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Total Synthesis of (−)-Stemospironine

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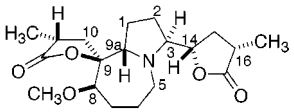
ABSTRACT



1 (−)-Stemospironine

A stereocontrolled total synthesis of the polycyclic *Stemona* alkaloid, (−)-stemospironine (1) has been achieved. Key transformations include the use of a Staudinger reaction leading to the aza-Wittig ring closure of the perhydroazepine system. Formation of the vicinal pyrrolidine butyrolactone is described via the stereoselective intramolecular capture of an intermediate aziridinium salt.

The roots and rhizomes of the plant family Stemonacae have provided a rich source of approximately 50 structurally novel, polycyclic alkaloids.[1] Interest in these substances, broadly described as *Stemona* alkaloids, originally stemmed from the use of plant materials in herbal teas used in Chinese folk medicine and from the extraordinary insecticidal activity detected among various alkaloids of the class.[2] Since the first complete structural elucidation of a *Stemona* alkaloid in 1967,[3] each example has been characterized with the identification of the 1-azabicyclo[5.3.0]decane nucleus embedded within the overall molecular architecture. In 1989, we achieved the first synthesis of a prototypical *Stemona* alkaloid as described by the enantiocontrolled total synthesis of (+)-croomine.[4] Over the past decade, a number of ingenious strategies have inspired successful syntheses of racemic stenine,[5] (−)-stenine,[6] (−)-stemoamide,[7] as well as its racemate,[8] (+)-croomine,[9] and (±)-isostemofoline.[10] Additionally, related synthesis studies have recently been described,[11] and a route for the preparation of the pair of racemic diastereomers, (±)-stemonamide and (±)-isostemonamide, has been reported.[12] Stemospironine **1** was isolated from methanolic extracts of the leaves of *Stemona japonica*, and issues of relative and absolute stereochemistry were unambiguously resolved by X-ray crystallographic analysis.[13] Herein, we report the first total synthesis of **1** via the stereoselective construction of a fully functionalized acyclic carbon chain followed by sequential ring closure reactions. Furthermore, our direct comparisons of naturally occurring stemonidine **2**[14] and synthetic **1** affirm the remarkable

(1) For recent examples, see: (a) Changying, Z.; Hongzheng, F.; Haimin, L.; Jun, L.; Wenhan, L. *J. Chinese Pharm. Sci.* **1999**, *8*, 185. (b) Wenhan, L.; Hongzheng, F. *J. Chinese Pharm. Sci.* **1999**, *8*, 1. (c) Zou, C.; Li, J.; Lei, H.; Fu, H.; Lin, W. *J. Chinese Pharm. Sci.* **2000**, *9*, 113. (d) For a related alkaloid, see: Sekine, T.; Ikegami, F.; Fukasawa, N.; Kashiwagi, Y.; Aizawa, T.; Fujii, Y.; Ruangrungsi, N.; Murakoshi, I. *J. Chem. Soc., Perkin Trans. 1* **1995**, 391.

(2) For recent reviews, see: (a) Pilli, R. A.; Ferreira de Oliveira, M. *Nat. Prod. Rep.* **2000**, *17*, 117. (b) Ye, Y.; Qin, G.-W.; Xu, R.-S. *J. Nat. Prod.* **1994**, *57*, 665.

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(9) Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299.

(10) Kende, A. S.; Smalley, T. L.; Huang, H. *J. Am. Chem. Soc.* **1999**, *121*, 7431.

(11) (a) Jung, S. H.; Lee, J. E.; Joo, H. J.; Kim, S. H.; Koh, H. Y. *Bull. Korean Chem. Soc.* **2000**, *21*, 159. (b) Rigby, J. H.; Laurent, S.; Cavezza, A.; Heeg, M. J. *J. Org. Chem.* **1998**, *63*, 5587. (c) Wipf, P.; Goldstein, D. M. *Tetrahedron Lett.* **1996**, *37*, 739. (d) Morimoto, Y.; Iwahashi, M. *Synlett* **1995**, 1221. (e) Beddoes, R. L.; Davies, M. P. H.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1992**, 538.

