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FACILE AND SIMPLE SYNTHESIS OF RING C AROMATIC DITERPENES: SYNTHESIS OF (+)-13-HYDROXYPODOCARPA-8,11,13-TRIENE AND (+)-7-DEOXYNIMBIDIOL

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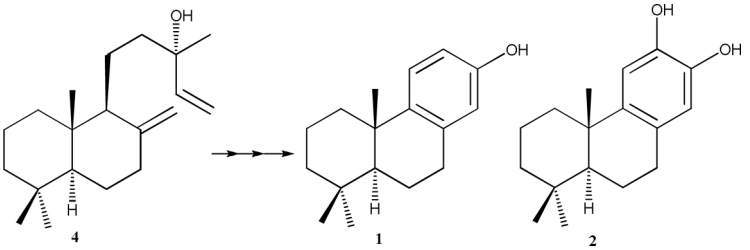
GRAPHICAL ABSTRACT



Abstract *A convenient synthesis of the natural* (+)*-13-hydroxypodocarpa-8,11,13-triene* ***1*** *and* (+)*-7-deoxynimbidiol* ***2*** *from* (+)*-manool* ***4*** *has been achieved in good overall yield.*

Keywords Abietane diterpenes; 7-deoxynimbidiol; nimbidiol; podocarpane diterpenes; synthesis

INTRODUCTION

Abietane and biosynthetically related polycyclic diterpenes constitute a major group of ring C aromatic diterpenes.[1] They have been reported to exhibit interesting biological properties such as antibiotic, antivirus, antioxidant, antimalarial, and cytotoxic activities.[2] Recently, some biologically active podocarpane phenols have been isolated. In 2000, Kuo et al. isolated from the bark of *Taiwania criptomeriodes* the podocarpane diterpene (+)-13-hydroxypodocarpa-8,11,13-triene **1**.[3] Recently,

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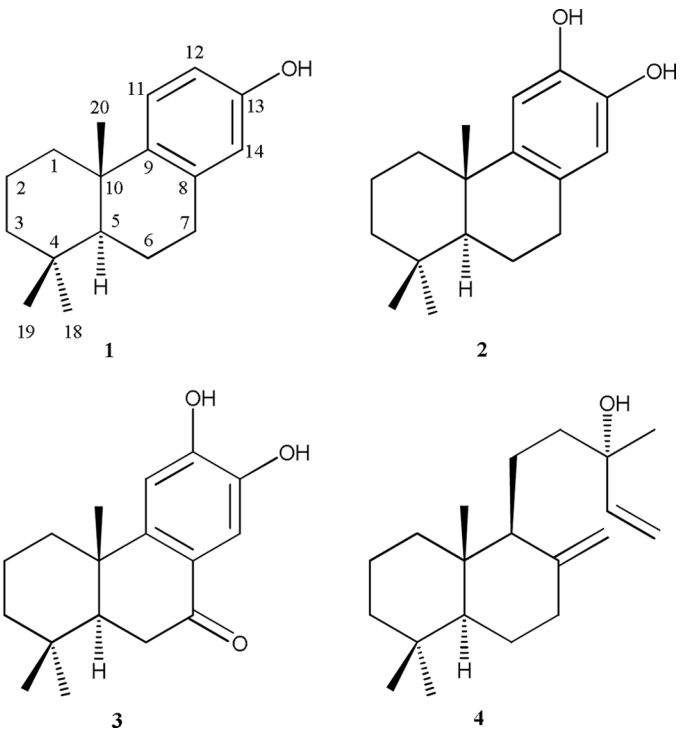
Xiong et al. isolated from the stalks of *Celastrus hypoleucus* the podocarpane diterpene (+)-7-deoxynimbidiol **2**, which has good antitumor activity[4] (Scheme 1).

