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ENANTIOSELECTIVE TOTAL SYNTHESES OF 13-ACETYL- 12-HYDROXY-PODOCARPANE- 8,11,13-TRIENE-7-ONE

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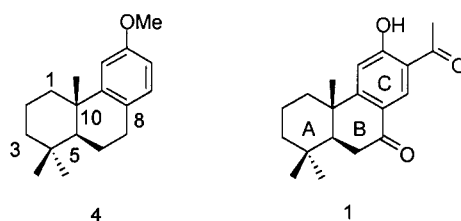
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ABSTRACT

A enantioselective total synthetic route to (+)-13-acetyl-12-hydroxy-podocarpene-8,11,13-triene-7-one **1a** and (–)-13-acetyl-12-hydroxy-podocarpene-8,11,13-triene-7-one **1b** from (*S*)-(–)- α -cyclocitral **8a** and (*R*)-(+)- α -cyclocitral **8b** was developed.

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Many diterpenoids exhibit significant bioactivities, such as: antibacterial,^{1,2} antidermatophytic,^{2,3} antioxidant,⁴ etc. Nimbosodione is a diterpenoid isolated by Siddiqui and his co-workers from the stem bark of *Azadirachta* and assigned the structure **1** based mostly on spectral evidence,⁵ but Sukumer et al. report the synthesis of the racemic dioxophenol **1** and the spectral data of which differ considerably from those reported for Nimbosodione.⁶ In order to study the relationship between the structure and bioactivities, and to further clarify the structure of Nimbosodione, it is desirable to develop a novel route to the *trans* isomer **4**. This key intermediate was obtained in low yield by King, but it is not stereospecific.⁷ In connection with our synthetic studies on a series of natural occurring diterpenes,^{8,9} we report herein a high yield stereoselective synthetic route to (+)-13-acetyl-12-hydroxy-podocarpene-8,11,13-triene-7-one **1a** and (–)-13-acetyl-12-hydroxy-podocarpene-8,11,13-triene-7-one **1b**.

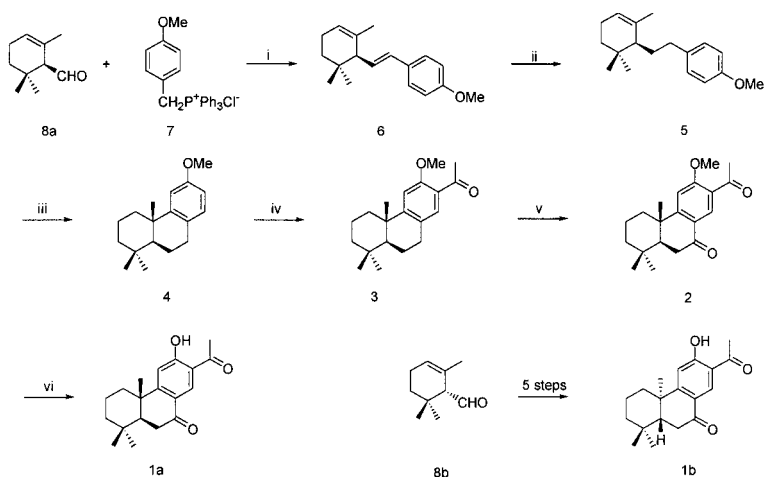


As shown in Scheme 1, our synthetic strategy to build the ring structure is AC \rightarrow ABC. We used *p*-anisic acid as the C ring starting material, (*S*)-(–)- α -cyclocitral **8a** and (*R*)-(+)- α -cyclocitral **8b** which were prepared from geranic acid according to reference¹⁰ as the A ring starting material.

Condensation of **8a** with **7** (prepared from Anisic acid via four steps in high yield) in the presence of *n*-BuLi/hexane afforded the desired stilbene derivative **6** in 70% yield. The ¹H-NMR of **6** reveals a *trans* double bond (the vicinal coupling constant of vinyl protons is 15.8 Hz). Selective hydrogenation of **6** over 5% Pd/C give the phenethyl derivative **5**. In the intracyclization step, in order to get all-*trans* figure, we found BF₃·Et₂O in CH₂Cl₂ at room temperature is better condition, which give sole *trans* (HPLC and ¹H-NMR⁷) isomer **4** in 93% yield. The compound **4** was acetylated by acetyl chloride and anhydrous AlCl₃ in CH₂Cl₂ in ice bath to give compound **3** in 90% yield. When the reaction was carried out at room temperature, demethylation took place to give **1a** from **2** in 95% yield. Oxidation of **3** by CrO₃/HOAc/H₂O give compound **2**. Although our spectrum data were not identical with Siddiqui's,⁵ same with Sukumer's.⁶



Thus the structure of Nimbosodione should not be the title compound 13-acetyl-12-hydroxy-podocarpene-8,11,13-triene-7-one **1**.



