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Flexible Approach to *Stemona* Alkaloids: Total Syntheses of (−)-Stemospironine and Three New Diastereoisomeric Analogs

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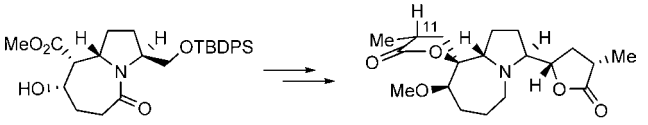
ABSTRACT



(-)-Stemospironine

Total syntheses of (−)-stemospironine and three new diastereoisomeric analogs have been completed through a flexible strategy devised for *Stemona* alkaloids. The azabicycle 7 is the pivotal intermediate, from which the sequence splits according to each particular target. The most remarkable differential feature for stemospironine is the installation of the spiranic γ-lactone through an intramolecular Horner−Wadsworth−Emmons olefination. The configuration of the stereogenic center at C-11 was controlled by fine-tuning of the synthetic sequence.

The extracts of several plants of the *Stemonaceae* family have long been used in East Asian countries for the treatment of respiratory disorders, as antihelmintics, and also as domestic insecticides. Significant constituents of these extracts are a series of structurally related alkaloids that may be responsible for their medicinal and antiparasitic properties, although studies on the specific activity of individual members of this alkaloid family are scarce.[1]

All the *Stemona* alkaloids are polycyclic and most of them enclose a pyrrolo[1,2-*a*]azepine core and one or more α-methyl-γ-butyrolactone units as the most characteristic structural features (Figure 1). Their intricate architectures have motivated the development of imaginative strategies for the construction of their skeletons.[2] Nevertheless, among the roughly 140 natural *Stemona* alkaloids currently known,[1a] the reported total syntheses target fewer than 20 members of the family, and in most of them, the azabicyclic skeleton is generated from a quite advanced intermediate, usually with several stereogenic centers, and, therefore, specifically assembled for one particular target.

Considering the high and continuously increasing number of *Stemona* alkaloids isolated from natural sources, and the subtle structural differences between some of them, we thought that a flexible synthetic design with some common intermediates was very desirable. Therefore, we devised a strategy in which the azabicyclic core was generated at an early stage of the sequence and the γ-butyrolactone moieties and other specific fragments were incorporated later (Scheme 1).[3] We planned the formation of the azabicycle via 1,3-dipolar cycloaddition of a pyrroline *N*-oxide to a suitable olefin, followed by reductive cleavage of the N−O bond and then 7-*exo*-*trig* cyclization. Previous studies regarding the cycloadditions of nitrones such as **4**, to electron-deficient olefins of type **3**, had indicated the relative trans configuration of the stereogenic centers at C-3 and C-9a would be attained as required for the target alkaloids.[3b,4]

With respect to their connectivity pattern[1b] and biogenetic relations,[1c] the *Stemona* alkaloids have been classified into several groups. The tuberostemospironine group is characterized by the presence of a spiro-γ-butyrolactone

(1) For comprehensive reviews, see: (a) Pilli, R. A.; Rosso, G. B.; de Oliveira, M. C. F. *Nat. Prod. Rep.* **2010**, *27*, 1908. (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, p 77. (c) Greger, H. *Planta Med.* **2006**, *72*, 99.

(2) For a recent review on synthetic strategies to *Stemona* alkaloids, see: Alibés, R.; Figueredo, M. *Eur. J. Org. Chem.* **2009**, 2421.

(3) (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.; Cąsas, E.; Closa, M.; de March, P.; Figueredo, M.; Font, J.; Sanfeliu, E.; Álvarez-Larena, A. *J. Org. Chem.* **2005**, *70*, 3157.

(4) (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.

