Formation of Nine-Membered Lactams by Oxidative Ring Expansion of 4-Hydroxyhydroindoles: A Biomimetic Approach toward the Tuberostemonone Ring System?

Peter Wipf* and Wenjie Li

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

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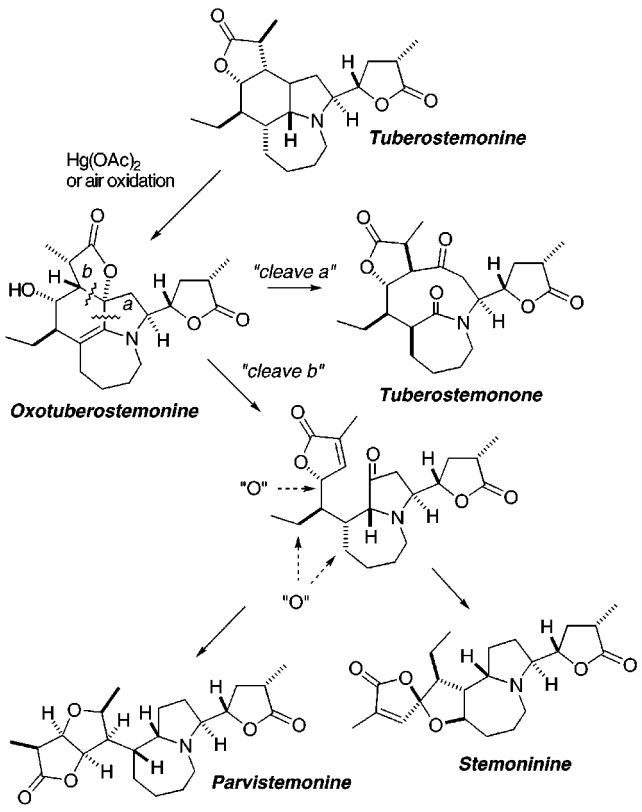
Extracts of *Stemona* have been used in Chinese and Japanese folk medicine as insecticides, as drugs for the treatment of respiratory diseases such as bronchitis, pertussis, and tuberculosis, and as antihelmintics. To date, the structures of more than 20 *Stemona* and related *Croomia* alkaloids have been elucidated by a combination of crystallographic, spectroscopic, and degradative techniques.[1,2] The polycyclic cores of these natural products pose challenging synthetic problems, and in recent years an impressive series of strategies has culminated in several total syntheses that showcase novel synthetic methodology.[3] As a continuation of our approach toward (−)-stenine and (−)-tuberostemonine,[3d,4] we now report the first preparation of the core bicyclic lactam ring system of tuberostemonone[5] by a novel hydroindole fragmentation reaction.

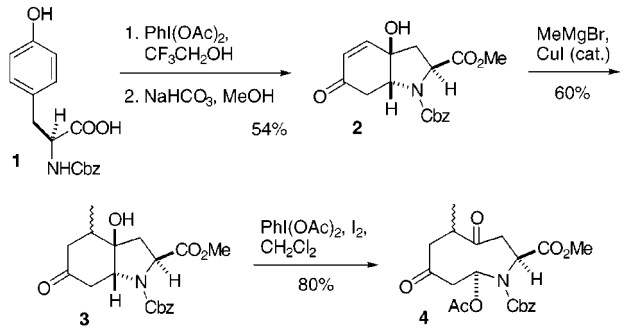
A key element of our retrosynthetic strategy is the hypothesis that both *Stemona* metabolites such as tuberostemonone and *Croomia* alkaloids such as stemoninine[6] and parvistemonine[7] could be derived from an oxidative ring cleavage of tuberostemonine[8] or related biosynthetic intermediates followed by a few further oxygenations and cyclizations (Scheme 1). In addition to the remarkable stereochemical correlations between *Stemona* and *Croomia* alkaloids, one of the linchpins of this hypothesis is the facile oxidative conversion of the major *Stemona* alkaloid tuberostemonine to oxotuberostemonine.[9] Accordingly, our presumed biomimetic synthetic approach focused on the fragmentation of hydroindole **3** (Scheme 2). Oxidative cyclization of Cbz-tyrosine (**1**) proceeded in 97% de as determined by HPLC analysis,[10] and copper(I)-catalyzed conjugate addition to enone **2** provided **3** as a mixture of diastereomers.[11]

Scheme 1



Treatment of this tertiary alcohol with iodobenzene diacetate and iodine indeed initiated a formal alkoxy radical fragmentation[12] and provided the nine-membered **4** in 80% yield as a separable 1.2:1 mixture of epimers.[13]

Scheme 2



The general scope of this novel ring expansion reaction of hydroindoles was subsequently confirmed by oxidative fragmentation of **5** (Scheme 3). The latter compound was obtained by successive ketone and alkene reductions of enone **2** and selective silylation of the secondary alcohol. Exposure of **5** to a mixture of iodobenzene diacetate and iodine in methylene chloride provided the azonane **9** as a

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(13) After crystallization from CH_2Cl_2/hexanes, an X-ray structure analysis of the major β-epimer of **4** confirmed the structure assignment for the fragmentation process.