Reagents and conditions: i) *n*-BuLi, *n*-hexane, r.t., 5 h (70%); ii) 5% Pd/C, ethanol (95%); iii) BF₃·Et₂O, CH₂Cl₂, 12 h (93%); iv) acetyl chloride, anhydrous AlCl₃, -5°C, 2 h, (90%); v) CrO₃/HOAc/H₂O, r.t., 0.5 h (90%); vi) anhydrous AlCl₃, CH₂Cl₂, r.t., 8 h (95%).

Scheme 1.

EXPERIMENTAL SECTION

The ¹H-NMR and ¹³C-NMR data were recorded in CDCl₃ solution with Bruker Am-80 or Am-400 MHz spectrometers. The chemical shifts are reported in ppm relative to TMS or CDCl₃. Mass spectrum were reported on a ZAB-Hs mass spectrometer (EI). Microanalyses were performed on a MOD-1106 elemental analyser. Optical rotations were determined on a JASCO J-20C polarimeter with a 0.2 dm tube. Chiral analysis was performed on a Varian Dynamax SD-300 using Chiralcel column CDMPC (150 × 4.6 mmD) with hexane/isopropyl alcohol as eluent.

3-(4-Methoxystyryl)-2,4,4-trimethyl-1-cyclohexene **6**

A solution of *n*-butyllithium in hexane (1.6 N, 5 mL) was added to a suspension of **7** (4.8 g, 11.5 mmol) in dry hexane (30 mL), under an



atmosphere of Ar and stirred at room temperature for 1 h. Then a solution of **8a** (1 g, 7 mmol) in dry hexane (15 mL) was added over 10 min. The solution was stirred for 4 h to complete the reaction then, poured into diluted HCl, the mixture was extracted with ether, the combined organic layer was washed with brine, dried with Na₂SO₄. The crude product was purified by column chromatography to give the desired compound **6** (1.2 g, 70%). ($[\alpha]_D^{25}$ -302 (c 0.25, CHCl₃), e.e. 90% by HPLC), ¹H-NMR (80 MHz, CDCl₃) δ ppm 0.94 and 1.00 (s, each 3H), 1.63 (bs, 3H), 3.83 (s, 3H), 5.50 (brs, 1H), 6.00 (dd, *J*=9.4, 15.8 Hz, 1H), 6.40 (d, *J*=15 Hz, 1H), 6.88 (d, *J*=8.9 Hz, 2H), 7.34 (d, *J*=8.9 Hz, 2H). MS (EI): 256, 200, 185, 121 and 91. (Found: C, 84.56; H, 9.40. C₁₈H₂₄O requires C, 84.32; H, 9.44%).

3-(4-Methoxyphenylethyl)-2,4,4-trimethyl-1-cyclohexene **5**

A suspension of **6** (1.0 g) and 5% Pd/C (0.3 g) in anhydrous ethanol (20 mL) was stirred at room temperature in an atmosphere of hydrogen. The reaction was monitored by TLC, when the reaction completed, the mixture was filtered. The filtrate was evaporated *in vacuo* to yield the desired compound **5** (0.95 g, 95%) as colorless oil. ($[\alpha]_D^{25}$ -132 (c 0.08, CHCl₃), e.e. 92%). ¹H-NMR (80 MHz, CDCl₃) δ ppm 0.91 and 1.00 (s, each 3H), 1.70 (bs, 3H), 3.80 (s, 3H), 5.34 (brs, 1H), 6.84 (d, *J*=8.6 Hz, 2H), 7.13 (d, *J*=8.6 Hz, 2H). MS (EI): 258, 243, 121, (Found: C, 83.55; H, 10.10. C₁₈H₂₆O requires C, 83.67; H, 10.14%).

12-Methoxyl-podocarpene-8,11,13-triene **4**

To a solution of **5** (0.8 g, 3.1 mmol) in CH₂Cl₂ (30 mL) was added BF₃·Et₂O (1.8 mL) dropwise. The mixture was stood overnight. Then 50 mL of ether was added and the solution was neutralized with saturated NaHCO₃. The mixture was extracted with ether and the combined organic layer was washed successively with saturated NaHCO₃ and brine, then dried with Na₂SO₄. Purification by column chromatography gave the all *trans* compound **4** (0.75 g, 93%). ($[\alpha]_D^{25}$ -32 (c 0.10, CHCl₃), e.e. 90%), ¹H-NMR (400 MHz, CDCl₃) δ ppm 0.99 (s, 6H), 1.24 (s, 3H), 1.32–2.37 (m, 11H), 3.82 (s, 3H), 6.70 (dd, *J*=8.0, 2.0 Hz, 1H), 6.85 (d, *J*=2.0 Hz, 1H), 6.93 (d, *J*=8.0 Hz, 1H). MS (EI): 258, 243, 187, 161, 121. (Found: C, 83.57; H, 10.09. C₁₈H₂₆O requires C, 83.67; H, 10.14%).



