a regioselective aldol condensation of triketone **3**.[10,11] In both the Kobayashi and the Ōmura−Smith syntheses, an asym-

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(2) Takamatsu, S.; Kim, Y.-P.; Enomoto, A.; Hayashi, M.; Tanaka, H.; Komiyama, K.; Ōmura, S. *J. Antibiot.* **1997**, *50*, 1069.

(3) Hayashi, M.; Rho, M.-C.; Enomoto, A.; Fukami, A.; Kim, Y.-P.; Kikuchi, Y.; Sunazuka, T.; Hirose, T.; Komiyama, K.; Ōmura, S. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 14728.

(4) Ōmura, S.; Hayashi, M.; Tomoda, H. *Pure Appl. Chem.* **1999**, *71*, 1673.

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(6) Zhang, X. G.; Bataille, R.; Jourdan, M.; Saeland, S.; Banchereau, J.; Mannoni, P.; Klein, B. *Blood* **1990**, *76*, 2599.

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(8) Sunazuka, T.; Hirose, T.; Shirahata, T.; Harigaya, Y.; Hayashi, M.; Komiyama, K.; Ōmura, S.; Smith, A. B., III *J. Am. Chem. Soc.* **2000**, *122*, 2122.

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(10) Hosokawa, S.; Sekiguchi, K.; Enemoto, M.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 6429.

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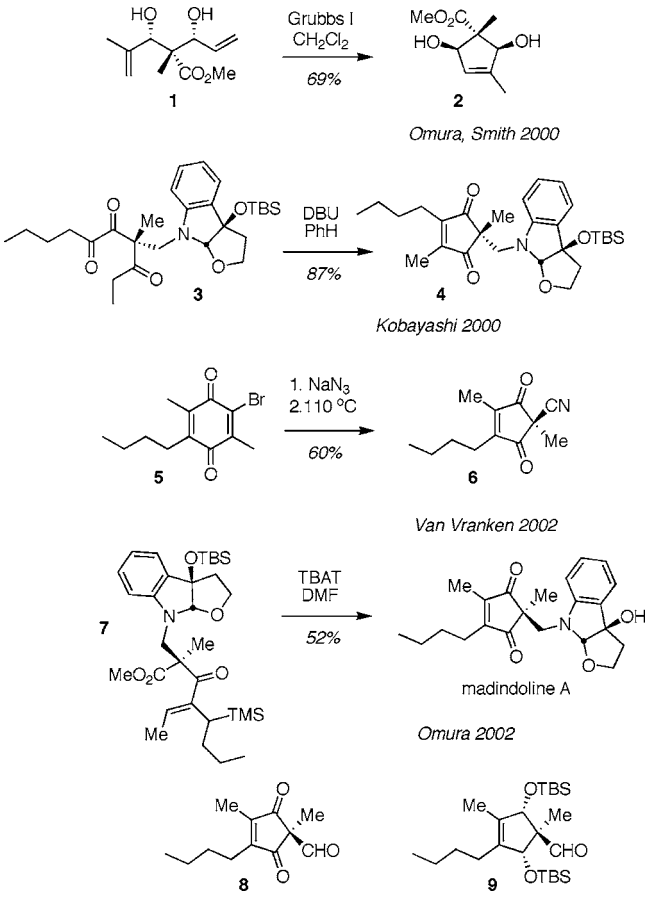
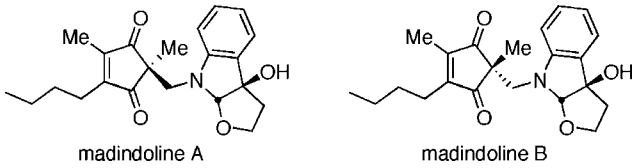
Scheme 1



metric Evans aldol reaction was employed. Van Vranken published a very clever synthesis of racemic madindolines A and B through a Moore ring contraction of **5** that led to **6**.[12] Ōmura's second-generation approach coupled a fluorodesilylation reaction of **7** with an intramolecular Claisen condensation to produce (+)-madindoline A.[13,14] Fluorodesilylation−Claisen condensation of a structural isomer of **7** gave (+)-madindoline B.