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

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

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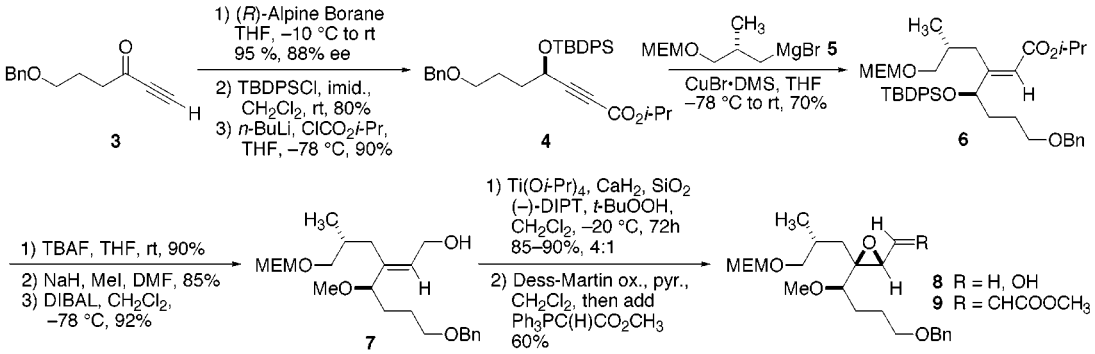
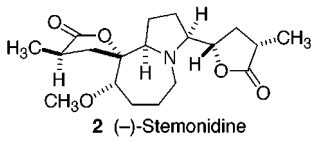
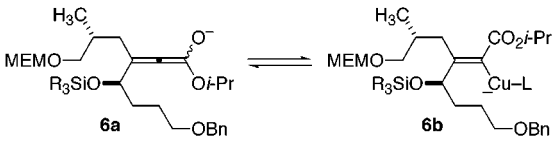
Scheme 1



similarities of these samples and support a detailed reexamination of stereochemical assignments purported for **2**.



The carbon connectivity of stemospironine was efficiently assembled as shown in Scheme 1. Since the methyl substituents of **1** at C_{11} and C_{16} could be incorporated into the target structure from (*S*)-(+)-methyl 3-hydroxy-2-methylpropionate and (*R*)-(−)-methyl 3-hydroxy-2-methylpropionate, respectively, we sought to establish the C_8, C_9, C_{9a} stereotriad at an early stage. Beginning with the readily available ketone **3**,[15] chirality at C_8 was introduced via Midland reduction[16] of the conjugated ynone with (*R*)-Alpine-Borane,[17] leading to **4** (88% ee).[18] The Grignard reagent **5** was prepared from the corresponding bromide[19] to set the stage for conjugate addition to the acetylenic ester **4**. It is widely appreciated that such reactions of copper-catalyzed nucleophilic attack proceed via syn addition at low temperatures.[20] However, the intermediate vinylic cuprate species can rapidly isomerize to O-coordinated allenic enolate **6a** via localized exotherms in the quenching process. Recent NMR investigations provide



evidence that thermodynamic equilibria may shuttle the initial *Z*-organocopper intermediate through the allenoate to *E*-alkenylcuprate **6b** for stereospecific protonation.[21] In our studies, exclusive *trans*-addition affording *E*-α,β-unsaturated ester **6** was observed upon slow warming from −78 to 23 °C prior to a protic quench and by the selection of the isopropyl ester and the sterically demanding *O*-silyl protection (C_8).[22]

Following fluoride-induced removal of the silyl ether, the C_8 allylic alcohol was treated with methyl iodide and sodium hydride to yield the required methyl ether. This transformation occurred with no evidence for olefin isomerization as facilitated via internal alkoxide conjugate addition and elimination. Hydride reduction subsequently gave the desired trisubstituted allylic alcohol **7**, which provided a 90% yield of oxiranes using the modified Sharpless asymmetric epoxidation system as described by Zhou and co-workers.[23] The major epoxide **10** was isolated as a pure diastereomer following flash silica gel chromatography of a mixture (4:1 ratio) of epoxide isomers. Oxidation of **8** with the Dess−Martin periodinane,[24] and in situ chain elongation via addition of (carbomethoxymethylene)triphenylphosphorane yielded *E*-unsaturated methyl ester **9** (60% for two steps).