13-Acetyl-12-methoxyl-podocarpene-8,11,13-triene **3**

At -10°C , to a solution of **4** (0.65 g, 2.5 mmol) in CH_2Cl_2 (30 mL), anhydrous AlCl_3 (400 mg) was added portionwise, then acetyl chloride (0.2 mL) was added dropwise to keep reaction temperature below -5°C . After stirring for 2 h at room temperature, the mixture was poured to ice-water, extracted with CH_2Cl_2 . The combined organic layer was successfully washed with saturated NaHCO_3 and brine, then dried with Na_2SO_4 . After column chromatography purification, the compound **3** was obtained as yellowish oil (0.65 g, 90%). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ ppm 0.91 (s, 3H), 0.95 (s, 3H), 1.21 (s, 3H), 1.32–2.37 (m, 11H), 2.58 (s, 3H), 3.87 (s, 3H), 6.83 (s, 1H), 7.44 (s, 1H). MS (EI): 300, 285, 256, 203, 163, 91. (Found: C, 79.73; H, 9.15. $\text{C}_{20}\text{H}_{28}\text{O}_2$ requires C, 79.96; H, 9.39%).

13-Acetyl-12-methoxyl-podocarpene-8,11,13-triene-7-one **2**

A solution of **3** (0.6 g, 2 mmol) in acetic acid (10 mL) was added CrO_3 (2.5 mmol) in acetic acid (10 mL and water 0.2 mL) at room temperature, the mixture was stirred for 0.5 h, then water was added to quench the reaction. After extraction with ether, the combined organic layer was washed with saturated NaHCO_3 and brine. Purification by column chromatography gave the compound **2** (0.58 g, 90%) as a white pellet crystals m.p. $190\text{--}192^{\circ}\text{C}$. ($[\alpha]_D^{25} + 54$ (c 0.05, CHCl_3), e.e. 90%, HPLC), $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ ppm 0.95 and 1.01 (s, each 3H), 1.27 (s, 3H), 1.27 (d, 3H), 1.29–2.57 (m, 7H), 2.58 (s, 3H), 2.60–2.74 (m, 2H), 3.98 (s, 3H), 6.89 (s, 1H), 8.38 (s, 1H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ ppm 18.76, 21.36, 23.12, 31.33, 32.51, 33.28, 36.87, 37.83, 38.78, 41.17, 49.10, 55.78, 106.02, 124.30, 126.79, 130.78, 162.00, 162.50, 197.37, 198.51. MS (EI): 314, 299, 217, 111, 85, 69, 43. (Found: C, 76.41; H, 8.29. $\text{C}_{20}\text{H}_{26}\text{O}_3$ requires C, 76.39; H, 8.33%).

(+)-13-Acetyl-12-hydroxy-podocarpene-8,11,13-triene-7-one **1a**

Under Ar, to a solution of **2** (315 mg, 1 mmol) in CH_2Cl_2 (15 mL), anhydrous AlCl_3 (400 mg) was added portionwise at -10°C , 10 min later, keep reaction at room temperature. After stirring overnight, the mixture was poured into ice-water, extracted with CH_2Cl_2 . The combined organic layer was successfully washed with saturated NaHCO_3 and brine, then dried with Na_2SO_4 . After column chromatography purification, the compound **1a** was obtained as white pellet (280 mg, 95%). m.p. $234\text{--}235^{\circ}\text{C}$. ($[\alpha]_D^{25} + 36$ (c 0.05, CHCl_3), e.e. 90%, HPLC) $^1\text{H-NMR}$



(400 MHz, CDCl_3) 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 (100 MHz, CDCl_3) 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 (EI): 300, 285, 217, 203, 189, 177, 91, 69, 43. (Found: C, 76.01; H, 8.02. $\text{C}_{19}\text{H}_{24}\text{O}_3$ requires C, 75.96; H, 8.05%).

(–)-13-Acetyl-12-hydroxy-podocarpene-8,11,13-triene-7-one 1b

Prepared by above method from compound **8b** ($[\alpha]_{\text{D}}^{25}$ -34 (c 0.05, CHCl_3), e.e. 90%).

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