A Radical Approach for the Construction of the Tricyclic Core of Stemoamide

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Abstract: A rapid synthesis of (±)-9,10-bis-*epi*-stemoamide is presented. Three of the four contiguous stereocenters of this compound were set in a diastereoselective radical 7-*exo*-trig cyclization, which also allowed the construction of the tricyclic core of the molecule.

Key words: radical cyclization, metathesis, stereoselective synthesis

Stemoamide (Figure 1) is the structurally simplest member of the large number of biologically active *Stemonaceae* alkaloids, which were obtained by extraction of the roots and rhizome of the *Stemona* and *Croomina* species. In traditional Chinese and Japanese folk medicine this extract is used for the treatment of respiratory diseases such as bronchitis, pertussis and tuberculosis and it has also been utilized as insecticide and antihelmintic.[1] To date more than forty biologically active alkaloids were isolated and characterized, few of them were prepared also by synthesis.[2] While there is a considerable amount of synthetic work in acceding to the racemic and optically active stemoamide,[1] little attention has been given to prepare synthetic analogs.[3e,f,4] In this communication we describe a short synthesis of the (±)-9,10-bis-*epi*-stemoamide using a radical cyclization as the key step.

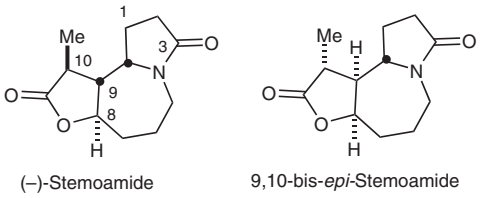
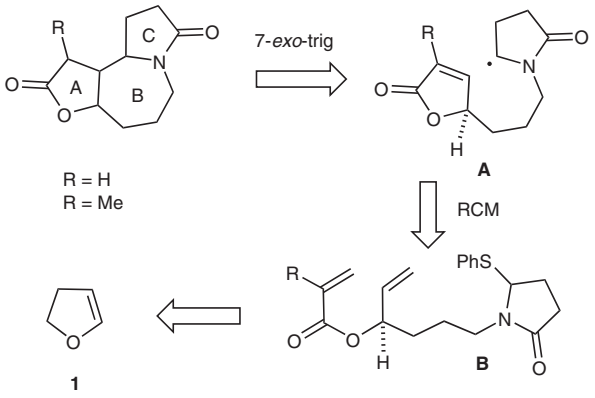


Figure 1

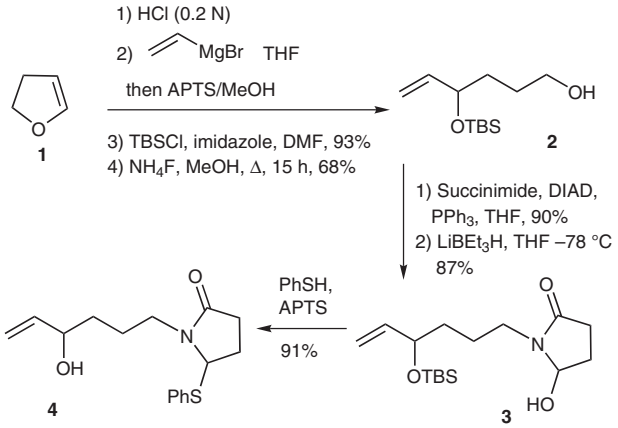
A retrosynthetic analysis of the tricyclic core of stemoamide is depicted in Scheme 1. The radical intermediate for the key cyclization reaction should be generated from the corresponding thiophenyl derivative.[5,7] The α,β-unsaturated lactone **A** could be prepared by ring-closing metathesis (RCM), and the unsaturated compound **B** should be easily accessible from dihydrofuran **1**.

The synthesis of the advanced intermediate **4** from dihydrofuran **1** is depicted in Scheme 2. Acid-catalyzed hydration of dihydrofuran, followed by addition of vinyl magnesium bromide to the hemiacetal afforded the corresponding diol,[6] which was converted selectively to the mono-protected alcohol **2** in two steps (TBSCl/imidazole followed by selective desilylation with NH_4F). This easily scalable sequence allowed the preparation of a multigram quantity of **2**.



