Bioinspired Synthesis

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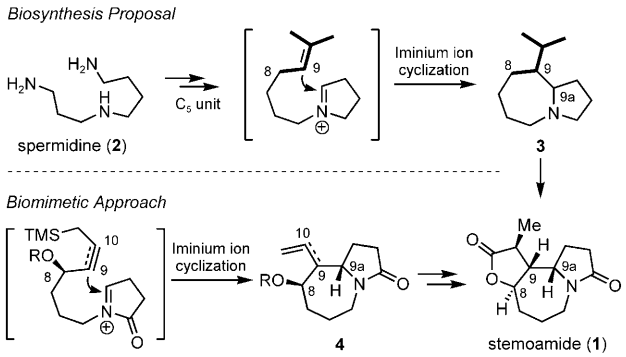
Bioinspired and Concise Synthesis of (±)-Stemoamide**

*Yan Wang, Lili Zhu, Yuying Zhang, and Ran Hong**

Dedicated to Professor Guo-Qiang Lin

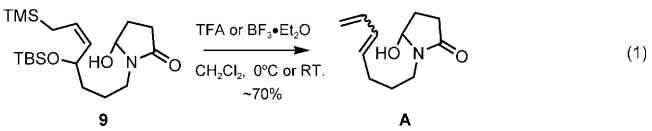
Stemona alkaloids have interesting biological properties and over 100 structurally diverse compounds have been identified so far.[1] The common pyrrolo[1,2-*a*]azepine core associated with the polycyclic architecture inspired many intriguing synthetic strategies. The innovation of powerful synthetic methods greatly improved the efficiency of the synthesis of these alkaloids.[2] In 1992, Xu and co-workers isolated the tricyclic stemoamide (**1**) from *Stemona tuberosa* Lour, the Chinese traditional medicine that has been used for the treatment of respiratory diseases such as asthma, bronchitis, petusis, and tuberculosis.[3] Since the first asymmetric total synthesis of (±)-stemoamide was completed by Williams et al., numerous efforts have been devoted to the efficient construction of this tricyclic system.[4,5] The ingenious seven-step racemic synthesis reported by Jacobi and Lee marks a milestone among these.[4d] Nevertheless, a general synthetic strategy remains elusive.

Seger et al. proposed an iminium-ion-based biosynthetic pathway from a putative precursor, spermidine (**2**).[6] This proposal suggests that the construction of the azepine ring **3** through an iminium ion is a stereochemical defining step (Scheme 1, top) in which preorganization of the reacting partners facilitated by an enzyme is most likely involved. The innovative radical-zipping strategy in which a reversal of the polar disconnection is executed by the groups of Cossy and Khim resulted in a *trans* configuration of C9 and C9a.[5] Inspired by the biogenetic proposal,[6] we envisioned a bioinspired approach in which the formation of the azepine **4** is accomplished through a cationic cyclization and then construction of the lactone ring by cyclocarbonylation[7] and reduction of the corresponding butenolide (Scheme 1, bottom) would furnish the target and diminish obstacles encountered in previous syntheses. Herein we describe the successful synthesis of (±)-stemoamide based on this approach.



Scheme 1. Biomimetic approach toward stemoamide (**1**).

To begin the synthesis, a modified procedure for the alkynylation of the aldehyde **6** with propargyl trimethylsilane (**5**) was undertaken.[8] The desired propargylic alcohol was obtained in 93% yield on a gram scale by careful control of the reaction temperature, reaction time, and exclusion of air and moisture (Scheme 2). After protection of the alcohol with TBS, the corresponding bromide **7** reacted with succinimide and subsequent reduction using $NaBH_4$ gave the hemiaminal **8** in excellent yield. Encouraged by the intramolecular cyclization of an allylsilane with an iminium ion as reported by the Speckamp group and others,[9] the requisite allylsilane **9** was prepared through hydrogenation using the Lindlar catalyst and subsequent reduction using the same protocol.[10] However, under these reaction conditions only the diene **A** was isolated as a single product [Eq. (1); TBS = *tert*-butyldimethylsilyl, TFA = trifluoroacetic acid, TMS = trimethylsilyl]. We reasoned that the allylic alcohol (or the masked allylic alcohol **9**) readily underwent elimination via an allylic cation intermediate. Gratifyingly, when the propargylsilane **8** was subjected to a $SnCl_4$-promoted cyclization,[11] the chlorinated product **B** was isolated in 56% yield[12] [Eq. (2)]. Lowering the reaction temperature and using 1.0 equivalent of $SnCl_4$ altered the product distribution to afford the allenic product **10** in 33% yield. After extensive experimentation,



