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Stereoselective Furan-Iminium Cation Cyclization in the Construction of the Core Structure of Manzamine A

Kazuyuki Tokumaru, Shigeru Arai, and Atsushi Nishida*

Graduate School of Pharmaceutical Sciences, Chiba University, 1-33, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

nishida@p.chiba-u.ac.jp

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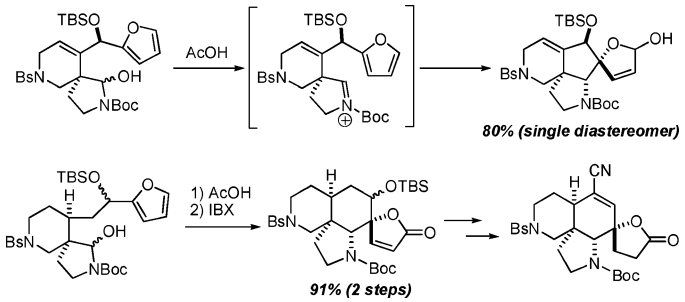
ABSTRACT



A new type of furan-iminium cation cyclization was developed and used to construct the ABC ring of manzamine A. The cyclization proceeded at the 2-position with complete regio- and stereoselectivity to give a spiro-center. The product was efficiently converted to the highly substituted core structure of manzamine A.

Manzamine alkaloids have attracted considerable attention because of their unique structure and diverse biological activities, and new related compounds continue to be isolated from marine sources.[1] Manzamine A, which was the first manzamine alkaloid isolated by Higa et al.[2] contains a 6/6/5/8/13 diazapentacyclic skeleton with a β-carboline ring and has shown a variety of biological activities, such as antitumor, antituberculosis, and strong antimalarial activities. Although many attempts have been made to construct this attractive molecule,[3] only Winkler and Martin have reported a total synthesis.[4]

Recently, we achieved the first total synthesis of a manzamine alkaloid, nakadomarin A, by two different synthetic pathways.[5] In our synthetic study of nakadomarin A, furan-iminium cation cyclization,[6] which is intramolecular nucleophilic addition of furan to acyl iminium cation, was found to be an efficient method for construction of the core 6/5/5/5 structure (Scheme 1). To expand the scope of this reaction to the synthesis of a 6/6/5 ring system, such as the ABC core of manzamine A, we have been studying two cyclization patterns. The cyclization of **1**, which has one carbon linker between a spiro-piperidine ring and a 2-furyl group, at the 3-position of furan would give tetracyclic furan **2**. The cyclization of **3**, which has two carbon linkers connecting the spiro-piperidine ring and 2-furyl group, might proceed at the 2-position of furan to result in the construction of the six-membered B ring of **4** with a tetra-substituted

(1) For review, see; Hu, J.-F.; Hamann, M. T.; Hill, R.; Kelly, M. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: New York, 2003; Vol. 60, p 207.

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

(3) For selected studies, see: (a) Pandit, U. K.; Overkleeft, H. S.; Borer, B. C.; Bieräugel, H. *Eur. J. Org. Chem.* **1999**, 959. (b) Magnier, E.; Langlois, Y. *Tetrahedron Lett.* **1998**, *39*, 837. (c) Brands, K. M. J.; DiMichele, L. M. *Tetrahedron Lett.* **1998**, *39*, 1677. (d) Nakagawa, M., Torisawa, Y., Uchida, H., Nishida, A. *J. Synth. Org. Chem. Jpn.* **1999**, *57*, 1004. (e) Li, S.; Yamamura, S. *Tetrahedron* **1998**, *54*, 8691. (f) Bland, D.; Chambournier, G.; Dragan, V.; Hart, D. J. *Tetrahedron* **1999**, 55, 8953. (g) Clark, J. S.; Townsend, R. J.; Blake, A. J.; Teat, S. J.; Johns, A. *Tetrahedron Lett.* **2001**, *42*, 3235. (h) Herdemann, M.; Al-Mourabit, A.; Martin, M.-T.; Marazano, C. *J. Org. Chem.* **2002**, *67*, 1890. (i) Magnus, P.; Fielding, M. R.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, *43*, 947. (j) Coldham, I.; Pih, S. M.; Rabot, R. *Synlett* **2005**, 1743.

