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# Synthetic Studies on (+)-Manzamine A: Stereoselective Synthesis of the Tetracyclic Core Framework

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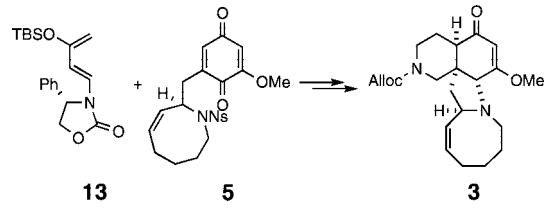
## ABSTRACT




**13** **5** **3**

**The stereoselective synthesis of the tetracyclic intermediate 3 for (+)-manzamine A (1) has been achieved. The key features of this stereoselective synthesis of 3 are the Rh-catalyzed asymmetric hydrogenation and a diastereoselective intermolecular Diels−Alder reaction. The 8-membered ring is efficiently constructed utilizing our Ns-strategy.**

Manzamine A (**1**), a naturally occurring $\beta$-carboline alkaloid isolated from a sponge of genus *Haliclona* by Higa[1] and from genus *Pellina* by Kobayashi,[2] has shown numerous biological activities, including cytotoxic,[1] antibacterial,[2] antimalarial,[3] insecticidal,[4] anti-inflammatory,[5] and anti-HIV[6] activities. The remarkable biological activities coupled with its highly complex structure have made it an attractive total synthesis target, and several synthetic studies on this family of compounds have been published.[7] However, only three total syntheses[8] have been reported to date. The crucial step in the synthesis of **1** should be the construction of the complex pentacyclic skeleton because the ready conversion from its biosynthetic precursor ircinal A (**2**) to **1** is known.[9] Herein, we report the stereocontrolled synthesis of tetracyclic intermediate **3** for the total synthesis of (+)-**1** (Scheme 1).

We envisioned that formation of the D ring and addition of the C1 unit to the vinylogous ester **3** could be achieved

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(1) (a) Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986**, *108*, 6404.

(2) Nakamura, H.; Deng, S.; Kobayashi, J.; Ohizumi, Y.; Tomotake, Y.; Matsuzaki, T.; Hirata, Y. *Tetrahedron Lett.* **1987**, *28*, 621.

(3) (a) Ang, K. K. H.; Holmes, M. J.; Higa, T.; Hamann, M. T.; Kara, U. A. K. *Antimicrob. Agents Chemother.* **2000**, *44*, 1645. (b) El Sayed, K. A.; Kelly, M.; Kara, U. A. K.; Ang, K. K. H.; Katsuyama, I.; Dunbar, D. C.; Khan, A. A.; Hamann, M. T. *J. Am. Chem. Soc.* **2001**, *123*, 1804. (c) Winkler, J. D.; Londregan, A. T.; Hamann, A. T. *Org. Lett.* **2006**, *8*, 2591. (d) Winkler, J. D.; Londregan, A. T.; Ragains, J. R.; Hamann, A. T. *Org. Lett.* **2006**, *8*, 3407. (e) Winkler, J. D.; Londregan, A. T.; Hamann, A. T. *Org. Lett.* **2007**, *9*, 4467.

(4) Edrada, R. A.; Proksch, P.; Wray, V.; Witte, L.; Müller, W. E. G.; Van Soest, R. W. M. *J. Nat. Prod.* **1996**, *59*, 1056.

(5) Mayer, A. M. S.; Gunasekara, S. P.; Pomponi, S. A.; Sennet, S. H. PCT Int. Appl., WO 0056304 A2 20000928, 2000.

(6) Rao, K. V.; Donia, M. S.; Peng, J.; Garcia-Palomero, E.; Alonso, D.; Martinez, A.; Medina, M.; Franzblau, S. G.; Tekwani, B. L.; Khan, S. I.; Wahyuono, S.; Willett, K. L.; Hamann, M. T. *J. Nat. Prod.* **2006**, *69*, 1034.

(7) For reviews of manzamine alkaloid, see: (a) Tsuda, M.; Kobayashi, J. *Heterocycles* **1997**, *46*, 725. (b) Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201.

(8) (a) Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425. (b) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C *J. Am. Chem. Soc.* **1999**, *121*, 866. (c) Humphrey, J.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584. (d) Tokumaru, K.; Arai; S., ; Nishida, A. 126th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, 2006; 028[F]-031.