Since Ōmura and Smith had shown that the hydroxyfuroindoline ring could be prepared easily and enantioselectively from commercially available tryptophol,[8,9] joining heterocycle and cyclopentane dione fragments by means of a reductive amination was attractive. However, Kobayashi found that aldehyde **8** was very unstable and underwent rapid decomposition upon standing at room temperature.[10] Deformylation is likely to be the dominant reaction pathway in any attempt to conduct the reductive amination of a substrate such as **8** that has the adjacent keto groups intact. By contrast, the reductive amination of formylcyclopentene **9** by Ōmura and Smith took place in high yield but necessitated reduction, protection, deprotection, and reoxidation steps in the synthesis.[8]

This was the backdrop against which our synthesis was designed. From the outset, there were two goals. The first was to use the allene ether version[15] of the Nazarov cyclization[16] for an efficient preparation of the cyclopentenone. The second was to install the heterocyclic fragment by means of a Mannich reaction. The ready availability of chiral, nonracemic hydroxyfuroindoline prompted us to develop the stereodivergent synthesis of (+)-madindolines A and B that is summarized in Scheme 2. Hexanamide **10** was formylated and converted to *E*-silyl enol ether **11** in 50% yield for the two steps. The geometry of the double bond depends on the base that is used in the second step (triethylamine led to a 3:1 *E*/*Z* mixture) and is important because our earlier work had shown that the Nazarov cyclization proceeds poorly from substrates derived from *Z*-enamides.[17] Treatment of **11** with methyllithium led to enone **12** in 70% yield. The substrate for the Nazarov cyclization (**13**) was formed by addition of 1-lithio-1-(methoxy)methoxyallene[18] to **12**. Upon exposure to trifluoroacetic anhydride and 2,6-lutidine, cyclization of **13** to **14** took place in 88% yield over the two steps.[18] No loss of the silyl ether protecting group was observed. The exocyclic double bond in **14** was saturated quantitatively and selectively by hydrogenation over palladium on carbon. Conversion of cyclopentenone **15** to triethylsilyl enol ether **16** turned out to be straightforward when the enolate was generated at −78 °C and trapped at −50 °C. Success of this step could not have been predicted from the outset because there are three sites where deprotonation of **15** could have occurred. Also, [1,5]-hydrogen shifts might have converted **16** to three isomeric silyl enol ethers.

Fortunately, these concerns proved to be unfounded. In the key Mannich reaction, the coupling of cyclopentane fragment **16** with chiral, nonracemic hydroxyfuroindoline fragment **27** took place in dichloromethane in the presence of $ZnBr_2$ at −30 °C.[19] Enol ether **16** was added to the solution last. The solution was heterogeneous but became homogeneous upon warming to 0 °C. It should be noted that the Mannich reaction failed to take place in THF. In both of the two major products, diastereomers **17** and **18**, the relative