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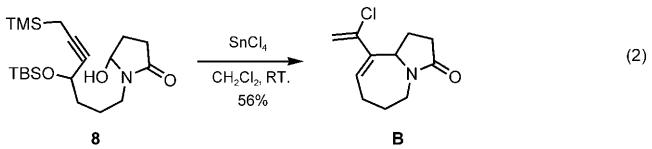

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[*] Y. Wang, L. Zhu, Y. Zhang, Prof. Dr. R. Hong
Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032 (China)
Fax: (+86) 21-6416-6128
E-mail: rhong@mail.sioc.ac.cn
Homepage: http://honglab.labways.com

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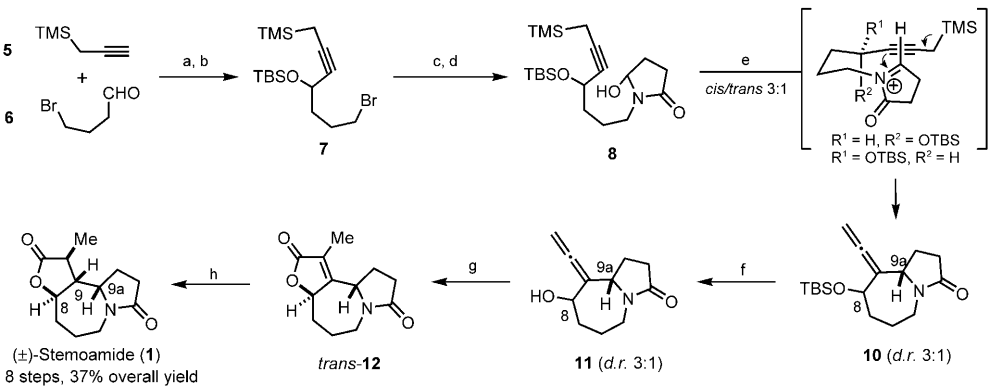
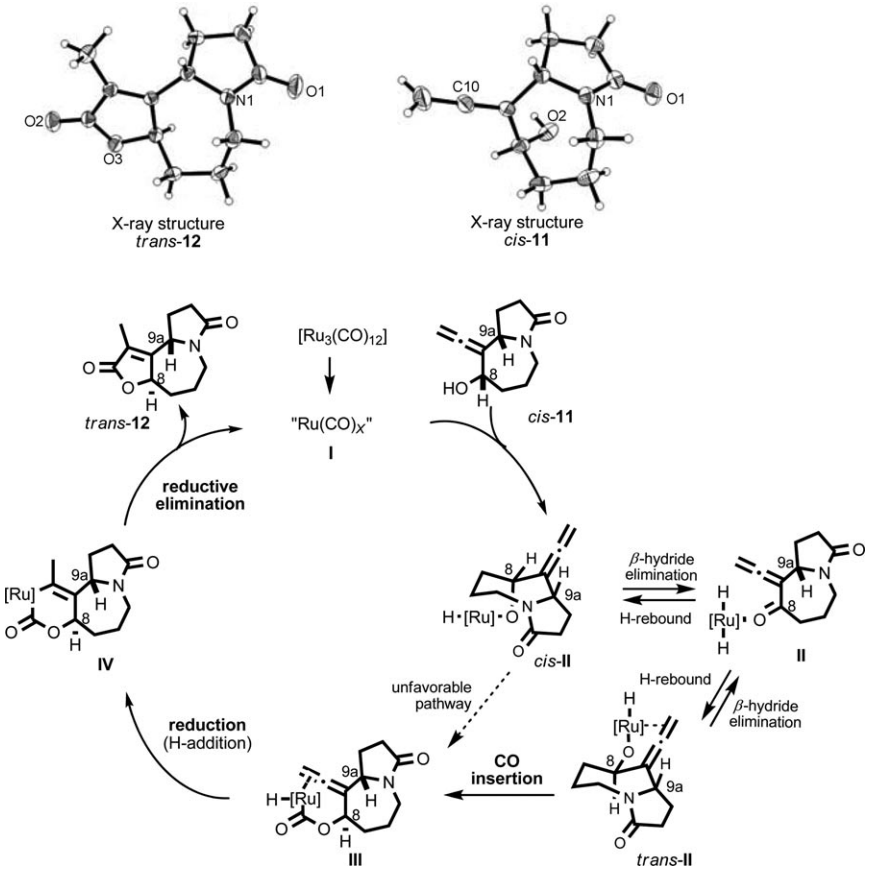