(9) (a) Kondo, K.; Shigemori, H.; Kikuchi, Y.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 2480. (b) Choo, Y.-M.; Hamann, M. T *Heterocycles* **2007**, *71*, 245.

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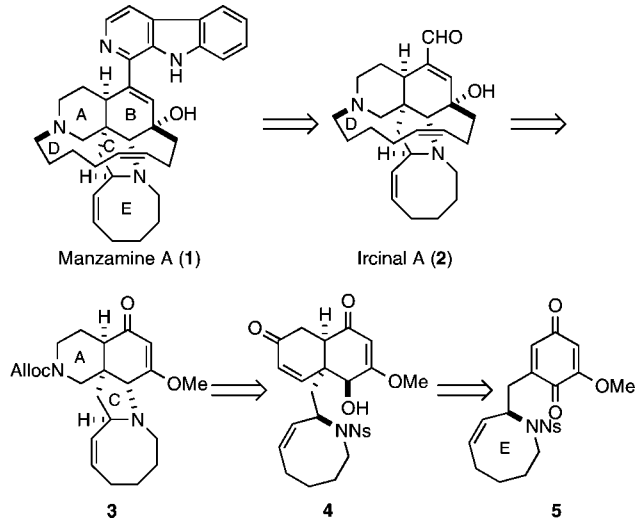
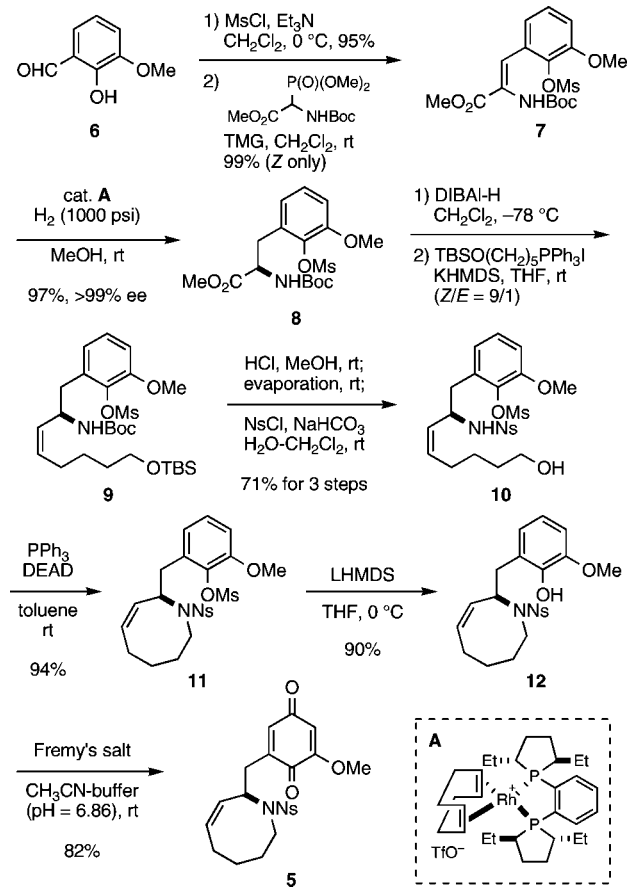
**Scheme 1.** Retrosynthetic Analysis




**Scheme 2.** Synthesis of the Quinone




in a later stage of the synthesis. Further disconnection led to tricyclic compound **4**. The C ring would form via $S_N2$ reaction from the secondary amine, and the A ring would result from conversion of the cyclohexenone. We assumed that asymmetric Diels−Alder reaction of quinone **5** and butadiene derivative was a key step for construction of the *cis*-decalin skeleton including quarternary carbon center. It seemed that an Ns-strategy[10,11] was suitable for formation of the remaining E ring. An asymmetric hydrogenation of an enamide ester mediated DuPHOS catalyst[12] would be suitable to prepare optically active **5** on a large scale.

