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Total Synthesis of (−)-Stemonine

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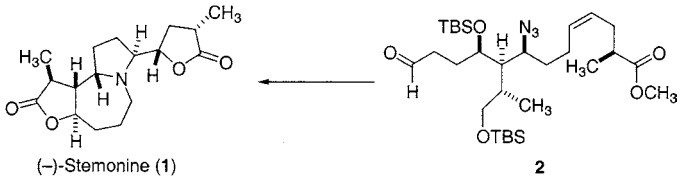
ABSTRACT



An enantioselective total synthesis of (−)-stemonine (1) is reported via a convergent assembly of the acyclic precursor 2. Key transformations include a Staudinger−aza-Wittig reaction to form the central perhydroazepine ring system and an iodine-induced tandem cyclization to construct the pyrrolidino-butyrolactone framework.

Stemona alkaloids represent a class of approximately 50 structurally novel, polycyclic metabolites isolated from monocotyledonous plants comprising the genera of *Stemona*, *Croomia*, and *Stichoneuron*.[1] Chinese and Japanese folk medicine has recorded the extensive use of extracts and herbal teas of *Stemonaceae* as remedies of respiratory diseases, including tuberculosis, and as anthelmintics.[2] Dried plant materials are utilized as powerful insecticidal materials for treatment of livestock throughout East Asia.[3] Stemonine (**1**), an important secondary metabolite of *Stemona japonica*, was isolated and investigated as early as 1929.[4,5] However, the characterization of relative and absolute stereochemistry remained unresolved until the report of the X-ray crystallographic study of stemonine hydrobromide hemihydrate by Koyama and Oda in 1970.[6] Progress toward the synthesis of *Stemona* alkaloids was elusive and uneventful until our account of the total synthesis of (+)-croomine in 1989.[7] Recent years have been marked by achievements of several notable total syntheses of members of this family.[8] Herein we disclose the first report of the total synthesis of (−)-stemonine (**1**) nearly 75 years after its initial discovery.

We have applied a thematic strategy for the preparation of *Stemona* alkaloids that has sought to assemble a fully functionalized acyclic carbon chain as a prelude to sequential, late-stage ring closure reactions. Since each alkaloid is characterized by the presence of a unique 1-azabicyclo[5.3.0]-decane as an integral part of the molecular architecture, the facile and stereocontrolled formation of this moiety is a key issue. In the case of (−)-stemonine (**1**), our retrosynthetic plan suggested a convergent construction of the acyclic precursor **2** from optically pure butyrolactone **3** and homoallylic iodide **4** (Scheme 1).

The convenient preparation of iodide **4** is summarized in Scheme 2, utilizing known aldehyde **6**.[9] The nonracemic tosylate **5** is readily available via hydroxyl protection of (*R*)-(−)-methyl-3-hydroxy-2-methyl propionate followed by hy-

(1) Dahlgren, R. M. T.; Clifford, H. T.; Yeo, P. F. *The Families of the Monocotyledons. Structure Evolution and Taxonomy*; Springer-Verlag: Berlin, 1985.

(2) (a) Sakata, K.; Aoki, K.; Chang, C.-F., Sakurai, A.; Tamura, S.; Murakoshi, S. *Agric. Biol. Chem.* **1978**, *42*, 457. (b) Shinozaki, H.; Ishida, M. *Brain. Res.* **1985**, *334*, 33. (c) Ye, Y.; Qin, G.-W.; Xu, R.-S. *Phytochemistry* **1994**, *37*, 1205.

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(5) Suzuki, K. *J. Pharm. Soc. Jpn.* **1931**, *51*, 419

