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An Efficient Total Synthesis of (±)-Stemonamine

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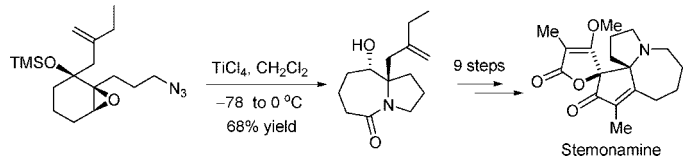
ABSTRACT



An efficient first approach to the Stemona alkaloid (±)-Stemonamine has been developed on the basis of a key $TiCl_4$ promoted tandem Semipinacol rearrangement/Schmidt reaction and a Dieckmann condensation reaction.

Stemonamine (**1a**, Figure 1), as a member of the Stemona family, was isolated from the roots of *Stemona japonica*, which was used in China and Japan for centuries as a drug for the treatment of respiratory diseases and insecticides.[1,2] The challenging molecular architecture containing two contiguous quaternary centers and a tetracyclic skeleton has attracted considerable interest to synthetic organic chemists.[2] Over the past years, several total syntheses of Stemona alkaloids have been reported,[3] but few total syntheses of alkaloids having the spirocyclic stemonamide nucleus have been revealed.

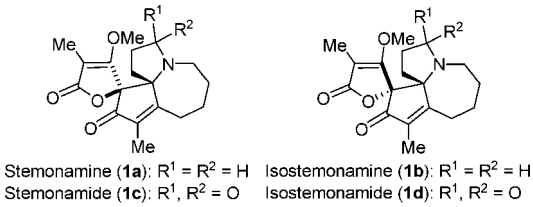


Figure 1. Stemonamine and related alkaloids.

The first total syntheses of (±)-stemonamide (**1c**) and (±)-isostemonamide (**1d**) have been disclosed on the basis of *N*-acyliminium chemistry and aldol spirocyclization by Kende et al. in 2001.[4] Recently, Ishibashi and co-workers developed another approach to (±)-**1c** and (±)-**1d** using a radical cascade strategy.[5] To the best of our knowledge, however, total synthesis of stemonamine (**1a**) has not yet been reported.

During the course of our studies on tandem reactions of α-hydroxy epoxides for constructing the 2-quaternary 1,3-diheteroatom units, we recently discovered a novel and highly efficient tandem semipinacol rearrangement/Schmidt reaction of α-siloxy epoxy azides (Scheme 1).[6] This synthetic method is powerful for the construction of functionalized azaquaternary carbon centers. Herein, we report the first total synthesis of (±)-**1a** as an application of this method.

As shown in Scheme 2, our retrosynthetic consideration of **1a** was focused on the efficient establishment of tetracyclic skeleton. We envisioned that the γ-lactone ring could be

(1) Iizuka, H.; Irie, H.; Masaki, N.; Osaki, K.; Ueno, S. *J. Chem. Soc., Chem. Commun.* **1973**, *125*.

(2) For recent reviews, see: (a) Pilli, R. A.; Ferreira de Oliveira, M. C. *Nat. Prod. Rep.* **2000**, *17*, 177. (b) Pilli, R. A.; Rosso, G. B.; de Oliveira, M. C. F. In *The Alkaloids*; Cordell, G. A., Ed.; Elsevier: New York, **2005**; Vol. 62, pp 77–173. (c) Greger, H. *Planta Med.* **2006**, *72*, 99.

(3) See also ref 2 and references cited therein.

(4) (a) Kende, A. S.; Martin Hernando, J. I.; Milbank, J. B. J. *Org. Lett.* **2001**, *3*, 2505. (b) Kende, A. S.; Martin Hernando, J. I.; Milbank, J. B. J. *Tetrahedron* **2002**, *58*, 61.

(5) Taniguchi, T.; Tanabe, G.; Muraoka, O.; Ishibashi, H. *Org. Lett.* **2008**, *10*, 197.

(6) Gu, P. M.; Zhao, Y.-M.; Tu, Y. Q.; Ma, Y. F; Zhang, F. M. *Org. Lett.* **2006**, *8*, 5271.

