Facile access to optically active ring C aromatic diterpenes from (+)-manool. Synthesis of (+)-13-hydroxypodocarpa-8,11,13-triene, (+)-7-deoxynimbidiol and (+)-nimbidiol

José E. Villamizar[a]*, Crisbel Montiel[a], Carlos Gamez[a], Antonio Alcalá[a], Yurimar Herrera[b], Franklin Salazar[a], Eleonora Tropper[a] and Nieves Canudas[b]

[a]*Centro de Química, Instituto Venezolano de Investigaciones Científicas (I.V.I.C.), Apartado 21827, Caracas 1020-A, Venezuela*

[b]*Departamento de Química, Universidad Simón Bolívar, Caracas, Venezuela*

A practical method for the synthesis of naturally occurring ring C aromatic diterpenes from (+)-manool *via* key intermediate β-enone is described. The natural (+)-13-hydroxypodocarpa-8,11,13-triene, the antitumour (+)-7-deoxynimbidiol, and (+)-nimbidiol were prepared in good overall yields.

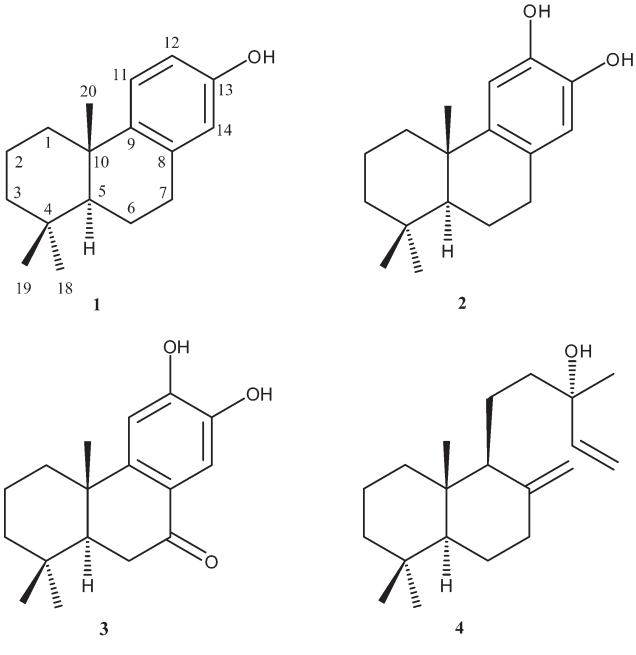
Keywords: podocarpane diterpenes, abietane diterpenes, nimbidiol, 7-deoxynimbidiol

Biologically active natural products can be regarded as chemical entities that were evolutionarily selected and validated for binding to particular protein domains. Therefore, they are already biologically validated, and the underlying structural architecture of such natural products may provide powerful guiding principles for drug discovery.[1] Abietane and the biosynthetically related polycyclic diterpenes constitute a major group of ring C aromatic diterpenes.[2] They have been reported to exhibit interesting biological properties such as antibiotic, anti-viral, anti-oxidant, anti-malarial and cytotoxic activity.[3–7] Some biologically active podocarpane phenols have recently been isolated. In 2000, Kuo *et al*. isolated the podocarpane diterpene (+)-13-hydroxypodocarpa-8,11,13-triene **1** from the bark of *Taiwania criptomeriodes*.[8] Recently, Xiong *et al.* isolated the podocarpane diterpene (+)-7-deoxynimbidiol **2** from the stalks of *Celastrus hypoleucus*, which showed good antitumour activity.[9] (+)-Nimbidiol **3** is a modified diterpenoid, isolated from the root-bark of *Azadirachta indica* (Indian 'neem').[10]

To date, a number of synthetic investigations of these biologically active podocarpane diterpenes have been reported by employing podocarpic acid, labdane diterpenes or via polyene cyclisation.[11–17] However, they generally require long reactions 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,[18,19] podocarpane-type terpenes[20,21] and labdane type diterpenes.[22–24] 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 a ring C aromatic diterpene derivative from (+)-manool **4** via unstable intermediates and its synthetic application to the formal synthesis of (+)-nimbidiol **3**.[25] Recently, Alvarez-Manzaneda *et al*. reported the synthesis of (+)-7-deoxynimbidiol **2** from (-)-sclareol in 10 steps.[26]

As a part of our research programme towards the synthesis of bioactive diterpene compounds starting from natural diterpenes, we are interested in developed a new route to ring C aromatic diterpenes, which are useful as medicinal compounds with potential antimicrobial and antioxidant activity. This paper presents an extension of our work to the synthesis of podocarpane diterpene (+)-13-hydroxypodocarpa-8,11, 13-triene **1**, (+)-deoxynimbidiol **2** and (+)-nimbidiol **3** from (+)-manool **4**.

