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An Approach to the Skeleton of the Securinega Alkaloids. The Total Synthesis of (±)-Securinine

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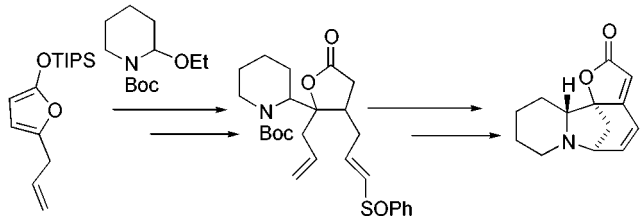
ABSTRACT



The concise total synthesis of securinine in nine steps from readily available starting materials is described. Key steps of the synthesis include an addition of a silyloxyfuran to an in situ generated iminium ion and a novel ring closing metathesis reaction.

Securinine (**1**, Figure 1) is a member of the Securinega family of alkaloids, and it embodies the basic structural features of this class of natural products. The compound is an architecturally interesting target, which contains an indolizidine skeleton, a butenolide moiety, and an azabicyclo [3.2.1] system. Securinine was isolated[4] in 1956, and its structure was elucidated in 1962 by degradation and by spectroscopic studies.[5] The structure of securinine was confirmed by X-ray crystallography in 1965.[6] To date, one total[7] and one formal[8] synthesis of securinine have been reported. Additionally, preliminary accounts toward the total synthesis of securinine have been disclosed.[9] Due to its compact nature and interesting structural characteristics, securinine lends itself as a challenging synthetic target and continues to attract the attention of synthetic chemists. In addition to its interesting structure, securinine possesses CNS biological activity as a GABA receptor antagonist.[10] In this Letter we will present a general approach to the skeleton of the Securinega alkaloids and the total synthesis of securinine in nine overall steps from readily available starting materials.

We envisioned an approach to securinine as depicted in Scheme 1. A stereoselective addition of silyloxyfuran **3** to an iminium ion generated in situ from substrate **4** would furnish a butenolide-containing intermediate with a quaternary carbon center, which would be converted to compound

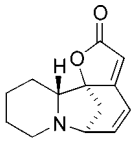


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Figure 1.

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(5) (a) Satoda, I.; Murayama, M.; Tsuji, Y.; Yoshii, E. *Tetrahedron Lett.* **1962**, *3*, 1199. (b) Nakano, T.; Yang, T. H.; Terao, S. *Tetrahedron* **1963**, *19*, 609.
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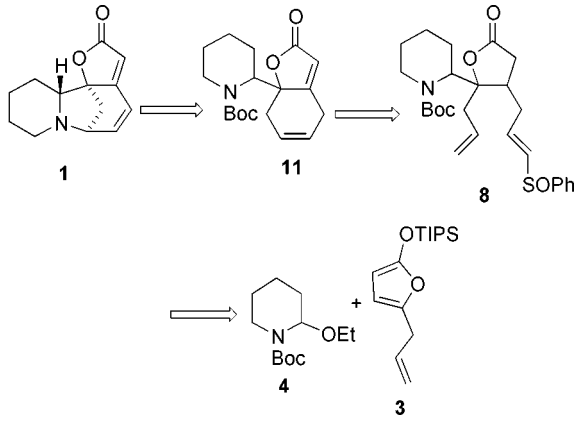
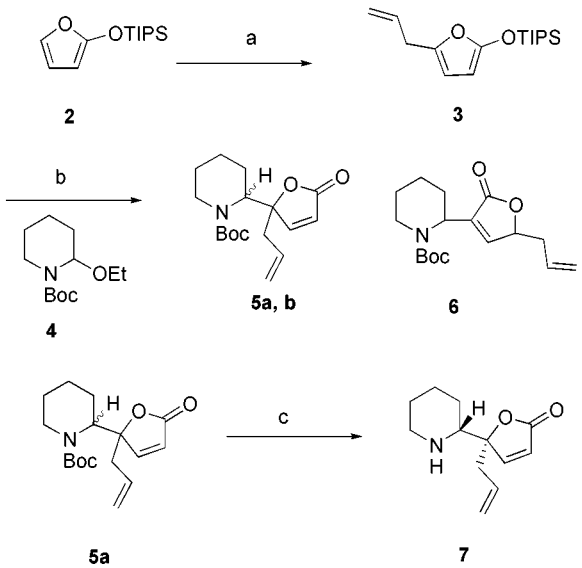
Scheme 1



