Total Synthesis of (+)-Podocarpic and (+)-Lambertic Acids

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A concise synthesis, from the chiral nitroalkene **1a**, of (+)-podocarpic acid is described. This was transformed into (+)-lambertic acid *via* a chromium complex.

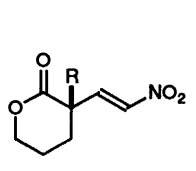
(+)-Podocarpic acid **2** is a typical tricyclic diterpenoid first isolated from *Podocarpus cupressina var. imbricata.*[1] Because of its abundance and typical skeleton, (+)-podocarpic acid **2** or methyl (+)-*O*-methylpodocarpate **3** has been widely used as a chiral starting material for the synthesis of diterpenoids such as callitricic acid **5**,[2] nagilactone F **6**,[3] maytenoquinone **7**,[4] taxodione **8**,[5] lambertianic acid **9**,[6] methyl (12*S*)- and (12*R*)-hydroxylabd-8(17)-en-19-oates **10a** and **10b**,[7] hinokino methyl ether **11**[8] and trachiloban-19-oic acid **12**.[9] Thus the total synthesis of (+)-podocarpic acid **2** constitutes the total syntheses of those diterpenoids in a formal sense. Although a number of papers have been published on the synthesis of (±)-podocarpic acid,[10] the total chiral synthesis of (+)-podocarpic acid **2** has been reported only once,[11] and that by a multi-step route giving a low overall yield.

Our recently developed method for the construction of chiral quaternary carbon centres through an addition–elimination process,[12] gives optically active nitroalkenes **1a** and **1b** which are versatile chiral building blocks for the syntheses of the Calabar bean alkaloids[13] and indole alkaloids of *Aspidosperma*- and *Hunteria*-type,[14] respectively. Here we report a general synthesis of (+)-podocarpic acid **2** and (+)-lambertic acid **4** from the nitroolefin **1a**,[15] a starting material particularly suitable for the synthesis of these molecules, since it has all of the carbon atoms of ring A as well as the correct absolute stereochemistry at C-4 for compounds **2** and **4**. Furthermore, the C(2)–C(6) unit necessary for the construction of rings B and C can be introduced to the β-position of the nitroalkene by a Michael addition.

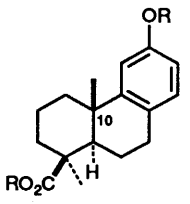
The synthetic route to compound **3** is shown in Scheme 1. Addition of the Grignard reagent **13** to the nitroalkene **1a** (87% ee) occurred smoothly to afford **14a** and the less polar isomer **14b** (3:2) whose stereochemistry will be discussed later. The lactone ring in the major isomer **14a** was opened with sodium methoxide–methanol to give the hydroxy ester **15a** which was then converted into the iodide **16a** by mesylation followed by substitution with sodium iodide (87% overall yield from **14a**). Treatment of the iodide **16a** with sodium hydride in dimethylformamide (DMF) gave the desired product **17a** (56%), the stereochemistry of whose nitro group was determined from its ^{1}H NMR spectrum [δ_H 5.13 (dt, *J*, 5, J_2 10, 1–H_{ax})]. Results of the latter suggest a *trans*-relationship between the nitro group and the β-arylethyl substituent, since the cyclohexane ring of **17a** should adopt a conformation in which the bulkiest β-arylethyl group is equatorial. Although the Nef reaction of **17a** by McMurry's method[16] did not work well, a slight modification involving the preformation of the nitronate anion gave **18a**†[17] quantitatively. The less polar isomer **14b** was converted into a mixture of **18a** and **b** (2:1, 42% overall yield) through the same sequence of reactions as for **14a**. Compounds **18a** and **b** were shown to establish an equilibrium in the ratio of 1:1 with toluene-*p*-sulfonic acid in refluxing methanol.

Addition of methylmagnesium iodide to **18a** gave the lactone **21**‡ in 59% yield, while **18b** gave a hydroxy ester **22**. These facts may be explained as follows. In both conformations of **18a** and **18b**, the bulky β-arylethyl group should take the equatorial conformation. For **18a**, the Grignard reagent attacked from the less hindered α-face of the carbonyl group to form intermediate

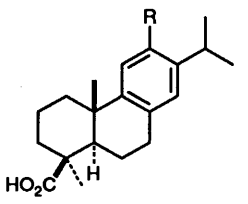
† Though racemic **18a** and **b** are known as a mixture, they are not characterized fully.
‡ This compound was reported in ref. 10(*f*). It was not characterized fully because it was contaminated with 10% of its C-2 epimer.