To date, a number of synthetic investigations of these biologically active podocarpane diterpenes employing podocarpic acid, labdane diterpenes, or via polyene cyclization have been reported.[5] However, they generally require long reaction sequences, and furthermore, almost all of them produce the racemic form of the natural substance.

(+)-Manool **4** is a readily available natural diterpene with established absolute stereochemistry. (+)-Manool **4** has been used as a starting material for the efficient syntheses of drimane-type sesquiterpenes,[6] podocarpane-type terpenes,[7] and labdane-type diterpenes.[8] In these studies, two cleavage reactions (oxidative and photochemical) were used sequentially to transform (+)-manool **4** to the unstable exocyclic diene in 52% overall yield. In 2003, Zambrano et al. reported the synthesis of ring C aromatic diterpene derivative from (+)-manool **4** via unstable intermediates and its synthetic application to the formal synthesis of (+)-nimbidiol **3**.[9] Recently, Alvarez-Manzaneda et al. reported the synthesis of (+)-7-deoxynimbidiol **2** from (−)-sclareol in 10 steps.[10]

As a part of our research program toward the synthesis of bioactive diterpene compounds starting from natural diterpenes, we were interested in developing a new route to ring C aromatic diterpenes, useful as a medicinal compound in which antimicrobial properties and antioxidant activity are expected. This article presents



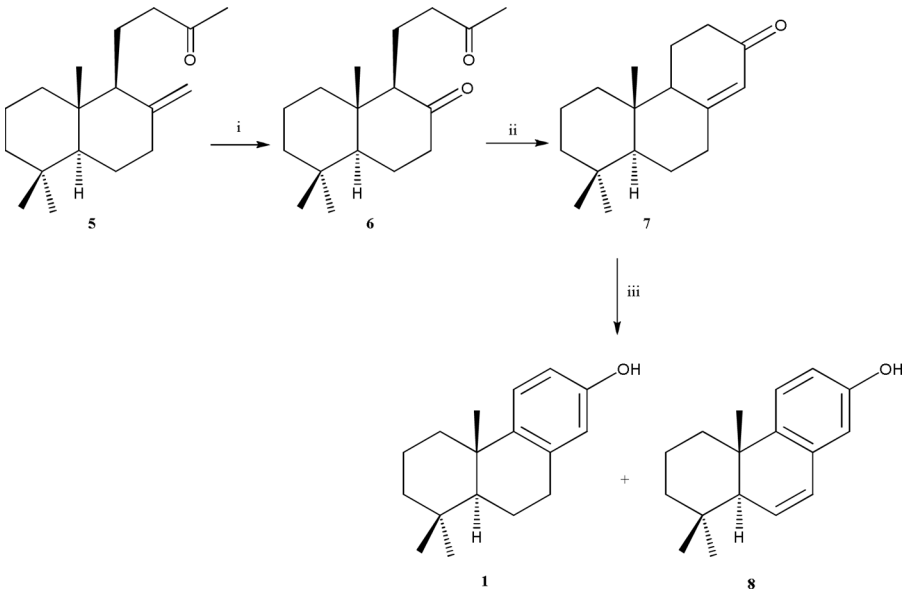
Scheme 1.

a further extension of our work to the synthesis of podocarpane diterpene (+)-13-hydroxypodocarpa-8,11,13-triene **1** and (+)-deoxynimbidiol **2** from (+)-manool **4**.