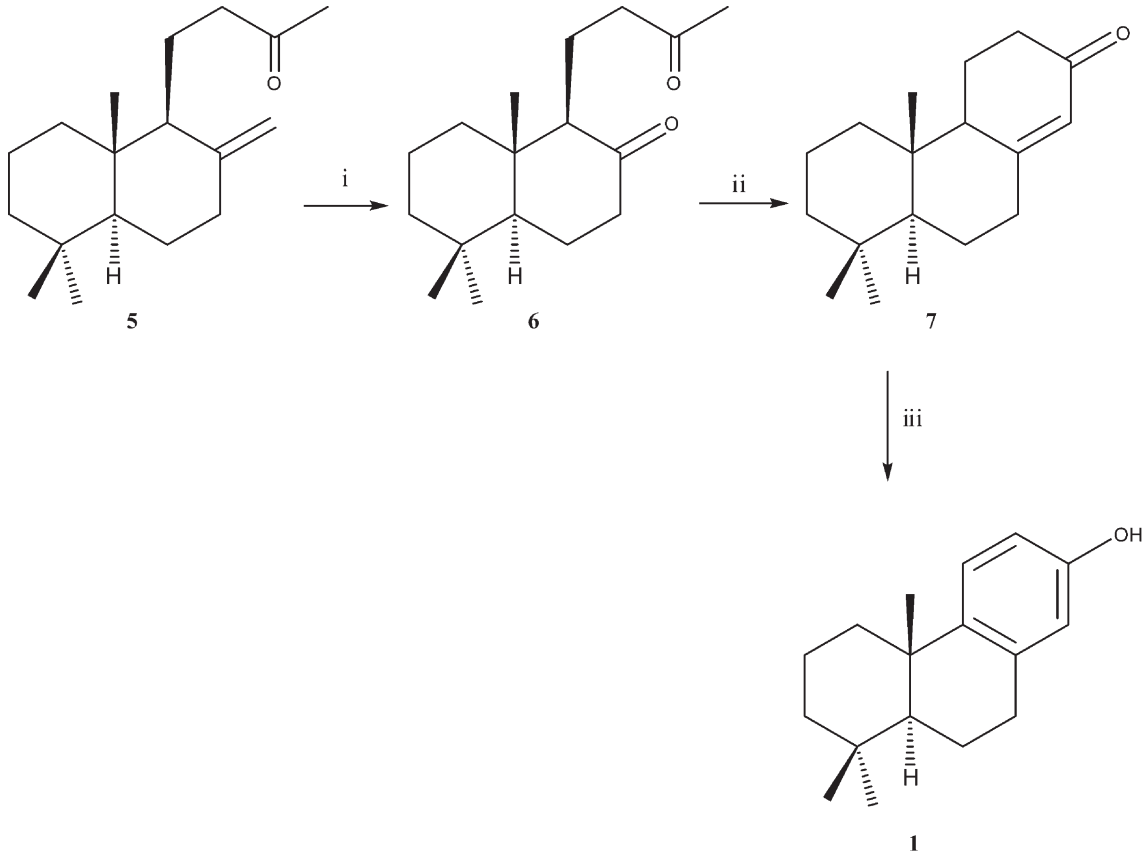


Scheme 1

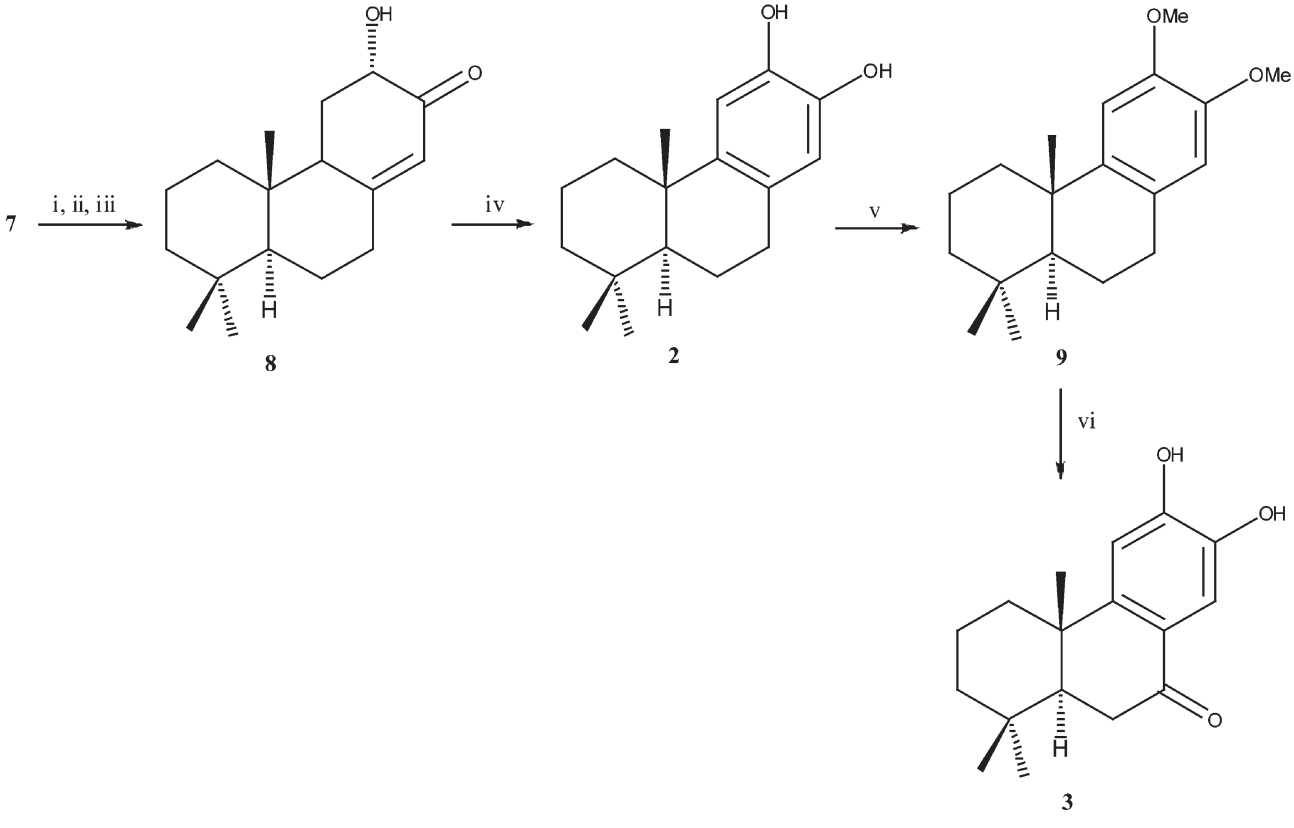
Results and discussion

Recently, a new route to compound **1** in seven steps via β-enone **7** from (+)-sclareol has been reported.[27] The key step involves the intramolecular aldol condensation of a trinorlabdane 1,5-diketone, aromatisation of the resulting β-enone, and benzylic oxidation. Previously Nakano *et al*.[28] 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 transfers catalyst $(CH_3)C_6H_5N^+Cl^-$ to obtain ketone **5** in 90% yield.[29] Ozonolysis of ketone **5** afforded diketone **6**.[27,28] Intramolecular aldol condensation utilising a dilute solution of H_2SO_4 afford the desired compound **7** in 80% yield.[30,31] To synthesise compound **1**, we first tried aromatisation of β-enone **7** with DDQ and SeO_2. However, these methods failed to give compound **1**. Aromatisation of ring C was finally achieved with LDA/PhSeCl[32] followed by oxidation of the selenide which was formedwith 30% hydrogen peroxide to obtain a selenoxide. The β-proton (H-11) was eliminated to give a cyclohexadienone system which subsequently isomerised to the corresponding phenol **1** in good yield. This had spectroscopic data identical with the natural phenol, except that the reported optical rotation value was observed ($[\alpha]_D$ +51, *c* 1.0,

* Correspondent: E-mail: jvillami@ivic.gob.ve