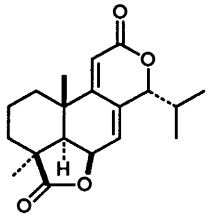
1a R = Me
b R = Et



2 R = H
3 R = Me



4 R = OH
5 R = H



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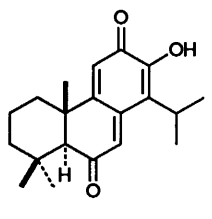

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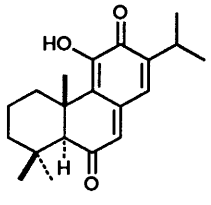

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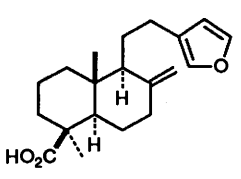

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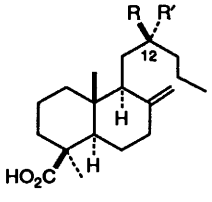
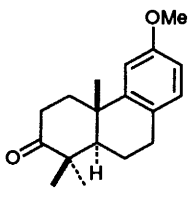


10a R = OH, R' = H
b R = H, R' = OH



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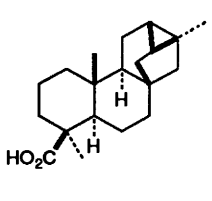

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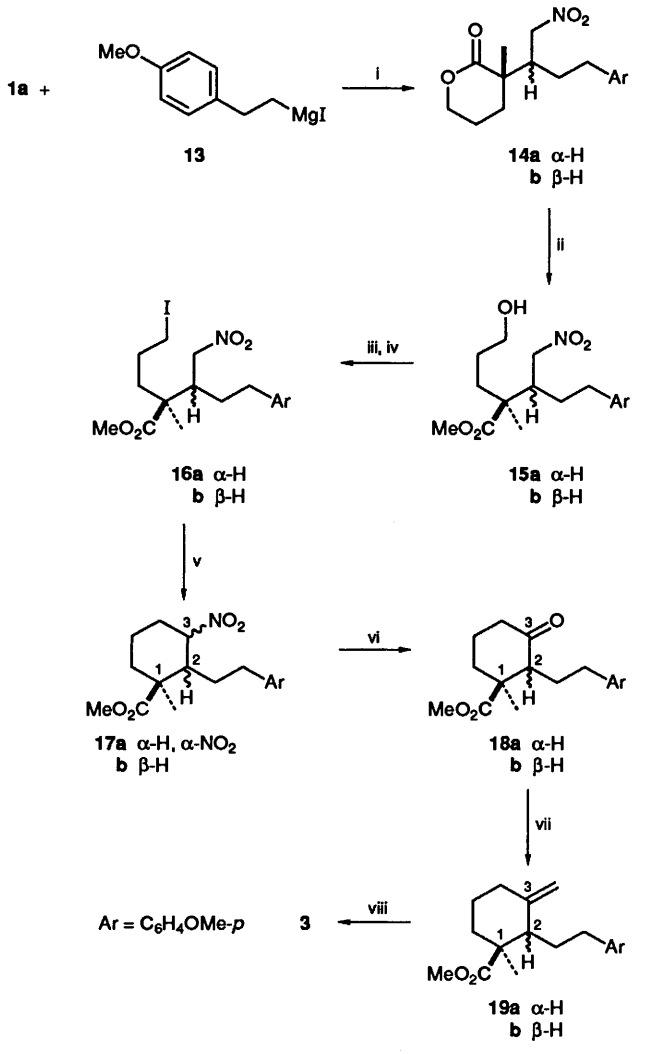


Scheme 1 Synthesis of (+)-podocarpic acid. *Reagents and conditions:* i, −78 °C; ii, NaOMe–MeOH; iii, MsCl; iv, NaI; v, NaH; vi, NaOMe–MeOH, then $TiCl_3$–NH_4OAc; vii, CH_2Br_2–Zn–$TiCl_4$; viii, MsOH–P_2O_5

20a, which could cyclise smoothly to give the lactone **21**. On the other hand, Grignard reagent attack from the β-face of the carbonyl group in **18b** would afford an intermediate **20b**. Lactonisation could not take place with this intermediate, but resulted in the hydroxy ester **22**. These results confirmed the (1*S*,2*S*)-configuration of **18a** and (1*S*,2*R*)-configuration of **18b** (Scheme 2). The Wittig reaction of **18a** gave a pair of isomers **19a** and **19b** resulting from epimerisation under the strongly basic conditions. Methylenation with the Nozaki's reagent[18] afforded **19a** in good yield.

