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Studies Toward The Synthesis of *Stemona* Alkaloids; A Short Synthesis Of The Tricyclic Core Of Tuberostemonines

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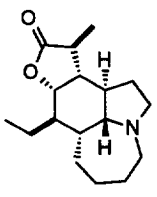
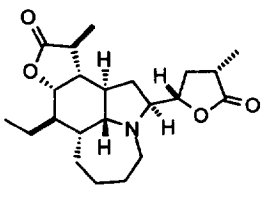
Abstract: The tricyclic hydroindole core system of the *Stemona* alkaloids was prepared in 9 steps from *N*-Aloc-tyramine. The synthesis features oxidation of tyramine with hypervalent iodine followed by intramolecular conjugate addition and Mitsunobu cyclization of an amino-alcohol as the key steps.

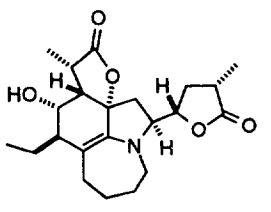
Extracts of *Stemona tuberosa* have yielded a structurally novel class of alkaloids used in traditional Chinese and Japanese medicine for the treatment of respiratory diseases such as bronchitis, pertussis, tuberculosis, and as antihelmintics.[1] A common structural feature shared by several *Stemona* alkaloids (i.e. stenine (**1**), tuberostemonine (**2**), oxotuberostemonine (**3**), and tuberostemonine L-G (**4**)) is the unusual azepinoindole skeleton. We have recently reported the first enantioselective total synthesis of (-)-stenine.[2] In this communication, we report an efficient general synthetic strategy for the construction of the core ring system of the *Stemona* alkaloids.[3]



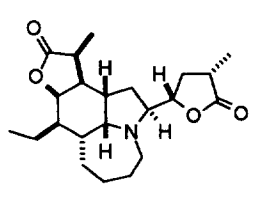
Stenine (**1**)



Tuberostemonine (**2**)



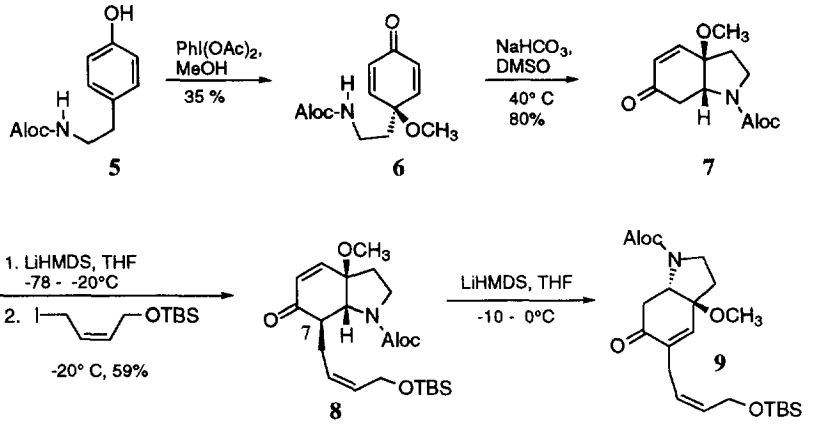
Oxotuberostemonine (**3**)



Tuberostemonine L-G (**4**)

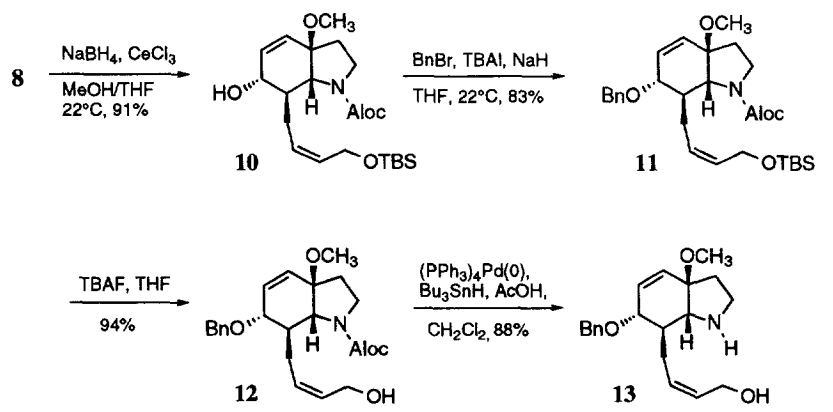
Using methodology previously reported by our laboratory,[4] the hydro-indolenone ring was constructed by the oxidation of *N*-Aloc-tyramine[5] with iodobenzene diacetate[6,7] to dienone **6** (35% yield), followed by intramolecular Michael cyclization of dienone **5** by treatment with $NaHCO_3$ in DMSO to give **7** in 80% yield. Under carefully controlled conditions, the lithium dienolate of bicycle **7** was allylated exclusively on the sterically less hindered β-face with *cis*-4-iodo-1-*t*-butyldimethylsilyloxy-2-butene[8] at -20 °C in 59% yield to give **8** as a single isomer. The configuration at C (7) was assigned by $^3J_{HH}$ analysis and by analogy to the facial selectivity observed previously in our laboratory on a similar system.[4] At elevated temperatures, or in the presence HMPA, subsequent β-elimination followed by Michael addition yielded the thermodynamically favored trisubstituted olefin **9** as the major product. Attempts to invert the stereochemistry at C(7) via reenolization of **7** and kinetic protonation were unsuccessful due to the facile formation of the β-elimination product **9**.

