

Facile Synthesis of a Benzindenoazepine Alkaloid, Bulgaramine, via Samarium Diiodide Promoted Ring Expansion of an α -Aminocarbonyl Compound

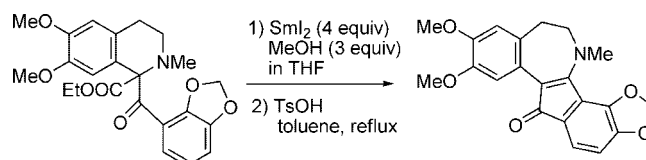
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ABSTRACT



A novel synthetic path to a benzindenoazepine alkaloid was established by employing a samarium diiodide promoted ring expansion reaction of an α -aminocarbonyl compound as a key reaction, in which a regioselective carbon–nitrogen bond cleavage followed by ring-closing reactions occurred to give the basic ring skeleton of the target compound. Bulgaramine was synthesized from the known tetrahydroisoquinoline derivative in 5 steps in 50% overall yield.

Plants of the genus *Fumaria* have been used in some parts of Asian and eastern European countries as folk medicines for their antipyretic, analgesic, and diuretic properties.¹ Because benzindenoazepines are expected to exhibit potential biological activities of medicinal interest, interest in the development of new synthetic methodology for this class of alkaloids continues unabated.²

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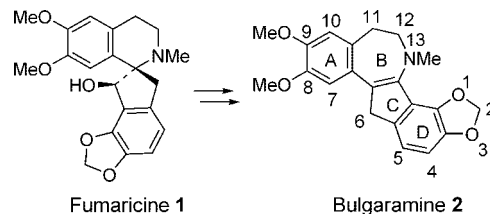
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Bulgaramine **2** was isolated from Herba *Fumaria officinalis*³ as a member of benzindenoazepines that are a distinct group of alkaloids, probably derived biogenetically from the rearrangement of spirobenzylisoquinolines.⁴ On the basis of this consideration, a spirobenzylisoquinoline alkaloid, fumaricine **1**, has been successfully transformed to bulgaramine, supporting the biogenetic hypothesis⁵ (Scheme 1). Furthermore, benzindenoazepine derivatives have been em-

Scheme 1. Conversion of Fumaricine to Bulgaramine

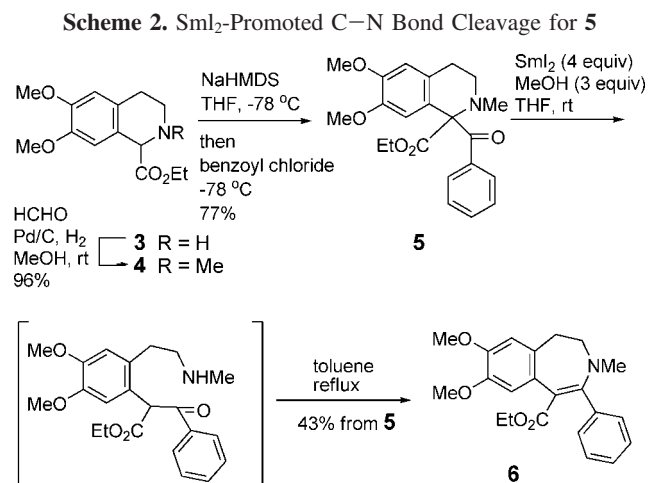


ployed as key intermediates for transformation to rhoeadine and protopine alkaloids.⁶

Total synthesis of bulgaramine **2** has recently been achieved by Giese and co-workers by using an intramolecular cyclopentannulation of the Fischer aminocarbene complex as a key reaction to give the desired ring system,⁷ and this is the only report of total synthesis for this alkaloid. The crucial step for synthesis of this class of alkaloids obviously lies in the facile construction of a benzindenoazepine ring system.⁸ In 1999, we developed a SmI₂-promoted regioselective carbon–nitrogen bond cleavage reaction of α -aminocarbonyl compounds.⁹ In relation to a project directed at the synthesis of bioactive alkaloids by application of this methodology,¹⁰ we are interested in establishing an entirely new, perhaps practical and general route for the total synthesis of a unique benzindenoazepine alkaloid, bulgaramine.

Prior to synthesis of the natural product, we decided to investigate efficient and mild reaction conditions for the SmI₂-promoted bond cleavage reaction of an ester **5** as follows. The known 1-ethoxycarbonyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **4**¹¹ was prepared by treatment of **3**¹² with 37% formalin in MeOH in the presence of a catalytic amount of 10% palladium on carbon under an atmospheric pressure of hydrogen in 96% yield. Installation of a benzoyl group was achieved by treatment of **4** with benzoyl chloride in the presence of NaHMDS in THF to give **5** in 77% yield. Attempted SmI₂-promoted reductive carbon–nitrogen cleavage reaction of **5** in THF at ambient temperature for 1 h in the presence of MeOH as a proton source afforded a bond-cleaved compound, which without further purification was subjected to a recyclization in refluxing toluene to give the desired product **6** in 43% yield from **5**.¹³ Thus, we were able to develop a new route for transformation of an isoquinoline skeleton to a functionalized

benzazepine ring system by simple reaction sequence (Scheme 2).