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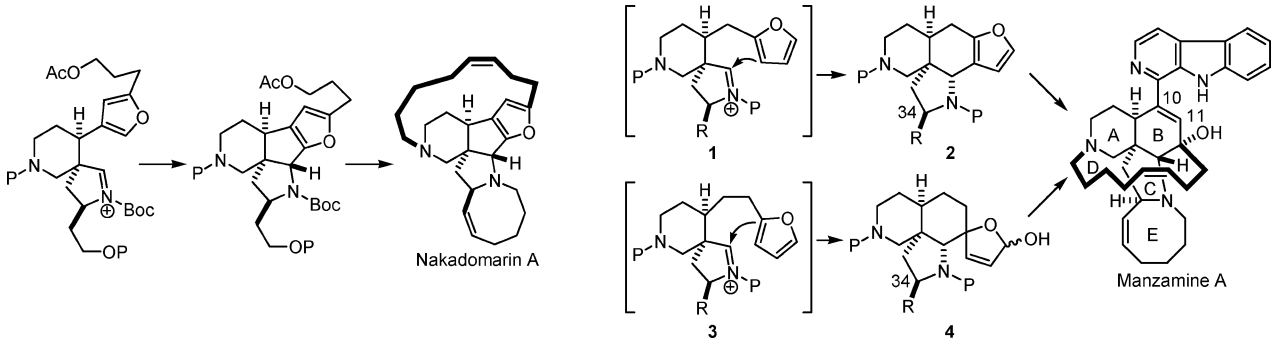
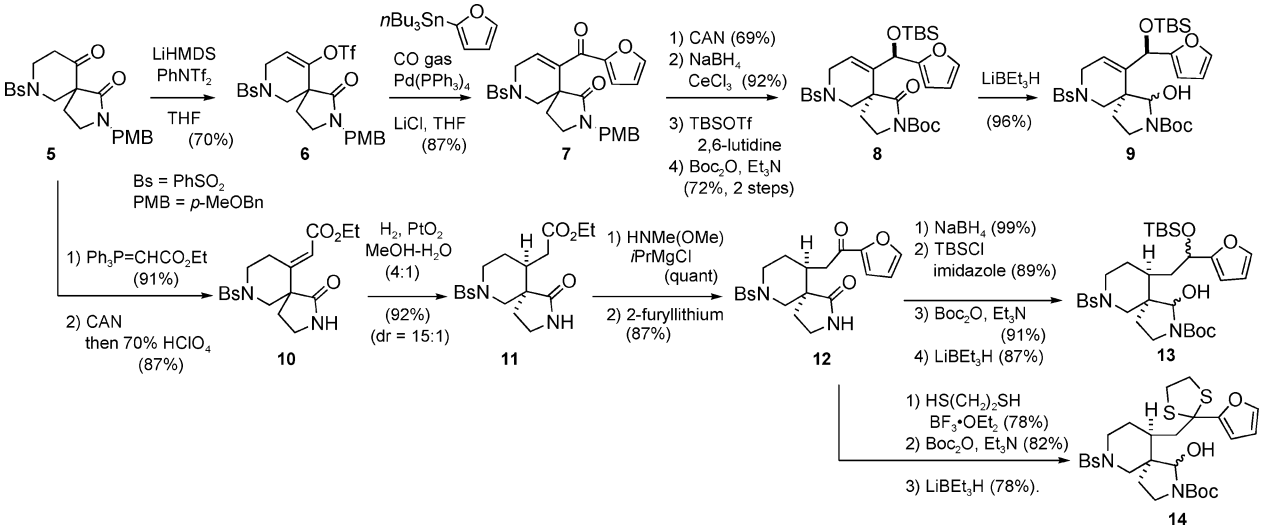
Scheme 1. Synthesis of Manzemine Alkaloids Using Furan-Iminium Cation Cyclization



Scheme 2. Synthesis of Cyclization Precursors



asymmetric center. In both reactions, the furan unit would be useful for constructing the D ring of manzamine A. Since the regio- and stereoselectivity of these cyclizations have not been clearly demonstrated before, we decided to start an initial model study using substrates that have no substituent at C34.

The synthesis of cyclization precursors is outlined in Scheme 2. Compound **5**[7] was converted to the enol triflate **6**, and one carbon linker and a 2-furyl group were then introduced by a carbonylative Stille coupling reaction[8] to give **7** in 87% yield. The ketone was reduced to increase the nucleophilicity of furan. After protection of the hydroxyl and lactam groups, *N*-Boc-lactam **8** was converted to hemiaminal **9**, an iminium cation precursor, by reduction using $LiBEt_3H$.[9]

Both precursors, **13** and **14**, which have two carbon linkers between a spiro-piperidine ring and a 2-furyl group, were also synthesized from **5**. Wittig reaction and diastereoselective hydrogenation[10] gave ester **11**, which was converted to 2-furyl ketone **12** via Weinreb amide.[11] After this ketone was converted to a thioketal or siloxy group, the same transformation of lactam as described above gave hemiaminals **13** and **14**.

Hemiaminals **9**, **13**, and **14** were then exposed to acidic media (Scheme 3). Depending on the structure of the substrates, cyclization conditions were modified slightly and cyclization occurred under mild acidic conditions without

(4) (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. M.; 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.

(5) (a) Nagata, T.; Nakagawa, M.; Nishida, A. *J. Am. Chem. Soc.* **2003**, *125*, 7484. (b) Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2020.