Scheme 2. Synthesis of (±)-stemoamide (**1**): a) *n*BuLi (1.0 equiv), THF, −78 °C, 93%; b) TBSCl (1.4 equiv), DBU (1.4 equiv), CH_2Cl_2, RT, 1 h, 87%; c) succinimide (2.0 equiv), K_2CO_3 (2.0 equiv), DMF, RT; d) $NaBH_4$ (5.0 equiv), EtOH, 0 °C, 93% (two steps); e) $FeCl_3$ (1.0 equiv), toluene, 0 °C, 2 h, 86%; f) TBAF (3.0 equiv), THF, RT, 96%; g) $[Ru_3(CO)_{12}]$ (3 mol%), CO (10 atm), TEA, 100 °C, 6 h, 81%; h) $NaBH_4$ (4.0 equiv), $NiCl_2$ (0.3 equiv), MeOH, RT, 2 h, 74% (recryst.). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMF = *N*,*N*′-dimethylformamide, TBAF = tetra-*n*-butylammonium fluoride, TEA = triethylamine, THF = tetrahydrofuran.

anhydrous $FeCl_3$ successfully promoted the cyclization to give **10** in a 3:1 d.r. with 86% yield in toluene.

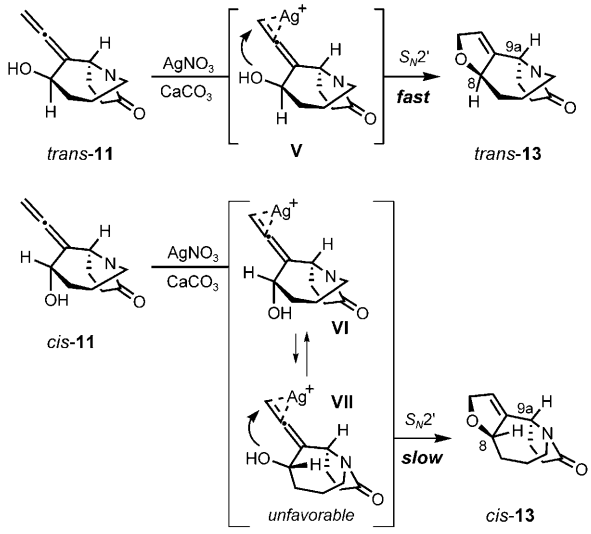
The subsequent removal of the TBS group, careful separation of the two diastereomers on silica gel, and product isolation allowed identification of the major isomer as *cis*-**11** as determined by X-ray diffraction analysis.[13] Based on the structure elucidation, we initially proposed that *trans*-**11** would preferentially undergo cyclocarbonylation through a metallacycle intermediate. Therefore, a proximity enabled carbonylation would preferentially convert the *trans* isomer into the desired butenolide. The mixture of the two distereoisomers of **11** (*cis*/*trans* = 3:1) was thereby subjected to the ruthenium-catalyzed CO-insertion reaction.[7a] Surprisingly, only *trans*-**12** was isolated, as was confirmed by X-ray analysis.[14] It is evident that the *cis*-**11** was also converted into *trans*-**12** during the carbonylation. To confirm this unprecedented epimerization of the allenic alcohol,[15] the pure *cis*-**11** was subjected to the reaction conditions and the *trans*-butenolide **12** was the only product isolated in 83% yield. The proposed mechanism indicates that an equilibrium between *cis*-**II** and *trans*-**II** allows both isomers of **11** to be converted into one diastereomer of **12** (Scheme 3). In the presence of CO gas, the active species "$Ru(CO)_x$"[16] would react with **11** to form the intermediate ruthenium alkoxy complex *cis*-**II**, and the subsequent CO-insertion is hindered because of the weak interaction between the allene moiety and the metal center; instead a β-hydride elimination is favored to afford the intermediate ketone and the Ru/hydride complex **II**. After the H-rebound, the corresponding intermediate *trans*-**II** would have a favorable conformation to promote the ruthenium-catalyzed CO insertion and subsequent reduction of the terminal alkene. Thus, the reductive elimination completes the catalytic cycle to generate the desired *trans*-**12**. When CO gas was excluded, the epimerization at C8 was not observed when using the pre-catalyst $[Ru_3(CO)_{12}]$ and only a small amount of diene product from the elimination of OH group was found.