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Total Synthesis of (–)-Stemoamide

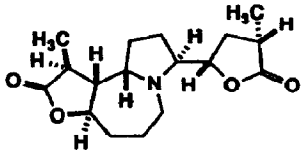
David R. Williams*, Jayachandra P. Reddy and George S. Amato

Department of Chemistry, Indiana University
Bloomington, Indiana 47405, U.S.A.

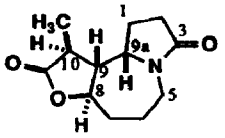
Key Words: Asymmetric aldol; chiral butyrolactone synthesis; selective 1,3-acyclic diol formation.

Abstract: *An enantiocontrolled total synthesis of the tricyclic alkaloid, stemoamide (2), is reported.*

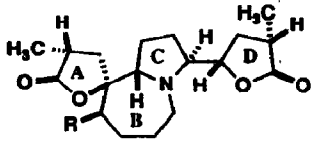
Roots and rhizomes of *Stemona* (*Stemonaceae*) have long been used as anthelmintics and as antitussives in traditional folk medicine of China and Japan. The extracts from this plant species have been found to contain, as their principal active constituents, a variety of alkaloids such as, stemonine **1**, stemoamide **2**, and stemospironine **3a**.[1,2] Several of these polycyclic alkaloids have been isolated and found to possess powerful insecticidal activity and/or neurotoxic properties.[3] Synthetic efforts targeting these molecules have appeared in the literature. We have previously reported the total synthesis of (+)-croomine **3b**, utilizing a Staudinger reaction followed by an iodine mediated bis-cyclization to create rings B, C, and D in two steps.[4] A total synthesis of (±)-stenine **4**, was completed by Chen and Hart, demonstrating ring closures by an intramolecular Diels-Alder cycloaddition-aminimide rearrangement sequence.[5] Herein we report the first total synthesis of stemoamide **2**.



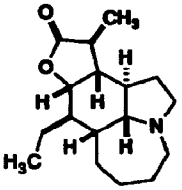
1 Stemonine



2 Stemoamide



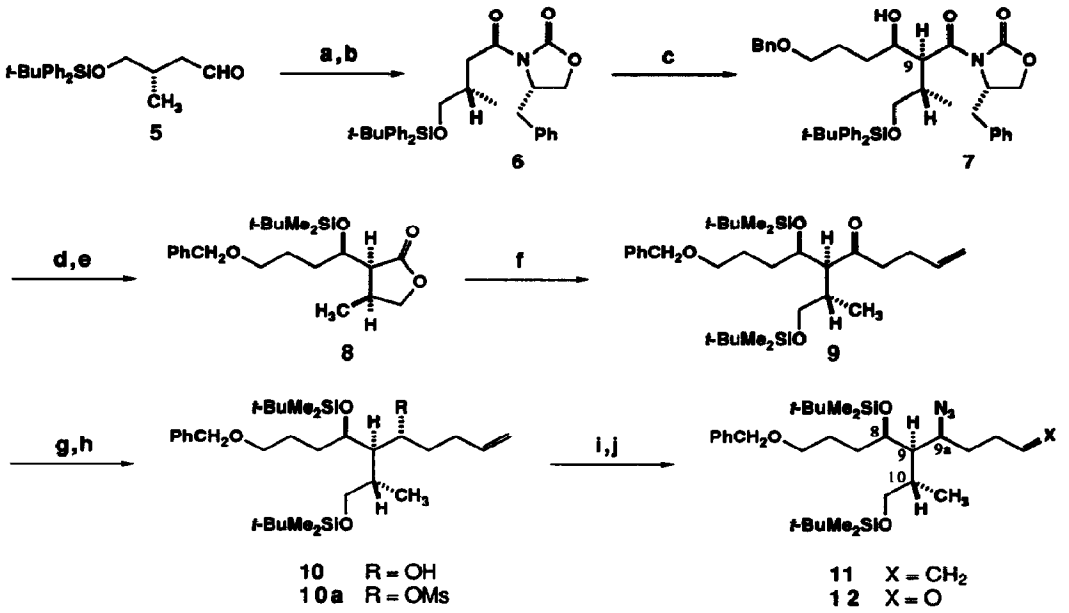
3a Stemospironine R = OCH_3
3b Croomine R = H



