ORGANIC LETTERS

2009
Vol. 11, No. 12
2547−2550

Stereoselective One-Step Construction of Vicinal Quaternary and Tertiary Stereocenters of the 5,10b-Ethanophenanthridine Skeleton: Total Synthesis of (±)-Maritidine

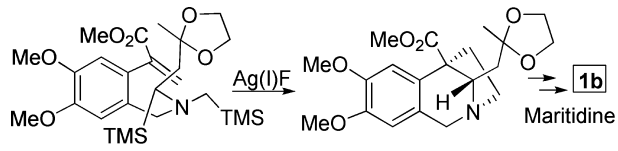
Ganesh Pandey,* Nishant R. Gupta, and Tukaram M. Pimpalpalle

Division of Organic Chemistry, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune-411 008, India

gp.pandey@ncl.res.in

Received April 13, 2009

ABSTRACT



The challenging vicinal quaternary and tertiary stereocenters of the 5,10b-ethanophenanthridine skeleton are created in a single step utilizing intramolecular [3 + 2]-cycloaddition of nonstabilized azomethine ylide as the key step. The application of the chemistry is demonstrated by synthesizing (±)-maritidine.

The Amaryllidaceae alkaloids[1] have long been the source of structurally intriguing target molecules due to their architectural diversity, limited supply, and promising biological activities. Crinine alkaloids[2] which belong to the biggest and truly representative class of this family comprises more than 50 members possessing immunostimulant, antitumor, and antiviral activities.[3] Maritidine (**1b**), isolated from *Pancratium maritimum*, *Pancratium tortuosum*, and *Zephyranthes* genera,[4] is the first alkaloid with a 5,10b-ethanophenanthridine nucleus containing dimethoxy rather than methylenedioxy substituents at C-8 and C-9 positions of the crinine skeleton (Figure 1). These alkaloids display adjacent quaternary and tertiary carbon stereocenters with a fused pyrrolidine ring whose stereochemical incorporation is the critical element in the synthesis of these types of alkaloids. Alkaloid **1b** is of particular interest due to its cytotoxic properties[5] and limited supplies from natural sources.[6] A literature survey has revealed that assembling of the core 5,10b-ethanophenanthridine skeleton of **1b** has utilized

(1) (a) Hoshino, O. *In The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, p 362. (b) Martin, S. F. *In The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, p 251. (c) Wildman, W. C. *In The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1960, Vol. VI, p 290. (d) Lewis, J. R. *Nat. Prod. Rep.* **1993**, *10*, 291. (e) Jin, Z. *Nat. Prod. Rep.* **2003**, *20*, 606. (f) Jin, Z. *Nat. Prod. Rep.* **2005**, *22*, 111. (g) Jin, Z. *Nat. Prod. Rep.* **2007**, *24*, 886. (h) Unver, N. *Phytochem. Rev.* **2007**, *6*, 125. (i) Jin, Z. *Nat. Prod. Rep.* **2009**, *26*, 363.

(2) For recent synthesis of Crinine-type alkaloids, see: (a) Tam, N. T.; Chang, J.; Jung, E.-J.; Cho, C.-G. *J. Org. Chem.* **2008**, *73*, 6258. (b) Bohno, M.; Sugie, K.; Imase, H.; Yusof, Y. B.; Oishi, T.; Chida, N. *Tetrahedron* **2007**, *63*, 6977, and references therein.

(3) (a) Tram, N. T. N.; Titorenkova, Tz. V.; Bankova, V. St.; Handjieva, N. V.; Popov, S. S. *Fitoterapia* **2002**, *73*, 183. (b) Fennell, C. W.; van Staden, J. J. *Ethnopharmacol.* **2001**, *78*, 15.

(4) (a) Sandberg, F.; Michel, K. -H. *Lloydia* **1963**, *26*, 78. (b) Rao, R. V. K.; Sheshagiri Rao, J. V. L. N. *Curr. Sci.* **1979**, *48*, 110. (c) Pacheco, P.; Silva, M.; Steglich, W.; Watson, W. H. *Rev. Latinoam. Quim.* **1978**, *9*, 28. (d) Toaima, S. M. *Alexandria J. Pharm. Sci.* **2007**, *21*, 61. (e) Zabel, V.; Watson, W. H.; Pacheco, P.; Silva, M. *Cryst. Struct. Commun.* **1979**, *8*, 371.