8 via the 1,4 addition of allyl phenyl sulfoxide. Compound **8** would be transformed to substrate **11** via a ring closing metathesis reaction and subsequent installation of the butenolide double bond. The total synthesis of securinine would result from an amino-cyclization reaction of an intermediate dibromide stemming from compound **11**.

The synthetic steps are described in the schemes below. The first step of the synthesis involved the preparation of silyloxyfuran **3**, which was produced in 82% yield upon treatment of the readily available silyloxyfuran **2**[11] with *sec*-BuLi and TMEDA at 0 °C in heptane followed by addition of allyl bromide (Scheme 2). The preparation of silyloxyfuran

Scheme 2[a]



[a] (a) *sec*-BuLi, TMEDA, allyl bromide, THF, 0 °C, 82%;(b) TIPSOTf, heptane, −78 °C, 78%; (c) HCl, EtOAc, rt, 85%.

3 set the stage for its addition to an iminium ion generated in situ from the readily available 2-ethoxy piperidine derivative **4**.[12] This reaction, described in the literature as a vinylogous Mannich reaction,[13] has been highlighted by Martin and co-workers as the key step in the elegant syntheses of other butenolide-containing natural products and advanced intermediates.[14] In the event, treatment of 2-ethoxy piperidine derivative **4** with furan **3** and several Lewis acids yielded variable mixtures of the diastereomeric butenolides **5a** and **5b** and a product consistent with the structure of furanone **6**. The effect of Lewis acids on the stereoselectivity of this transformation will be discussed in subsequent communications.[15] Optimum reaction conditions that minimized the formation of furanone **6** were discovered when a mixture of furan **3** with 2-ethoxy piperidine **4** in heptane at −78 °C was treated with 0.1 equiv of TIPSOTf. Under these reaction conditions a 78% yield of butenolides **5a**, **5b**, and **6** was obtained in a ratio of 8:2:1, respectively. Substrates **5a**, **5b**, and **6** were separated by flash chromatography.

The stereochemistry of the major adduct **5a** was determined from a crystal structure of the amine hydrochloride **7** (Figure 2). Compound **7** was produced by removal of the

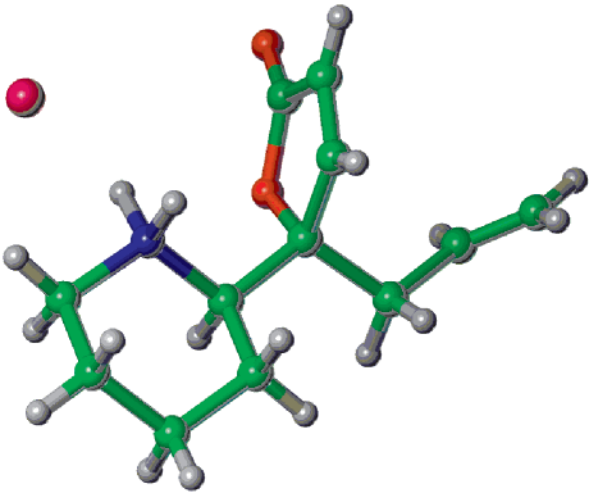


Figure 2.

N-Boc group in **5a** with HCl in ethyl acetate at room temperature in 85% yield. The X-ray structure of compound **7** confirmed that the stereochemical relationship of the piperidine group and the butenolide moiety in the major isomer **5a** is consistent with the stereochemical relationship of the piperidine and butenolide moieties found in securinine.

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(13) For reviews, see: (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. (b) Martin, S. F. *Pure Appl. Chem.* **1997**, *69*, 571.