4 Stenine

Asymmetric synthesis of an acyclic carbon chain precursor is outlined in Scheme I for construction of the key intermediate, azido aldehyde **12**. Aldehyde **5** was prepared in 91% overall yield from (*R*)-(–)-methyl 3-hydroxy-2-methylpropionate in 5 steps.[6] Permanganate oxidation of aldehyde **5** gave the corresponding carboxylic acid which was then transformed to the imide **6** via the mixed pivalic anhydride.[7] The asymmetric Evans aldol reaction[7] of **6** with 4-benzyloxybutanal, required freshly distilled di-*n*-butylboron triflate and proceeded to give the expected *syn*-aldol derivative **7** as the exclusive product in 88% yield. When commercial dichloromethane solutions of di-*n*-butylboron triflate were used or when di-*n*-butylboron triflate was not freshly distilled, the reagent would cleave the terminal silyl ether of **6** which could then intramolecularly cyclize to give a butyrolactone.[8] Deprotection of the silyl ether of **7** with aqueous HF was followed by careful addition of potassium carbonate to basify the reaction mixture in order to release the chiral auxiliary and yield the disubstituted butyrolactone which was then converted to its *t*-butyldimethylsilyl ether **8** in standard fashion.[9] Neither epimerization at C-9 nor elimination to give the α,β-unsaturated carbonyl compound was detected in this sequence.

Scheme I[a]



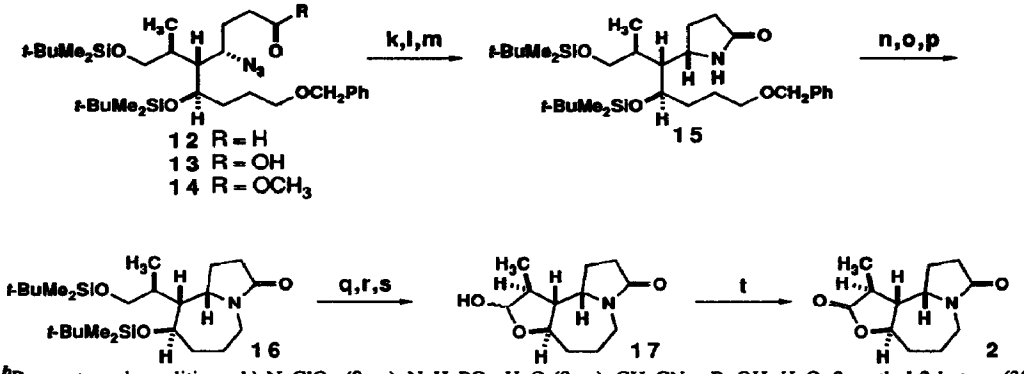
[a]Reagents and conditions: a) 1M $KMnO_4$, 0.5M NaH_2PO_4, *t*-BuOH, 15 min; b) *t*-BuC(O)Cl (1 eq), Et_3N (1.3 eq), THF, 0 °C→rt, 30 min; then cool to –78 °C and add premixed solution of (*S*)-4-(benzyl)-2-oxazolidinone (1.1 eq) and *n*-BuLi (1.1 eq), THF, –78 °C; then warm to rt, 2h, 94% from **5**; c) *n*-Bu_2BOTf (1.2 eq), CH_2Cl_2, –78 °C, 1h; then Et_3N (1.6 eq), –78 °C→0 °C, 1h; then 4-benzyloxybutanal (1.5 eq), –78 °C→0 °C, 1h, 88%; d) 48% aq HF (17 eq), CH_3CN, 20 min, rt; then sat aq $NaHCO_3$ (0.9M, 0.7 eq), K_2CO_3 (18 eq), 2h, 82%; e) *t*-$BuMe_2SiOTf$ (1.3 eq), collidine (1.5 eq), CH_2Cl_2, –78 °C→rt, 97%; f) 4-Iodo-1-butene (2.1 eq), *t*-BuLi (2.1 eq), Et_2O, –100 °C, 45 min; then add **8** (1 eq), –100 °C→–78 °C, 1.5 h; then collidine (3.4 eq), *t*-$BuMe_2SiOTf$ (3.2 eq), –78 °C→rt, 2.5h, 78%; g) $LiEt_3BH$ (1.4 eq), THF, –78 °C, 30 min; then warm to rt, 1.5h, 91%; h) MsCl (1.6 eq), pyridine, rt, 12h, 96%; i) NaN_3 (20 eq), HMPA, rt, 9h; j) O_3, CH_2Cl_2/CH_3OH (3:1), –78 °C; then Me_2S, –78 °C→rt, 3h, 49% from mesylate.