(5) (a) Alarcon, M.; Cea, G.; Weigert, G. *Environ. Contam. Toxicol.* **1986**, *37*, 508. (b) Pacheco, P.; Silva, M.; Steglich, W.; Watson, W. H. *Rev. Latinoam. Quim.* **1978**, *9*, 28. (c) Elgorashi, E. E.; Stafford, G. I.; Jager, A. K.; van Staden, J. *Planta Med.* **2006**, *72*, 470 (inhibition of [3*H*]citalopram binding to the rat brain serotonin transporter). (d) Cea, G.; Alarcon, M.; Weigart, G. *Med. Sci.* **1986**, *14*, 90 (clastogenic effect/mutagenic).

10.1021/ol900806m CCC: $40.75
Published on Web 05/18/2009

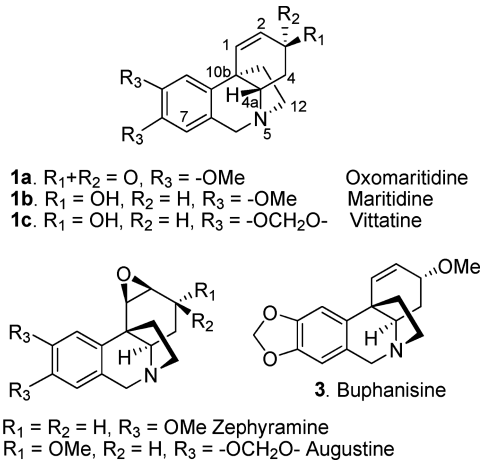
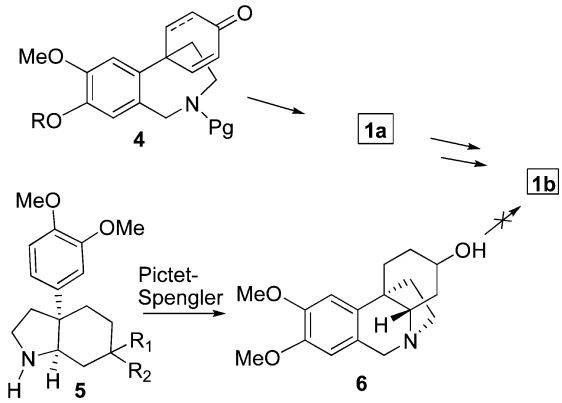


Figure 1. Representative structures of 5,10b-ethanophenanthridine alkaloids.

essentially two approaches. While the majority of approaches used spiro-fused dienone **4** to elaborate to **1b**, few strategies have also employed the Pictet−Spengler cyclization of 3-aryl-substituted hydroindole derivatives **5** into dihydromaritidine **6**. Spiro-fused **4** has been synthesized employing phenolic oxidative para−para coupling[7−10,14] and photochemical cyclization[11] of norbelladine derivatives. Other routes to **4** involve intramolecular Heck coupling[12] or the cyclization of an intermediate iron carbonyl complex.[13] The synthesis of **5** involved key reactions such as regioselective reduction of 1-methyl-3,3-disubstituted pyrrolidine-2,5-dione,[15a] intramolecular ene cyclization of an appropriately constructed acylnitroso olefin,[15b] or condensation of 3-arylated Δ^1-pyrrolinium salts with the *tert*-butyl 3-oxopent-4-enoate[15c] (Scheme 1).

Scheme 1. Various Approaches Towards Maritidine



From the preceding discussion, it is apparent that these strategies employed stepwise generation of vicinal quaternary and tertiary stereocenters along with the use of a cyclic precursor for C-ring formation. Moreover, the Pictet−Spengler cyclization route has produced only the dihydromaritidine whose oxidative conversion to **1b** has remained unsuccessful to date.

Our continuing interest in exploring the application of nonstabilized azomethine ylides generated by sequential double desilylation of α,α′-bis(trimethylsilylmethyl)alkylamines[16] in the total synthesis of alkaloids[17] with complex architectures and the need to develop a concise and versatile strategy to synthesize these types of alkaloids led us to envisage the synthesis of **1** through an intramolecular 1,3-dipolar cycloaddition of a nonstabilized azomethine ylide (AMY) as shown retrosynthetically in Scheme 2. This proposed strategy originated from our recently accomplished formal synthesis of the fused polycyclic 5,11-methanomorphanthridine skeleton of (±)-pancracine.[18]

Regio- as well as stereochemical issues, the two important aspects of this cycloaddition strategy, were evaluated at the planning stage of the synthesis itself. The origin of the 5,10b-ethanophenanthridine regiochemistry during cycloaddition, in contrast to the 5,11-methanophenanthridine skeleton,[18] was speculated based on the change in the LUMO energy of the dipolarophile due to its conjugation with the aromatic ring and ester moiety present on the same carbon. Cycloaddition reaction of **8** was visualized to generate the vicinal quaternary

