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Chiral Synthesis of 13-Acetyl-12-hydroxy-podocarpane-8, 11,13-triene-7-one

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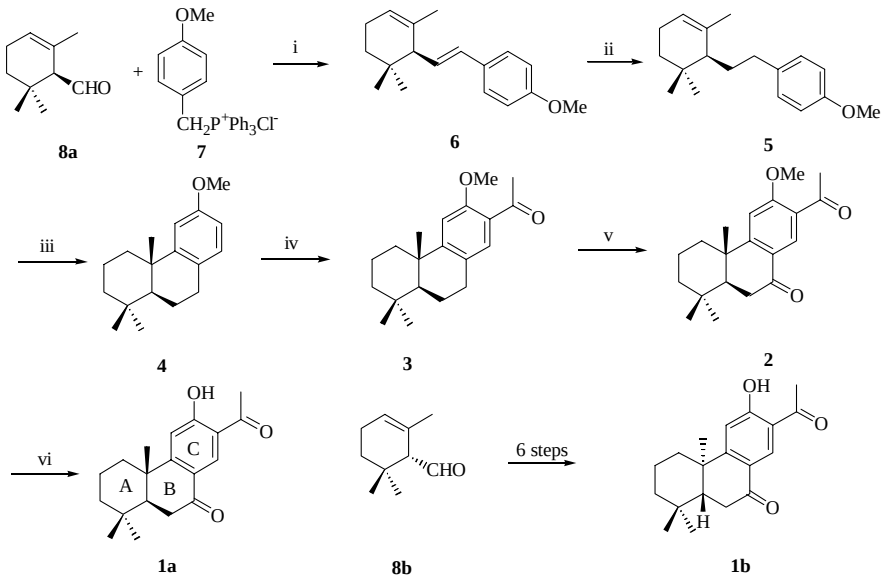
Abstract: An enantioselective synthetic route to (+)-13-acetyl-12-hydroxy-podocarpane-8,11,13-triene-7-one **1a** and (-)-13-acetyl-12-hydroxy-podocarpane-8,11,13-triene-7-one **1b** was developed from (S)-(-)-α-cyclocitral **8a** and (R)-(+)-α-cyclocitral **8b**.

Keywords: Synthesis, enantioselective, podocarpane, anisic, chiral.

Most diterpenoids exhibit significant bioactivities, such as: antibacterial[1,2], antidermatophytic[2,3], antioxidant[4], *etc*. 13-Acetyl-12-hydroxy-podocarpane-8,11,13-triene-7-one is a diterpene which has been synthesized by Sukumer *et al*. from the racemic *trans* isomer **4**[5].

Scheme 1



Reagents and conditions: i) n-BuLi, n-hexane , r.t., 4 h (70%); ii) 5% Pd/C, ethanol (95%); iii) $BF_3 \cdot Et_2O$, CH_2Cl_2, r.t., 12 h (93%); iv) acetyl chloride, anhydrous $AlCl_3$, -5°C, 4 h (90%); v) CrO_3/

HOAc/H_2O, r.t., 0.5 h (90%); vi) anhydrous $AlCl_3$, CH_2Cl_2, r.t. 5 h (95%).

Based on our synthetic studies on the natural occuring diterpenes[6-8], we report a high yield enantioselective synthetic route to (+)-13-Acetyl-12-hydroxy-podocarpane-8,11,13-triene-7-one **1a**[9] and (-)-13-Acetyl-12-hydroxy-podocarpane-8,11,13-triene-7-one **1b**[10].

As shown in **scheme 1**, our synthetic strategy is AC→ABC. Compound **7** was obtained through four steps from *p*-anisic acid as the C ring starting material. (S)-(-)-α-cyclocitral **8a** and (R)-(+)-α-cyclocitral **8b** were prepared according to Charles' method[11] as the A ring starting material. In the intracyclization step of compound **5**, we found $BF_3 \cdot Et_2O$ in CH_2Cl_2 is the better condition, after the mixture stood overnight at room temperature, all-*trans* isomer **4** (HPLC and ^{1}HNMR[12]) was obtained in 93% yield. Compared with Sukumer's method, we introduced acetyl group before oxidation at C-7. Compound **4** was acetylated by acetyl chloride and anhydrous $AlCl_3$ in CH_2Cl_2 in ice bath to afford compound **3** in 90% yield. Compound **3** was oxidized by CrO_3 in HOAc to afford compound **2**. At the last step, we found demethylation of **2** was achieved with $AlCl_3$ at room temperature in higher yield than BBr_3 which has been reported by Sukumer *et al*. Our spectrum data agree with Sukumer's. By the same route as compound **8a** to **1a** we obtained compound **1b** from **8b**.

Acknowledgments

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References and Notes

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9. **1a**: m.p. 234-235°C; $[\alpha]_D^{25}$ +36 (c 0.05, $CHCl_3$), (e.e.>90% HLPC); ^{1}H-NMR δ ppm 0.90 (s, 3H), 0.95 (s, 3H), 1.18 (s, 3H), 1.23-2.26 (m, 7H), 2.63 (s, 3H), 2.55-2.66 (m, 2H), 6,89 (s, 1H), 8.43 (s, 1H), 12.55 (s, 1H). ^{13}C-NMR δ ppm 18.56, 21.26, 22.76, 26.43, 32.58, 33.24, 35.69, 37.40, 38.53, 41.32, 48.45, 112.78, 117.64, 123.10, 131.35, 164.24, 166.19, 197.04, 204.41. MS (*m/z*) (EI): 300, 285, 217, 203, 189, 177, 91, 69, 43. IR (film) 1670, 1640, 1595 cm^{-1}.
10. **1b**: $[\alpha]_D^{25}$ -35 (c 0.05, $CHCl_3$), (e.e.>90%). Other spectra data were the same as those in ref. 8.
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