As shown in Scheme 2, synthesis of **5** was commenced with commercially available *o*-vanillin (**6**). After protecting the phenol of **6** with a mesyl group, the aldehyde was subjected to Horner−Emmons reaction with a phosphonate[13] to give (*Z*)-dehydrophenylalanine derivative **7**. Catalytic asymmetric hydrogenation of **7** proceeded smoothly in the presence of [((COD)-(*R*,*R*)-Et-DuPHOS)Rh]$^+$OTf$^-$ under 1000 psi of hydrogen to afford the amino ester **8**. After treating **8** with DIBAL, the resulting aldehyde was subjected to the Wittig reaction to predominantly afford the *cis*-alkene **9**. After switching from the Boc group of **9** to the Ns group and upon treating **10** with DEAD and $PPh_3$, the desired cyclization reaction proceeded smoothly to afford 8-membered ring **11** in excellent yield.[14] Removal of the Ms group was achieved by treatment with LHMDS[15] because utilizing basic hydrolysis conditions, such as KOH in MeOH, resulted in the $\beta$-elimination of the Ns group by deprotonation the allylic hydrogen. Subsequent oxidation of **12** with Fremy's salt[16] furnished quinone **5** in good yield.

With desired quinone **5** in hand, we then focused on the stereoselective construction of the tetracyclic ring system of **3**, as shown in Scheme 3. The critical intermolecular Diels−Alder reaction was achieved by utilizing optically active diene **13** reported by Rawal.[17] Upon treatment of diene **13** and quinone **5**, a facial selective Diels−Alder reaction proceeded smoothly at room temperature to provide **14** as a single isomer in 92% yield. Successively treating ketone **14** with $NaBH_4$ enabled the diastereoselective reduction from the less hindered *exo*-face of the molecule to afford the alcohol as a single product. In this reaction, undesired reduction of the vinylogous ester was not observed. Subsequent removal of the TBS group by TBAF and simultaneous elimination of oxazolidinone proceeded to afford enone **4** in good yield.

The next challenge in the synthesis was oxidative cleavage of the opening reaction cyclohexenone skeleton **4** to convert

(10) For a review on Ns chemistry, see: (a) Kan, T.; Fukuyama, T. *J. Syn. Org. Chem., Jpn.* **2001**, *59*, 779. (b) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 1204.

(11) (a) Fukuyama, T.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1995**, *36*, 6373. (b) Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831. (c) Fukuyama, T.; Cheung, M.; Kan, T. *Synlett* **1999**, 1301. (d) Kurosawa, W.; Kan, T.; Fukuyama, T. *Org. Synth.* **2002**, *79*, 186.

(12) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.

(13) Schmidt, U; Lieberknecht, A; Wild, J. *Synthesis* **1984**, 53.

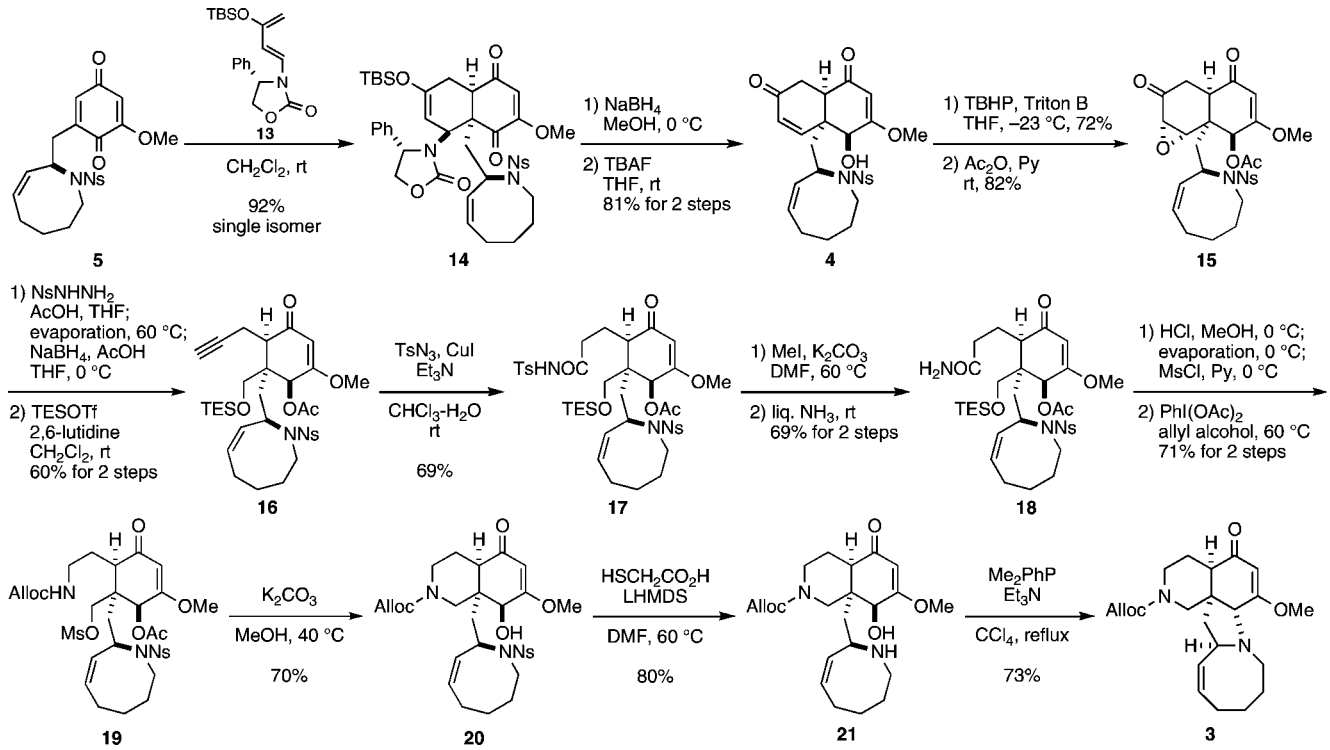
(14) For construction of 8-membered ring by Ns-strategy, see: (a) Kan, T.; Kobayashi, H.; Fukuyama, T. *Synlett* **2002**, 697.