(6) Maritidine: (a) Tani, S.; Kobayashi, N.; Fujiwara, H.; Shingu, T.; Kato, A. *Chem. Pharm. Bull.* **1981**, *29*, 3381. (b) Hung, S.; Ma, G.; Sung, G. *Huaxue Xuebao* **1981**, *39*, 529. (c) Ghosal, S.; Ashutosh, R.; Razdan, S. *Phytochemistry* **1985**, *24*, 635. (d) Ma, G.; Li, H. Y.; Lu, C.; Yang, X.; Hong, S. *Heterocycles* **1986**, *24*, 2089. (e) Ghosal, S.; Singh, S.; Srivastava, R. S. *Phytochemistry* **1986**, *25*, 1975. (f) Kihara, M.; Koike, T.; Imakura, Y.; Kia, K.; Shingu, T.; Kobayashi, S. *Chem. Pharm. Bull.* **1987**, *35*, 1070. (g) Bastida, J.; Llabres, J. M.; Viladomat, F.; Codina, C.; Rubiralta, M.; Feliz, M. *Planta Med.* **1988**, *54*, 524. Oxomaritidine: (h) Herrera, M. R.; Brun, R.; Villadoma, F.; Codina, C.; Bastida, J. *Planta Med.* **2001**, *67*, 191.

(7) Schwartz, M. A.; Holton, R. A. *J. Am. Chem. Soc.* **1970**, *92*, 1090.

(8) (a) Kotani, E.; Takeuchi, N.; Tobinaga, S. *J. Chem. Soc., Chem. Commun.* **1973**, 550. (b) Kotani, E.; Takeuchi, N.; Tobinaga, S. *Tetrahedron Lett.* **1973**, *29*, 2735.

(9) Kita, Y.; Takada, T.; Gyoten, M.; Tohma, H.; Zenk, M. H.; Eichhorn, J. *J. Org. Chem.* **1996**, *61*, 5857.

(10) (a) Ley, S. V.; Schucht, O.; Thomas, A. W.; Murray, P. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1251. (b) Baxendale, I. R.; Deeley, J.; Griffiths-Jones, C. M.; Ley, S. V.; Saaby, S.; Tranmer, G. K. *Chem. Commun.* **2006**, 2566.

(11) (a) Kametani, T.; Kohno, T.; Shibuya, S.; Fukumoto, K. *Chem. Commun.* **1971**, *14*, 774. (b) Kametani, T.; Kohno, T.; Shibuya, S.; Fukumoto, K. *Tetrahedron* **1971**, *27*, 5441.

(12) Bru, C.; Thal, C.; Guillou, C. *Org. Lett.* **2003**, *5*, 1845.

(13) Roe, C.; Stephenson, G. R. *Org. Lett.* **2008**, *10*, 189–192.

(14) (a) Yamada, S.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1976**, *1*, 57. (b) Yamada, S.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1976**, *1*, 61. (c) Tomioka, K.; Koga, K.; Yamada, S. *Chem. Pharm. Bull.* **1977**, *25*, 2681. (d) Tomioka, K.; Shimizu, K.; Yamada, S.; Koga, K. *Heterocycles* **1977**, *6*, 1752.

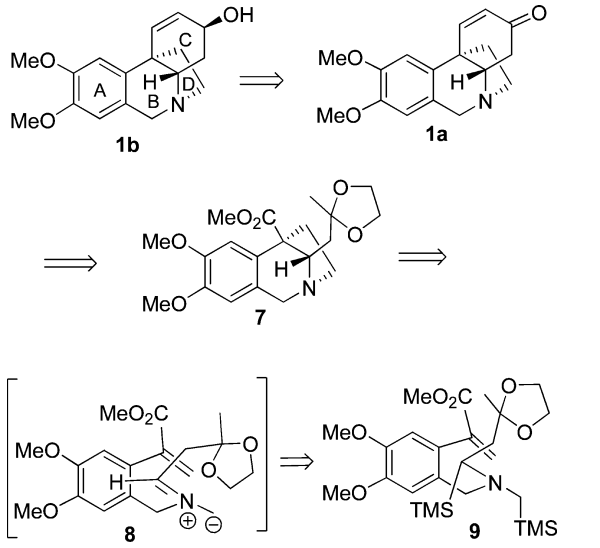
(15) (a) Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 2579. (b) Keck, G. E.; Webb, R. R. *J. Org. Chem.* **1982**, *47*, 1302. (c) Michael, J. P.; Howard, A. S.; Katz, R. B.; Zwane, M. I. *Tetrahedron Lett.* **1992**, *33*, 6023.