By establishing a synthetic route to the basic skeleton of the natural product, we started the synthesis of bulgaramine as follows. Our synthesis was launched with the preparation of the known acid chloride **7**.¹⁴

Treatment of tetrahydroisoquinoline derivative **4** with 2,3-methylenedioxybenzoyl chloride **7** in THF in the presence of NaHMDS in THF afforded the 1-benzoyl derivative **8** in 83% yield. Reductive carbon–nitrogen bond cleavage reaction of **8** with SmI₂ (4 equiv) in THF in the presence of MeOH (3 equiv) as the proton source at room temperature for 30 min gave a secondary amine, which on treatment with *p*-TsOH monohydrate (0.1 equiv) in refluxing toluene furnished the desired benzindenoazepine-type compound **9** directly in 68% yield from **8**.

It is noteworthy that the bond-cleaved compound was converted to benzindenoazepin-6-one **9** by treatment with *p*-TsOH in reasonable yield, probably due to the presence of an electron-donating methylenedioxy group on the D-ring, which might facilitate the cyclization of a relatively unstable enamino-ester to the more stable tetracyclic compound **9** (Scheme 3). Actually, when this cyclization was attempted in toluene in the absence of *p*-TsOH, enamino-ester **10** was isolated in 40% yield as the major product, which could be transformed to **9** in refluxing toluene containing *p*-TsOH in 81% yield. The plausible reaction mechanism is depicted in Scheme 4.

Finally, reduction of the carbonyl group of **9** at the 6-position was investigated under various reaction conditions. Usually, reduction of enamines with various hydride donors, such as lithium borohydride, sodium borohydride, zinc borohydride, sodium acetoxyborohydride, or lithium aluminum hydride, provides the corresponding carbon–carbon double bond reduced ketones or corresponding alcohols,¹⁵

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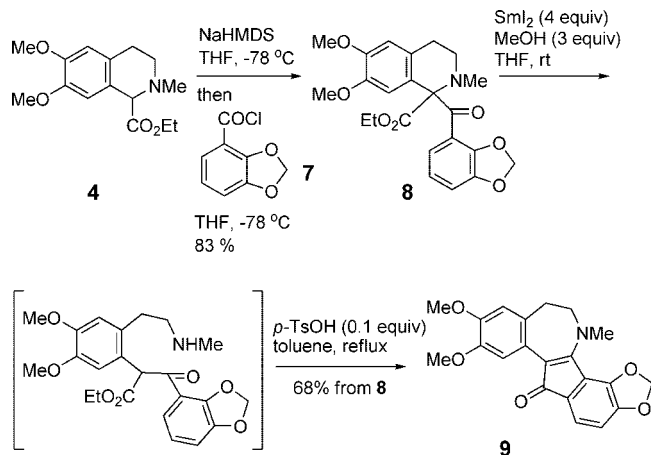
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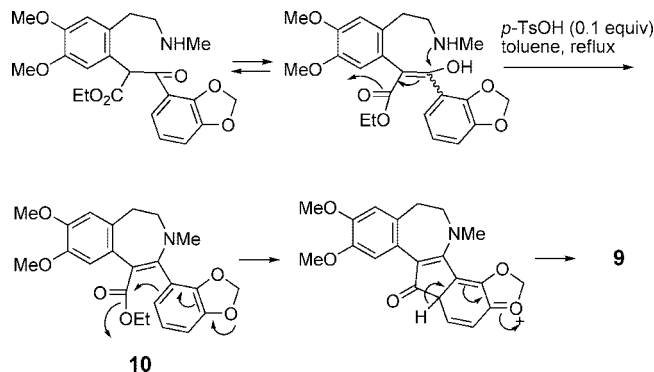
Scheme 3. Sml₂-Promoted Ring Transformation of **8**



but the attempted reduction of **9** under similar reaction conditions did not give any reduced products. Fortunately, we are able to find a practical route for the conversion of **9** to the target compound **2** in which DIBAL was employed as the reducing agent.

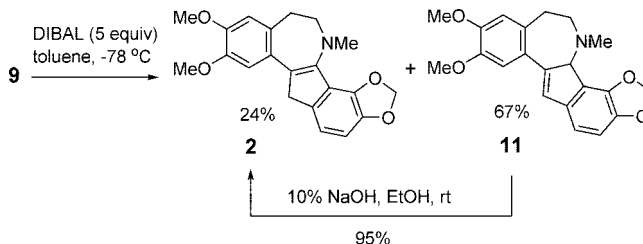
Thus, the reduction of ketone **9** with DIBAL (5 equiv) in toluene at $-78\text{ }^{\circ}\text{C}$ for 24 h afforded bulgaramine **2**, in 24%

Scheme 4. Plausible Reaction Mechanism for Formation of **9**



yield, together with the isomer **12**^{5,7} in 67% yield. Further transformation of **11** to **2** was achieved by treatment with 10% NaOH in EtOH at room temperature for 19 h in 95% yield (Scheme 5).

Scheme 5. Synthesis of Bulgaramine **2**



The spectroscopic data of the synthesized compound including its melting point, $205\text{--}206\text{ }^{\circ}\text{C}$ (lit.⁴ mp $209\text{ }^{\circ}\text{C}$), were identical to those reported in the literature.⁴

In summary, we were able to establish a facile and entirely new route for construction of a benzindenoazepine ring skeleton in a small number of steps with reasonably high yield, in which a Sml₂-promoted regioselective carbon–nitrogen bond cleavage reaction, followed by acid-catalyzed formation of a benzindenoazepin-6-one ring system, was involved as the key step. By exploiting this strategy, we succeeded in a concise synthesis of a benzindenoazepine alkaloid, bulgaramine, starting from the known tetrahydroisoquinoline derivative **4** in 4 or 5 steps in 50% overall yield. Further utilization of this strategy in the synthesis of other types of biologically active alkaloids is in progress in our laboratory.

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Supporting Information Available: Experimental details and compound characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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