10.1021/ol800433r CCC: $40.75
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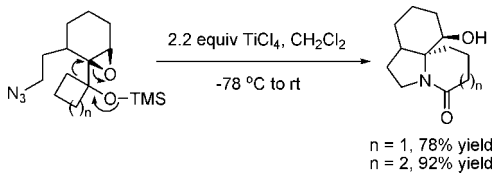
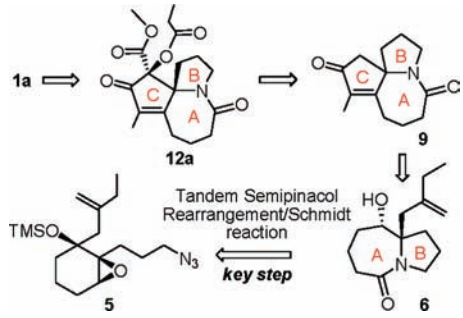
Scheme 1. Tandem Semipinacol Rearrangement/Schmidt Reaction of α-Siloxy Epoxy Azides



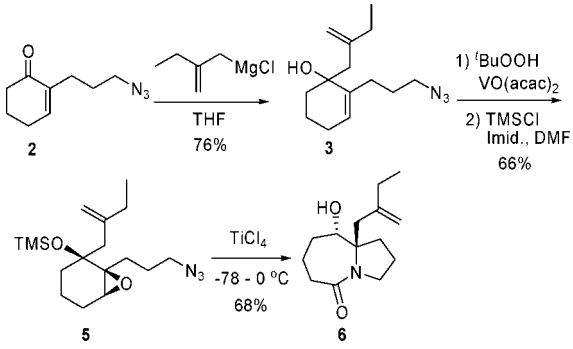
Scheme 2. Retrosynthetic Analysis of (±)-Stemonamine



viable through a Dieckmann condensation reaction, and ring C could be achieved from **6** through several transformations including oxidation and aldol cyclization. As a key strategy-level step, the Lewis acid-promoted tandem semipinacol rearrangement/Schmidt reaction of α-siloxy epoxy azide **5** would provide the desired azaquaternary bicyclic precursor **6**.

As depicted in Scheme 3, our synthesis commenced with a Grignard addition of substituted allylmagnesium chloride[7]

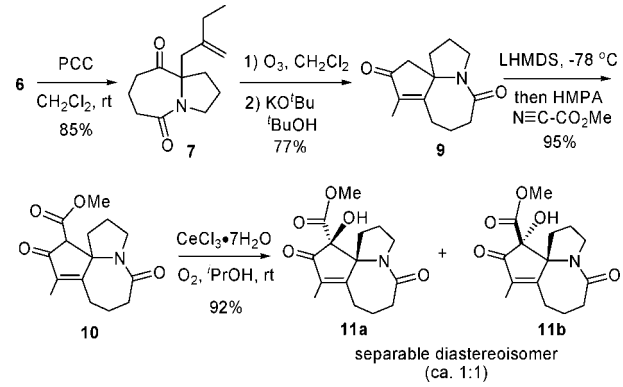
Scheme 3



to known compound **2**.[8] The epoxidation of the resulting allylic alcohol **3**, followed by protection with TMSCl, afforded α-siloxy epoxy azide **5** in 66% overall yield from **3**. With **5** in hand, the key tandem semipinacol rearrangement/Schmidt reaction was investigated. As expected, **5** was treated with 2.2 equiv of $TiCl_4$ in CH_2Cl_2 at −78 to 0 °C for 2 h, giving the desired amide **6** in 68% yield as a white solid.

Oxidation of alcohol **6** with PCC gave rise to the corresponding ketone **7**. Ozonolysis and subsequent aldol condensation afforded **9** in 65% overall yield from **6** (Scheme 4). After achieving the crucial tricyclic intermediate **9**, we

Scheme 4



then turned our attention to construction of γ-lactone ring. Treatment of ketone **9** with LHMDS and Mander reagent[9] at −78 °C for 0.5 h gave the acylation product **10** in 95% yield as a single diastereoisomer. In order to introduce the second quaternary carbon center, an epoxidation was attempted. However, the initial epoxidation of the enolate of β-ketoester **10** with *m*-CPBA failed. To our delight, the desired hydroxylation was accomplished under an atmosphere of oxygen with catalytic amounts of $CeCl_3 \cdot 7H_2O$, giving **11a** and its diastereoisomer **11b** in a total yield of 92% (Scheme 4).[10] These two epimers were readily separated by column chromatography on silica gel. The relative configuration of **11a** was subsequently assigned by the later X-ray analysis of the hydrochloride dihydrate of **1a** (see Figure 2).