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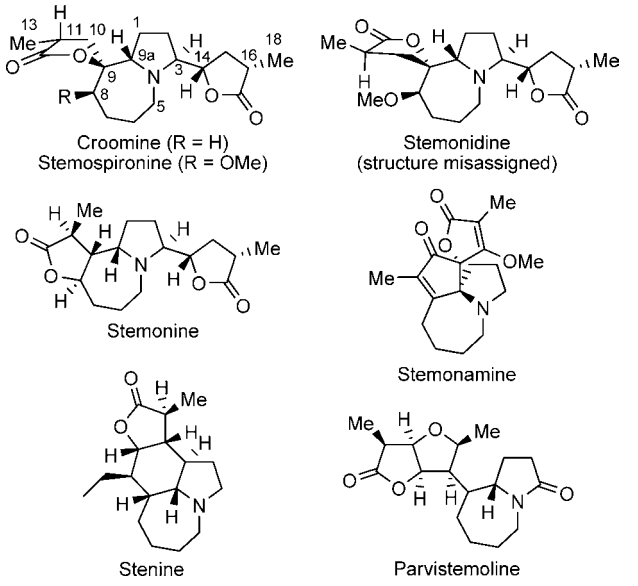
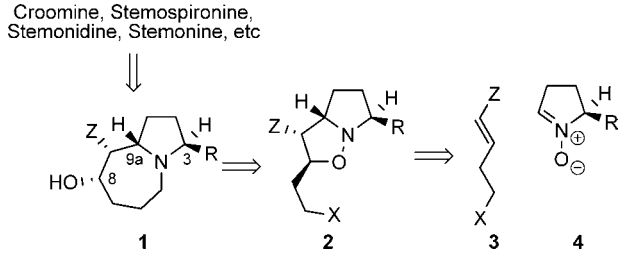


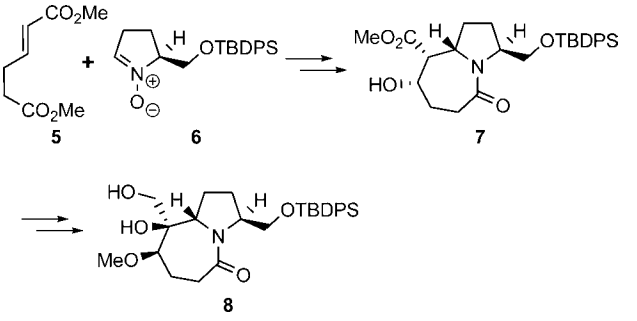
Figure 1. Some representative examples of *Stemona* alkaloids.

Scheme 1. Retrosynthetic analysis for some *Stemona* alkaloids



attached to C-9 and includes 12 members. Within this group, only four successful total syntheses have been described to date. The first one (which was also the first described synthesis of any *Stemona* alkaloid) was that of (+)-croomine reported by Williams and co-workers in 1989,[5] through an impressive 24-step linear sequence, involving the preliminary construction of a branched carbon chain, followed by consecutive ring closures to generate each heterocycle. Some years later, the same group completed, by an analogous pathway, the synthesis of (−)-stemospironine.[6] A second synthesis of (+)-croomine, starting from L-pyroglutamic acid, was described by Martin and Barr.[7] We recently described the synthesis of the proposed stemonidine[8] and, in so-doing, demonstrated that the hypothetical stemonidine was in fact stemospironine, as had been previously suggested.[6] Starting from diol **8**, an intermediate en route to stemonidine, we have now completed the synthesis of stemospironine and three additional analogs, thus demonstrating the flexibility of our synthetic design.