Scheme 1



Luche reduction[9] of the enone **8** afforded the equatorial allylic alcohol **10** as the major stereoisomer in 91% yield. Protection of the hydroxyl group as its benzyl ether with benzyl iodide gave **11** in 83% yield. Deprotection of the silyl ether with TBAF led to **12** in 94% yield, and subsequent palladium(0)-catalyzed hydrostannolytic cleavage[10] of the allyloxycarbonyl moiety provided the amino alcohol **13** in 88% yield. Mitsunobu[11] cyclization of the allylic alcohol afforded the undesired S_N2' product **14** in 55% yield as a single isomer. The relative stereochemistry of **14** was unambiguously determined by chemical shift analysis, $^3J_{HH}$ analysis, and 2D NOESY studies.

Scheme 2

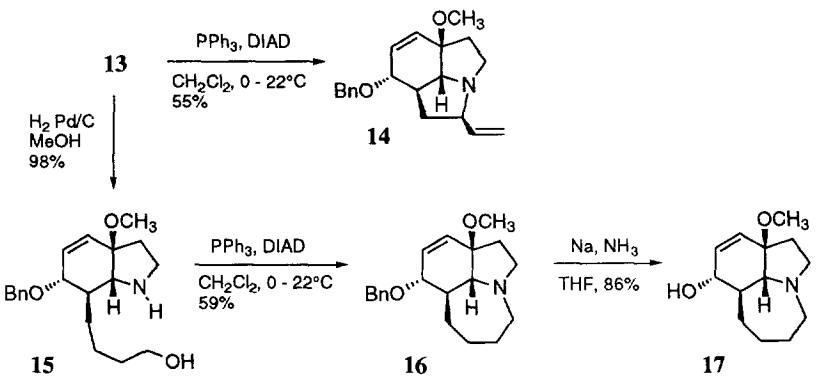


For the preparation of the desired azepine ring system, the side chain olefin of **13** had to be selectively hydrogenated in the presence of the endocyclic double bond. This was accomplished by controlled hydrogenation with 10% Pd/C for 1 h at room temperature to give **14** in 98% yield. Mitsunobu cyclization of the resulting amino alcohol **15** afforded the desired tricyclic core **16** in 59% yield. The success of this approach

demonstrates the utility of the Mitsunobu reaction to effect macrocyclization of amino-alcohols, the scope of which has yet to be further investigated.[12] The success of such cyclizations, however, appears to require considerable conformational preorganization of the amino alcohol as attempts to close a similar *trans*-hydroindole **18** as well as simple linear alkylamino alcohols to seven-membered heterocycles failed.[13,14]

Birch reduction of the benzyl ether afforded alcohol **17** in 82% yield. The stereochemical assignment of **17** was based on the correlation of the experimentally determined coupling constants with the values calculated for the geometry of **17**.[15]

Scheme 3



In conclusion, we have demonstrated an efficient method for the synthesis of the tricyclic perhydroindole core of the *Stemona* alkaloids from readily available starting materials. This synthetic strategy appears especially suitable for the preparation of oxotuberostemonine and tuberostemonine L-G. Further studies toward these natural products will be reported in due course.

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References and Notes

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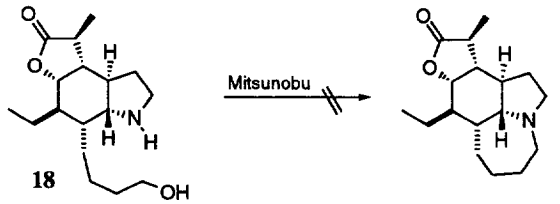
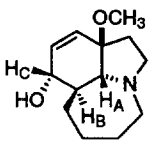


14 Bernotas, R. C.; Cube, R. V. *Tetrahedron Lett.* **1991**, *32*, 161-64.

15 $^3J_{HH}$ Calculations according to: Haasnoot, C.A.G.; De Leeuw, F.A.A.M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783. This isomer is the only one possible with all trans diaxial proton-proton coupling constants between H_A-H_B-H_C.



	J_{HH} (obs)	$^3J_{HH}$ (calc)
J_{AB}	= 10.8 Hz	= 11.9 Hz
J_{BC}	= 10.0 Hz	= 10.8 Hz

IR (neat) 3400, 3025, 2930, 2847, 2818, 2745, 1456, 1385, 1338, 1261, 1215, 1165, 1147, 1122, 1069, 991, 804, 745 cm^{-1}; ^1H NMR δ 5.91 (d, 1 H, *J* = 10.2 Hz), 5.51 (dd, 1 H, *J* = 10.2, 2.3 Hz), 3.72 (dd, 1 H, *J* = 10.0, 2.3 Hz), 3.07 (s, 3 H), 2.97 (m, 2 H), 2.76 (d, 1 H, *J* = 10.6 Hz), 2.75 (m, 1 H), 2.55 (m, 1 H), 2.26 (m, 1 H), 1.90-1.50 (m, 8 H), 1.19 (m, 1 H); ^{13}C NMR δ 137.2, 127.3, 84.6, 71.7, 66.0, 54.1, 53.7, 51.2, 49.6, 36.6, 32.9, 28.5, 23.6; MS (EI) *m/z* (rel intensity) 223 ($M^{\bullet+}$, 35), 193 (62), 174 (40), 110 (100), 84 (60); HRMS *m/z* calcd for $C_{13}H_{21}O_2N$: 223.1572, found: 223.1570.

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