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Total Synthesis of the Putative Structure of Stemonidine: The Definitive Proof of Misassignment

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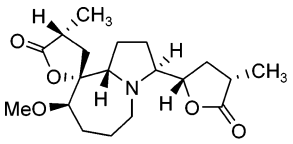
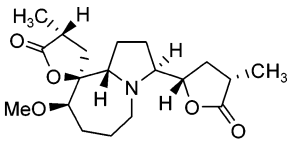
ABSTRACT



stemonidine
putative structure



stemospironine

The total synthesis of the putative structure of the *Stemona* alkaloid stemonidine has been completed. The key transformations include a 1,3-dipolar cycloaddition of a chiral nitrone derived from (*S*)-prolinol and a spirolactonization process involving the generation of the critical stereocenter. The NMR data of the synthetic material do not match those reported for the natural product. It is concluded that the structure assigned to stemonidine is incorrect, and it must be reassigned as stemospironine.

The extracts of several plants of the *Stemonaceae* family have long been used in Chinese and Japanese traditional medicine for the treatment of respiratory disorders, as antihelmintics and also as insecticides.[1] Significant constituents of these extracts are a series of structurally related alkaloids, which may be responsible for their medicinal properties. Nowadays, around 90 *Stemona* alkaloids are known, whose structures were elucidated by X-ray analysis, spectroscopic techniques, and/or chemical correlation, but there is a continuous flow in the literature of new reports describing the isolation of previously unknown members of the family. All the *Stemona* alkaloids are polycyclic, and most of them present a central pyrrolo[1,2-*a*]azepine system as a common characteristic structural feature. The majority also incorporates at least one substructure of α-methyl-γ-butyrolactone, which can be linked to the azabicyclic core in a spiro or fused manner or as a substituent. Considering their structural diversity, Pilli and co-workers have recently classified the *Stemona* alkaloids in eight groups,[1a] whereas Greger has suggested a different classification in only three groups taking into account their biosynthetic connections.[1b] One of these groups, the tuberostemospironine[1a] or croomine[1b] type, concurs in both classifications and is characterized by the inclusion of a spiro-γ-lactone at C_9 of the basic azabicyclic nucleus (Figure 1).

In 1982, Xu and co-workers assigned to stemonidine, an alkaloid isolated from the roots of *Stemona tuberosa*, the structure depicted as **1**, on the basis of its ^{1}H NMR data.[2] Later on, the same group revised the former stereochemical assignment and proposed the new structure that is depicted as **2**.[3] More recently, Williams and co-workers completed the first synthesis of (−)-stemospironine and found that its spectral and physical data matched those reported for the natural material, whose structure had been unequivocally established by X-ray analysis.[4] They also found that the ^{13}C NMR spectra of synthetic stemospironine and natural stemonidine were virtually identical; the authors did not exclude the possibility of the two compounds being spirocyclic diastereomers. Herein, we describe the total synthesis and

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(1) For recent reviews, see: (a) 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. (b) Greger, H. *Planta Med.* **2006**, *72*, 99.

(2) Xu, R.; Lu, Y.; Chu, J.; Iwashita, T.; Naoki, H.; Naya, Y.; Nakanishi, K. *Tetrahedron* **1982**, *38*, 2667.

(3) He, X.; Lin, W.; Xu, R. *Huaxue Xuebao* **1990**, *48*, 694.

(4) (−)-Stemospironine: Williams, D. R.; Fromhold, M. G.; Early, J. D. *Org. Lett.* **2001**, *3*, 2721.