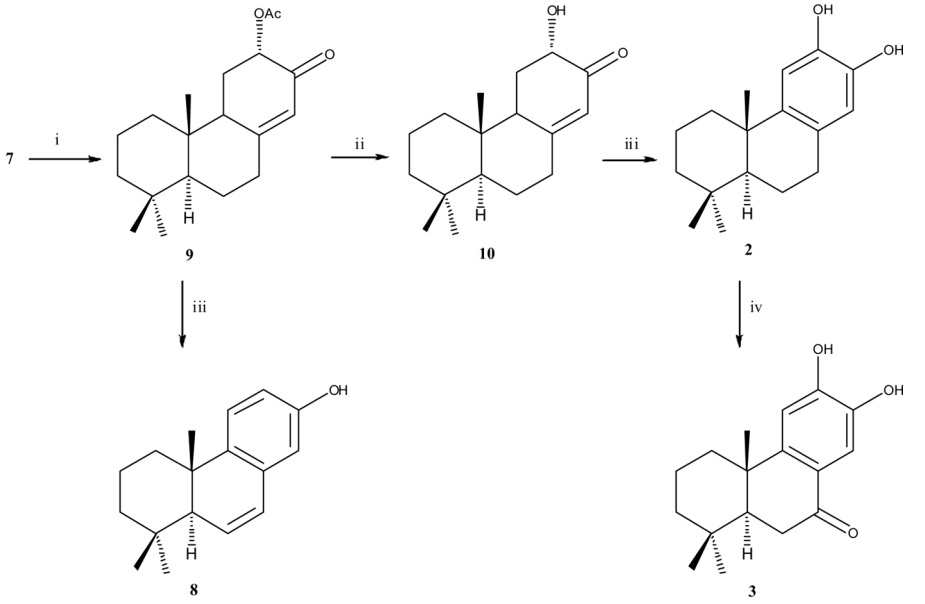
RESULTS AND DISCUSSION

Recently, Alvarez-Manzaneda Roldan et al. reported a new route to compound **1** in seven steps via β-enone **7** from (+)-sclareol.[11] The key step involves the intramolecular aldol condensation of a trinorlabdane 1,5-diketone, aromatization of the resulting β-enone, and benzylic oxidation. Previously, Nakano et al.[12] reported the synthesis of β-enone **7** from (+)-manool **4** in three steps. In an attempt to increase the yield of the β-enone **7**, (+)-manool **4** was oxidized with anhydrous $KMnO_4$ in the presence of phase-transfer catalyst $(CH_3)C_6H_5N^+Cl^-$ to obtain ketone **5** in 90% yield.[13] Ozonolysis of ketone **5** afforded diketone **6**. Intramolecular aldol condensation utilizing a diluted solution of H_2SO_4 afford the desired compound **7** in 80% yield.[14] To synthesize compound **1**, we first tried aromatization of β-enone **7** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and SeO_2. However, these methods failed to give compound **1**. Aromatization of ring C was finally achieved with a $CuBr_2$/LiBr system,[15] yielding the desired compound **1** in 83% yield along with only small amounts of compound **8** (Scheme 2). The spectroscopic data were identical with the natural phenol, except the reported optical rotation value was observed ($[\alpha]_D + 51$, *c* 1.0, $CHCl_3$, lit.[3] $[\alpha]_D + 16.7$, *c* 0.43, $CHCl_3$). Probably, the difference between the optical rotation values can be due to the fact that the compound **1**, isolated by Kuo et al.,[3] was not pure and thus exhibits different values.

Compound **2** was synthesized via the 12-hydroxy-enone **10**, which was obtained from β-enone **7**. Oxidation of compound **7** with manganese(III) acetate



Scheme 2. (i) O_3, CH_2Cl_2, −78 °C, 1 h; Zn, AcOH; (ii) H_2SO_4, MeOH, reflux; and (iii) $CuBr_2$, LiBr, CH_3CN, rt, 10 min.



Scheme 3. (i) $Mn(OAc)_3$, AcOH, benzene, reflux; (ii) K_2CO_3, MeOH, rt; (iii) $CuBr_2$, LiBr, rt, 30 min; and (iv) Ref. 5 [5g, 9, 10].

afforded acetate **9** in 80% yield.[16] To synthesize compound **2**, we first tried aromatization of acetate **9** with a $CuBr_2$/LiBr system,[15] but unfortunately this method gave the phenol **8**. Deprotection of the acetate group of compound **9** with K_2CO_3 and aromatization of ring C of 12-hydroxy-enone **10** with $CuBr_2$/LiBr system[15] in CH_3CN afforded the (+)-deoxynimbidiol **2** in 61% yield, whose physical and spectroscopic data were identical to those reported.[4] The three-step conversions of **2** to (+)-nimbidiol **3** has been previously reported.[5g,9,10]

