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Development of the Intramolecular Prins Cyclization/Schmidt Reaction for the Construction of the Azaspiro[4,4]nonane: Application to the Formal Synthesis of (±)-Stemonamine

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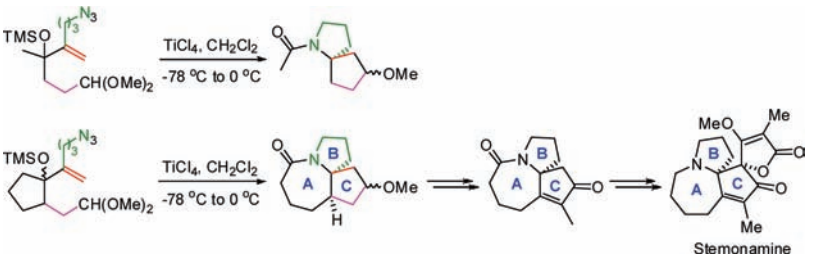
ABSTRACT



A $TiCl_4$-promoted tandem intramolecular Prins cyclization/Schmidt reaction has been designed and developed to be an efficient method for the construction of the azaspiro[4,4]nonane. The present tandem protocol has been employed to construct the tricyclic azaquaternary skeleton (ring A, B, and C) of stemonamine.

Herbal extracts of the Stemonaceae plant have long been used in traditional medicine in East Asia for the treatment of respiratory diseases and as domestic insecticides. More than 130 *Stemona* alkaloids have been isolated to date from the monocotyledonous family Stemonaceae.[1] The Stemonamine group alkaloids[2] **1a**−**1g** (Figure 1), which are characterized by the presence of the cyclopenta[1,2-*b*]-pyrrolo[1,2-*a*]azepine nucleus, represent a class of polycyclic *Stemona* alkaloids and have been synthetic targets in organic chemistry for many years. In the past decade, five different strategies toward the syntheses of the Stemonamine group alkaloids have been accomplished based on rational design and fundamental research.[3]

Previous investigations in our laboratory showed that the **A** and **B** rings of stemonamine (**1a**) could be established based on a cascade semipinacol rearrangement/Schmidt reaction or a desymmetric intramolecular Schmidt reaction,[4] and the construction of ring **C** would need more

(1) For recent reviews, see: (a) Pilli, R. A.; de Oliveira, M. C. F. *Nat. Prod. Rep.* **2000**, *17*, 117. (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. (d) Pilli, R. A.; Rosso, G. B.; de Oliveira, M. C. F. *Nat. Prod. Rep.* **2010**, *27*, 1908.

(2) Pilli et al. have classified Stemona alkaloids into eight groups according to their structural features. See ref 1a and 1d for more details.

(3) (a) Kende, A. S.; Hernando, J. I. M.; Milbank, J. B. J. *Org. Lett.* **2001**, *3*, 2505. (b) Kende, A. S.; Hernando, M. J. I.; Milbank, J. B. J. *Tetrahedron* **2002**, *58*, 61. (c) Zhao, Y.-M.; Gu, P. M.; Tu, Y.-Q.; Fan, C.-A.; Zhang, Q.-W. *Org. Lett.* **2008**, *10*, 1763. (d) Taniguchi, T.; Tanabe, G.; Muraoka, O.; Ishibashi, H. *Org. Lett.* **2008**, *10*, 197. (e) Taniguchi, T.; Ishibashi, H. *Tetrahedron* **2008**, *64*, 8773. (f) Zhao, Y.-M.; Gu, P. M.; Zhang, H.-J.; Zhang, Q.-W.; Fan, C.-A.; Tu, Y.-Q.; Zhang, F.-M. *J. Org. Chem.* **2009**, *74*, 3211. (g) Chen, Z.-H.; Zhang, Y.-Q.; Chen, Z.-M.; Tu, Y.-Q.; Zhang, F.-M. *Chem. Commun.* **2011**, DOI:10.1039/C0CC02612C.

(4) For the intramolecular Schmidt reaction, see: (a) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965. (b) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449.