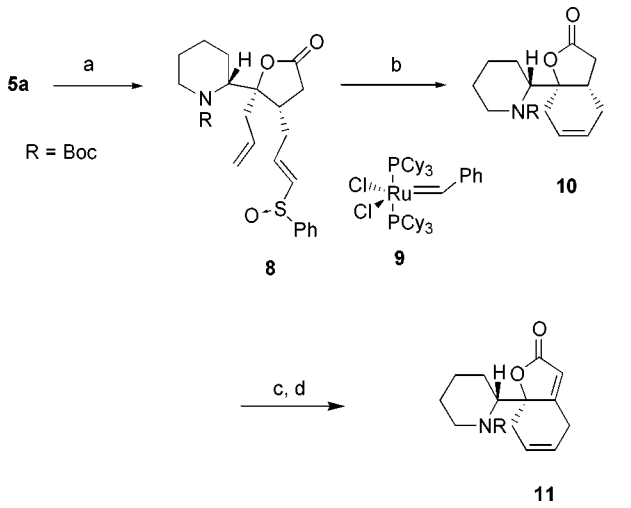
(14) For selected examples, see: (a) Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990. (b) Martin, S. F.; Liras, S. *J. Am. Chem. Soc.* **1993**, *115*, 10450. (c) Martin, S. F.; Bur, S. K. *Tetrahedron Lett.* **1997**, *38*, 7641.

(15) For a rationale regarding the diastereoselectivity of silyloxyfuran additions to related cyclic iminium ions, see: Martin, S. F.; Bur, S. K. *Org. Lett.* **2000**, *2*, 3445.

Our attention was subsequently turned to the elaboration of **5a** into a ring closing metathesis (RCM) precursor. Efforts to convert the major stereoisomer **5a** into the desired substrate by addition of allyl cuprate reagents were unsuccessful. Adduct **5a** was converted into a ring closing metathesis reaction precursor via the 1,4-addition of the anion of allyl phenyl sulfoxide.[16] Thus, compound **8** was prepared in 71% yield by treatment of excess allyl phenyl sulfoxide (2 equiv) with LiHMDS (2.1 equiv) in THF at −78 °C followed by addition of 1 equiv of **5a** in THF and stirring of the reaction mixture at −45 °C for 5 h. Compound **8**, which represents a novel substrate for a ring closing metathesis reaction by virtue of its terminal vinyl sulfoxide functionality, was recovered as a single diastereomer on the basis of NMR spectroscopic analysis. With compound **8** available, we sought to develop conditions for the crucial RCM transformation. Numerous elegant applications of the ring closing metathesis reaction in the total synthesis of natural products have recently been reported.[17] In this instance, treatment of compound **8** with 0.2 equiv of the Grubbs reagent **9**[18] in refluxing 1,2-dichloroethane yielded an approximately 15% yield of the desired product **10**. Gratifyingly, treatment of **8** with a full equivalent of the Grubbs reagent furnished **10** in 79% yield. Efforts to optimize the efficiency of this transformation utilizing the recently reported reagents with increased reactivity[19] will be described in due course.

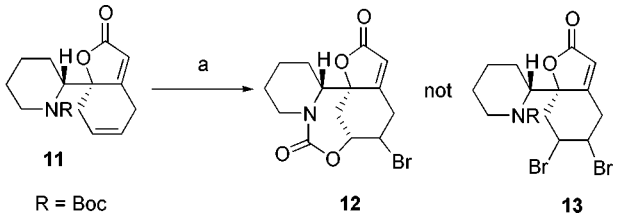
With compound **10** in hand, our attention was turned to the installation of the butenolide double bond. Thus, treatment of **10** with LiHMDS and phenyl selenyl bromide in THF at −78 °C followed by oxidative elimination of an intermediate phenyl selenide under the influence of H_2O_2 in dichloromethane at 0 °C furnished **11** in a 43% yield overall (Scheme 3).

