

First Total Synthesis of (\pm)-13-Hydroxy-8 (14)-abietene

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Abstract: The first total synthesis of (\pm)-13-hydroxy-8 (14)-abietene was accomplished in 20.1% yield *via* a strategy of AC \rightarrow ABC, in which the reduction of compound **5** with Li/NH₃ gave the key intermediate **6** and the title compound was then obtained by the reaction of compound **6** with Grignard reagent.

Keywords: Total synthesis, (\pm)-13-hydroxy-8 (14)-abietene, diterpene.

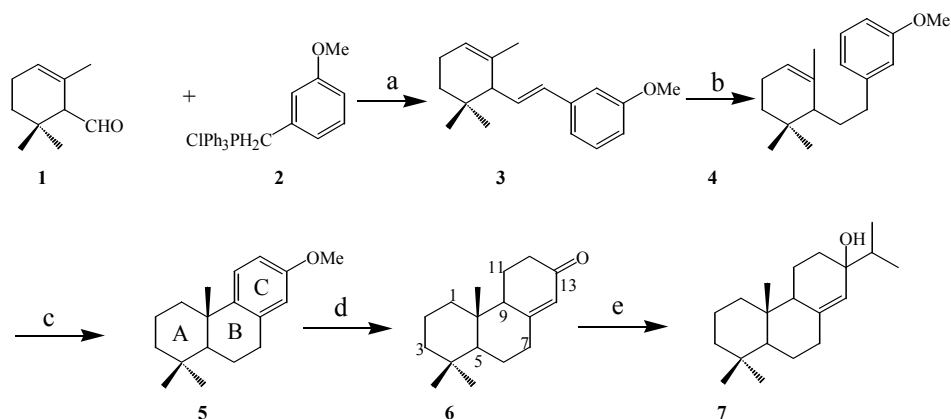
(\pm)-13-Hydroxy-8 (14)-abietene, a rare alicyclic diterpene possessing an isopropyl group and a hydroxy group at the C-13 position, was isolated from *Solidago missouriensis nutt*¹. Many diterpenes exhibit significant bioactivities, such as antibacterial. As a part of our synthetic studies on the naturally-occurring diterpenes, we are attempting the synthesis of the rare natural compound. To our knowledge no total synthetic work has been reported yet. In order to study the further relationship between the structure and bioactivities, we develop a novel route which was simple and (\pm)-13-hydroxy-8 (14)-abietene **7**² could be obtained in good yield. The synthesis of the title compound was achieved through the AC \rightarrow ABC ring construction strategy.

As shown in **Scheme 1**, we used α -cyclocitral **1** as A ring synthon and the compound **2** as the C ring synthon. The synthesis of the target compound **7** was based on our previous work³⁻⁶.

Condensation of compound **1** with **2** in dry THF in the presence of *n*-BuLi in an argon atmosphere afforded the desired compound **3** in 73% yield. Partial hydrogenation of **3** in anhydrous ethanol at room temperature over 10% Pd/C gave compound **4** in 98% yield. The reagent BF₃·Et₂O was used in the intramolecular cyclization step (B ring) at room temperature to afford the product **5** that was in *trans* form in 89% yield. The *trans*-configuration of A/B ring junction in **5** was characterized specifically by the upfield signal of the C_{4 α} methyl group at 1.0 ppm. According to the literature⁷, when the A/B ring is in *trans* junction, the C₄- α -methyl group is slightly deshielded by the aromatic ring C, the δ value of C₄- α -methyl group will appear at about 1.0 ppm. When A/B ring is a *cis* junction, the C_{4 α} methyl group remains within the sphere of magnetic influence of aromatic ring C, the chemical shift of C_{4 α} methyl group appears at about 0.40 ppm. Reduction of compound **5** with Li/NH₃ afforded α , β -unsaturated ketone **6** in

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Scheme 1



Reagents and conditions: (a) *n*-BuLi, THF, r. t., 73%; (b) 10% Pd/C, EtOH, r. t., 98%; (c) BF₃·Et₂O, CH₂Cl₂, r. t., 89%; (d) Li, NH₃, r. t., 93%; (e) Mg, *i*-PrBr, CeCl₂, THF, 0°C, 2 h, 34%.

good yield. Compound **6** reacted with *iso*-PrMgBr (THF, 0°C, 2 h) gave the target compound **7**.

In conclusion, in the present work, a simple convergent synthetic route has been developed for the discovered diterpenoid.

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References and Notes

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2. (±)-13-Hydroxy-8 (14)-abietene: yellow crystal, m.p.144-147°C. IR (KBr), v/cm⁻¹: 3418 (OH). ¹H NMR (CDCl₃, δ ppm) : 0.86 (s, H-19), 0.93 (s, H-18), 0.87 (d, 3H, *J*=7.0 Hz), 0.96 (d, 3H, *J*=7.0 Hz), 1.83 (sept, 1H, *J*=7.0 Hz), 1.42-2.39 (m, 1H, *J*=6.9 Hz), 4.79 (dd, *J*=10, 7.2 Hz, H-7), 7.07 (dd, 1H, *J*=8.0, 1.8 Hz), 7.15 (d, *J*=8.0 Hz, 15H), 2.35-2.47 (m, 1H), 6.90-7.06 (m, 1H). ¹³C NMR, δ: 16.2 (C-17), 17.3 (C-16), 18.5 (C-11), 19.2 (C-2), 20.7 (C-18), 22.9 (C-19), 23.1 (C-20), 28.5 (C-12), 30.1 (C-6), 33.2 (C-4), 37.8 (C-15), 38.0 (C-10), 38.6 (C-1), 41.2 (C-3), 45.6 (C-7), 47.4 (d, C-9), 49.2 (C-5), 71.3 (C-13), 135.6 (C-8), 141.8 (C-14); HRMS (positive-SIMS): 291.4846 (M+1) (Calcd.For: C₂₀H₃₄O: 290.4840). The above data were consistent with the literature¹.
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