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Expedient Construction of the Ziegler Intermediate Useful for the Synthesis of Forskolin via Consecutive Rearrangements

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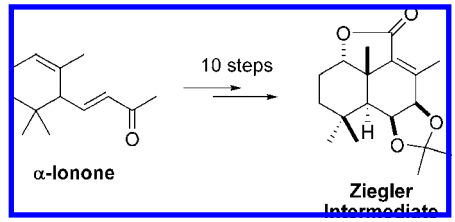
ABSTRACT



The Ziegler intermediate, useful for the total synthesis of forskolin, was synthesized in 10 reaction steps starting from commercially available α-ionone. This highly efficient synthesis relies on the success of two consecutive highly regio- and stereoselective rearrangements. The current synthesis has not only established an efficient synthetic route to access the Ziegler intermediate but it has also paved a way to the structural optimization of forskolin.

The Ayurvedic herb *Coleus forskohlii*, a member of the mint family growing in the subtropical areas in India, Burma, and Thailand, has been utilized as a traditional folk medicine to treat disorders of the digestive organs.[1] Forskolin (**1**) (Figure 1), a highly oxygenated labdane diterpene isolated in 1977 from the roots of *C. forskohlii*[2] by a research group from Hoechst, India, has been shown to have therapeutic potential against glaucoma, congestive heart failure, bronchial asthmas,

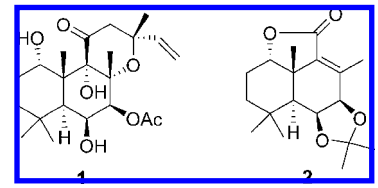


Figure 1. Chemical structures of forskolin (**1**) and the Ziegler intermediate **2**.

etc.[3] In addition, forskolin, together with a few other congeners, is a unique and potent stimulator of the enzyme adenylate cyclase in various tissues.[4] For example, it has been shown to be effective for lowering blood pressure,

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(2) (a) Bhat, S. V.; Bajwa, B. S.; Dornauer, H.; de Souza, N. J.; Fehlhaber, H.-W. *Tetrahedron Lett.* **1977**, 1669–1672. (b) Paulus, E. F. *Z. Krisalloar.* **1980**, *152*, 239–245; *153*, 43−49. (c) Bhat, S. V.; Bajwa, Dornauer, B. S. H.; de Souza, N. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, *76*, 7–771.

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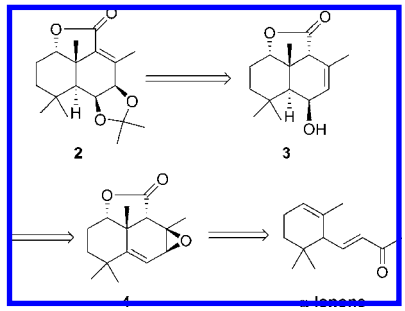
inhibiting platelet aggregation, improving heart function, and possibly increasing nitric oxide levels.[5] Further, it has been used as a standard when a lipolytic agent is examined.[6]

Owing to its broad range of physiological activities and unique structural features, forskolin has been the subject of many synthetic efforts.[7] So far, four different total syntheses of this highly challenging target have been completed,[8] and the first three have proceeded through the intermediacy of lactone (**2**), first synthesized[9] by the Ziegler group. Consequently, this advanced intermediate has emerged as a highly attractive target for substantial synthetic investigation.[10]

We have been interested in designing efficient synthetic strategies. In a previous paper, we proposed a standard to gauge the efficiency of synthetic strategies.[11] According to that standard, we started to work on the synthesis of intermediate **2** and the retrosynthetic analysis is shown in Scheme 1.

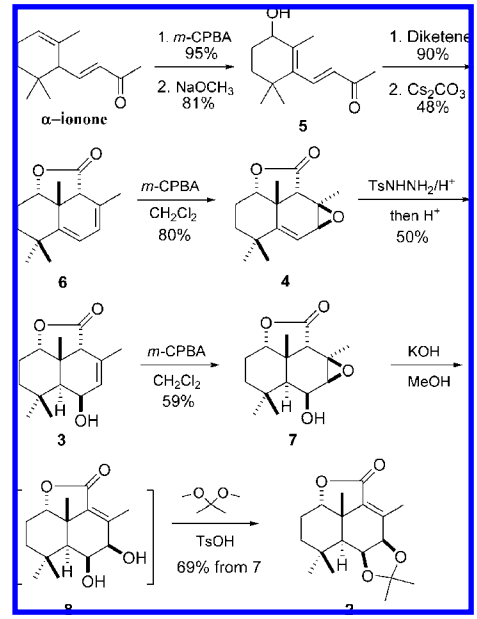
Scheme 1. Retrosynthetic Analysis of the Ziegler Intermediate



After a brief literature comparison, we have found that some of the key intermediates in our synthetic design are known, though the transformations that we plan to use are different. α-Ionone is a commercial material which may be converted into intermediate **4** in five steps as documented in the literature. While transformation of **4** into **3** is established, it takes six reaction steps. Thus, there is still considerable room to enhance the efficiency of the entire synthetic strategy, which is the main point of this paper. Subsequent conversion of **3** into **2** is also known.