(16) (a) Pandey, G.; Lakshmaiah, G.; Kumaraswamy, G. *J. Chem. Soc. Chem. Commun.* **1992**, 1313. (b) Pandey, G.; Lakshmaiah, G. *Tetrahedron Lett.* **1993**, *34*, 4861.

(17) (a) Pandey, G.; Laha, J. K.; Lakshmaiah, G. *Tetrahedron* **2002**, *58*, 3525. (b) Pandey, G.; Sahoo, A. K.; Bagul, T. D. *Org. Lett.* **2000**, *2*, 2299. (c) Pandey, G.; Laha, J. K.; Mohankrishnan, A. K. *Tetrahedron Lett.* **1999**, *40*, 6065. (d) Pandey, G.; Sahoo, A. K.; Gadre, S. R.; Bagul, T. D.; Phalgune, U. D. *J. Org. Chem.* **1999**, *64*, 4990. (e) Pandey, G.; Bagul, T. D.; Sahoo, A. K. *J. Org. Chem.* **1998**, *63*, 760. (f) Pandey, G.; Lakshmaiah, G.; Ghatak, A. *Tetrahedron Lett.* **1993**, *34*, 7301.

(18) Pandey, G.; Banerjee, P.; Kumar, R.; Puranik, V. G. *Org. Lett.* **2005**, *7*, 3713.

Scheme 2. Retrosynthetic Analysis



and tertiary stereocenters in one step with the orientation of substituents in the dipole deciding the stereochemical outcome at the C_{4a} position. For illustration, it was hypothesized that the alkyl ketal moiety of the dipole in AMY may experience severe stereoelectronic conjestion with the tethered aromatic ring flanked between the dipole and the dipolarophile as shown in TS-I (Figure 2) resulting in

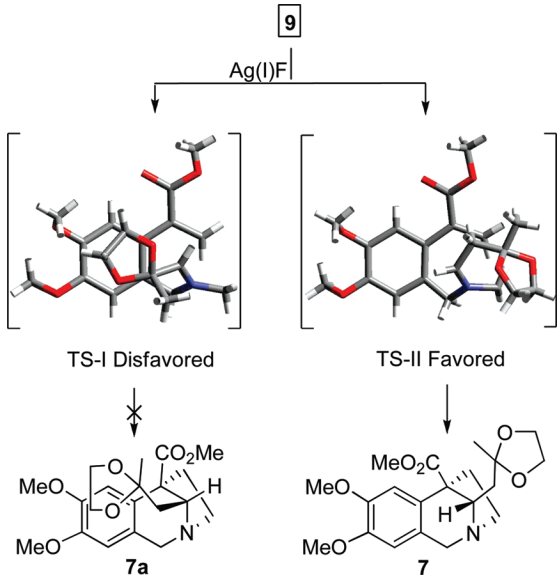
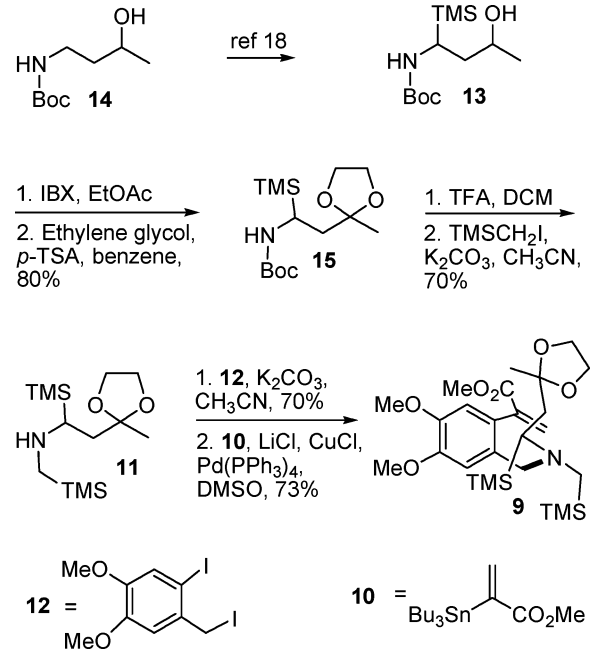


Figure 2. Proposed transition state model of the [3 + 2] cycloaddition step.

epimeric C_{4a} stereochemistry in cycloadduct **7a**. On the other hand, TS-II, in which the alkyl ketal side chain and the aromatic ring are distantly away from each other, may generate the desired C_{4a} stereochemistry (**7**). Thus, we anticipated that the substrate-controlled stereoelectronic favor during the cycloaddition of **8** would reinforce the stereochemical outcome in the tricyclic skeleton with suitable stereochemical disposition of substituents required for assembling the C-ring of the target alkaloid.