Scheme 1

The C-ring of stemoamide was introduced with a Mitsunobu-type substitution of the primary alcohol with succinimide followed by selective reduction of one of the carbonyl functionality using superhydride ($LiBEt_3H$, THF, –78 °C) producing **3** in 87% yield. Preliminary studies indicated that thioaryl ethers are convenient sources of radicals from pyrrolidinones, thus thiophenyl derivative **4** was selected for further studies. Intermediate **4** was prepared by treatment of **3** with PhSH in the presence of APTS[7] and, under these acidic conditions, the silyl protecting group was also cleaved (91%, overall yield).



Scheme 2

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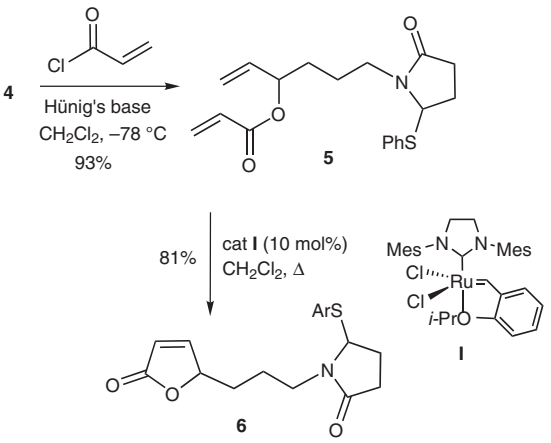
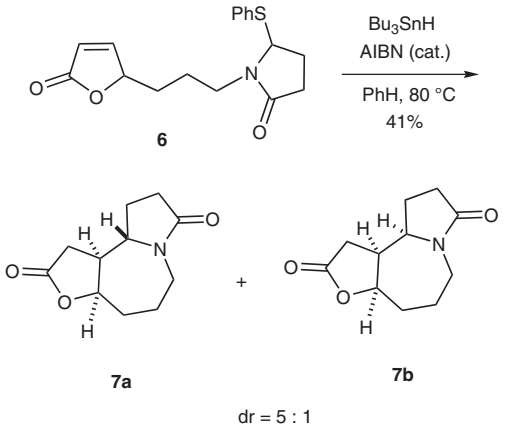
In order to test the radical cyclization, the synthesis of the *nor*-C(10) stemoamide from derivative **6** was first considered (Scheme 3).[7] The requisite α,β-unsaturated lactone (stemoamide A-ring) was assembled in 2 steps from the corresponding allylic alcohol **4** by esterification using an excess of acryloyl chloride and Hünig's base followed by a ring-closing metathesis (RCM). In this latter reaction, Grubbs' catalysts first and second generation[8] afforded **6** only in moderate yields (around 50%) from the unsaturated compound **5** while Hoveyda's catalyst[9] **I** afforded **6** in good yield (81%).



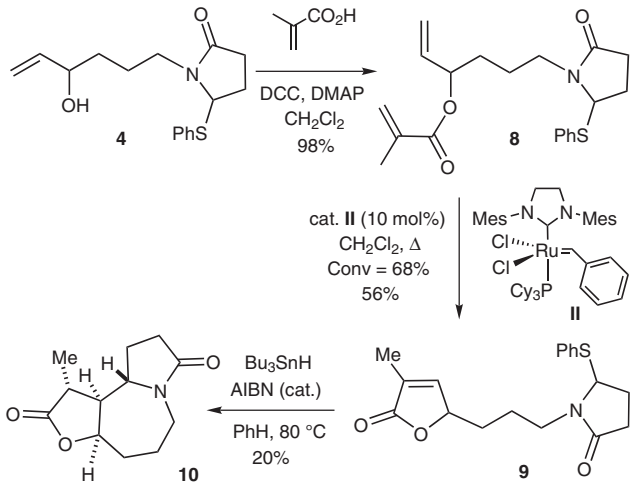
Scheme 3

The radical cyclization of **6** was realized in benzene under high dilution conditions (5.6 mM) at reflux temperature by slow addition of a Bu_3SnH solution (0.2 M) and AIBN (cat.) (Scheme 4).[10] The reaction afforded a 5:1 mixture of two diastereomers in 41% yield. The structure of the two isomers was assigned by analyzing the ^1H NMR coupling constants of **7a** and **7b**.