Scheme 2. Preparation of Diol **8**

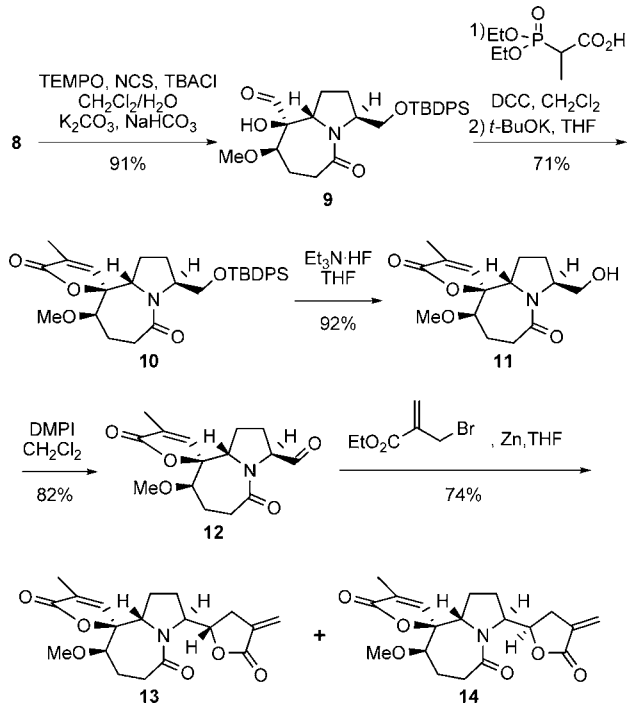


Stemospironine possesses a methoxy group at C-8 with the same stereochemical orientation as that of the putative stemonidine, but requires the formation of the spiranic lactone with the opposite configuration. We envisaged the installation of this lactone through an intramolecular Horner–Wadsworth–Emmons olefination of a derivative of the common intermediate **8**, which was prepared from the α,β-unsaturated diester **5** and the enantiomerically pure nitrone **6**,[9] derived from L-(+)-prolinol, as previously reported (Scheme 2).[8] It is remarkable that, after the initial formation of the azabicycle **7**, the inversion of configuration at C_8 and the diastereofacial oxidation at C_9 was efficiently accomplished in a cooperative manner through dehydration and subsequent dihydroxylation. The "eastern" lactone, appended to the pyrrolidine ring, features identically in both alkaloids.

Progression of our synthesis of stemospironine was attempted as shown in Scheme 3. The oxidation of alcohol **8** with *N*-chlorosuccinimide in the presence of TEMPO and tetrabutylammonium chloride in basic medium and a biphasic system[10] provided aldehyde **9** in 91% yield. Spirolactonization was accomplished by esterification of the tertiary alcohol by reaction with 2-(diethoxyphosphoryl)-propanoic acid and cyclohexylcarbodiimide,[11] followed by a basic treatment of the intermediate phosphonate, in 71% yield. Next, the silyl protection was removed and the primary alcohol was oxidized to the corresponding aldehyde **12**, which treated with ethyl bromomethylacrylate and zinc[12] furnished a roughly 1:1 mixture of bislactones **13** and **14** in 74% overall yield. The relative erythro/threo configuration of **13** and **14** was tentatively assigned by NMR in comparison with literature data[7,13] and unambigously established in a more advanced intermediate (*vide infra*).

(5) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923.
(6) Williams, D. R.; Fromhold, M. G.; Early, J. D. *Org. Lett.* **2001**, *3*, 2721.
(7) Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299.
(8) Sánchez-Izquierdo, F.; Blanco, P.; Busqué, F.; Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Parella, T. *Org. Lett.* **2007**, *9*, 1769.
(9) Gella, C.; Ferrer, E.; Alibés, R.; Busqué, F.; de March, P.; Figueredo, M.; Font, J. *J. Org. Chem.* **2009**, *74*, 6365.
(10) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J.-L. *J. Org. Chem.* **1996**, *61*, 7452.
(11) Nahmany, M.; Melman, A. *Org. Lett.* **2001**, *3*, 3733.
(12) Rauter, A. P.; Figueiredo, J.; Ismael, M.; Canda, T.; Font, J.; Figueredo, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1131.

Scheme 3. Preparation of Bislactones **13** and **14**



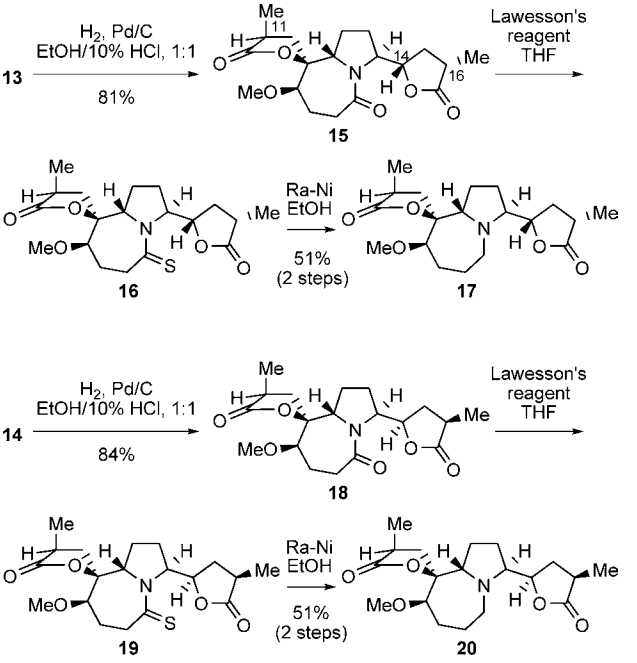
From the threo isomer **13**, the remaining transformations to conclude the synthesis of stemospironine were, theoretically, the hydrogenation of the endo- and exocyclic C−C double bonds and the deoxygenation of the lactam. These transformations were undertaken from both epimeric bislactones, **13** and **14**, separately (Scheme 4).

