Bioinspired Synthesis

DOI: 10.1002/ange.201005833

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

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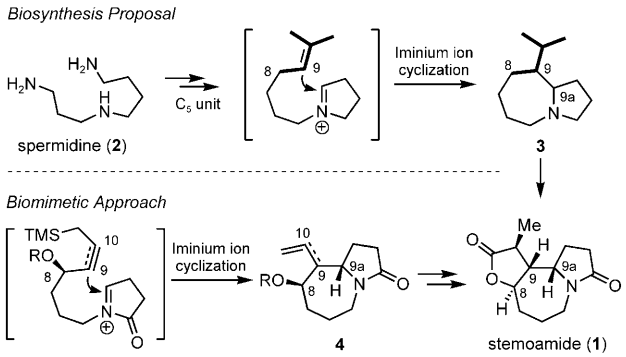
Dedicated to Professor Guo-Qiang Lin

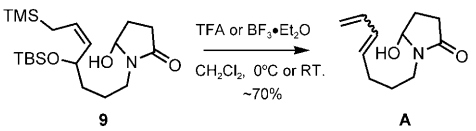
Stemona alkaloids have interesting biological properties and over 100 structurally diverse compounds have been identified so far.[1] The common pyrrolo[1,2-*a*]azepine core associated with the polycyclic architecture inspired many intriguing synthetic strategies. The innovation of powerful synthetic 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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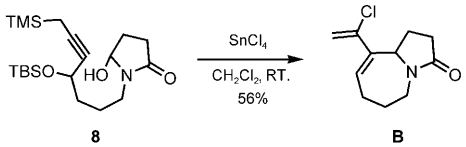

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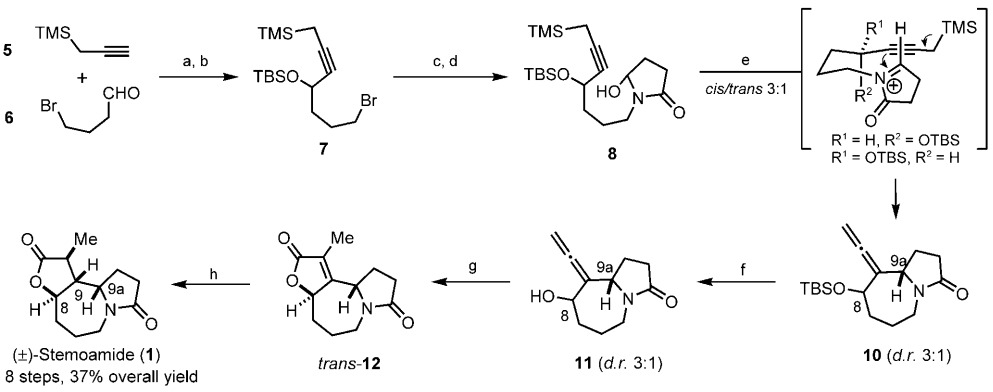
[**] We are grateful to the National Basic Research Program of China (2010CB833200), the Shanghai Rising Star Program (08A14079), the National Natural Science Foundation of China (20702058 and 20872157), and CAS for their generous financial support. We thank Dr. Jie Sun (SIOC) for X-ray analysis and Dr. Rob Hoen (Barcelona Science Park, Spain) for helpful discussions.

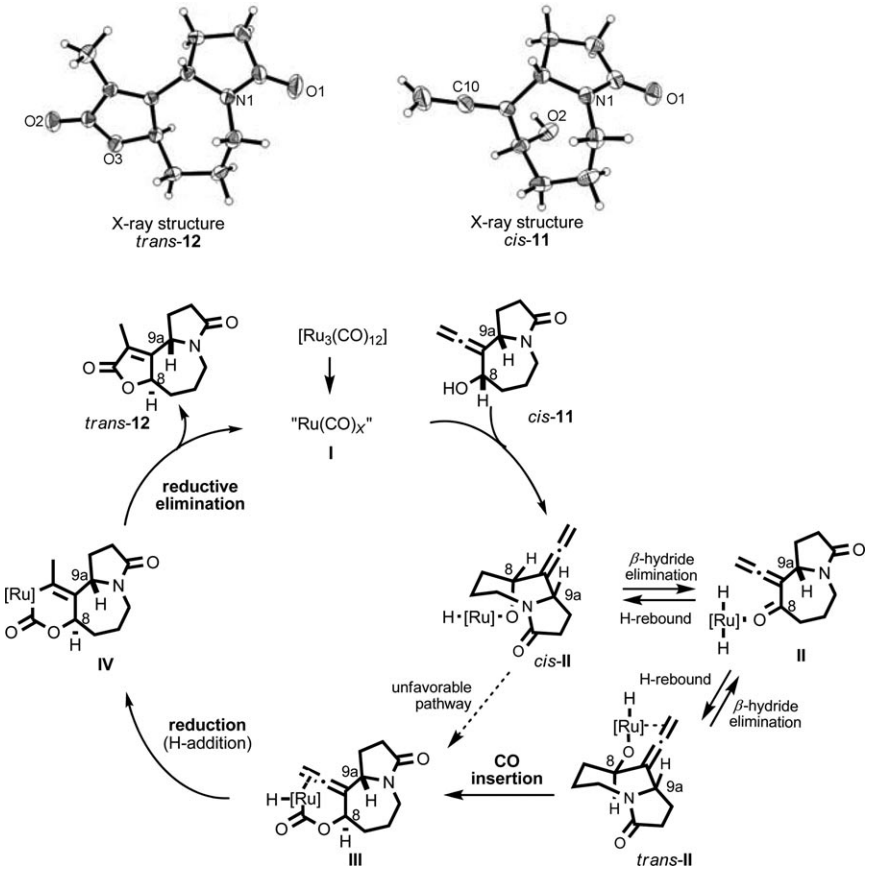
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201005833.



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.

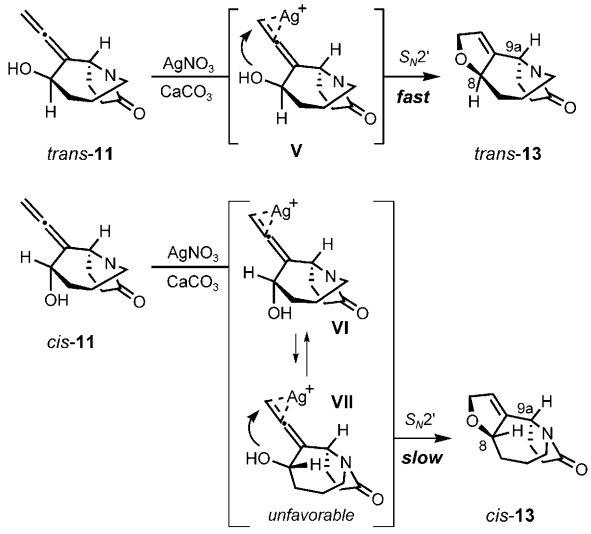
The subsequent removal of the TBS group, careful separation of the two diastereomers on silica gel, and product isolation allowed identification of the major isomer as *cis*-**11** as determined by X-ray diffraction analysis.[13] Based on the structure elucidation, we initially proposed that *trans*-**11** 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.

Received: September 17, 2010
Revised: December 20, 2010
Published online: February 17, 2011

Keywords: carbonylation · cyclization · epimerization · natural products · total synthesis

[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.