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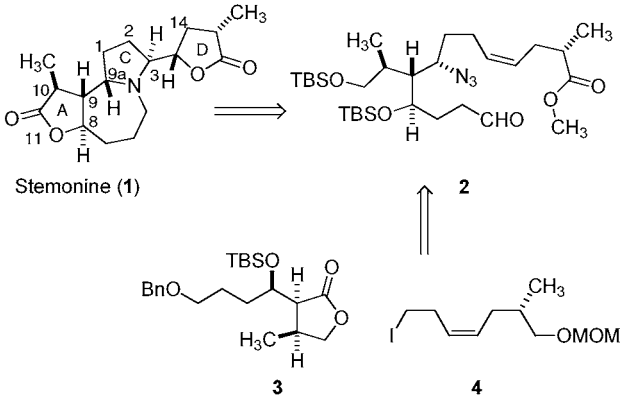
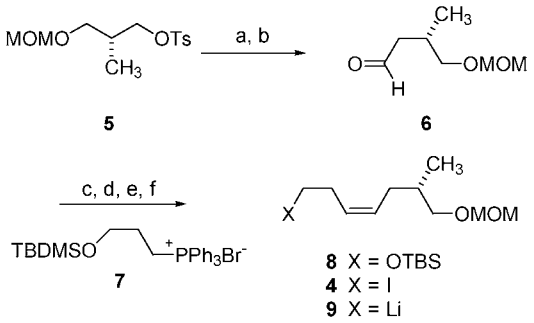
Scheme 1. Retrosynthetic Analysis of (−)-Stemonine



Scheme 2 [a]



[a] Reaction conditions: (a) NaCN, DMSO, 70 °C. (b) DIBAL, Et_2O, −78 °C to room temperature, then H_3O^+, 86% (four steps). (c) To **7** was added KHMDS, Et_2O, −78 °C, then **6**. (d) TBAF, THF, 0 °C to room temperature. (e) PPh_3, I_2, imidazole, CH_2Cl_2, 0 °C, 80% (two steps). (f) ^{t}BuLi, −78 °C.

dride reduction ($LiAlH_4$) and conversion to **5**. Cyanide displacement followed by DIBAL reduction provided **6**, which was subjected to a Wittig reaction with ylide generated from phosphonium salt **7**[10] to afford (*Z*)-olefin **8** in 85% yield and 95:5 *Z*:*E* selectivity. The (*Z*)-isomer was purified via flash silica gel chromatography and transformed to iodide **4** uneventfully. This sequence of five steps from **5** provided iodide **4** in high purity on a preparative scale with excellent overall yield (59%).

The condensation of components **3** and **4**, which required formation of an effective homoallyl carbanion, was initially problematic. Halogen−metal exchange of the corresponding bromide of **4** to provide an active organolithium or Grignard species led to several observed side products, including E_2 elimination and protonation, as well as Wurtz coupling. These difficulties were overcome by modification of the procedures of Bailey[11a] and Negishi[11b] for essentially quantitative metalation of **4** to **9** (Scheme 2) using ^{t}butyllithium (2.05 equiv added dropwise) in diethyl ether at −78 °C.

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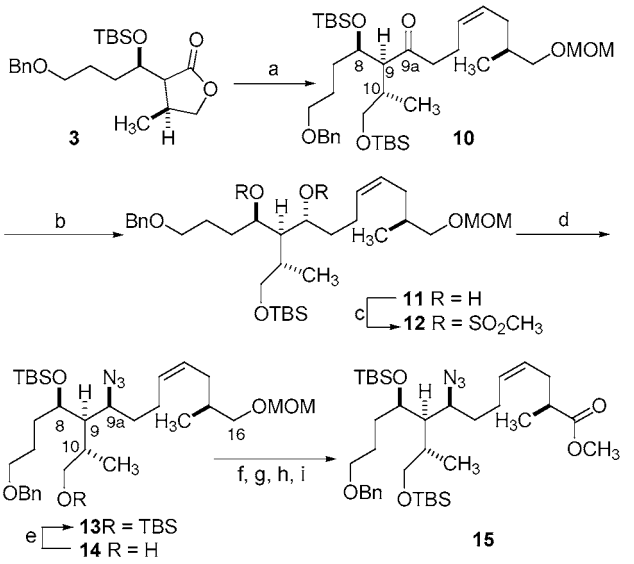
Scheme 3 [a]