In summary, this work provides a short synthesis of natural ring C aromatic diterpenes from (+)-manool **4** (Scheme 3). The key intermediate for such preparation is β-enone **7**, which was easily prepared from (+)-manool **4**. Utilizing this, the syntheses of (+)-13-hydroxypodocarpa-8,11,13-triene **1** and (+)-7-deoxynimbidiol **2** have been accomplished (54% and 32% overall yields from (+)-manool **4**). (+)-Nimbidiol **3** has also been prepared (14% overall yield from (+)-manool **4**).

EXPERIMENTAL

Melting points were measured with a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded with Bruker Avance-300 and Avance-500 spectrometers. Infrared (IR) spectra were recorded using a Nicolet Magna 560 Fourier transform (FT)–IR spectrometer. High-resolution mass spectra (HRMS) were obtained on a Jeol JMS-AX505WA mass spectrometer. Optical rotations were obtained for $CHCl_3$ solutions on a Perkin-Elmer 341 polarimeter, and their concentrations are expressed in g/100 mL. Manool resin was purchased from Westchem

Industries, Ltd., and purified to obtain (+)-manool, $[\alpha]_D^{24} + 28$ (*c* 1.5, $CHCl_3$). Tetrahydrofuran (THF) and benzene were freshly distilled from Na-benzophenone before use. CH_2Cl_2 was distilled from CaH_2 under argon. All other solvents and reagents were obtained from commercial suppliers and used without further purification. Merck silica gel (70–230 mesh ASTM) was used for column chromatography. Thin-layer chromatography (TLC) was performed on Analtech silica gel 60 G_{254}, and the spots were observed either by exposure to iodine or by ultraviolet (UV) light. All organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure below 60 °C.

14,15-Bisnorlabd-8(20)-ene-13-one (5)

$KMnO_4$ (0.51 g, 3.22 mmol) and $(CH_3)_3C_6H_5N^+Cl^-$ (0.56 g, 3.25 mmol) were added to a solution of manool **4** (1.04 g, 3.58 mmol) in $CHCl_3$ (15 mL) and stirred for 24 h at 10 °C. The reaction mixture was filtered through silica gel, and the filtrate was evaporated. The resulting crude product was chromatographed over silica gel, and elution with 4% ether in hexane afforded ketone **5** (0.85 g, 90%) as a colorless oil. The spectroscopic properties were similar to those reported in the literature.[1]

15,16,17-Trinorlabdane-8,13-dione (6)

A flow of ozone was applied to a solution of **5** (0.2 g, 0.76 mmol) in CH_2Cl_2 (5 mL) at 0 °C until the solution became blue in color. The reaction mixture was immediately degassed with N_2 for 15 min, followed by dropwise addition of Zn (200 mg) in AcOH (2 mL). The solution was allowed to warm to room temperature, and stirring was continued for 2 h. The reaction mixture was filtered to remove the Zn, after which 1.0 M $NaHCO_3$ was added over 15 min and extracted with $CHCl_3$. The resulting crude product was chromatographed over silica gel, and elution with 5% ether in hexane afforded diketone **6** (0.180 g, 90%) as a colorless oil. The spectroscopic properties were similar to those reported in the literature.[11,12]

Podocarp-8(14)-en-13-one (6)