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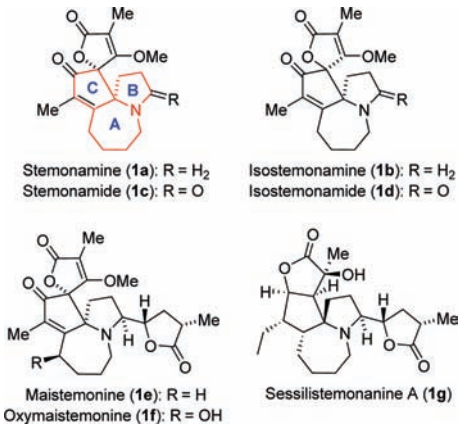


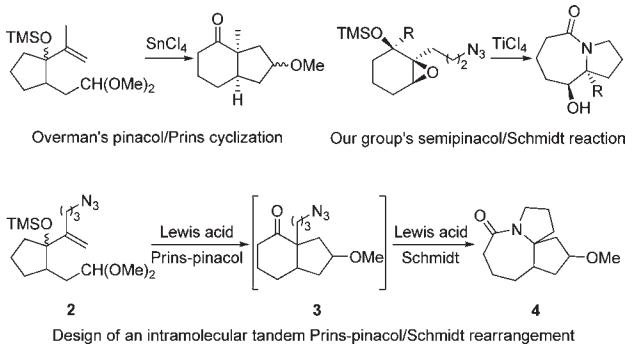
Figure 1. Seven alkaloids of the stemonamine group.

manipulations involving an aldol cyclization.[3c,f] However, a more efficient approach to forge the tricyclic azaquaternary core of **1a** was still a challenging task to us, especially via a tandem reaction of a readily available substrate. In connection with Overman's pinacol-terminated Prins cyclizations[5] and our previous studies on a semipinacol rearrangement/Schmidt reaction,[6] we envisioned that an intramolecular cascade Prins-pinacol/Schmidt rearrangement could lead to the tricyclic skeleton of **1a**.[7,8] Herein, we wish to present our study on this tandem protocol and its application to the formal synthesis of (±)-stemonamine (**1a**).

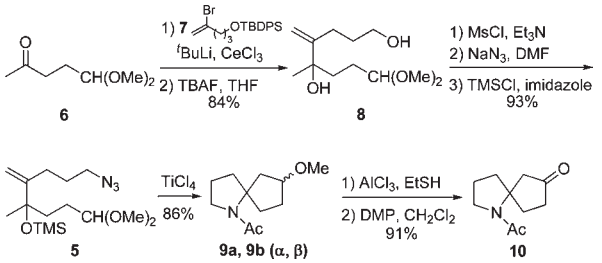
The designed tandem reaction is shown in Scheme 1. We conceived that the azido-acetal compound **2** would undergo a Prins-pinacol cyclization promoted by a Lewis acid to generate an azido-ketone intermediate **3**, which was expected to subsequently undergo an intramolecular Schmidt reaction under the same conditions to give the desired tricyclic product **4**.

According to the aforementioned idea, we initially started our investigation using a relatively simple linear substrate **5**, which could be conveniently obtained from ketone **6**[9] (Scheme 2). Thus, 1,2-addition of the vinyl cerium reagent[10] derived from **7**[11] to **6**, followed by removal of TBDPS group afforded diol **8**. Selective mesylation of **8** and

Scheme 1. Design of an Intramolecular Tandem Prins-Pinacol/Schmidt Rearrangement to Forge the Tricyclic Skeleton of **1a**



Scheme 2. Model Study of the Cascade Protocol



subsequent displacement with NaN_3, followed by TMS protection of tertiary alcohol resulted in the formation of azido-acetal **5** in 78% overall yield from **6**. With **5** in hand, the key Prins-pinacol/Schmidt reaction was attempted. To our delight, the rearrangement was enabled by treatment of **5** with 1.1 equiv of $TiCl_4$ (−78 to 10 °C, then quenched with water). Purification of the resulting product on silica gel gave the desired azaspiro adducts in 86% yield (separable diastereoisomers **9a** and **9b** in the ratio of 1.3:1). Next, the mixture of **9a** and **9b** was subjected to demethylation with $AlCl_3$ in ethanethiol[12] and oxidation using Dess−Martin periodinane[13] to yield ketone **10**. The efficient construction of the azaspiro[4,4]nonane **10** not only was a model study used to determine the possibility of the cascade course but also afforded a viable synthetic intermediate for advancement to the alkaloids containing an azaspirocyclic system, such as cephalotaxine.[14]

Based on the success of the model system, we attempted to incorporate the cyclopentane unit required for forming the tricyclic core of **1a** via a tandem reaction. As shown in Scheme 3, treatment of the known compound **11**[5a] with the cerium reagent and then TBAF furnished compounds **12a** and **12b** in the ratio of 5:1, which were readily separated by column chromatography.