Scheme 2 (i) O_3, CH_2Cl_2, –78 °C, 1h; Zn, AcOH (ii) H_2SO_4, MeOH, reflux. (iii) LDA, THF, –78 °C, 15 min, PhSeCl, THF; H_2O_2, THF, –15 °C, 40 min.



Scheme 3 (i) LDA, THF, –78 °C, 1 h; TMSCl, rt, 1h (ii) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, –15 °C, 2h;(iii) Et_3NF, CH_2Cl_2, rt, overnight; (iv) $CuBr_2$, LiBr, MeCN, rt, 10 min; (v) ref. 11; (vi) ref. 17.

$CHCl_3$) lit.[8] $[\alpha]_D$ +16.7, *c* 0.43, $CHCl_3$). It is probably that the difference between the optical rotation values is due to the fact that the compound **1**, isolated by Kuo *et al.*[8] was not pure and thus exhibited a different value.

Compound **2** was synthesised *via* the 12-hydroxy-enone **8**, which was obtained from β-enone **7**.[28] Aromatisation of ring C was achieved with $CuBr_2$/LiBr system in CH_3CN[33] to give the (+)-deoxynimbidiol **2** in 61% yield whose physical and spectroscopic data were identical to those reported.[9] Dimethylation of **2** afforded the dimethyl derivative **9**, whose transformation into (+)-nimbidiol **3** has been reported previously.[17]

This work provides a short synthesis of natural ring C aromatic diterpenes from (+)-manool **4**. The key intermediate for such preparation is β-enone **7**, which was easily prepared from (+)-manool **4**. Utilising this, the synthesis of (+)-13-hydroxypodocarpa-8,11,13-triene **1**, (+)-7-deoxynimbidiol **2**, and (+)-nimbidiol **3**, starting from (+)-manool **4**, have been accomplished.