Despite the fact that the hydrogenation reaction generates two new stereogenic centers at C_{11} and C_{16}, lactams **15** and **18** were exclusively isolated from **13** and **14**, respectively, in good yields. The configuration at C_{16} was consistent with the approach of the hydrogen by the less hindered face of the "eastern" lactone, as expected,[8] while a rational explanation of the configuration at C_{11}, which is the opposite in stemospironine, may be found by observation of a simple tridimensional molecular model of compound **13** (Figure 2) that shows how the pyrrolidine ring obstructs one of the faces of the "western" lactone. Although other reduction protocols were tried, the C_{11} epimers of **15** or **18** were never detected. The deoxygenation of lactams **15** and **18**, accomplished by treatment with Lawesson's reagent and then Ra−Ni, gave 11-*epi*-stemospironine, **17**, and 11-*epi*-14-*epi*-16-*epi*-stemospironine, **20**, respectively. The structural assignment of all the intermediates was confirmed by X-ray analysis of thiolactam **19** (Figure 3).

In view of the high diastereoselectivity accomplished in the reduction of the C_{10}−C_{11} double bond, we reasoned that the methylation of an enolate formed by deprotonation of C_{11} should occur with the same facial selectivity, leading to the correct stemospironine-like configuration.

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

Scheme 4. Synthesis of 11-*epi*-Stemospironine, **17**, and 11-*epi*-14-*epi*-16-*epi*-Stemospironine, **20**



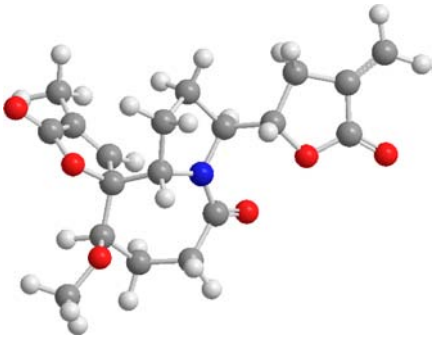


Figure 2. Molecular model of bislactone **13** (ChemBio3D Ultra 12.0).

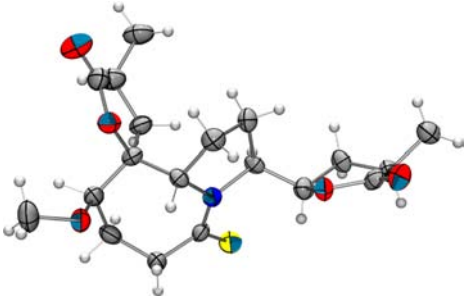
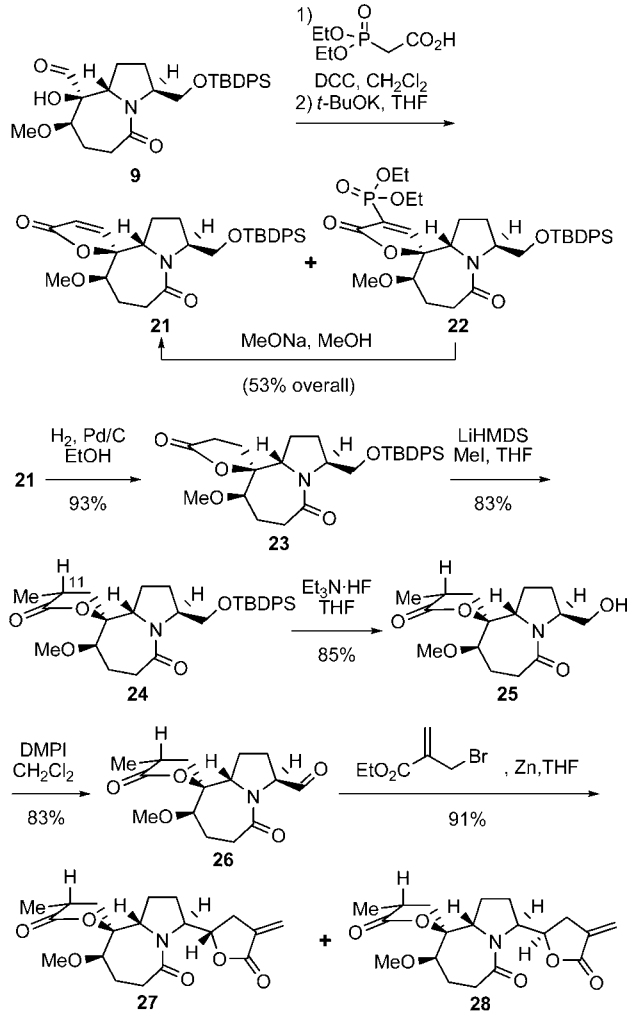


Figure 3. Crystal structure of thiolactam **19**.