The elaboration of the carbon skeleton began with reduction of the unsaturated ester and protection of the resulting

(15) Ketone **3** was prepared by the addition of ethynylmagnesium bromide to 4-benzyloxybutenal (THF, 0 °C, 80%) and subsequent Jones oxidation at 0 °C (85%).

(16) Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1371.

(17) Alpine-Borane is a trademark of Aldrich Chemical Co. Our reductions were conducted with neat reagent, freshly prepared from (+)-α-pinene (97% ee).

(18) Enantiomeric excess was determined using the Mosher ester analysis of (*R*)-α-methoxy-α-(trifluoromethyl)phenyl acetates by proton NMR integration of the acetylenic hydrogens. The minor (*S*)-isomer gave a signal at 2.50 ppm whereas the major (*R*)-isomer appeared at 2.55 ppm. (See: Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165.)

(19) The optically pure bromide and its corresponding Grignard reagent **5** were prepared from (*S*)-(+)-methyl-3-hydroxy-2-methylpropionate in four steps (84% overall yield) via protection, hydride reduction, tosylation, and exchange with LiBr (D'Antuono, J. Ph.D. Thesis, Indiana University, 1988). For use of the related Gilman reagent, see: Williams, D. R.; Turske, R. A. *Org. Lett.* **2000**, *2*, 3217.

(20) Selected examples: (a) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851. (b) Piers, E.; Gavai, A. *J. Org. Chem.* **1990**, *55*, 2374. (c) Crimmins, M. T.; Nantermet, P. G.; Trotter, B. W.; Vallin, I. M.; Watson, P. S.; McKerlie, L. A.; Reinhold: T. L.; Cheung, A. W. H.; Steton, K. A.; Dedoponlou, D.; Gray, J. L. *J. Org. Chem.* **1993**, *58*, 1038. (d) Millar, J. G. *Tetrahedron Lett.* **1997**, *38*, 7971.

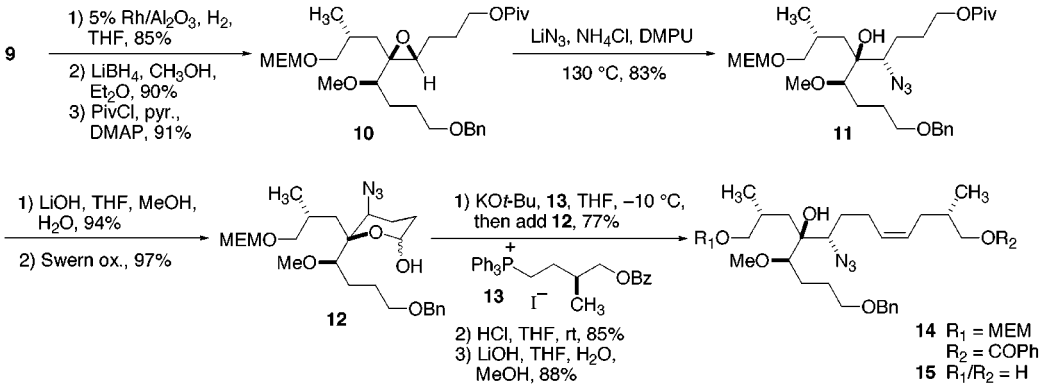
(21) Nilsson, K.; Andersson, T.; Ullenius, C.; Gerold, A.; Krause, N. *Chem. Eur. J.* **1998**, *4*, 2051.

(22) The use of the *tert*-butyldimethyl silyl ether (TBS) at C_8 was also effective for production of the *E*-enoate. However, combinations of bulky silyl ethers at C_8 and ethyl/methyl esters analogous to **4** or the incorporation of the desired C_8 methoxy group in tandem with the choice of an isopropyl ester resulted in mixtures of *E*/*Z*-products.