Scheme 4

In the aim of synthesizing stemoamide, the methacrylate **8** was prepared by condensation of the parent alcohol with methacrylic acid (Scheme 5). The ring-closing metathesis was more suitable with Grubbs' catalyst **II** and the reaction provided lactone **9** in 56% (conversion 68%). The radical cyclization of **9** was achieved with Bu_3SnH, AIBN (cat.) in refluxing benzene, and afforded the tricyclic compound **10** in a non-optimized 20% yield as a single diastereoisomer.[11] It is worth noting that we were not able to isolate other diastereomers in this cyclization reaction. The stereochemistry of the newly formed centers in **10** was assigned on the basis of ^1H NMR coupling constants and by comparison with the ^1H NMR and ^{13}C NMR spectrum described in the literature.[3e]



Scheme 5

In this radical cyclization, the *cis*-fused AB ring of the *epi*-stemoamide was formed according to a 7-*exo*-trig process. The relative *trans*-stereochemistry of the methyl substituent at C(10) and the hydrogen H^a can be the consequence of a kinetic control with preferred reduction of the radical from the *endo* face. The unfavorable 1,3-interaction between the methyl at C(10) and the hydrogen H^a in the transition state renders intermediate **C** energetically less favorable (Figure 2).

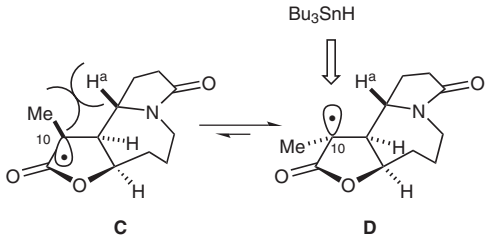


Figure 2

In summary, a diastereoselective synthesis of the (±)-9,10-bis-*epi*-stemoamide was realized in 10 steps. The sequence was based on a 7-*exo*-trig radical cyclization, which allowed the control of three of the four contiguous stereocenters of the molecule. The synthesis of (–)-stemoamide is underway in the laboratory and will be reported in due time.

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(10) For general conditions of cyclization see ref.[11]

(11) **9,10-bis-*epi*-Stemoamide (10):**
To a stirred solution of **9** (48 mg, 0.15 mmol) and AIBN (5 mg, 0.03 mmol) in degassed benzene (30 mL) at reflux, a solution of Bu_3SnH (100 μL, 0.37 mmol) in benzene (3 mL) was added over 4 h via a syringe pump. The crude mixture was treated with a sat. aq solution of KF, extracted by CH_2Cl_2, dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by chromatography on silica gel (gradient: CH_2Cl_2 then CH_2Cl_2–MeOH 95:5) to afford compound **10** (6.7 mg, 0.03 mmol, 20%) as a single diastereomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 7.2 Hz, 3 H), 1.61–2.15 (br m, 5 H), 2.23–2.62 (m, 5 H), 2.78 (ddd, *J* = 13.9, 10.4, 3.4 Hz, 1 H), 3.63 (dd, *J* = 9.0, 7.2 Hz, 1 H), 4.18 (dt, *J* = 13.9, 4.5 Hz, 1 H), 4.62 (ddd, *J* = 10.6, 7.9, 3.0 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.9, 24.0, 25.5, 28.9, 30.1, 39.1, 44.1, 50.9, 60.5, 80.7, 174.6, 177.9. MS (EI, 70eV): *m/z* (%) = 224 (12) [MH^+], 223 (87) [M^+], 208 (41), 180 (44), 98 (100), 97 (59).