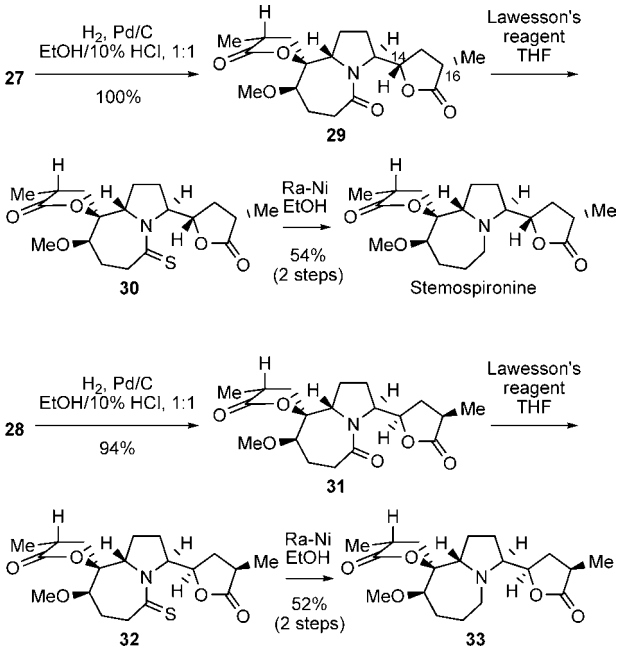
Scheme 5. Preparation of Bislactones **27** and **28**



To test this hypothesis, we decided to investigate the spirolactonization of aldehyde **9** with diethoxyphosphorylacetic acid (Scheme 5). This reaction delivered the expected lactone **21**, along with the undesired Knoevenagel product **22**, and despite many attempts including changing the base, solvent, and other experimental conditions, this competitive pattern could not be completely inhibited. Fortunately, compound **22** could be recycled to **21** by treatment of the former with MeONa in MeOH to afford the latter in a reasonable 53% yield. Catalytic hydrogenation furnished the saturated lactone **23**, which was α-methylated without problems and with the previously predicted stereoselectivity to furnish **24** in good yield. Installation of the second lactone was made, as before, by desilylation of **24**, followed by oxidation to the aldehyde **25** and then reaction with ethyl bromomethylacrylate and zinc. As expected, this last reaction furnished a mixture of the threo, **27**, and erythro, **28**, epimers in a roughly 1:1 ratio and excellent overall yield. The stereochemical assignment of these bislactones was confirmed by their conversion to the target alkaloids (Scheme 6).

The syntheses of stemospironine and 14-*epi*-16-*epi*-stemospironine, **33**, were completed using the previously

Scheme 6. Synthesis of Stemospironine and 14-*epi*-16-*epi*-Stemospironine, **33**



established protocols, namely, catalytic hydrogenation of the precursor bislactones **27** and **28**, followed by deoxygenation via the corresponding thiolactams **30** and **32**, respectively. The analytical data of our synthetic stemospironine including optical rotation, $[\alpha]_D^{20}$ −8.6 (*c* 0.23, $CHCl_3$), are in total agreement with those described for the natural alkaloid, $[\alpha]_D^{27}$ −8.2 (*c* 0.92, $CHCl_3$).[14]

In summary, we have accomplished the syntheses of stemospironine and the three additional diastereoisomers 11-*epi*-stemospironine, **17**, 11-*epi*-14-*epi*-16-*epi*-stemospironine, **20**, and 14-*epi*-16-*epi*-stemospironine, **33**, through a flexible strategy, which allows the preparation of different *Stemona* alkaloids by splitting the sequence in the appropriate late-stage step. The configuration of the stereogenic center at C_{11} has been totally controlled by a fine-tunning of the synthetic pathway.

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Supporting Information Available. Experimental details, spectral data and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) Sakata, K.; Aoki, K.; Chang, C.-F.; Sakurai, A.; Tamura, S.; Murakoshi, S. *Agric. Biol. Chem.* **1978**, *42*, 457.

The authors declare no competing financial interest.