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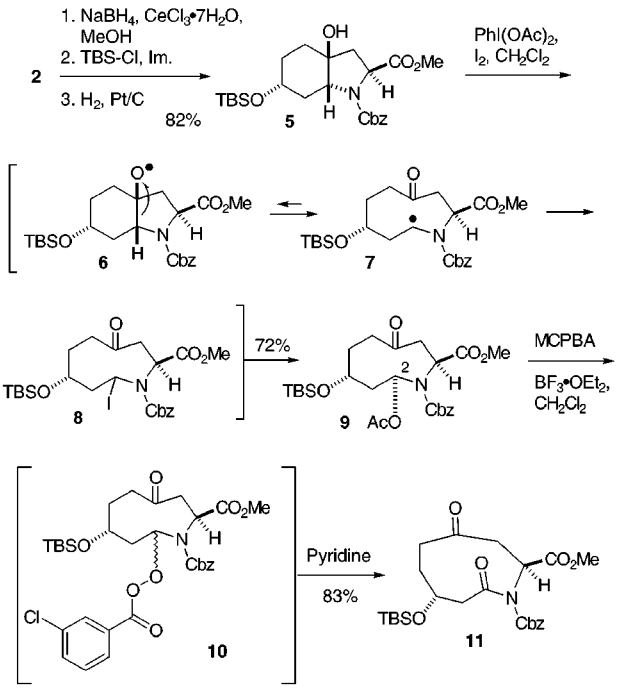
Scheme 3

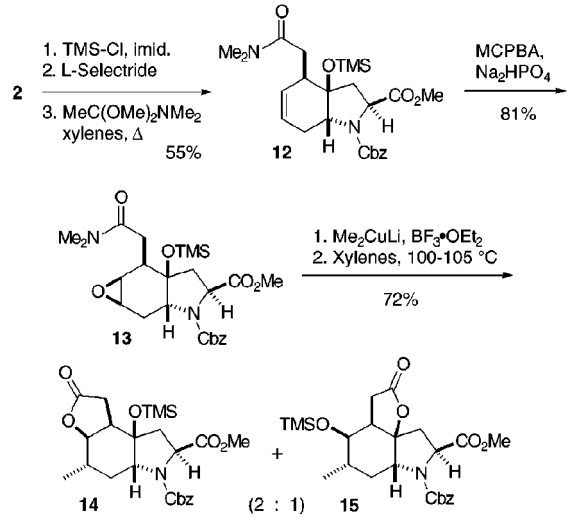


single isomer, presumably the thermodynamically preferred anomer derived from oxygen- and carbon-centered radicals **6** and **7** via the unstable iodine trapping product **8**. The configuration at C(2) of **9** was tentatively assigned as shown on the basis of the X-ray structure analysis of the major isomer of **4**.[13]

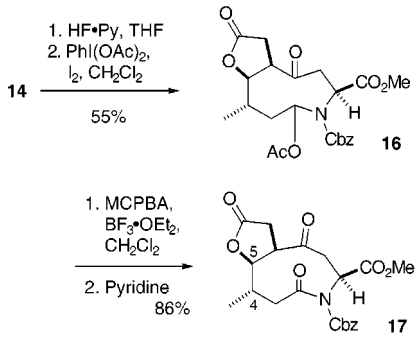
The planned further conversion of the unusual mixed carbamate−ester acetal functionality in **9** to the lactam moiety of the tuberostemonone target structure was largely unprecedented. Any base hydrolysis of **9** was expected to fragment this mixed acetal and open, perhaps irreversibly, the strained nine-membered ring. However, since regular acetals, in particular glycosides, can directly be converted to lactones in the presence of Lewis acids and peracids,[14] we decided to apply analogous conditions for the oxidation of C(2) in **9**. Exposure of a solution of **9** in CH_2Cl_2 to *m*-chloroperbenzoic acid and BF_3−etherate led to a rapid conversion to an new intermediate that was tentatively assigned as peroxy acetal **10**. Without isolation, the crude material was treated with neat pyridine to provide the desired keto−lactam **11** in 83% overall yield (Scheme 3).[15]

The successful radical fragmentation−oxidation of bicycles **3** and **5** underlined the feasibility of our retrosynthetic approach toward tuberostemonone. For the investigation of a model system more closely related to the polycyclic tuberostemonone scaffold, we protected the tertiary alcohol in **2** and used L-selectride for the preparation of the axial allylic alcohol (Scheme 4). Subsequent Eschenmoser Claisen rearrangement[3c,d,16] provided amide **12** in 55% overall yield. Epoxidation proceeded exclusively from the convex face of bicycle **12**, but methyl cuprate ring opening of **13** led to a 2:1 mixture of silyl ethers. After thermal lactonization, lactones **14** and **15** were isolated in a combined 72% yield based on epoxide **13** and could readily be separated by chromatography on SiO_2.

Scheme 4



Scheme 5



Lactone **14** was desilylated with HF/pyridine and subjected to our radical fragmentation conditions (Scheme 5). The nine-membered heterocycle **16** was isolated in 55% yield, and peracid-mediated oxidation of the mixed acetal moiety provided the fused-ring system **17** in 86% yield after pyridine-mediated decomposition of the peroxide intermediate. The structure of **17** was secured by X-ray analysis.

In conclusion, the successful conversion of the aromatic amino acid tyrosine into the saturated medium-ring core system of the alkaloid tuberostemonone in a few steps underlines the efficacy of our unified synthetic approach toward the *Stemona* and *Croomia* alkaloids.[3d,4] Specifically, we have developed a novel strategy for radical fragmentation of hydroxyl-substituted hydroindoles that provides a versatile access to highly functionalized azonanes. In addition, the two-step conversion of mixed carbamate−ester acetals to lactams is likely to find general use in medium-ring synthesis where hydrolytic conditions can lead to ring opening and lactamization of *seco*-acids is disfavored due to ring strain. We are currently extending this synthetic strategy toward the preparation of stereoisomers at C(4) and C(5) of **17** necessary for a completion of the total synthesis of tuberostemonone.

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Supporting Information Available: Experimental details and characterization data for all new compounds, ^1H and ^{13}C NMR spectra, and crystal structure data and ORTEP drawings for **4** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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