As shown in Scheme 2, chemoselective epoxidation of α-ionone provided (95%) the desired epoxide intermediate,

Scheme 2. Synthesis of the Ziegler Intermediate



treatment of which with sodium methoxide produced intermediate **5** in 81% yield. Upon reaction with diketene, intermediate **5** was converted into an acetoacetyl ester (90%), which afforded intermediate **6** after treatment with a mixture of anhydrous potassium carbonate−cesium carbonate (4:1 mol ratio) in refluxing acetonitrile in 48% yield. We had some difficulty in optimizing the reaction yield to what was reported in the literature, though the effort of optimization is still being continued. Chemoselective oxidation of **6** with *m*-CPBA led to the formation of epoxide **4** in 80% yield. The key reaction of this synthesis was designed to proceed through the following sequence:

Regio- and stereoselective addition of tosylhydrazine to the epoxide was catalyzed by TsOH. The newly formed hydrazine derivative decomposed under the reaction condi-

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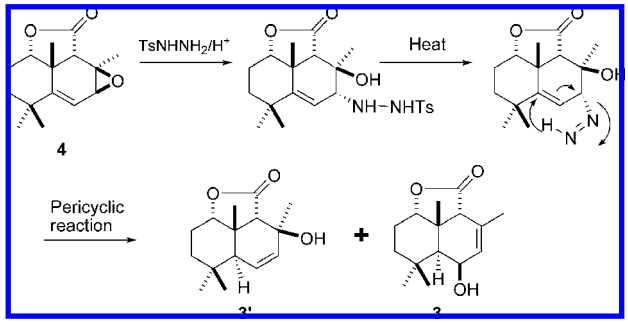
tions, leading to a diimine derivative. The latter was unstable and underwent an electrocyclic reaction to afford intermediate **3′** (Scheme 3). The stereochemistry of the bridgehead hydrogen depends on that of the imine derivative.

Scheme 3. Mechanistic Rationale of the Stereocontrolled Hydrogen Atom Transfer

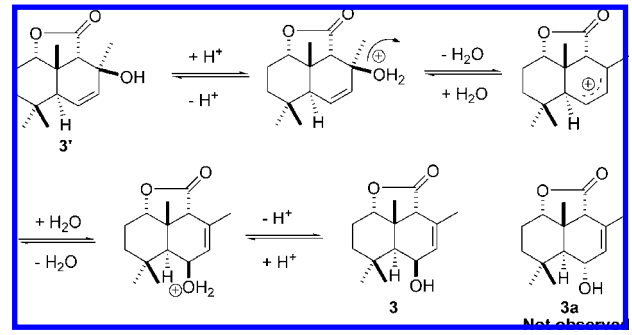


Although intermediate **3′** was the initially desired product from the rearrangement, during the course of the reaction, a small amount of a new product was detected and was identified to be **3**. We believed that intermediate **3** was produced from the hydroxyl rearrangement of **3′** under the reaction conditions. Much to our delight, when it was treated with an aqueous sulfuric acid solution (1%), **3′** was converted into **3** in high yield. A possible mechanism of this rearrangement is proposed as shown in Scheme 4.

The driving force for this rearrangement to occur is perhaps due to the strain release from **3′** to **3** and the thermodynamic stability difference of the carbon−carbon double bond between **3′** and **3**. The stereochemistry of the hydroxyl group was identified by comparison of its spectroscopic data with those reported and by conversion of **3** into the Ziegler intermediate, whose spectroscopic data were in full agreement with those reported in the literature. The reason for such an outcome to occur is perhaps due to the difference in the torsional strain of the developing transition state to form **3** as is compared to its epimer **3a**.

Based on the above analysis, conversion of **3′** into **3** was achieved when the reaction mixture from the first step was treated with dilute sulfuric acid prior to purification.

Scheme 4. Possible Mechanism of the 1,3-Rearrangement Leading to Intermediate **3**



Oxidation of **3** with *m*-CPBA afforded the epoxide intermediate, **7**, in 59% yield. Without optimization, the latter was treated with KOH in methanol to furnish the desired diol **8**, which was converted into the Ziegler intermediate upon treatment with a catalytic amount of toluenesulfonic acid and dimethoxypropane in 69% overall yield from intermediate **7**. The spectroscopic data of the final product are in full agreement with those reported.

Although this paper describes a racemic synthesis of the Ziegler intermediate, an asymmetric synthesis may be achieved by using chiral **6**, which is readily accessible through a known procedure.[12]

In summary, we have achieved an efficient synthesis of the Ziegler intermediate. Conversion of this intermediate into forskolin is under way and will be presented for publication in due course.

Acknowledgment. This work was supported by a grant from GIBH.

Supporting Information Available: Experimental procedures, analytical data, and copies of ^{1}H and ^{13}C NMR spectra for **2**−**4** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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