(15) Similar deprotection of Ms group by LDA, see: (a) Ritter, T.; Stanek, K.; Larrosa, I.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1513.

(16) For a review, see: Zimmer, H.; Lankin, D. C.; Horgan, S. W *Chem. Rev.* **1971**, *71*, 229.

(17) Janey, J. M.; Iwama, T.; Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **2000**, *65*, 9059.

**Scheme 3.** Synthesis of the Tetracyclic Core of Manzamine A




to the piperidine ring without affecting the reactive double bond of the E ring. Epoxy ketone **15** was converted by stereoselective oxidation of enone **4** with TBHP in the presence of Triton B and subsequent protection with acetate. Upon treatment of **15** and nosyl hydrazide in acidic conditions, the desired Eshcenmoser−Tanabe fragmentation occurred smoothly to give the desired alkyne, and subsequent reduction of the resulting aldehyde and protection with TES group afforded **16**. Chemoselective conversion from alkyne **16** to *N*-tosylimide **17** was performed according to Chang's protocol.[18] Upon treatment with **16** and tosyl azide in the presence of copper iodide, the desired cycloaddition reaction and rearrangement proceeded smoothly to give **17**. Because the direct ammonolysis of Ts-imide **17** was difficult, *N*-methylation and subsequent treatment with excess ammonia gave primary amide **18**. After one-pot switching from the TES ether to mesylate, treating the amide with $PhI(OAc)_2$ in the presence of allyl alcohol enabled the crucial Hofmann rearrangement to proceed smoothly to afford **19**. The piperidine ring was constructed by treating allyl carbamate **19** with potassium carbonate and concomitant of hydrolysis of the Ac group to give **20**. Due to its steric hindrance, removing the Ns group was extremely troublesome under typical conditions.[11d] After several attempts, it was found that a combination of thioglycolic acid and LHMDS allowed a smooth deprotection reaction to provide **21**. Upon treatment with **21** with dimethylphenylphosphine[19] in carbon tetrachloride, the cyclization reaction proceeded to provide **3** in excellent yield.

In conclusion, an enantioselective ABCE ring of Manzamine A (**1**) has been accomplished in 24 steps from *o*-vanillin (**6**). Our stereoselective synthesis features a DuPHOS-mediated catalytic asymmetric hydrogenation, efficient construction of the E ring by employing our Ns-strategy, and a diastereoselective Diels−Alder reaction to construct a functionalyzed *cis*-decalin skeleton. Sequential Eschenmoser−Tanabe fragmentation, Chang's amide formation, and Hofmann rearrangement converted piperidine **20** from cyclohexanone **4** even in the presence of the labile double bond of the E-ring. Further investigation of the total synthesis of Manzamine A (**1**) by introducing the C1 unit at the vinylogous ester and constructing the D ring are currently underway in our laboratory.

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**Supporting Information Available:** Available detailed experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) (a) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046. (b) Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1897.

(19) Utilizing other phosphines or employing typical Mitsunobu conditions did not provide the desired product.