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First synthesis of 1,9-dideoxyforskolin from ptychantin A

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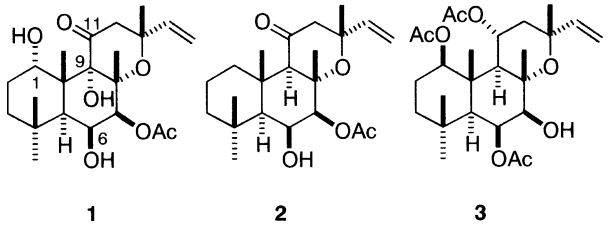
Abstract—1,9-Dideoxyforskolin **2** has been synthesized starting from ptychantin A **3**.

During the course of investigation of antihypertensive and cardioactive substances in nature, de Souza et al. isolated several labdane diterpenoids[1] from *Coleus forskohlii*, which has been used as a folk medicine in India. One major constituent, forskolin **1** (Fig. 1) showed significant blood pressure lowering properties.[2] In addition, a wide variety of biological activities were observed by raising the level of cAMP and, as a result, activating protein kinase. Due to such activities, more than 1,500 citations dealing with the physiological properties of forskolin **1** appeared in *Chemical Abstracts* in 2001. The physiological importance in addition to the highly oxygenated structure of forskolin **1** stimulated the interest of synthetic organic chemists and there has been a surge of synthetic studies.[3]

One other major constituent, 1,9-dideoxyforskolin **2**, was not potent in antihypertensive activity. However, attention was recently focused on **2** because it has been found to inhibit glucose transports in rats adipocytes in micromolar range.[4] The activity is expected to treat some diseases (Alzheimer, diabetes, cancer) caused by abnormal glucose uptake.[5]



1 2 3

Figure 1.

Alternatively, five new labdane diterpenoids have been isolated from liverwort *Ptychanthus striatus*.[6] All of them have closely related structures to forskolins, although antihypertensive activities have not yet been found in these compounds. The major constituent, ptycanthin A **3** easily available in large quantity (0.45%) from the liverwort, would be a good starting material for syntheses of forskolin and its derivatives.

Recent results of synthetic study as well as the importance of physiological activity of 1,9-dideoxyfoskolin **2**[7] prompted us to report synthesis of **2** from ptychantin A **3** which is described in Scheme 1. One major problem in the present synthesis was selective transformation of a hydroxy and three acetoxy groups, especially selective oxidation at C-11, by discriminating the subtle difference in the environment around each functional group.

Selective hydrolysis of the 6-acetoxy group by potassium hydroxide proceeded quantitatively owing to the highly congested nature of the acetoxy group at C-6 to give diol **4** whose 6,7-diol moieties were protected as an acetonide in 91% yield by 2,2-dimethoxypropane. The resulting acetonide **5** was reduced with lithium aluminumhydride to provide diol **6** in 97% yield. After several attempts, selective oxidation of the hydroxyl group at C-11 was fortunately accomplished by PCC to give ketone **7** in 71% yield. The densely substituted nature of the β-face of **6** may allow such selective oxidation of the α-equatorial hydroxy group at C-11.