With the above premises, we began our synthetic endeavor by synthesizing key precursor **9** (73% yield) by modified Stille coupling between appropriately substituted aryl iodide and vinyl stannane **10** by following Corey's protocol.[19] The Stille precursor was obtained in 70% yield by N-alkylation of **11** with **12** in the presence of anhydrous K_2CO_3 in CH_3CN. Secondary amine **11** was synthesized from **13** as shown in Scheme 3. Compound **13** was readily obtained by following

Scheme 3. Synthesis of Cycloaddition Precursor

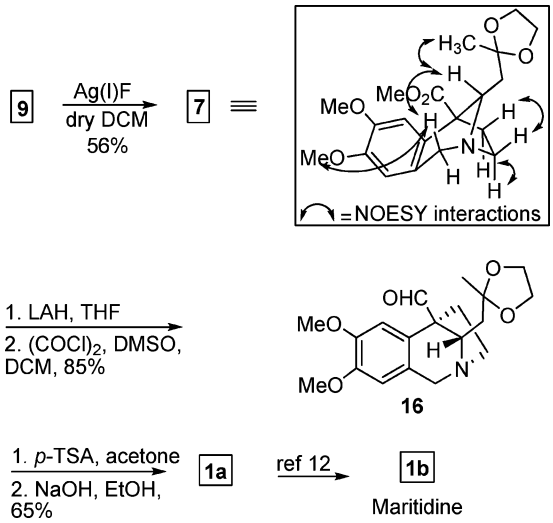


our earlier protocol[18] from **14**. Compound **14** in turn was obtained in 70% yield by aza-Michael reaction between $BocNH_2$ and methyl vinyl ketone followed by $NaBH_4$ reduction. Compound **13** on IBX oxidation followed by ketalization gave ketal **15** in 80% yield. N-Boc deprotection of **15** followed by N-alkylation with iodomethyltrimethylsilane gave bis-silylated compound **11** in 70% yield.

The key cycloaddition reaction was performed by dropwise addition of **9** dissolved in DCM to a stirring mixture of flame-dried Ag(I)F in dry DCM. To our delight, the reaction conferred desired cycloadduct **7** in 56% isolated yield along with other minor unidentifiable impurities. The cycloadduct was completely characterized by ^1H and ^{13}C NMR experiments. The stereochemical assignment of cycloadduct was based on extensive COSY, NOESY, and HETCOR NMR studies.[20]

(19) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.

Scheme 4. Synthesis of Maritidine



To proceed further along the proposed synthesis, cycloadduct **7** was subjected to DIBAL reduction. However, this reaction led to the reduction of ester functionality along with ketal deprotection presumably via coordination of alkoxy aluminum with ketal oxygen followed by deprotection of the ketal group to give a stable hemi ketal. Thus, we were compelled to adopt a two-step protocol to obtain **16**. LAH reduction of the ester moiety of **7** followed by Swern oxidation produced aldehyde-ketal **16** in 85% yield. In an attempt to perform one-pot ketal deprotection and aldol condensation, **16** was stirred overnight with 80% acetic acid. However, this reaction produced only a ketal-deprotected compound in poor yield along with traces of **1a**. Therefore, **16** was subjected to *trans*-ketalization using *p*-TSA and acetone to obtain the corresponding δ-keto-aldehyde which was immediately treated with NaOH/EtOH to obtain **1a** in 65% yield. The spectral data of **1a** are in excellent agreement with the reported one.[12] Compound **1a** on subjecting to Luche reduction[21] and mesylation followed by substitution using CsOAc and saponification of the resultant acetate gave **1b** in 45% yield[12] (Scheme 4). The spectral data of **1b** are in good agreement with those of the reported one.[12]

In conclusion, we have successfully developed a conceptually new and versatile protocol for the construction of 5,10b-ethanophenanthridine alkaloids. The significance of the approach is demonstrated by synthesizing (±)-maritidine. The versatility of this strategy is being elaborated to the asymmetric synthesis of this class of alkaloids and will be shortly revealed in a full paper.

Acknowledgment. The authors are thankful to Dr. Prabal Banerjee (Purdue University, USA) and Alok Singh (Hankook University of Foreign Studies, South Korea) for initiating this project. N.R.G. thanks CSIR, New-Delhi, for the Research Fellowship. The support of DST for funding our research program is also greatly acknowledged.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900806M

(20) For details, see Supporting Information.

(21) Luche, J. L.; Rodriguez-Hahn, L.; Crabbe, P. *J. Chem. Soc. Chem. Commun.* **1978**, 601.