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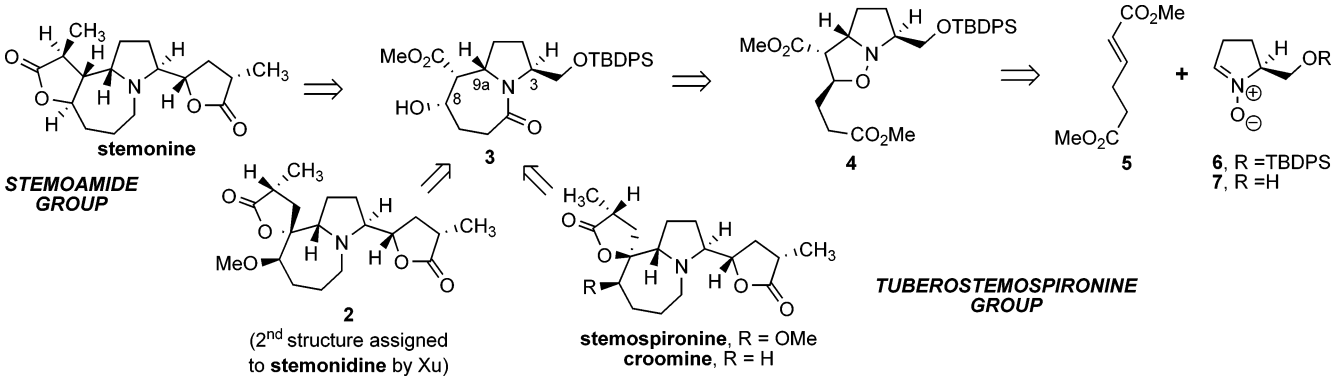
Scheme 1. Retrosynthetic Analysis for Some *Stemona* Alkaloids



NMR data of the putative structure of stemonidine **2**, which are definitive proof of the incorrect original assignments of the natural product.

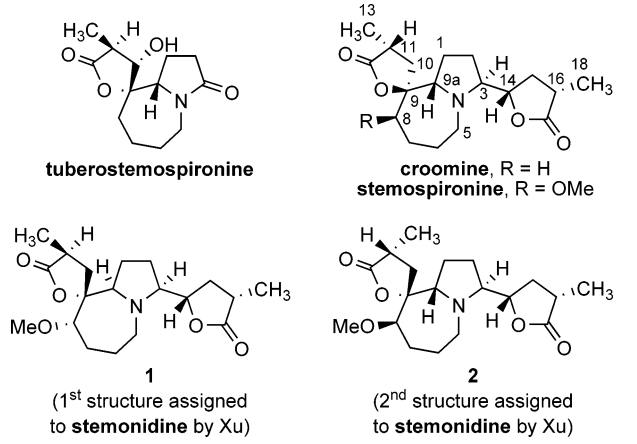


Figure 1. Some alkaloids of the tuberostemospironine group.

The challenging molecular architecture of the *Stemona* alkaloids has attracted considerable interest among synthetic organic chemists, and several total syntheses have been published, although they are limited to a quite small number of targets.[4−12] We designed a strategy in which the azabicyclic core was generated at an early stage of the sequence and the α-methyl-γ-butyrolactone and other specific fragments were then incorporated, with the aim of developing a flexible approach, with some intermediates being common precursors of various alkaloids (Scheme 1).[13]A main advantage of this methodology is the high antifacial selectivity accomplished in the 1,3-dipolar cycloadditions of nitrones such as **6** to electron-deficient olefins of type **5**, delivering isoxazolidine adducts **4** with relative trans configuration of the stereogenic centers at C_3 and C_{9a}, as required for the target alkaloids.[13b,14]

Previously, we have reported the one-step preparation of (*S*)-5-hydroxymethyl-1-pyrroline *N*-oxide, **7**, by treatment of L-prolinol, **8**, with dimethyldioxirane in acetone at low temperature and its isolation in 32% yield.[14a] Although this straightforward methodology competed favorably with other preparations of related nitrones in terms of brevity and yield, difficulties associated with the purification of **7** and scaling-up of the procedure led us to temporarily abandon its use and explore different alternatives. However, recent reports disclosing a new protocol for in situ dioxirane reactions[15] led us to reinvestigate the possibility of preparing the required nitrone by direct oxidation of a prolinol derivative. Hence, the TBDPS derivative of L-prolinol **9** was prepared[16] and treated with Oxone under different reaction conditions (Scheme 2). As the best result, it was found that 2.1 equiv of the oxidant in THF−CH_3CN (1:4) in the presence of

(5) (+)-Croomine: (a) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923. (b) Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299.