Keywords: 1,9-dideoxyforskolin; ptychantin A; labdane; forskolin.
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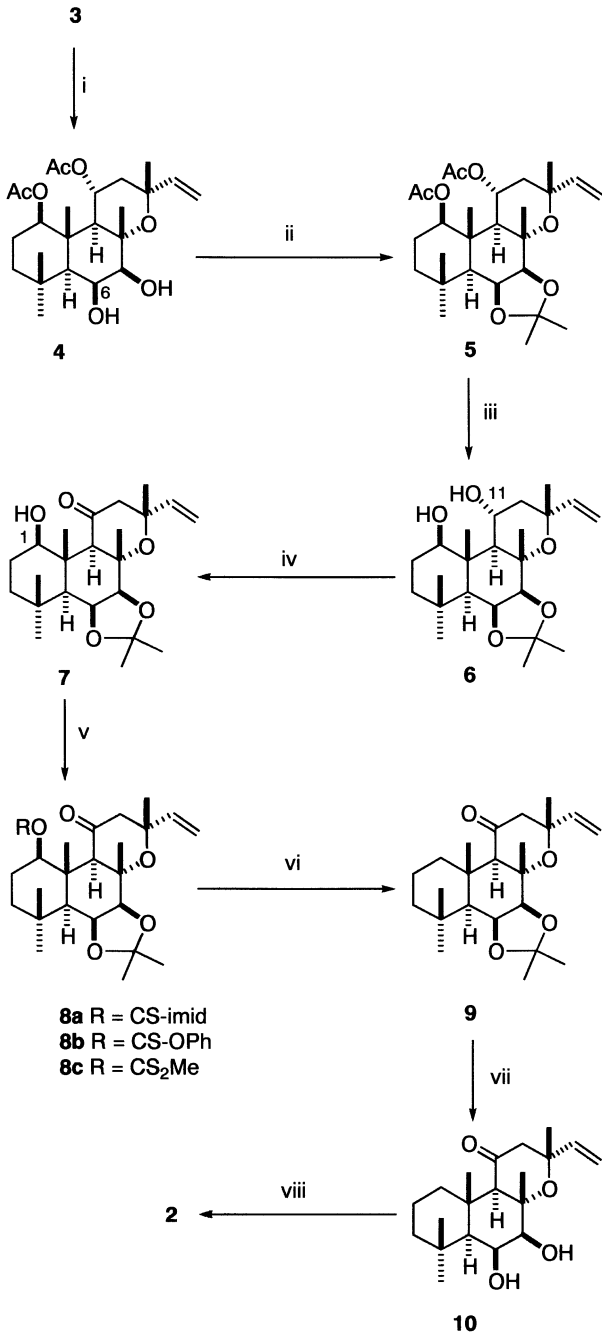

Scheme 1. *Reagents, conditions and yields*: (i) KOH/MeOH, rt, 13 h, 100%; (ii) 2,2-dimethoxypropane, PTSA, rt, 91%; (iii) LAH, Et_2O, rt, 2.5 h, 97%; (iv) PCC/AcONa, CH_2Cl_2, rt, 3 h, 71%; (v) thiocarbonyldiimidazolide, DMAP, 2 h, 82% for **8a**; phenylchlorothionoformate, DMAP, $CHCl_3$, reflux, 23 h, 54% for **8b**; *n*-BuLi/CS_2/MeI, THF, 0°C, 4 h, 33% for **8c**; (vi) AIBN/*n*-Bu_3SnH, toluene, 100–120°C, 30–45 min, 83% from **8a**, 41% from **8b**, 72% from **8c**; (vii) 10% $HClO_4$/THF (1:2), rt, 7 days, 100%; (viii) Ac_2O/Pyr./DMAP, 0°C, 1 h, 86%.

Then, in order to remove the hydroxyl group at C-1, the alcohol **7** was transformed into thiocarbonylimidazolide **8a** by solid-state reaction,[8] thiocarbonylformate **8b** or xanthate **8c** by conventional procedure in 82, 54 or 33% yield, respectively. Radical cleavage of **8a**, **8b** or **8c** with *n*-tributyltinhydride in the presence of AIBN furnished **9** in 83, 41 or 72% yield respectively. Hydrolysis of the acetonide **9** proceeded very slowly but quantitatively by dilute $HClO_4$ to give diol **10**. Finally, selective acetylation of the less hindered hydroxy group at C-6 of the diol **10** completed the synthesis of 1,9-dideoxyforskolin **2** in 86% yield. The spectral data of the synthetic **2** were identical with those of natural **2** $\{[\alpha]_D^{25}$ −89.2, lit.[1] −89.4$\}$ kindly supplied by Dr. Rosner.

In summary, we have completed the first synthesis of 1,9-dideoxyforskolin **2** in 37% overall yield in eight steps from ptychantin A **3**. Since ptychantins are available in large quantity, present protocol offers enough supply of physiologically potent compounds.

Acknowledgements

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