(23) (a) Wang, Z.-M.; Zhou, W.-S.; Lin, G.-Q. *Tetrahedron* **1987**, 2935. (b) Wang, Z.-M.; Zhou, W.-S. *Synth. Comm.* **1989**, 2627.

(24) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

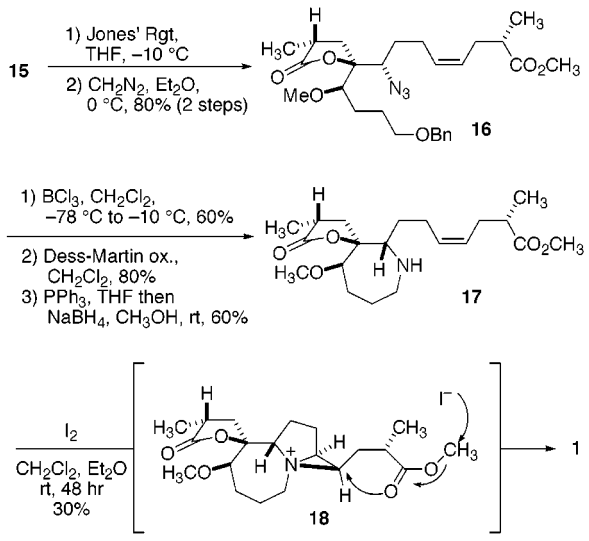
Scheme 2



primary alcohol as its corresponding pivaloate **10** (Scheme 2). Selection of the *tert*-butyl ester blocking unit is significant as bulky silyl ethers underwent facile cleavage in the subsequent azide displacement reaction, which led to substantial amounts of tetrahydrofuran ring formation owing to the proximate oxirane. This side reaction was completely suppressed in the case of pivaloate **10** as epoxide opening occurred in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU, Aldrich) with 5 equiv of solid ammonium chloride to provide the azido alcohol **11** (85%). Saponification of the ester followed by the Swern oxidation[25] of the resulting primary alcohol led to the isolation of a mixture (3:1 ratio) of diastereomeric lactols **12** and hydroxy-aldehyde in high yield. Treatment of this equilibrating mixture with the triphenylphosphorane derived from **13**[26] in THF at −10 °C provided sole formation of *Z*-alkene **14**. Hydrolysis of the β-methoxyethyl ether was accomplished by treatment of **14** in THF with aqueous HCl at room temperature. Our attempts to utilize various Lewis acids under mild conditions proved problematic, featuring formation of a 1,3-dioxepane as the major product.[27] Subsequent removal of the primary benzoate gave desired triol **15** for ring closure studies.

Oxidation of triol **15** proceeded in THF solution at −10 °C in the presence of a suspension of Celite via the dropwise addition of a slight excess of Jones reagent (Scheme 3). Dilution with ethyl acetate and filtration through Celite led to a concentrate for treatment with ethereal diazomethane directly yielding the lactone methyl ester **16** (80%). Cleavage of the benzyl ether at low temperature was followed by Dess−Martin oxidation[23] of the resulting primary alcohol to give the crucial azido-aldehyde intermediate for the aza-Wittig process. Thus, a Staudinger reduction was initiated by the addition of triphenylphosphine, leading to an aza-ylide for intramolecular condensation providing a seven-membered imine for in situ reduction yielding azepine **17**. Finally, synthetic stemospironine **1** was produced by the iodine-induced double cyclization reaction of **17**. Our previous studies have documented the expected high regio- and stereoselectivity for formation of *trans*-2,5-disubstituted pyrrolidino iodides from related bis-homoallylic (*Z*)-*N*-alkoxylalkenylamines.[28] Nucleophilic anchimeric assistance by the tertiary amine leads to aziridinium species **18** for capture by the neighboring methyl ester for net retention of C_{14} stereochemistry. Modest, albeit reproducible, yields (30%) of synthetic **1** were isolated owing to the ease of over-oxidation of the pyrrolidine product.[29] Comparisons of spectral data of our synthetic **1** ($[\alpha]^{24}_D$) −7.5° (*c* 0.85 mg/mL, $CHCl_3$)) with data reported for natural (−)-stemospironine ($[\alpha]^{27}_D$) −8.2° (*c* 0.92 mg/mL, $CHCl_3$)) showed these substances to be identical in all respects.[30] In fact, these efforts were guided by our previous total synthesis of (+)-croomine (8-desmethoxystemospironine), for which we had also secured unambiguous confirmation of stereochemical assignments at C_3, C_9, C_{9a}, and C_{14} through our independent X-ray analysis.[4]

Scheme 3



(25) Mancuso, A. J.; Huang, S. L.; Swern, D. J. *J. Org. Chem.* **1978**, *43*, 2480.