(6) (±)-Stenine: (a) Chen, C.-Y.; Hart, D. J. *J. Org. Chem.* **1990**, *55*, 6236. (b) Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515. (c) Golden, J. E.; Aubé, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4316. (−)-Stenine: (d) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106. (e) Morimoto, Y.; Iwahashi, M.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 904.

(7) (±)-Stemoamide: (a) Kohno, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2063. (b) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **1997**, *119*, 3409. (−)-Stemoamide: (c) Williams, D. R.; Reddy, J. P.; Amato, G. S. *Tetrahedron Lett.* **1994**, *35*, 6417. (d) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356. (e) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **2000**, *122*, 4295. (f) Gurjar, M. K.; Reddy, D. S. *Tetrahedron Lett.* **2002**, *43*, 295. (g) Sibi, M. P.; Subramanian, T. *Synlett* **2004**, 1211. (h) Olivo, H. F.; Tovar-Miranda, R.; Barragán, E. *J. Org. Chem.* **2006**, *71*, 3287. (i) Bogliotti, N.; Dalko, P. I.; Cossy, J. *J. Org. Chem.* **2006**, *71*, 9528.

(8) (±)-Isostemofoline: Kende, A. S.; Smalley, T. L., Jr.; Huang, H. *J. Am. Chem. Soc.* **1999**, *121*, 7431.

(9) (±)-Stemonamide and (±)-isostemonamide: Kende, A. S.; Hernando, J. I. M.; Milbank, J. B. J. *Org. Lett.* **2001**, *3*, 2505.

(10) (−)-Tuberostemonine: Wipf, P.; Rector, S. R.; Takahashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 14848.

(11) (−)-Stemonine: Williams, D. R.; Shamim, K.; Reddy, J. P.; Amato, G. S.; Shaw, S. M. *Org. Lett.* **2003**, *5*, 3361.

(12) (±)-Didehydrostemofoline and (±)-isodidehydrostemofoline: Brüggemann, M.; McDonald, A. I.; Overman, L. E.; Rosen, M. D.; Schwink, L.; Scott, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 15284.

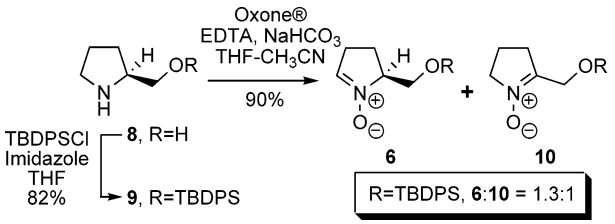
(13) (a) Cid, P.; Closa, M.; de March, P.; Figueredo, M.; Font, J.; Sanfeliu, E.; Soria, A. *Eur. J. Org. Chem.* **2004**, 4215. (b) Alibés, R.; Blanco, P.; Çasas, E.; Closa, M.; de March, P.; Figueredo, M.; Font, J.; Sanfeliu, E.; Ávarez-Larena, A. *J. Org. Chem.* **2005**, *70*, 3157.

(14) (a) Closa, M.; de March, P.; Figueredo, M.; Font, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1031. (b) Busqué, F.; de March, P.; Figueredo, M.; Font, J.; Gallagher, T.; Milán, S. *Tetrahedron: Asymmetry* **2002**, *13*, 437.

(15) (a) Evarts, J. B.; Fuchs, P. L. *Tetrahedron Lett.* **2001**, *42*, 3673. (b) Li, W.; Fuchs, P. L. *Org. Lett.* **2003**, *5*, 2853.