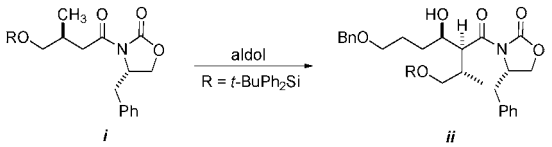
[a] Reaction conditions: (a) To a 0.25 M solution of **9** in Et_2O at −78 °C was added **3**, 0.5 h; then collidine, TBSOTf, −78 °C to room temperature, 86%. (b) $LiEt_3BH$, THF, −78 °C to room temperature, 94%, anti:syn = 17:1. (c) MsCl, pyridine, rt, 95%. (d) NaN_3 (3 equiv), 15-crown-5 (3 equiv), HMPA, rt, 65%. (e) TBSOTf, collidine, −78 °C, 97%. (f) Me_2BBr, CH_2Cl_2, Et_3N (0.3 equiv), −78 °C, 5 min, 76%. (g) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt. (h) $NaClO_2$, NaH_2PO_4, ^{t}BuOH, CH_3CN, 2-methyl-2-butene, 0 °C. (i) CH_2N_2, Et_2O, 83% (three steps).

Introduction of enantiopure lactone **3**[12] into a 0.25 M solution of **9** at −78 °C (Scheme 3) efficiently provided a single carbonyl addition reaction, which permitted in situ protection of the resulting primary alkoxide as the ^{t}butyldimethylsilyl ether **10** in 86% overall yield from iodide **4**.

Reduction of ketone **10** with lithium triethylborohydride (Super Hydride) at −78 °C proceeded with high diastereoselectivity, yielding **11** as the major product (17:1 dr). The (*R*)-configuration of the C_{9a} alcohol **11** was rationalized as the expected product of Felkin−Anh addition where the C_8 carbon appendage bearing the β-TBS ether is designated as the large substituent. Since the reduction yielded 1,3-anti and 1,3-syn diol derivatives, the assignment of stereochemistry was confirmed by ^{13}C NMR analysis of the corresponding acetonides following deprotection of the secondary TBS ether.[13]

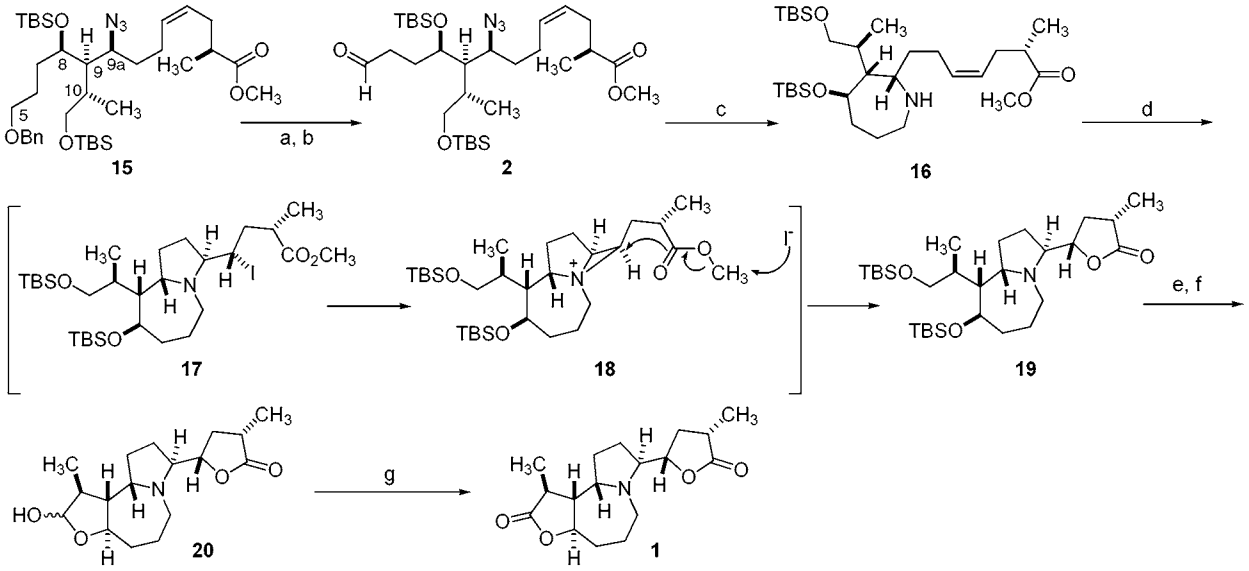
Stereocontrolled introduction of nitrogen was accomplished by azide displacement of the C_{9a} mesylate of **12**

(12) Lactone **3** has been previously described via the asymmetric aldol condensation of imide ***i*** to give ***ii*** followed by silyl ether cleavage. Williams, D. R.; Reddy, J. P.; Amato, G. S. *Tetrahedron Lett*. **1994**, *35*, 6417.