H_2SO_4 (0.6 mL) was added dropwise to a solution of diketone **6** (76 mg, 0.28 mmol) in methanol (5 mL) at room temperature. The solution was refluxed for 2 h, diluted with water, and extracted with ether. The organic extract was dried and evaporated, and the product was chromatographed over silica gel. Evaporation of the hexane/ether (4%) elute afforded β-enone **7** (57 mg, 81%) as white crystals (hexane): mp 90–91 °C; IR (KBr) ν_{max} 1674, 1617; HRMS *m/z* 246.1822 (M^+, $C_{17}H_{26}O$ requires 246.1830); EIMS *m/z* 247 (45), 246 (14), 213 (6), 175 (5), 161 (7), 137 (60), 123 (60), 110 (100), 81 (62); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.76, 0.83, 0.88 (3H each, s, CH_3), 2.04 (1H, m, H-9), 2.25 (1H, m, Hα-12), 2.52 (1H, ddd, $J = 15.4$, 4.71, 1.7 Hz, Hβ-12), 5.82 (1H, dd, $J = 2.08$, 1.88 Hz, H-14); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 15.23, 18.68, 20.45, 21.89, 22.00, 33.32, 33.57, 35.58, 36.74, 38.90, 39.25, 41.71, 51.58, 53.85, 125.80, 165.64, and 199.76.

(+)-13-Hydroxypodocarpa-8,11,13-triene (1)

The β-enone **7** (50 mg, 0.20 mmol) in dry CH_3CN (2 mL) were added to $CuBr_2$ (94.71 mg, 0.40 mmol) and LiBr (17.6 mg, 0.20 mmol), and the reaction mixture was stirred for 10 min at room temperature. The reaction mixture was diluted with AcOEt, washed with brine, dried, and evaporated, and the product was chromatographed over silica gel. Elution with 3% ethyl acetate in hexane yielded only small amounts of compound **8**. Elution with 5% ethyl acetate in hexane afforded compound **1** (41 mg, 83%) as white crystals (hexane): mp 125–127 °C; ($[\alpha]_D + 51$, *c* 1.0, $CHCl_3$) lit.[3] ($[\alpha]_D + 16.7$, *c* 0.43, $CHCl_3$); IR (KBr) ν_{max} 3264, 3052, 2995, 1585, 1238; HRMS *m/z* 244.1822 (M^+, $C_{17}H_{24}O$ requires 244.1830); EIMS *m/z* 244 (14), 229 (M-CH_3, 100), 201 (7), 159 (34), 147 (54), 133 (52), 91 (11); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89, 0.92, 1.13 (3H each, s, CH_3), 4.51 (1H, bs, OH), 6.48 (1H, d, *J* = 2.6 Hz), 6.58 (1H, dd, *J* = 8.5 2.6 Hz), 7.09 (1H, d, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 18.95, 19.31, 21.57, 24.94, 30.44, 33.30, 33.38, 37.27, 39.09, 41.69, 50.55, 112.84, 114.83, 125.65, 136.89, 142.91, and 152.77.

Podocarp-8(14)-en-13-one-12α-yl Acetate (9)

Manganese(III) acetate (1.75 g, 6.52 mmol) in acetic acid (5 mL) was added to a solution of the β-enone **7** 0.541 g (2.2 mmol) in dry benzene (5 mL). The resulting suspension was heated to 80 °C for 48 h. The reaction mixture was filtered through silica gel and eluted with AcOEt, and the filtrate was washed with HCl 2 M solution, saturated 10% $NaHCO_3$ solution, and brine, which were evaporated under reduced pressure. The product was chromatographed over silica gel. Elution with 5% AcOEt in hexane afforded acetate **9** (0.520 g, 78%) as a white crystals (hexane): mp 117–119 °C; $[\alpha]_D - 56$ (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 2923, 1740, 1685, 1618; HRMS *m/z* 327.3712 ($[M + Na]^+$ $C_{18}H_{29}O_3Na$ requires 327.4260); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82, 0.88, 0.95 (3H each, s, CH_3), 2.08 (3H, s, $COCH_3$), 2.49 (1H, dd, *J* = 11.49 1.86 Hz), 5.35 (1H, *J* = 11.10 5.49 Hz), 5.85 (1H, s, H-14); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 15.85, 18.87, 20.89, 21.73, 23.41, 26.63, 33.44, 33.68, 36.58, 39.53, 41.33, 41.78, 50.40, 54.52, 71.29, 123.20, 166.14, 170.15, and 193.63.