Scheme 3[a]



[a] (a) Allyl phenyl sulfoxide, LiHMDS, THF, −78 to −45 °C, 71%; (b) Grubbs catalyst **9**, 1,2-dichloroethane, 70 °C, 79%; (c) LiHMDS, THF, phenyl selenyl bromide, −78 °C to rt; (d) H_2O_2, dichloromethane, 0 °C, 43% for steps c and d.

Scheme 4[a]



[a] (a) Bromine, chloroform, 0 °C to rt.

With the formation of compound **11** secured, the aminocyclization reaction and the installation of the conjugated diene functionality remained as the final obstacles to the completion of the total synthesis of securinine. We envisioned dibromide **13**, resulting from selective bromination of the nonconjugated olefin in **11**, as the precursor to a final tandem cyclization−dehydrohalogenation step. Conversion of a related dibromide to securinine, albeit in low yields, has been reported.[7] However, in an attempt to obtain the target dibromide by treatment of **11** with bromine in chloroform we obtained the cyclic carbamate **12** in nearly quantitative yield (Scheme 4). The structure of **12** was verified by X-ray crystallography (Figure 3).

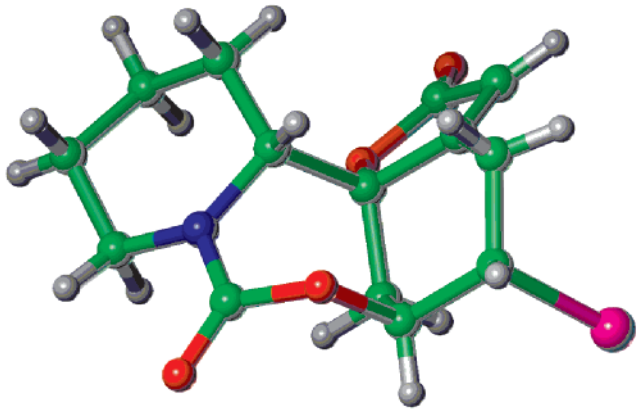


Figure 3.

The total synthesis was subsequently completed by reversal of the reaction sequence. Thus, removal of the nitrogen-protecting group of **11** with trifluoroacetic acid in dichloromethane at ambient temperature and treatment of the crude trifluoroacetate salt **14** with bromine in chloroform afforded dibromide **15** (Scheme 5). Treatment of the crude dibromide **15** with K_2CO_3 in DMF at 70 °C yielded securinine in 78% yield for the three final steps, thus completing the total synthesis in nine overall steps. The proton and carbon NMR

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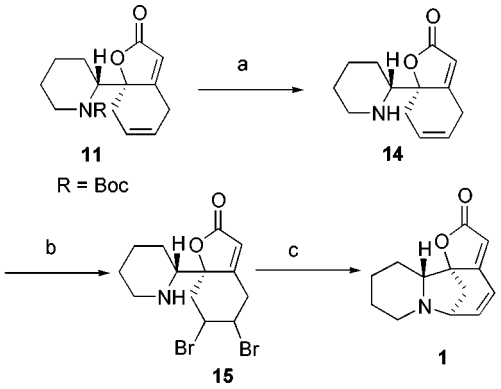
Scheme 5[a]



[a] (a) TFA, dichloromethane; (b) bromine, chloroform, −10 °C to rt; (c) K_2CO_3, DMF, 70 °C, 78% for steps a−c.

spectra obtained from the synthetic securinine were identical to the spectra obtained from a sample of commercially available securinine (Sigma).

In conclusion, the concise total synthesis of the alkaloid natural product securinine has been accomplished in nine overall chemical steps from readily available materials. Key steps of the synthesis included a stereoselective addition of a silyloxyfuran to an iminium ion, a stereoselective 1,4 addition of phenyl allyl sulfoxide to a butenolide moiety, and a novel ring closing metathesis reaction. The approach described herein represents a general strategy for the synthesis of additional members of the Securinega alkaloid family such as norsecurinine.

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Supporting Information Available: Representative experimental procedures for the preparation of compounds **5a**, **8**, **10**, and **1** and copies of NMR spectra for compounds **3**, **5a**, **7**, **8**, **10**, **11**, **14**, **15**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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