The condensation of the lactone **8** with 4-bromo-1-butene (*via* halogen-metal exchange to give the corresponding organolithium or Grignard) proved to be problematic. Various side reactions arising from Wurtz coupling and reduction of the primary halide, were observed. In addition, the yield from these reactions was variable. However, the procedures of Bailey[10a] and Negishi[10b] modified and applied to 4-iodo-1-butene produced the primary alkyllithium in diethylether at low temperatures and cleanly gave an intermediate alcohol which was protected as its *t*-butyldimethylsilyl ether in the same reaction pot to afford **9** in excellent reproducible yields. Reduction of ketone **9** by treatment with Super-Hydride® at –78 °C resulted in the formation of alcohol **10** as the exclusive product. The stereoselective formation of the 1,3-*anti*-diol derivative **10** is noteworthy. The *R*-alcohol configuration (at C-9a) is generated *via* a Felkin-Anh hydride addition, in which the β-*t*-butyldimethylsilyl ether predetermines the assignment of the C-8 carbon appendage as the larger substituent. Elucidation of stereochemistry at C-9a was made by ^{13}C-NMR analysis of the corresponding 1,3-acetonide.[11,12] This may offer a general strategy for production of 1,3-*anti*-diols from *syn*-aldol adducts.

Displacement of the methanesulfonate of **10** with sodium azide proceeded uneventfully with inversion of configuration to yield **11**, which was unstable when stored at room temperature or when purified through silica gel.[13] In practice, the azido alkene **11** was directly subjected for ozonolysis of the terminal olefin to produce **12**.

The strategy for sequential operations of ring cyclizations to afford stemoamide was crucial. As shown in Scheme II, sodium chlorite oxidation of **12** followed by esterification of the resulting carboxylic acid **13** gave methyl ester **14**. Mild reduction of the azide functionality with triphenylphosphine and hydrolysis of the resulting iminophosphorane led to the *in situ* cyclization to lactam **15**. Hydrogenation of **15** and conversion of the primary alcohol to the corresponding mesylate with subsequent treatment with sodium hydride afforded the 1-azabicyclo[5.3.0]decanone **16** in 71% overall yield from **15**.[14]

Scheme II[b]



[b]Reagents and conditions: k) $NaClO_2$ (9 eq), $NaH_2PO_4 \cdot H_2O$ (8 eq), CH_3CN, *t*-BuOH, H_2O, 2-methyl-2-butene (300 eq), 0 °C, 30 min; l) CH_2N_2 (xs), Et_2O, 0 °C, 15 min, 96% from **12**; m) PPh_3 (6.5 eq), THF/H_2O (100:1), 10^{-2}M, reflux, 48h, 87%; n) H_2, 10% Pd-C, EtOH, 24h; o) MsCl (3 eq), pyridine, rt, 15 min; p) NaH (xs), THF 10^{-2}M, rt, 1.5h, 71% from **15**; q) HF•NEt_3 (xs), CH_3CN, rt, 7h, 63% (78% based on recovered **15**); r) Dess-Martin periodinane (1.6 eq), pyridine (20 eq), CH_2Cl_2, rt, 30 min; s) *n*-Bu_4NF (xs), THF, rt, 15 min, 94% (2 steps); t) PDC (3 eq), CH_2Cl_2, reflux, 1.5h, 80%.

