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An Improved Method of Total Synthesis of 2-Methoxypodocarpane-8,11,13-triene

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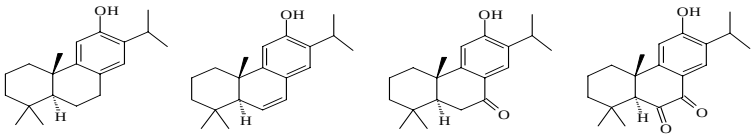
Abstract: 12-Methoxypodocarpane-8,11,13-triene **1**, the key intermediate in the synthesis of some important diterpenes, was synthesized in an efficient way, which has the characteristics of short route, simple operation and high yield.

Keywords: Synthesis, diterpenes, 12-methoxypodocarpane-8,11,13-triene, cyclization.

12-Methoxypodocarpane-8,11,13-triene **1** is the key intermediate for synthesis of some important diterpenoids, such as Ferruginol **2**[1], 6,7-dehydroferruginol **3**[1], sugiol **4**[2], 5-epixanthoperol **5**[3] *etc*. These compounds posses significant bioactivities, such as fungicidal[1], antimicrobial[1] and cytotoxic activity[2]. Some methods of synthesis of the title compound **1** were reported, but the process is laborious and the yield is low. In connection with our effort to discovery and develop new anti-HIV drugs, a number of analogs of the compound **1** were needed to evaluate their structure-active relationship. Here we report a facile stereoselective synthetic route to compound 1.

Scheme 1

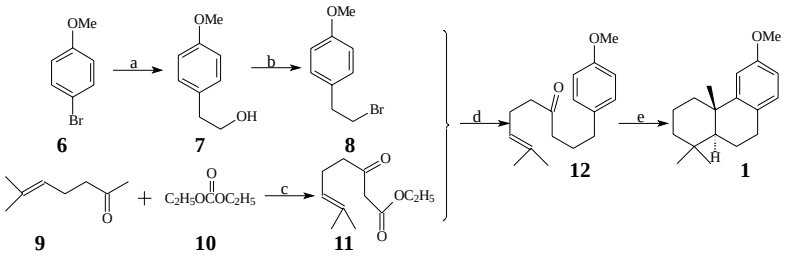


2 **3** **4** **5**

The synthetic route is illustrated in **scheme 2**. Compound **7** was easy obtained from unexpensive material **6** in 95% yield. The bromination of **7** was carried out according to literature method[5] with 85% yield. In the course of synthesis of compound **11**, it was found that benzene was more proper than ether , which was always used in the literature[6]. When using benzene as solvent, **11** was obtained in 92% yield. After alkylation of **8** and **11**, without separation, the mixture was directly hydrolyzed in refluxing EtOH with KOH to give **12** in 75% overall yield. **12** was added with excess

CH_3Li, then the mixture was directly refluxed with PPA[4] at 80-90℃ for 2 h to give the title compounds **1**[7] in 42% overall yield. The stereoselectivity of cyclization is 100% *trans*, if there is A/B *cis* isomer, the chemical shift of 4α-CH_3 shielded by the aromatic group is about 0.54 ppm[8], which was not found. The final stage work of coverting **1** to other diterpenes is in progress.

Scheme 2



Reagents and conditions: (a) Mg, THF, ethylene oxide, 95%; (b) Ph_3P, Br_2, CH_2Cl_2, 85%; (c) NaH, C_6H_6, reflux,92%; (d) i) NaH, THF; ii) EtOH/KOH/H_2O, reflux, 75%; (e) i) excess CH_3Li, THF; ii)PPA, 80-90℃, 42%.

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References and Note

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7. Spectra data of **1**: δ_H (300 MHz, $CDCl_3$): 0.93 (s,6H), 1.18 (s,3H), 1.10-2.90 (m,11H), 3.77 (s,3H), 6.60 (1H,dd,J = 8.0,2.0 Hz), 6.80 (1H,d,J = 2.0 Hz), 6.90 (1H,d,J = 8.0 Hz); EI-MS(*m/z*): 258 (M^+,100), 243 (73), 187 (65), 174 (73), 161 (85), 91 (18); IR (film, cm^{-1}): 2928, 1578, 1462,1360,1244.
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