(13) (a) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.

Scheme 4 [a]

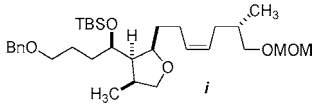


[a] Reaction conditions: (a) DDQ, CH_2Cl_2, ^tBuOH, H_2O, rt, 56%. (b) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 86%. (c) $EtPPh_2$, benzene, rt, 18 h; the mixture was then concentrated in vacuo, and THF, $NaBH_4$, and MeOH were added, 70%. (d) I_2, CH_2Cl_2/Et_2O (2.5:1), rt, 48 h, 42%. (e) TBAF, THF, rt, 77%. (f) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 69%. (g) CrO_3, aq H_2SO_4, acetone, THF, rt, 68%.

(Scheme 3). In fact, a number of issues were overcome to ensure the feasibility of this S_N2 process. Initially, solvents that provided for the dissolution of **12** and sodium or lithium azide, including combinations of THF and 2-propanol, ethanol, or NMP and DMPU, led to very poor yields of **13**. Reactions in anhydrous HMPA (NaN_3; 6 equiv) at 40 °C gave approximately 40 to 45% yields of **13** and significant amounts (30−35%) of the corresponding C_{11} primary alcohol **14**, as well as several minor products. Shorter reaction times at elevated temperatures resulted in reduced yields of **13** and products of intramolecular 1,3-dipolar cycloaddition. Experimentally, it was found that the addition of equimolar quantities of 15-crown-5 facilitated reactions at 22 °C with a 50% reduction of the starting sodium azide (3 equiv) to yield desired **13** (65%).[14] Varying amounts of mesylate **12** (10−15%) were recovered along with 15% of the C_{11} alcohol **14**. On a preparative scale, protection of the latter, followed by subjection of recovered mesylate to the reaction conditions, provided azide **13** in an overall yield of 82%. Selective cleavage of the C_{16} methoxymethyl ether in the presence of the C_{11} primary TBS ether necessitated the inclusion of triethylamine during brief exposure of **13** to Me_2BBr at low temperature.[15] The resulting C_{16} alcohol was oxidized and converted to the methyl ester, which provided for the fully functionalized acyclic precursor **15**.

The systematic ring closure of **15** to provide natural product **1** relied upon our prior experience in the case of (+)-croomine.[7] Attempted removal of the C_5 benzyl ether of **15** by brief exposure to boron trichloride in CH_2Cl_2 at −78 °C in the presence of Proton Sponge followed by the addition of cold MeOH gave the desired alcohol, which was contaminated by diol resulting from cleavage of the primary TBS group. This task was cleanly accomplished upon treatment of **15** with DDQ[16] (Scheme 4), and subsequent Dess−Martin oxidation yielded aldehyde **2**.[17] Cyclization to the perhydroazepine **16** via the Staudinger reaction of aldehydic azide **2** with ethyldiphenylphosphine proceeded with nitrogen evolution and generated the seven-membered imine by an intramolecular aza-Wittig process.[18] After imine formation, reactions were concentrated in vacuo, and the addition of THF was followed by an immediate reductive quench with $NaBH_4$ (1.5 equiv) and methanol (1.5 equiv) giving the amine **16** (70% yield). Stereocontrolled formation of the pyrrolidino-butyrolactone C−D ring system occurred in a single step as a consequence of an iodine-induced cyclization. Treatment of amine **16** with I_2 in a solution of CH_2Cl_2 and Et_2O (2.5:1) for 48 h at 22 °C led to formation of **19** in reproducible yields of 42% along with 20% recovery of starting material. Excellent stereoselectivity is observed by kinetic formation of 2,5-trans-disubstituted pyrrolidine **17** following the highly reversible π-complexation of iodine.[19a] The tertiary amine can initiate a nucleophilic backside

(14) Optimal results were obtained with freshly opened bottles of 15-crown-5 (Aldrich), which may provide traces of water. However, older bottles of 15-crown-5 led to reduced yields of **15**. Small amounts (4−8%) of the tetrahydrofuran ***i*** were also obtained as a minor product.



i

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(16) Schreiber, S. L.; Ikemoto, N. *J. Am. Chem. Soc.* **1992**, *114*, 2535.