As demonstrated in Scheme 5, treatment of **11a** with propionic anhydride, Et_3N, and DMAP (cat.) in dry CH_2Cl_2 at room temperature afforded **12a** in 95% isolated yield. The next crucial step of the current total synthesis involved a Dieckmann condensation to access the key tetronic acid ring system. Reaction of **12a** with 18-crown-6 and KO^{t}Bu in dry benzene at room temperature for 2 h, followed by *O*-methylation, proceeded in moderate yield to afford **13a**. To complete the synthesis, treatment of lactam **13a** with Lawesson's reagent and reduction of thiolactam using W-2 Raney Ni in THF gave the racemic stemonamine (**1a**) in 93% yield over two steps. The structure of our synthetic stemonamine (**1a**) was confirmed by the X-ray crystallographic analysis of its hydrochloride dihydrate (Figure 2).

Given the fact that the γ-lactone ring in **1a** could be established by the Dieckmann condensation of **12a**, the same cyclization condition (KO^{t}Bu and 18-crown-6 in benzene at

(7) For large-scale preparation of 2-(chloromethyl)but-1-ene, see: (a) Green, M. B.; Hickinbottom, W. J. *J. Chem. Soc.* **1957**, 3262. (b) Magid, R. M.; Fruchey, O. S.; Johnson, W. L.; Allen, T. G. *J. Org. Chem.* **1979**, *44*, 359.

(8) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449–10459.

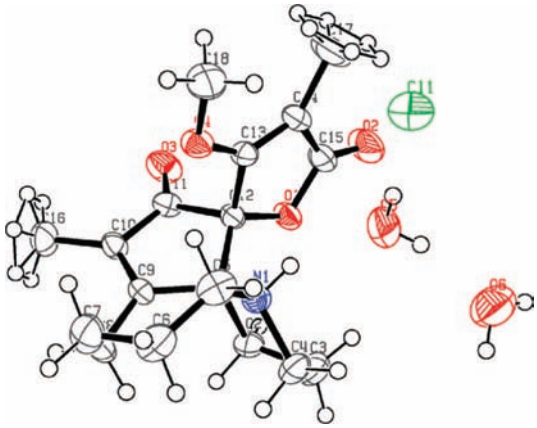


Figure 2. X-ray structure of stemonamine hydrochloride dihydrate.

rt) was subsequently applied to the corresponding propionate product **12b**,[11] which resulted from the acylation of **11b**. Surprisingly, however, only degradation of starting material was observed. A series of bases (LDA, LHMDS, $NaN\{Si(CH_3)_3\}_2$, $KN\{Si(CH_3)_3\}_2$, NaH, KH, or NaOMe) with the combination of various solvents (Et_2O, THF, benzene, toluene, or HMPA) were carefully examined in the present cyclization, and no improved results were obtained. Currently, we are seeking insight into this unusual reactivity of two epimers (**12a** and **12b**) in Dieckmann condensation by the computation chemistry in our laboratory.

In summary, a concise and efficient total synthesis of stemonamine (**1a**) was achieved for the first time in 13 steps from the known compound **2** in an overall yield of 3.7%, featuring a tandem semipinacol rearrangement/Schmidt reaction and a Dieckmann condensation.

Acknowledgment. We gratefully acknowledge financial support from the NSFC (No. 30271488, 20911001) and the Chang Jiang Scholars Program.

Supporting Information Available: General experimental procedures, characterization data for all compounds, and X-ray crystallographic data for the hydrochloride dihydrade of **1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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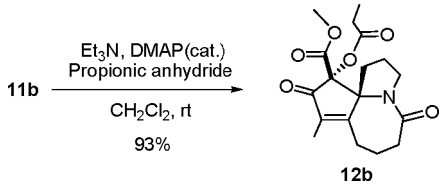
(9) Crabtree, S. R.; Mander, L. N.; Sethi, S. P. *Org. Synth.* **1990**, *70*, 256.

(10) (a) Christoffers, J.; Werner, T. *Synlett* **2002**, 119–121. (b) Christoffers, J.; Werner, T.; Unger, S.; Frey, W. *Eur. J. Org. Chem.* **2003**, 425–431.

(11) For the preparation of **12b**, see below:



Scheme 5