Selective deprotection of the primary silyl ether was realized with excess HF•Et_3N in acetonitrile, and oxidation of the resulting alcohol using the Dess-Martin periodinane[15] gave an intermediate aldehyde. Deprotection of the remaining silyl ether at C-8 using tetra-*n*-butylammonium fluoride directly gave a 1:1 mixture of lactols. Finally, pyridinium dichromate oxidation of the lactols in refluxing dichloromethane gave stemoamide **2**, which crystallized as colorless needles from diethylether, mp 190-191 °C (dec).[16] Single crystal x-ray analysis provided unambiguous confirmation of the structure of **2**.[17] Proton and carbon NMR data was in agreement with the reported spectral characterization of the natural product.[2]

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6. The five step transformation involved: i) *t*-$BuPh_2SiCl$ (1 eq), imidazole (2 eq), DMF, 0 °C→rt, 1.5h; ii) $LiBH_4$ (1 eq), CH_3OH (1 eq), Et_2O, reflux, 2h; iii) *p*-TsCl (1 eq), pyridine, 0 °C→rt, 12h; iv) NaCN (1.5 eq), DMSO, 70 °C, 2h; v) *i*-Bu_2AlH (1.1 eq), Et_2O, –78 °C→rt, 1.5 h, then H_3O^+. All new compounds were purified and characterized by ^1H (400 or 500 MHz), ^{13}C (100 or 125 MHz) NMR, IR and MS.
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8. These attempts also recorded cleavage of MEM and MOM ethers upon addition of the di-*n*-butylboron triflate reagent.
9. The usual techniques for selective hydrolysis or hydride reduction of **7** led to exclusive reactions of the oxazolidinone carbonyl as a result of steric hindrance.
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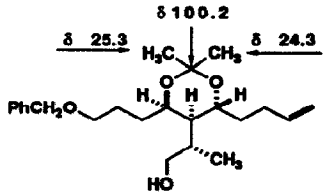
11. Key ^{13}C NMR data for the acetonide of **10** are shown. Our assignment was made by comparisons with data for a closely related pair of 1,3-*syn* and *anti*-acetonides available from our synthesis efforts toward stemonine **1**.



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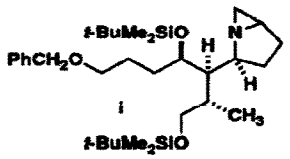
13. We speculate transformation of **11** to **i**, based upon ^1H, ^{13}C NMR and DEPT analysis. Rapid evolution of nitrogen is observed upon attempted silica gel chromatography of **11**.



14. For an example of a similar reaction: Aratani, M.; Dunkerton, L. V.; Fukuyama, T.; Kishi, Y.; Kakoi, H.; Sugiura, S.; Inoue, S. *J. Org. Chem.* **1975**, *40*, 2009.
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16. Data for **2**: mp 190-191 °C (Et_2O); $[\alpha]_D^{26}$ –141 ° (c = 0.19, CH_3OH) and $[\alpha]_D^{26}$ –181 ° (c = 0.89, CH_3OH); R_f (10% THF/EtOAc) 0.15; ^1H NMR (500 MHz, $CDCl_3$) δ 1.31 (d, *J* = 7 Hz, 3H), 1.45-1.55 (m, 2H), 1.72 quintet, *J* = 11 Hz, 1H), 1.85-1.9 (m, 1H), 2.03-2.08 (m, 1H), 2.38-2.45 (m, 4H), 2.60 (dq, *J* = 6.9, 12.4 Hz, 1H), 2.66 (broad dd, *J* = 14, 12 Hz, 1H), 4.0 (dt, *J* = 6.4, 10.7 Hz, 1H), 4.13-4.18 (m, 1H), 4.21 (dt, *J* = 3, 10.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 174.0, 55.8, 52.7, 40.2, 37.3, 34.8, 30.6, 25.6, 22.6, 14.1; IR ($CHCl_3$) ν (cm^{-1}) 3027, 3005, 2944, 1771, 1682; EIMS m/z (relative intensity) 223 (M^+, 42), 208 (11), 180 (7), 138 (6), 124 (14), 110 (26), 98 (100), 84 (17); HRMS m/z -223.1216 (Calcd for $C_{12}H_{17}NO_3$ -223.1209).
17. Complete X-ray crystallographic data are available from the Indiana University Chemistry Library. Request Molecular Structure Center Report 94134.

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