(17) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(18) Imine could be isolated following rapid purification via flash silica gel chromatography but decomposed within 2 h at room temperature. Spectral data for characterization of the imine are included in Supporting Information.

displacement of the vicinal iodide in **17** leading to aziridinium salt **18**.[19b] This event ensures net retention of C_{13} stereochemistry, as the ester carbonyl participates in butyrolactone ring closure, yielding **19**. Excess iodine, utilized in attempts to consume all starting amino-alkene, led to multiple side products from further oxidations. In the course of these studies, the A ring trans-fused lactone related to **16** was readily obtained via the Staudinger reaction. However, the analogous iodine-induced cyclization was not observed, giving way to slow oxidative decomposition of the starting azepine.

We speculate that conformations of the azepine must permit a favorable backside trajectory for intramolecular opening of the iodonium complex, which provides for the minimization of nonbonded interactions. Our models (Figure 1) indicate that the *trans*-2,5-pyrrolidine **17** is favored via

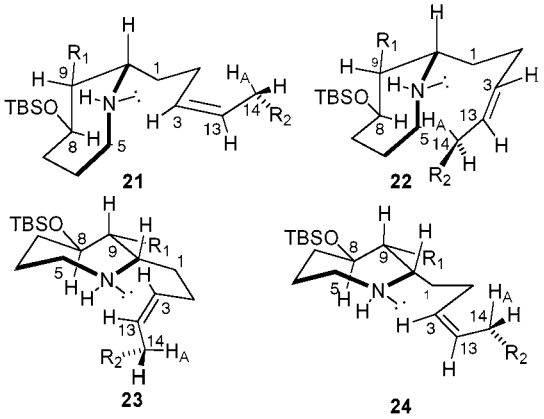

Figure 1.

the iodonium species derived from conformer **21**, in which R_1 and OTBS substituents on the azepine ring are pseudoequatorial and allylic A(1,3) strain is minimized. A reversal of face selectivity, leading to *cis*-2,5-pyrrolidine, would stem from conformer **22**. However, the geometry of the (*Z*)-olefin in **22** creates nonbonded interactions of C_5 and R_2 in the ring closure event. Nitrogen lone pair inversion leads to the consideration of structures **23** and **24**, but both of these conformers have nonbonded eclipsing interactions of C_1 and R_1. In addition, the (*Z*)-olefin places R_2 under the azepine ring in a reaction profile developed from **23**.

Finally, the synthesis of **1** was completed by simultaneous deprotection of TBS ethers at C_8 and C_{11} followed by Dess−Martin oxidation,[20] which resulted in isolation of the stable lactol **20**. Brief exposure to Jones reagent gave synthetic (−)-stemonine (**1**), which proved to be identical in all respects to an authentic sample.[21]

In summary, a highly stereocontrolled total synthesis of (−)-stemonine (**1**) has been accomplished in 23 steps along the longest linear sequence from known materials. We have documented the preparative generation of a useful homoallyllithium reagent via iodide−lithium exchange. Efforts have demonstrated the use of the Staudinger reaction as a versatile technique for the synthesis of complex alkaloids, and our overall concept for the tandem, iodine-induced cyclization of the pyrrolidino-butyrolactone system has proven to be particularly noteworthy for its bond constructions and stereoselectivity.

Acknowledgment. We thank Bryan Stroup for his assistance in preparing **3** and **4** and gratefully acknowledge the National Institutes of Health (GM-41560) for generous support of this work.

Supporting Information Available: Experimental details for compound **16**, spectral data for coumponds **4**, **6**, **10**, **11**, **13**, **15**, **16**, **19**, and **1**, and the proton NMR spectrum of synthetic **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Selective oxidation of the C_{11} primary alcohol over the secondary C_8 alcohol was possible by portionwise (0.5 equiv at a time) addition of Dess Martin periodinane under buffered conditions (10 equiv of $NaHCO_3$) with careful monitoring by TLC.

(21) We gratefully acknowledge Professor Yang Ye of Shanghai Institute of Materia Medica for kindly providing an authentic sample of (−)-stemonine, as well as ^{1}H NMR, IR, and mass spectra of the natural product.