(11) Hosokawa, S.; Sekiguchi, K.; Hayase, K.; Hirukawa, Y.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 6435.
(12) McComas, C. C.; Perales, J. B.; Van Vranken, D. L. *Org. Lett.* **2002**, *4*, 2337.
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(14) Hirose, T.; Sunazuka, T.; Yamamoto, D.; Kaji, E.; Ōmura, S. *Tetrahedron Lett.* **2006**, *47*, 6761.
(15) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284.
(16) For reviews of the Nazarov reaction, see: (a) Habermas, K. L.; Denmark, S.; Jones, T. K. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons, Inc.: New York, 1994; Vol. 45, pp 1−158. (b) Harmata, M. *Chemtracts* **2004**, *17*, 416. (c) Frontier, A.; Collison, C. *Tetrahedron* **2005**, *61*, 7577. (d) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479. (e) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193.
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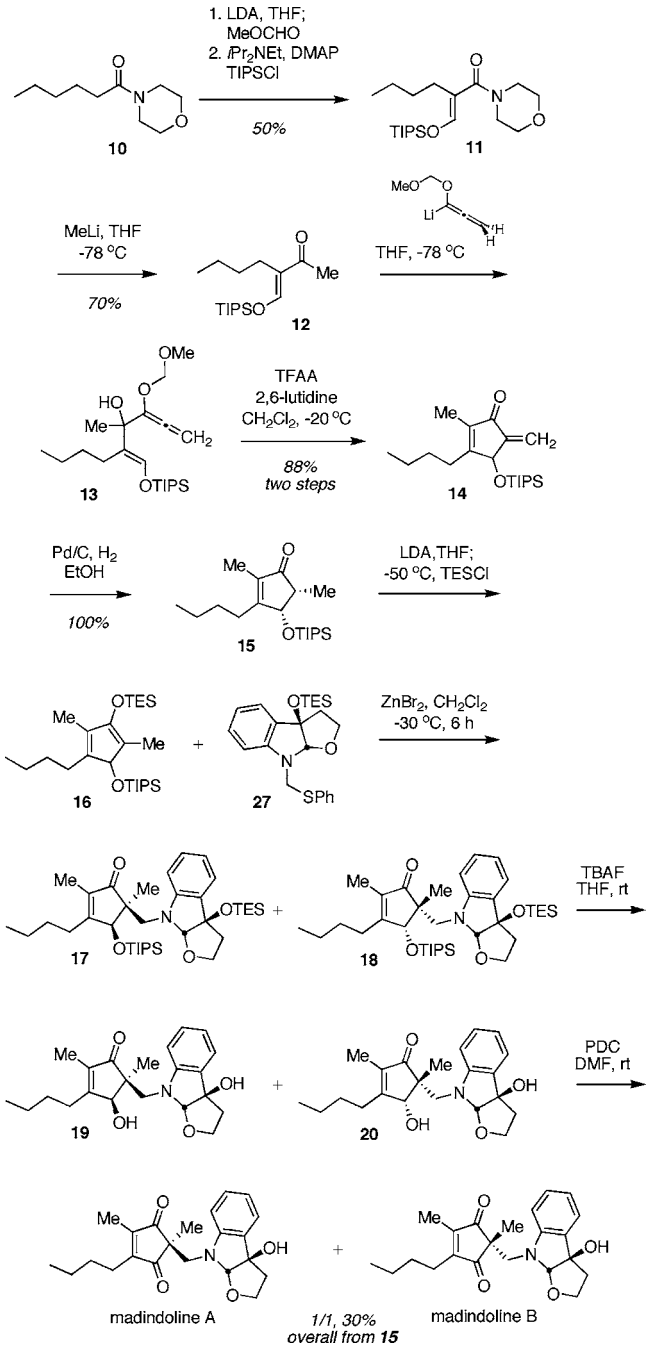
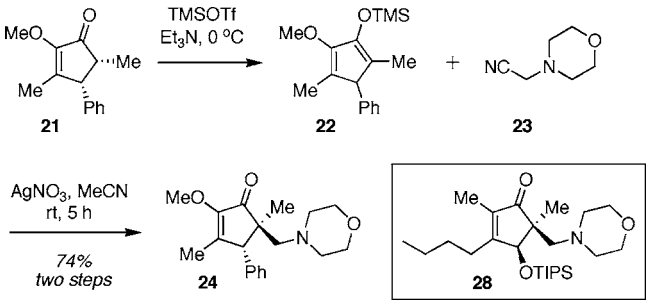
Scheme 2



stereochemistry for the Mannich reaction was cis. This was ascertained by observing a positive NOE of the signal for the cyclopentane methine proton upon irradiation of the quaternary methyl group in **19** and **20**. The stereochemistry was not the one predicted on the basis of the model study summarized in Scheme 3. The Mannich reaction of silyl enol ether **22** with α-aminonitrile **23** took place in the presence of $AgNO_3$ in acetonitrile to produce aminocyclopentane **24** in good yield. The stereochemistry of product **24** was consistent with addition of the electrophile trans to the phenyl substituent and is the one expected for **17** and **18** (Scheme 2). The difference in stereochemical outcomes (**24** vs **17** and