[10] This observation suggests that the CO insertion of *trans*-**II** may be the driving force for the complete conversion of *cis*-**II** into *trans*-**II**. Notwithstanding, the epimerization of the allenic alcohol remains obscure and requires additional mechanistic studies. When *trans*-**12** was subjected to a known nickel-catalyzed reduction[4b] and



Scheme 3. Proposed mechanism for the dynamic ruthenium-catalyzed CO insertion into **11**. The thermal ellipsoids of the X-ray structures are shown at 50% probability.

subsequent recrystallization, (±)-stemoamide (**1**) was isolated in 74% yield and was identical to the natural product.[3,4i]

To secure a future asymmetric synthesis of stemoamide,[17] the resolution of **11** was pursued. The compound *trans*-**11** was envisioned to undergo a favorable cyclization with the participation of the pseudoequitorial C8–OH group. To our delight, preliminary screening showed that upon treatment of **11** (*cis*/*trans* = 77:23) with $AgNO_3$ (0.8 equiv) and $CaCO_3$ (0.8 equiv; Marshall's conditions),[18] *trans*-**11** was preferentially transformed into the tricylic *trans*-**13**, and *cis*-**11** was recovered in good yield (64%, >98% d.r.) after 32 hours.[10] The carbophilic silver catalyst activates the distal double bond as shown in the intermediates **V** and **VI** (Scheme 4). The former silver complex is thought to undergo an S_N2'-type



Scheme 4. Proposed mechanism for the silver-mediated cyclization of an allenic alcohol.

cyclization with the proximal OH group to give *trans*-**13**.[19] However, in the case of **VI**, the pseudoaxial C8-OH group would have to adopt the unfavorable conformer **VII** that would then lead to *cis*-**13**.[20] Clearly, the later cyclization is slow because of the high energy barrier, and as a consequence *cis*-**11** would not undergo reaction and *trans*-**11** would be transformed into the cyclized product. Through this mode of reaction, stemoamide can be enantioselectively synthesized from a chiral propargylic alcohol.[21]

In summary, the concise synthesis of (±)-stemoamide was achieved in eight steps and 37% overall yield from commercially available propargylsilane. The bioinspired iminium ion cyclization in combination with the ruthenium-catalyzed cyclocarbonylation of an allenic alcohol ensured the convergence of the synthesis. This easily scaled-up synthesis can be combined with the silver-mediated cyclization to obviate the installation of the stereocenter at C9a as done in previous syntheses and pave the way to the synthesis of more complex stemona alkaloids.