(6) For selected examples of furan-iminium cation cyclization, see: (a) Cassidy, M. P.; Özdemir, A. D.; Padwa, A. *Org. Lett.* **2005**, *7*, 1339. (b) Tanis, S. P.; Deaton, M. V.; Dixon, L. A.; McMills, M. C.; Raggon, J. W.; Collins, M. A. *J. Org. Chem.* **1998**, *63*, 6914. (c) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895.

(7) Nagata, T.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **2001**, *42*, 8345.

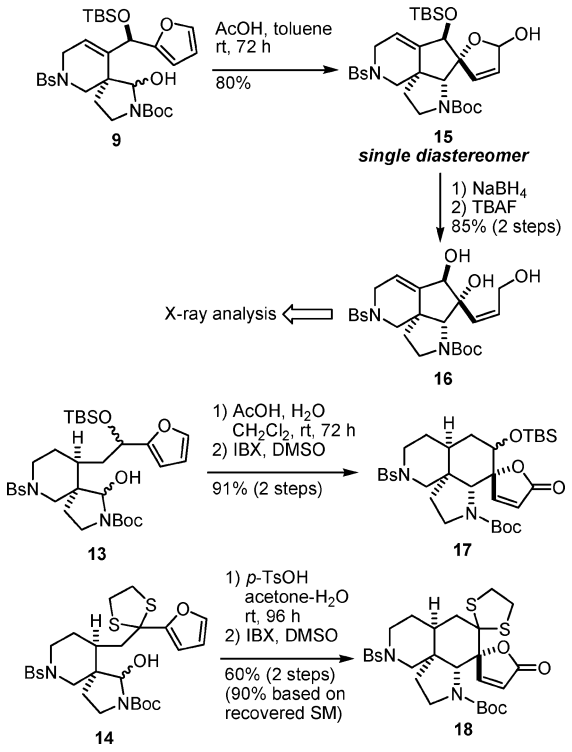
(8) Farina, V.; Krishnamurthy, V.; Scott, W. J. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1997; Vol. 50, p 1.

(9) Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreño, M. C.; Ruano, J. L. G. *Tetrahedron Lett.* **1994**, *35*, 2053.

(10) The diastereoselectivity of hydrogenation was catalyst- and solvent-dependent. For example, hydrogenation using Pd/C as a catalyst in AcOEt gave the product in 84% yield and α-H:*β*-H ratio was 1:1.5.

(11) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.

Scheme 3. Furan-Iminium Cation Cyclizations



deprotection of acid-sensitive TBS and Boc groups. All of these reactions proceeded in a regioselective manner completely at the 2-position of furan regardless of the length of the carbon tether to generate new spiro-centers. Furthermore, the stereochemistry of the newly formed tetrasubstituted spiro-centers was also completely controlled and consistent with the corresponding stereocenter of manzamine A (C12). The structure of each cyclized product was determined by X-ray or NMR analysis.[12]

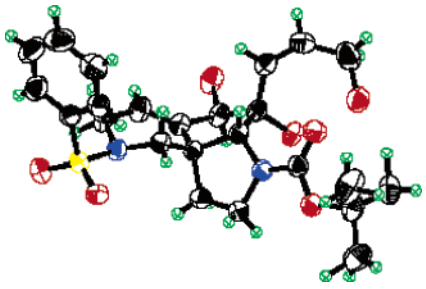


Figure 1. ORTEP Presentation of compound **16**.

The observed stereoselectivity could be explained by Diels−Alder-type transition states (Figure 2). The face selectivity of furan might be controlled by interaction with

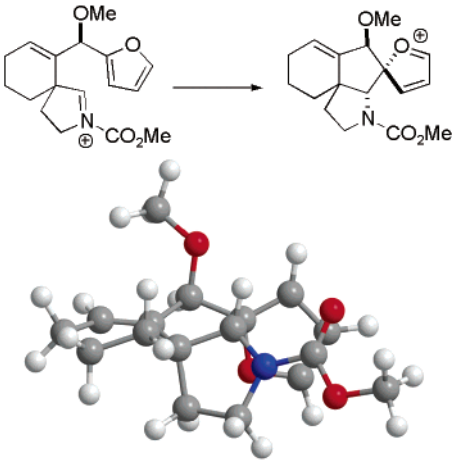


Figure 2. Transition state model of simplified substrate.

an acyl group attached to the iminium nitrogen.[6c,13] Several types of intramolecular furan-iminium cation cyclizations have been reported, for example, cyclization of 3-substituted furan at the 2-position,[6b] cyclization of 2-substituted furan at the 3-position,[6a,b] and cyclization of 2-substituted 5-siloxy furan at the 2-position.[6c] However, intramolecular furan-iminium cation cyclization of 2-monosubstituted furan at the 2-position has not been reported, and the high level of diastereoselectivity in this reaction is noteworthy.