Scheme 3

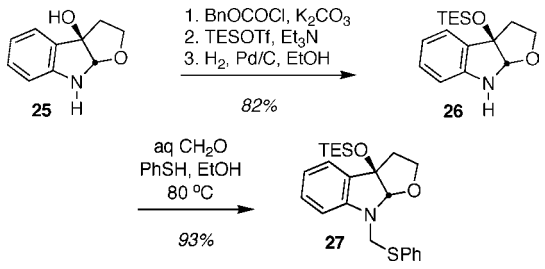


18) for the Mannich reactions is probably not related to the source of the iminium ion. Exposure of **16** to α-aminonitrile **23** in the presence of $AgNO_3$ in acetonitrile led to aminocyclohexane **28** (Scheme 3) in 66% overall yield from **15**. The stereochemistry of **28** reflects the influence of the silyloxy group and results from cis addition. This effect may be due to an electrostatic attraction between the positively charged iminium ion and the partial negative charge on the silyloxy oxygen atom.[20] Woerpel and co-workers[21] have demonstrated that strategically placed alkoxy substituents on oxocarbenium ions can powerfully influence the stereochemical course of *nucleophilic* additions in a contrasteric sense. It remains to be seen whether the present work is related to his. If the effect is general, it could be useful in a broader context.

Fluorodesilylation of the mixture of **17** and **18** followed by oxidation with pyridinium dichromate led to a 1:1 mixture of (+)-madindolines A and B in 30% overall yield for the four steps from **15**. The two products were separated by flash column chromatography and were found to have properties matching the published data for the two natural products.

The preparation of **27** is summarized in Scheme 4. Twice

Scheme 4



recrystallized hydroxyfuroindoline **25**[8,9] (>98% ee) was converted to the benzyloxy carbamate and then exposed to triethylsilyl triflate and triethylamine. Hydrogenolytic cleavage of the carbamoyl group led to **26** in 82% overall yield. Attempts to convert the hydroxyl group in **25** to the silyl ether in the presence of the free amine invariably led to lower

(20) We thank a referee for suggesting this explanation.

(21) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879.

yields of material that was difficult to purify. Heating an ethanolic solution of **26** in the presence of thiophenol and aqueous formaldehyde gave **27** in 93% yield as an isolable and stable precursor of the iminium ion.

This concludes a brief (10 steps) enantiodivergent synthesis of (+)-madindoline A and (+)-madindoline B in 9.2% overall yield from **10**. The use of cyclopentadiene **16** as a key intermediate as well as the diastereoselective Mannich reaction that produces **17** and **18** are noteworthy. Because the Mannich reaction is diastereoselective, there is an opportunity to use the asymmetric version of the Nazarov[22] reaction to form **16**, or its equivalent, for an asymmetric total synthesis targeted solely at (+)-madindoline A, or at (+)-madindoline B.

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Supporting Information Available: Experimental procedures for **11**−**20**, **26**, **27**, (+)-madindoline A, and (+)-madindoline B; ^{1}H and ^{13}C NMR, HRMS, and IR data for **11**, **12**, **14**, **15**, **26**, **27**, (+)-madindoline A, and (+)-madindoline B; and reproductions of ^{1}H and ^{13}C NMR spectra for **11**, **12**, **14**, **15**, **26**, **27**, (+)-madindoline A, and (+)-madindoline B. This material is available free of charge via the Internet at http://pubs.acs.org.

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