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[1] Reviews: a) R. A. Pilli, M. C. F. de Oliveira, G. B. Rosso in *The Alkaloids*, *Vol. 62*, (Ed.: G. A. Cordell), Academic Press, New York, **2005**, p. 77; b) H. Greger, *Planta Med.* **2006**, *72*, 99.
[2] Reviews: a) R. A. Pilli, M. C. F. de Oliveira, *Nat. Prod. Rep.* **2000**, *17*, 117; b) E. Jezek, O. Reiser, *Chemtracts* **2005**, *18*, 200; c) R. Alibés, M. Figueredo, *Eur. J. Org. Chem.* **2009**, 2421.
[3] W.-H. Lin, Y. Ye, R.-S. Xu, *J. Nat. Prod.* **1992**, *55*, 571.
[4] Stemoamide: a) D. R. Williams, J. P. Reddy, G. S. Amato, *Tetrahedron Lett.* **1994**, *35*, 6417; b) Y. Kohno, K. Narasaka, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2063; c) A. Kinoshita, M. Mori, *J. Org. Chem.* **1996**, *61*, 8356; d) P. A. Jacobi, K. Lee, *J. Am. Chem. Soc.* **1997**, *119*, 3409; e) P. A. Jacobi, K. Lee, *J. Am. Chem. Soc.* **2000**, *122*, 4295; f) M. K. Gurjar, D. S. Reddy, *Tetrahedron Lett.* **2002**, *43*, 295; g) M. P. Sibi, T. Subramanian, *Synlett* **2004**, 1211; h) H. F. Olivo, R. Tovar-Miranda, E. Barragán, *J. Org. Chem.* **2006**, *71*, 3287; i) N. Bogliotti, P. I. Dalko, J. Cossy, *Synlett* **2006**, 2664; j) N. Bogliotti, P. I. Dalko, J. Cossy, *J. Org. Chem.* **2006**, *71*, 9528; k) S. Torssell, E. Wanngren, P. Somfai, *J. Org. Chem.* **2007**, *72*, 4246; l) R. W. Bates, S. Sridhar, *Synlett* **2009**, 1979.
[5] *epi*-Stemoamide: a) N. Bogliotti, P. I. Dalko, J. Cossy, *Synlett* **2005**, 349; b) S.-K. Khim, A. G. Schultz, *J. Org. Chem.* **2004**, *69*, 7734; c) P. Gao, Z. Tong, H. Hu, P.-F. Xu, W. Liu, C. Sun, H. Zhai, *Synlett* **2009**, 2188.
[6] a) C. Seger, K. Mereiter, E. Kaltenegger, T. Pacher, H. Greger, O. Hofer, *Chem. Biodiversity* **2004**, *1*, 265; b) The C3 lactone unit of stemonine was recently proposed from leucine, see: H. Greger, J. Schinnerl, S. Vajrodaya, L. Brecker, O. Hofer, *J. Nat. Prod.* **2009**, *72*, 1708.
[7] a) Ruthenium-catalyzed cyclocarbonylation: E. Yoneda, T. Kaneko, S.-W. Zhang, K. Onitsuka, S. Takahashi, *Org. Lett.* **2000**, *2*, 441, and references therein; b) Pd-catayzed cyclocarbonylation: H. Alper, D. Leonard, *J. Chem. Soc. Chem. Commun.* **1985**, 511; c) Radical lactonization: M. D. Bachi, E. Bosch, *J. Org. Chem.* **1992**, *57*, 4696.
[8] A. Blum, W. Hess, A. Studer, *Synthesis* **2004**, 2226.
[9] a) H. Hiemstra, W. N. Speckamp, *Tetrahedron Lett.* **1983**, *24*, 1407; b) H. Hiemstra, M. H. A. M. Sno, R. J. Vijn, W. N. Speckamp, *J. Org. Chem.* **1985**, *50*, 4014. For selected reviews on iminium ion cyclization, see: c) B. E. Maryanoff, H.-C. Zhang, J. H. Cohen, I. J. Turchi, C. A. Maryanoff, *Chem. Rev.* **2004**, *104*, 1431; d) J. Royer, M. Bonin, L. Micouin, *Chem. Rev.* **2004**, *104*, 2311; e) W. N. Speckamp, M. J. Moolenaar, *Tetrahedron* **2000**, *56*, 3817; f) H. Hiemstra, W. N. Speckamp in *Comprehensive Organic Synthesis*, *Vol. 2* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, UK, **1991**, p. 1047.
[10] See the Supporting Information for details.
[11] a) C. Li, X. Li, R. Hong, *Org. Lett.* **2009**, *11*, 4036; b) X. Li, C. Li, W. Zhang, X. Lu, S. Han, R. Hong, *Org. Lett.* **2010**, *12*, 1696.
[12] The chlorination was proposed to proceed through a close-S_N2' pathway; see: a) J. Pornet, *Tetrahedron Lett.* **1981**, *22*, 453; b) J. Pornet, L. Miginiac, K. Jaworski, B. Randrianoelina, *Organometallics* **1985**, *4*, 333; c) Y. Deng, X. Jin, S. Ma, *J. Org. Chem.* **2007**, *72*, 5901.
[13] The *cis* configuration of **11** referred to the protons at C8 and C9a, each on the same side. The data for *trans*-**11** was identical to that reported in the literature (see Ref. [4n]). CCDC 799348 (*cis*-**11**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge

Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] CCDC 799392 (*trans*-**12**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] Dynamic kinetic resolution involving allenic alcohol is extremely rare. See a recent chemoenzymatic approach: J. Deska, C. del Pozo Ochoa, J. E. Bäckvall, *Chem. Eur. J.* **2010**, *16*, 4447.

[16] The precise structure of "$Ru(CO)_X$" is not clear. See a discussion on multinuclear or mononuclear complexes: N. Chatani, T. Fukuyama, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **1996**, *118*, 493.

[17] The two diastereomers of **10** are inseparable, and the separation of *cis*-**11** and *trans*-**11** on a silica gel column is also very tedious. Moreover, the configuration at C9a could not be epimerized later in the synthetic route. For a gram scale synthesis, starting from optically pure **7**, the resulting stemoamide would be only 50% *ee* (% *ee* = 100% (3−1)/(3+1)) if both isomers of **11** were carried through the synthesis.

[18] a) L. I. Olsson, A. Claesson, *Synthesis* **1979**, 743; b) J. A. Marshall, X. Wang, *J. Org. Chem.* **1990**, *55*, 2995; c) J. A. Marshall, K. G. Pinney, *J. Org. Chem.* **1993**, *58*, 7180; d) J. A. Marshall, R. H. Yu, J. F. Perkins, *J. Org. Chem.* **1995**, *60*, 5550; e) For reviews on silver-mediated reactions, see: M. Naodovic, H. Yamamoto, *Chem. Rev.* **2008**, *108*, 3132; f) J.-M. Weibel, A. Blanc, P. Pale, *Chem. Rev.* **2008**, *108*, 3149; g) M. Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García, *Chem. Rev.* **2008**, *108*, 3174; h) Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3199.

[19] Gold catalysts (e.g. $AuCl_3$) also exhibit excellent reactivity toward this cyclization; see the Supporting Information for details. The exploration on asymmetric kinetic resolution of allenic alcohol will be reported in due course.

[20] The relative configuration of *cis*-**13** was assigned based on the cross-peak between H8 and H9a as observed in the two-dimensional NOE experiment (see the Supporting Information for details).

[21] For the synthesis of chiral propargylic alcohol through asymmetric reduction: a) E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092; *Angew. Chem. Int. Ed.* **1998**, *37*, 1986; b) asymmetric alkynylation: D. E. Frantz, R. Faessler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806, and references therein.