Experimental

Melting points were measured with a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded with a Bruker Avance-300 and Avance-500 spectrometers. IR spectra were recorded using a Nicolet Magna 560 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, $[\alpha]^{24}_D$ +28 (*c* 1.5, $CHCl_3$). THF was 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. TLC was performed on Analtech silica gel 60 G_{254} and the spots were observed either by exposure to iodine or by UV light. All organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure below 60 °C.

Oxidative cleavage of manool **4** *with* $KMnO_4/(CH_3)_3C_6H_5N^+Cl^-$: A solution of manool **4** (1.04 g, 3.58 mmol) in $CHCl_3$ (15 mL) was treated with $KMnO_4$ (0.51 g, 3.22 mmol) and $(CH_3)_3C_6H_5N^+Cl^-$ (0.56 g, 3.25 mmol) 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. Elution with 4 % ether in hexane afforded ketone **5** (0.85 g, 90 %) as a colourless oil. The spectroscopic properties were similar to those reported in the literature.[2]

Ozonoyisis of ketone **5***:* A solution of **5** (0.2 g, 0.76 mmol) in CH_2Cl_2 (5 mL) at 0 °C was treated with a stream of ozone until the solution became blue in colour. The reaction mixture was immediately degassed with N_2 for 15 min followed by the 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. The product was extracted with $CHCl_3$.The resulting crude product was chromatographed over silica gel. Elution with 5% ether in hexane afforded diketone **6** (0.180 g, 90 %) as colourless oil. The spectroscopic properties were similar to those reported in the literature.[27,28]

Intramolecular aldol condensation of diketone **6**: To a solution of diketone **6** (76 mg, 0.28 mmol) in methanol (5 mL) was added dropwise H_2SO_4 (0.6 mL) at room temperature. This mixture was refluxed for 2 h. then water was added and extracted with ether. The solution was refluxed for 2 h., diluted with water and extracted with ether. The organic extract was dried, 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): m.p. 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); ^{1}H 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.

Aromatisation of β*–enone* **7** *with PhSeCl/LDA:* The β-enone **7** (380 mg, 1.54 mmol) in dry THF (3 mL) was added a stirred solution of LDA [prepared *in situ* by addition of *n*-BuLi (1.23 mL of 1.4M solution in hexane, 1.72 mmol) to di-isopropylamine (215 mg, 2.12 mmol) in dry THF (3 mL) at –78 °C] under nitrogen at –78 °C. After keeping the mixture for 10 min at –78 °C, phenylselenyl chloride (396 mg, 2.06 mmol) in THF (3 mL) was added rapidly. The resulting solution was washed with an excess of 0.1 N HCl and extracted with ether. The combined organic layers were washed with saturated sodium chloride solution, dried and the solvent was evaporated under pressure. The residue was oxidised with 30% hydrogen peroxide (2 mmol) in THF (3 mL) at –15 °C for 40 min. The reaction was allowed to warm up to room temperature, acidified with 0.1 N HCL and extracted with ether. The solvent was evaporated under reduced pressure. The product was chromatographed over silica gel. Elution with 4% ether in hexane afforded the aromatic product **1** (290 mg, 77 %) as white crystals (hexane): m.p. 128–129 °C, lit.[8] 125–127 °C; $[\alpha]_D$ +51 (*c* 1.0, $CHCl_3$), lit.[8] $[\alpha]_D$ +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.

Aromatisation of 12-hydroxy-enone **8** *with* $CuBr_2$*/LiBr:* The 12-hydroxy-enone **8** (40 mg, 0.15 mmol) in dry CH_3CN (2 mL) was treated with $CuBr_2$ (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): m.p. 88–90 °C, lit.[9] 90–92 °C; $[\alpha]_D$ +38 (*c* 1.0, MeOH), lit.[9] $[\alpha]_D$ +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); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88, 0.91, 1.12 (3H each, s, CH_3), 1.33 (1H, ddd, *J* = 13.6, 13.6, 4 Hz), 1.45 (1H, bd, *J* = 13.6 Hz), 2.12 (1H, bd, *J* = 12.8 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.

This research was supported by grant from FONACIT (Misión Ciencia 2007000960).

Received 6 May 2010; accepted 7 June 2010
Paper 1000107 doi: 10.3184/030823410X12792754099464
Published online: 30 August 2010

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