(5) (a) Hirst, G. C.; Howard, P. N.; Overman, L. E. *J. Am. Chem. Soc.* **1989**, *111*, 1514. (b) Ando, S.; Minor, K. P.; Overman, L. E. *J. Org. Chem.* **1997**, *62*, 6379. (c) Gahman, T. C.; Overman, L. E. *Tetrahedron* **2002**, *58*, 6473.

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

(7) In the course of our investigation for the intramolecular tandem Prins-pinacol/Schmidt rearrangement, the Aubé group reported an intermolecular Prins/Schmidt reaction. See: Meyer, A. M.; Katz, C. E.; Li, S.-W.; Velde, D. V.; Aubé, J. *Org. Lett.* **2010**, *12*, 1244.

(8) For a cascade reaction involving an intramolecular Schmidt reaction, see: (a) Golden, J. E.; Aubé, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4316. (b) Zeng, Y.; Reddy, D. S.; Hirt, E.; Aubé, J. *Org. Lett.* **2004**, *6*, 4993. (c) Zeng, Y.; Aubé, J. *J. Am. Chem. Soc.* **2005**, *127*, 15712. (d) Frankowski, K. J.; Golden, J. E.; Zeng, Y.; Aubé, J. *J. Am. Chem. Soc.* **2008**, *130*, 6018 and ref 6.

(9) Sworin, M.; Neumann, W. L. *J. Org. Chem.* **1988**, *53*, 4894.

(10) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.

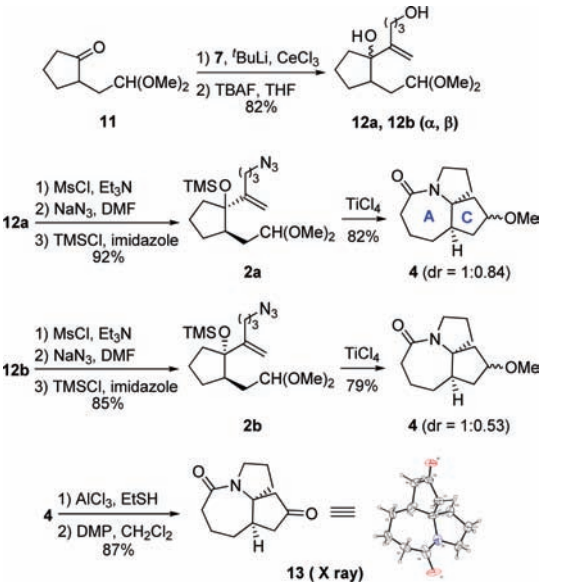
(11) Pihko, A. J.; Lundell, K.; Kanerva, L.; Koskinen, A. M. P. *Tetrahedron: Asymmetry* **2004**, *15*, 1637.

(12) Node, M.; Nishide, K.; Sai, M.; Ichikawa, K.; Fuji, K.; Fujita, E. *Chem. Lett.* **1979**, *8*, 97.

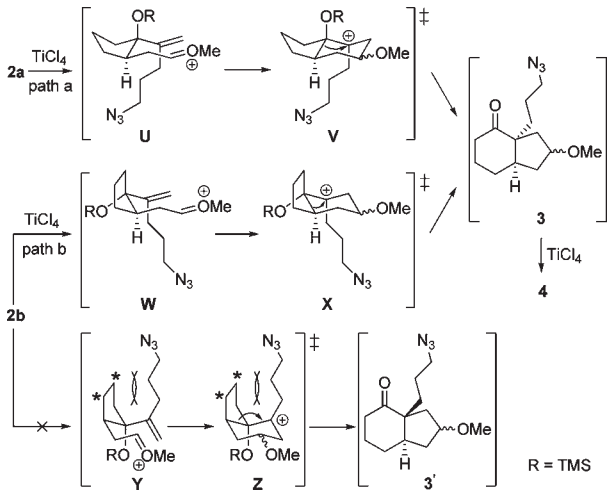
(13) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(14) (a) Middleton, D. S.; Simpkins, N. S.; Terrett, N. K. *Tetrahedron Lett.* **1989**, *30*, 3865. (b) Li, W.-D. Z.; Wang, X.-W. *Org. Lett.* **2007**, *9*, 1211. (c) For a recent review about construction of azaspirocycles, see: Dake, G. *Tetrahedron* **2006**, *62*, 3467.