(16) Gerasyuto, A. I.; Hsung, R. P.; Sydorenko, N.; Slafer, B. *J. Org. Chem.* **2005**, *70*, 4248.

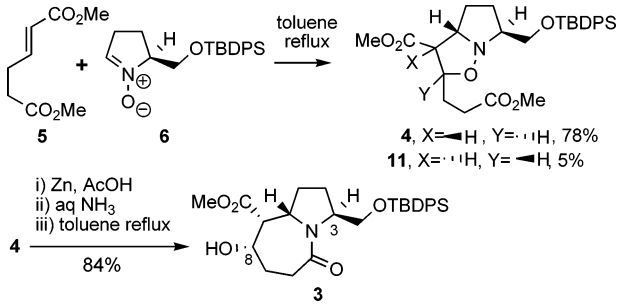
Scheme 2. Preparation of Nitrone **6** from L-Prolinol



EDTA and $NaHCO_3$ at 0 °C furnished a chromatographically separable mixture of nitrones **6** and **10** in 1.3:1 ratio and 90% total yield.

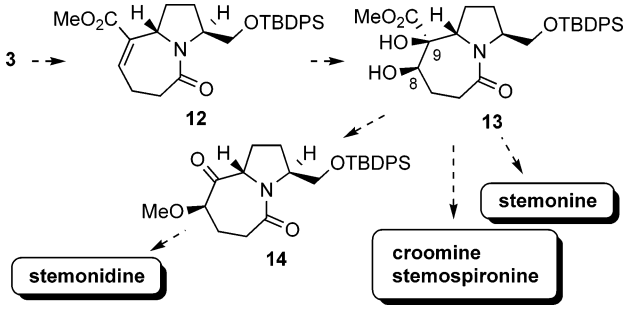
According to the plan, the first step in the synthesis of stemonidine was the 1,3-dipolar cycloaddition between nitrone **6** and diester **5**. This reaction was performed in toluene at reflux for 10 h and delivered the endo isoxazolidine **4** as the major product as expected,[17] along with a minor quantity of the exo isomer **11** (Scheme 3). Hydrogenolysis of **4**, performed by treatment with Zn in glacial acetic acid, followed by basic treatment, and then heating furnished lactam **3** in 84% overall yield.

Scheme 3. Construction of the Azabicyclic Core



Once the azabicyclic core had been elaborated, the formation of the surrounding γ-lactones was our next concern. Obviously, the silyloxymethyl substituent at C_3 in **3** should work as the pivotal feature to install the east-side lactone, which is common to all the target alkaloids shown in Scheme 1, as well as to many other *Stemona* alkaloids. Conversely, the lactone at the west region differs from one alkaloid to another and its formation must be specifically devised for each target. However, for both the tuberostemospironine and stemoamide groups, all the alkaloids bearing an oxygen atom at C_8 present the same configuration at this center, opposite to that in compound **3**. On the other hand, preliminary studies with model compounds had shown that attempted manipulation of the hydroxyl group at C_8 for further synthetic elaboration usually led to elimination products,[13a] and a simple conformational analysis of the perhydropyrroloazepinone skeleton of these compounds shows that the concave face is relatively inaccessible. Taking these facts into account, it seemed to us that dehydration of **3** followed by diastereoselective dihydroxylation could be a good strategy for further studies (Scheme 4). Diol **13** was considered a suitable precursor for stemospironine because it would present the correct configuration at C_8 and a convenient functionalization to form the spirolactone with the appropriate configuration at C_9. Conversely, spirolactonization on ketone **14**, available from **13**, should presumably proceed to give the opposite configuration at the spiro stereocenter, as required for stemonidine.