13-Hydroxypodocarpa-6,8,11,13-tetraene (8)

$CuBr_2$ (71.36 mg, 0.32 mmol) and LiBr (14 mg, 0.16 mmol) were added to a solution of the acetate **9** (50 mg, 0.16 mmol) in dry CH_3CN (3 mL) and stirred for 30 min at room temperature. The reaction mixture was diluted with AcOEt washed with brine, dried, evaporated under reduced pressure, and chromatographed over silica gel. Elution with 4% ethyl acetate in hexane afforded compound **8** (23 mg, 58%) as an oil; IR (KBr) ν_{max} 3264, 3052, 2995, 1585, 1238; HRMS *m/z* 242.1670 (M^+, $C_{17}H_{22}O$ requires 242.3540); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96, 1.02, 1.03 (3H each, s, CH_3), 2.10 (1H, bs), 2.15 (1H, m), 4.94 (1H, bs, OH), 6.02 (1H, dd, *J* = 9.63 2.67 Hz), 6.45 (1H, dd, *J* = 9.63 2.67 Hz), 6.53 (1H, d, *J* = 2.7 Hz), 6.54 (1H, dd, *J* = 8.31 2.7 Hz), 7.02 (1H, d, *J* = 8.31 Hz); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 18.94, 20.47, 22.47, 32.56, 32.73, 36.12, 37.42, 40.97, 51.33, 113.01, 113.78, 123.08, 127.23, 131.31, 134.21, 141.10, and 153.27.

Podocarp-8(14)-en-12α-hydroxy-13-one (10)

Acetate **9** (121 mg, 0.40 mmol) was treated with K_2CO_3 (50 mg, 0.43 mmol) in MeOH (3 mL) and stirred at room temperature for 1 h. The solution was then acidified with hydrochloric acid, diluted with water, and extracted with AcOEt. The organic extracted was dried, evaporated under reduced pressure, and chromatographed over silica gel. Elution with 10% AcOEt in hexane afforded compound **10** (101 mg, 97%) as a colorless oil. The spectroscopic properties were similar to those reported in the literature.[12]

(+)-Deoxynimbidiol (2)

The 12-hydroxy-enone **10** (40 mg, 0.15 mmol) in dry CH_3CN (2 mL) were added to $CuBr_2$ (66 mg, 0.29 mmol) and LiBr (13 mg, 0.15 mmol), and the reaction mixture was stirred for 10 min at room temperature. The reaction mixture was diluted with water and extracted with AcOEt. The organic extract was washed with brine, evaporated, and chromatographed over silica gel. Elution with ethyl acetate in hexane (1:1) afforded compound **2** (24 mg, 61%) as crystal (hexane): mp 88–90 °C; $[\alpha]_D + 38$ (*c* 1.0, MeOH), lit.[4] $[\alpha]_D + 49.44$ (*c* 0.1, MeOH); IR (KBr) ν_{max} 3360, 1609, 1520; HRMS *m/z* 283.1669 ($[M + Na]^+$ $C_{17}H_{24}O_2Na$ requires 283.1670); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88, 0.91, 1.12 (3H each, s, CH_3), 1.45 (1H, bd, $J = 13.8$ Hz), 2.12 (1H, bd, $J = 12$ Hz), 2.74 (1H, m), 2.80 (1H, m), 4.99 (2H, bs, OH), 6.50 (1H, s), 6.74 (1H, s); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 19.32, 19.50, 21.81, 25.10, 30.01, 33.52, 33.60, 37.64, 39.35, 41.88, 50.82, 111.72, 115.43, 128.33, 141.28, 141.58, and 143.59.

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