Scheme 3. Construction of Tricyclic Core **13**



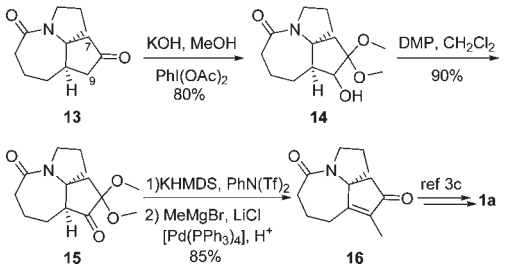
Scheme 4. Possible Reaction Mechanism



The isomers **12a** and **12b** were converted to azido-acetal **2a** and **2b** through several transformations mentioned above in the yield of 92% and 85%, respectively. Next, the key rearrangement to access the core of **1a** was attempted. Gratifyingly, reactions of **2a** and **2b** with $TiCl_4$ in CH_2Cl_2 at −78 to 10 °C both provided the fused tricyclic compounds **4** with different diastereomeric ratios in high yields. Demethylation of **4** followed by oxidation gave ketone **13** as a single diastereoisomer. The X-ray crystallographic analysis of **13** verified the stereospecificity of the tandem reactions of substrates **2a** and **2b**, namely, the *cis*-fused bicycle (ring **A** and C in **4**) was forged in the rearrangement.

(15) For the mechanism of the intramolecular Schmidt reaction, see: Sahasrabudhe, K.; Gracias, V.; Furness, K.; Smith, B. T.; Katz, C. E.; Reddy, D. S.; Aubé, J. *J. Am. Chem. Soc.* **2003**, *125*, 7914 and ref 4b.

Scheme 5. Synthesis of Enone **16**



A possible sequential mechanism of this cascade reaction was proposed on the basis of the above experimental results and the literature reports[5c,15] (Scheme 4). The $TiCl_4$-promoted Prins cyclization of ring-enlarging cyclopentane annulations of **2a** and **2b** took place through path **a** and path **b** to deliver the same *cis*-fused intermediate **3**, which then underwent an intramolecular Schmidt reaction promoted by the same Lewis acid to afford the rearrangement product **4**. In the absence of overriding steric effects, the Prins cyclization should occur preferentially through a stereoelectronically favored pathway. For substrate **2a**, the transition state of the Prins cyclization would adopt the **U** to **V** pathway in order to favor the stereoelectronic effect and avoid steric destabilization. In the case of substrate **2b**, the Prins cyclization would took place through a stereoelectronically less favored pathway (**W** to **X**). It was assumed that the steric destabilization between the original azido-chain and two carbons of the cyclopentane ring (the starred carbons of **Y** and **Z**) might retard the occurrence of the transition state **Y** to **Z**.

To complete the formal synthesis of stemonamine, the final challenge was dehydrogenation and introduction of a methyl group on ring **C** of **13** (Scheme 5). α-Methylenation of ketone **13** with a series of bases (KHMDS, LHMDS, KH, or NaH) and Eschenmoser's salt[16] afforded the undesired C-7 methylenation product. Similar α-methylenation using *t*-BuOK and paraformaldehyde gave a complex mixture of products. Gratifyingly, treatment of ketone **13** with $KOH/PhI(OAc)_2$[17] afforded a C-9 hydroxy dimethylketal **14** in 80% yield, which was subsequently oxidized by Dess−Martin periodinane to ketone **15** in 90% yield. Ketone **15** was converted into its enol triflate using $KHMDS/PhN(Tf)_2$, and the methyl moiety was introduced via Kumada coupling[18] (quenched under acid conditions to remove the dimethylketal group) to give the desired intermediate **16** in 53% overall yield from **4**, which could be conveniently converted to **1a** according to our previously reported procedure.[3c]

In summary, we have designed and developed a new Lewis acid promoted tandem intramolecular Prins

(16) Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed.* **1971**, *10*, 330.

(17) Moriarty, R. M.; Hu, H.; Gupta, S. C. *Tetrahedron Lett.* **1981**, *22*, 1283.

(18) Clark, J. S.; Berger, R.; Hayer, S. T.; Thomas, L. H.; Morrison, A. J.; Gobbi, L. *Angew. Chem., Int. Ed.* **2010**, *49*, 9867.

cyclization/Schmidt reaction. This protocol was efficiently employed to synthesize the azaspiro[4,4]nonane which might be a viable synthetic intermediate and to construct the azaquaternary tricyclic skeleton in the formal synthesis of stemonamine. Furthermore, a possible mechanism of this cascade process has been proposed in the present report. Efforts toward the total synthesis of other alkaloids based on the present tandem reaction is currently underway in our group.

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Supporting Information Available. General experimental procedures, characterization data for all products, and X-ray crystallographic data for compound **13**. This material is available free of charge via the Internet at http://pubs.acs.org.