Scheme 4. Synthetic Plan from **3** to the Target Alkaloids



Dehydration of **3** was accomplished in 88% yield under Mitsunobu conditions and, as anticipated, the dihydroxylation of the α,β-unsaturated ester **12** occurred with complete facial selectivity in 92% yield (Scheme 5). From the crucial intermediate **13**, we pursued the synthesis of stemonidine to shed light on its uncertain stereochemical assignment. Regioselective methylation of diol **13** delivered the corresponding methyl ether **15**, which was converted to the ketone **14** by consecutive treatment with $LiBH_4$ and then lead tetraacetate. Treatment of **14** with ethyl bromomethylacrylate, **17**, and zinc in THF[18]gave the spiro-α-methylen-γ-lactone **18** with complete facial selectivity in 86% yield. After removal of the protecting silyl group, Dess−Martin oxidation furnished aldehyde **20**, where the configuration of the spiro stereocenter was unambiguously ascertained by the remarkable NOE between H_{9a} and one of the protons H_{10}. Further treatment of **20** with **17** and zinc produced a roughly 1:1 mixture of bislactones **21** and **22** in 73% overall yield. Their relative erythro/threo configuration was established by NMR and comparison with literature data.[5b,19] Thus, the proton H_3 in the erythro isomer **21** (δ 4.24) is upfield shifted in relation to the threo isomer **22** (δ 4.51), whereas the opposite occurs for the carbon atom C_3 (δ 62.0 and 60.4, respectively). This assignment is consistent with NOE experiments performed in subsequent derivatives.

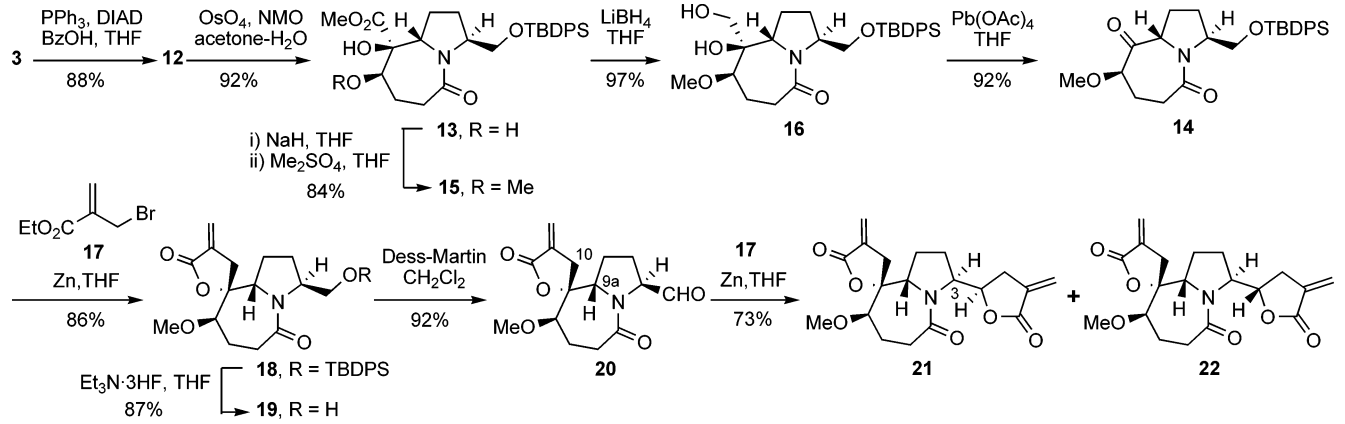
All that remained to convert the threo bislactone **22** into stemonidine was to reduce the lactam and the C−C double bonds. Preparation of the corresponding thiolactam followed by treatment with Ra−Ni was devised as a straightforward manner to achieve this goal, and this protocol was tested starting from the erythro isomer **21**. Thus, treatment of **21**

(17) de March, P.; Figueredo, M.; Font, J. Electron-deficient 1,2-disubstituted olefins of *E* configuration lead mainly to the formation of endo cycloadducts. *Heterocycles* **1999**, *50*, 1213 and references therein.

(18) Rauter, A. P.; Figueiredo, J.; Ismael, M.; Canda, T.; Font, J.; Figueredo, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1131.

