An Efficient Total Synthesis of (\pm) -Stemonamine

Yu-Ming Zhao, Peiming Gu, Yong-Qiang Tu,* Chun-An Fan, and Qingwei Zhang

State Key Laboratory of Applied Organic Chemistry and Department of Chemistry, Lanzhou University, Lanzhou 730000, P. R. China

tuyq@lzu.edu.cn

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TMSO $N_3 \xrightarrow{\text{TiCl}_4. \text{ CH}_2\text{Cl}_2}_{-78 \text{ to } 0 \text{ }^{\circ}\text{C}} \xrightarrow{\text{HO}}_{0} \xrightarrow{\text{9 steps}} \xrightarrow{\text{Me}}_{0} \xrightarrow{\text{OMe}}_{\text{Me}} \xrightarrow{\text{N}}_{\text{Me}}$ M_{E} $M_$

ABSTRAC

An efficient first approach to the Stemona alkaloid (\pm) -Stemonamine has been developed on the basis of a key TiCl₄ 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 chal-



Figure 1. Stemonamine and related alkaloids.

lenging 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.

The first total syntheses of (\pm) -stemonamide (1c) and (\pm) 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 (\pm) -1c and (\pm) -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 1,3diheteroatom 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 (\pm)-**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

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

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Scheme 1. Tandem Semipinacol Rearrangement/Schmidt Reaction of α-Siloxy Epoxy Azides



Scheme 2. Retrosynthetic Analysis of (\pm) -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 chloride⁷



to known compound 2⁸ The epoxidation of the resulting allylic alcohol 3, followed by protection with TMSCl,

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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 TiCl₄ in CH₂Cl₂ 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



then turned our attention to construction of γ -lactone ring. Treatment of ketone **9** with LHMDS and Mander reagent⁹ 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 CeCl₃•7H₂O, 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, Et₃N, and DMAP (cat.) in dry CH₂Cl₂ 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'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'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.

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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(CH₃)₃}₂, KN{Si(CH₃)₃}₂, NaH, KH, or NaOMe) with the combination of various solvents (Et₂O, THF,

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





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.

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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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