(26) The requisite phosphonium salt **13** was prepared from known (2*S*)-2-methyl-4-penten-1-ol (see: Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506). Formation of the benzoate, ozonolysis, and sodium borohydride reduction gave the primary alcohol for conversion to the corresponding iodide and triphenylphosphine displacement. Details will be provided in the full account of this work.

(27) Formation of the seven-membered cyclic ether occurs with retention of stereochemistry at C_9.

With assistance of colleagues in Shanghai,[31] spectra and a sample of (−)-stemonidine (**2**) were obtained, permitting direct comparisons of proton NMR data with our synthetic material. In this regard, we were unable to confirm differences in chemical shifts or coupling patterns. The remarkable similarities of these samples support a claim that they share a common structure, **1**. Likewise, the comparisons in Table 1 for the ^{13}C NMR data published for stemospironine and the corresponding ^{13}C NMR data that we have obtained for synthetic **1** and (−)-stemonidine exhibit a close correlation. However, we cannot eliminate the coincident possibility that these natural products may be spirocyclic diastereomers.[32,33]

In summary, we have reported the first total synthesis of (−)-stemospironine via an enantiocontrolled pathway featuring a *trans*-selective conjugate addition, an intramolecular aza-Wittig process, and the iodine-initiated, single-step formation of the pyrrolidino butyrolactone system.

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

stemospironine[13]	synthetic **1**	stemonidine
179.5 (2)	179.4 (2)	179.3 (2)
90.5	90.5	90.3
85.2	85.3	85.2
80.0	80.0	80.0
67.7	67.7	67.7
63.1	63.0	63.0
58.0	58.0	58.0
48.9	48.8	48.9
35.7	35.7	35.7
35.0	35.1	35.1
35.0	35.0	35.0
34.6	34.6	34.6
27.0	27.0	27.0
26.5	26.5	26.5
25.7	25.7	25.6
22.4	22.3	22.3
17.5	17.6	17.6
14.8	14.8	14.8

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Supporting Information Available: Experimental procedures and spectral data for compounds **6**−**11**, **14**−**17**, and synthetic **1** with comparison data and proton NMR spectra for natural stemonidine. This material is available free of charge via Internet at http://pubs.acs.org.

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(28) Williams, D. R.; Osterhout, M. H.; McGill, J. M. *Tetrahedron Lett.* (a) **1989**, *30*, 1327; (b) **1989**, *30*, 1331.

(29) Previously we had shown (ref 4) that it was advantageous to introduce limited amounts of iodine solution and quench cyclizations at approximately 50% completion, yielding the desired product (30−35%) and recovered starting material (50−55%) for resubmission. In the case of stemospironine, limited quantities of **18** precluded this approach, and the complete consumption of starting alkene led to numerous polar byproducts.

(30) Although we were unable to procure a sample of stemospironine from the original laboratories (ref 12), our synthetic material provided spectra and physical data which were completely consistent with data reported for the natural product as assigned by X-ray diffraction.

(31) We gratefully acknowledge the assistance of Professor Yang Ye, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, for providing spectra and an authentic sample of (−)-stemonidine.

(32) Professor R.-S. Xu has indicated ongoing revisions of **2**. See: He, X.; Lin, W.-H.; Xu, R.-S. *Acta Chim. Sin.* **1990**, *48*, 694.

(33) We can visualize slight differences in the line art of the proton NMR spectra of **1** and (−)-stemonidine (see Supporting Information). However, small differences in chemical shifts and coupling constants are within the tolerances and limits of error of our instrumentation. Small quantities of these samples have precluded additional experiments.