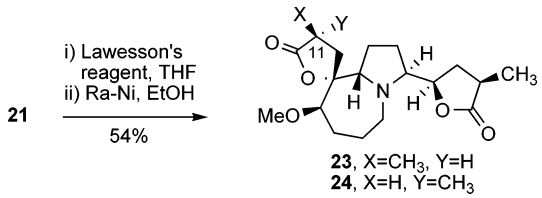
(19) Blanco, P.; Busqué, F.; de March, P.; Figueredo, M.; Font, J.; Sanfeliu, E. *Eur. J. Org. Chem.* **2004**, 48.

Scheme 5



with Lawesson's reagent furnished the expected thiolactam, which by reaction with Ra−Ni in EtOH delivered a mixture of amines **23** and **24**, epimers at C_{11}, in 54% total yield for the two steps (Scheme 6). Unfortunately, when the same

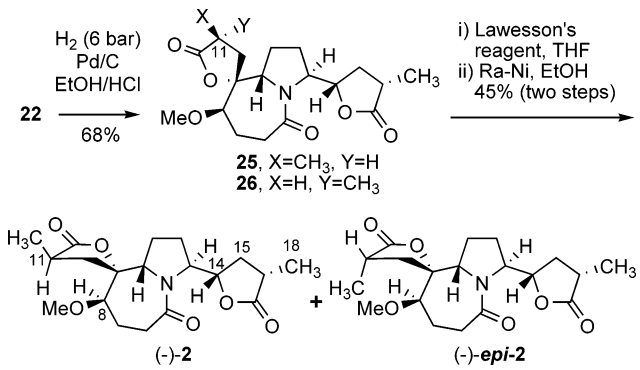
Scheme 6



procedure was applied to the threo bislactone **22**, the corresponding thiolactam underwent rapid decomposition. We found that hydrogenation of **22** under 6 bar pressure in the presence of Pd/C in EtOH/2 M HCl produced a mixture of C_{11}-epimeric azepinones **25** and **26** in 68% yield. Formation of the derived thiolactams and then treatment with Ra−Ni furnished the corresponding azepines in 45% yield for the two steps (Scheme 7). Analytical samples of each isomer could be chromatographically isolated.

The structure of the less-polar isomer was established as **2** by NMR techniques. A remarkable NOE between H_8 and

Scheme 7



H_{11} evidences the configuration of the α-carbonyl stereocenter at C_{11}, whereas that of the east-side lactone is proved by complementary NOEs from H_{14} or $(CH_3)_{18}$ to either proton at C_{15}. A comparison of the ^{13}C NMR data of **2**, $[\alpha]^{20}_D = -16$ (*c* 0.25, acetone), and natural stemonidine, $[\alpha]^{24}_D = -5.4$ (*c* 0.9, acetone)[2] (Table 1), definitively shows that the

Table 1. Comparison of ^{13}C NMR Data (δ) in $CDCl_3$

stemonidine[4]	stemospironine[4]	synthetic **2**	***epi*-2**
179.3 (2)	179.5 (2)	180.8	180.6
		179.5	179.5
90.3	90.5	90.8	91.3
85.2	85.2	87.2	85.9
80.0	80.0	79.1	79.6
67.7	67.7	69.3	69.3
63.0	63.1	68.5	68.1
58.0	58.0	57.5	57.4
48.9	48.9	52.1	51.8
35.7	35.7	35.69	35.5
35.1	35.0	35.67	35.0
35.0	35.0	35.60	34.9
34.6	34.6	34.8	33.9
27.0	27.0	28.3	27.4
26.5	26.5	26.9	26.83
25.6	25.7	26.9	26.79
22.3	22.4	25.3	25.4
17.6	17.5	16.8	16.4
14.8	14.8	14.8	14.8

structure assigned to the alkaloid isolated from natural sources is incorrect and that it must be reassigned as stemospironine.

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Supporting Information Available: Experimental procedures, listing of physical data of new compounds, and significant ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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