We also studied the introduction of a C1 unit at the B ring, which is a key functional group for preparing β-carboline (Scheme 4). Unfortunately, the thioketal group of **18** could not be deprotected effectively. Deprotection of the TBS group of **17** followed by hydrogenation of olefin in the lactone ring gave secondary alcohol **19** quantitatively as a 1:1 mixture of diastereomeres. Thus, a secondary alcohol of **19** at C11 was oxidized to ketone **20**, whose structure was determined by X-ray analysis. However, all attempts to introduce a C1 unit by α-acylation of **20** were unsuccessful.[14] We next synthesized epoxide **23** from **19b** by dehydration to give **22** followed by epoxidation using DMDO. Although **19a** could not be directly used to synthesize **23**, **19a** could be converted to **19b** via **20** by an oxidation−reduction sequence. Regioselective nucleophilic epoxide opening was accomplished using the method reported by Utimoto[15] to give β-cyanohydrin **24**. Finally, usual dehydration gave α,β-unsaturated nitrile **25**, which has all of the functional groups necessary to synthesize the manzamine A structure except for the E ring.

In summary, we have developed a new synthetic pathway to the ABC core skeleton of manzamine A. A noteworthy feature of this synthesis is the highly regio- and stereoselective furan-iminium cation cyclization under mild acidic

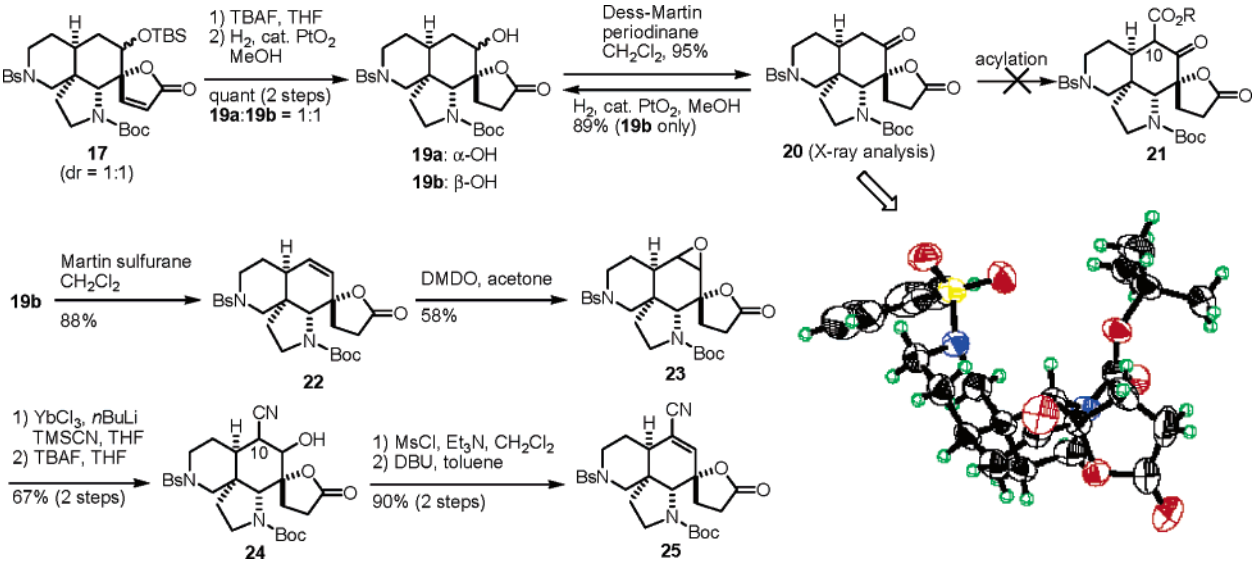
(12) The structure of **15** and **17** were determined by X-ray analysis after conversion to **16** and **20** (Figure 1 and Scheme 4). The structure of **18** was determined by NMR analysis (see Supporting Information).

(13) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1987**, *109*, 7881.

(14) Both Winkler and we successfully introduced C1 unit at C10 by α-acylation. See refs 3e and 4a. These unsuccesssful results might be attributed to the bulkiness of the tetrasubstituted center at C12.

(15) Matsubara, S.; Onishi, H.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6209.

Scheme 4. Functionalization of the B Ring



conditions. The reaction was used to construct two contiguous stereocenters including a tetrasubstituted stereocenter corresponding to the B ring of manzamine A. The total synthesis of manzamine A using this methodology is now under investigation.

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Note Added after ASAP Publication. There was an error in Figure 2 in the version published ASAP December 8, 2005; the corrected version was published ASAP December 13, 2005.

Supporting Information Available: Experimental procedures, X-ray analysis data (**11**, **16**, and **20**) in CIF format, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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