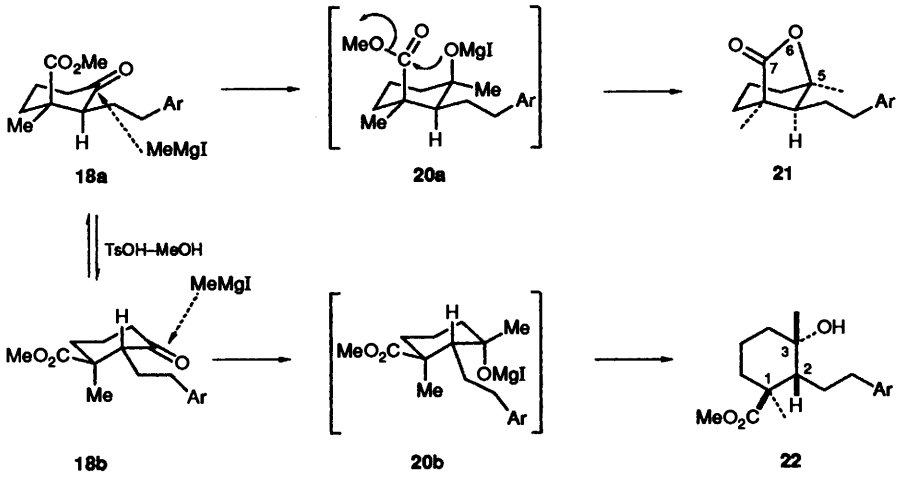
The acid catalysed Friedel–Crafts cyclization is known to be an important method for the synthesis of tricyclic diterpenoids. The stereochemistry of the A/B-ring junction can be controlled by the proper choice of the acid[19] or by the substitution pattern of an aromatic ring in open chain substrates.[20] The *cis*- or *trans*-product has been obtained with Lewis or protic acid catalysts respectively.[21] Treatment of **19a** with modified polyphosphoric acid[22] provided methyl (+)-*O*-methylpodocarpate **3** selectively. The desired A/B ring junction with *S*-configuration at C-10 could be explained by the neighboring group participation of the methoxycarbonyl group (see Scheme 3). Since the bulkiest β-arylethyl group should take an equatorial conformation in the intermediate carbenium ion, the methoxycarbonyl group is automatically disposed to interact axially with the cationic centre to form a stable intermediate **23**. The anisole ring attacked from the opposite side to the methoxycarbonyl group to form the spiro intermediate **24** with the A/B ring in a *trans*-orientation. Dienone–phenol rearrangement *via* **25** yields **3**. A combination reagent system of aluminium bromide and diethyl sulfide[23] cleaved both the methyl ether and ester in **3** to give (+)-podocarpic acid **2** (98%).

(+)-Lambertic acid **4** was isolated from *Podocarpus lambertius* in 1976.[24] The synthetic problem was the introduction of the isopropyl group at C-13 for the formation of (+)-lambertic acid **4** from methyl (+)-*O*-methylpodocarpate **3**. Instead of typical Friedel–Crafts alkylation[25] we used the chromium complex **26**[26] as a starting material (Scheme 4). The chromium complex **26** was treated with BuLi to form a lithio anion *ortho* to the methoxy group,[27] which reacted with acetone to furnish **27**[25] (55%) after decomplexation in refluxing pyridine. Reductive removal of the hydroxy group in **27** was accomplished by ionic hydrogenation with triethylsilyl hydride in trifluoroacetic acid[28] to give the known compound **28**[25,29] which was converted into (+)-lambertic acid **4** (identified by optical rotation and spectroscopic data) (82%) by demethylation with aluminium chloride and ethanethiol.[23]

Experimental

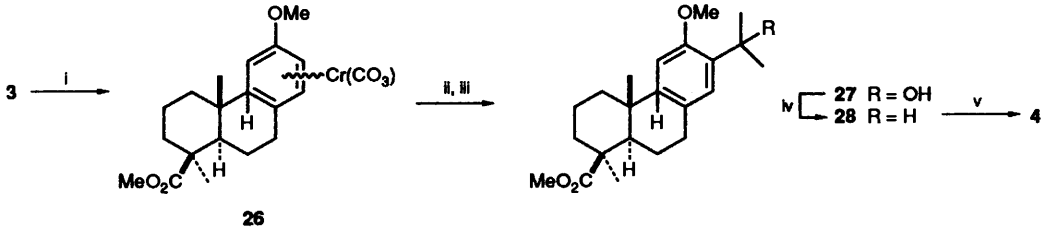
General.—M.p.s were measured on a Yanagimoto apparatus and are uncorrected. IR spectra were recorded on a JASCO IR-810 spectrophotometer. ^1H NMR spectra were measured in the indicated solvents with a JEOL JMN-FX 100 (100 MHz), JEOL JMN-GX 400 (400 MHz) or Varian GEMINI 200 (200 MHz) spectrometer, signals are given in ppm using $SiMe_4$ as internal standard. *J*-Values in Hz. MS were recorded on a JEOL JMS-DX 300 mass spectrometer. Combustion analyses were performed with a Yanaco CHN corder MT-3. Optical rotations were recorded on a JASCO DIP-181 polarimeter in the indicated solvents. All reactions were monitored by TLC carried out on 0.25 mm E. Merck silica gel plates (60F-254) with UV light or 10% ethanolic phosphomolybdic acid–heat as developing agent. Preparative TLC was performed on 0.5 mm × 20 cm × 20 cm E. Merck silica gel plates (60F-254). Short column chromatography was carried out on E. Merck silica gel (60H, Art 7736). Tetrahydrofuran (THF), Et_2O and Bu_2O were distilled from sodium diphenyl ketyl under N_2. Et_3N, pyidine, DMF and CH_2Cl_2 were distilled from CaH_2. Me_2CO was distilled from P_2O_5. MeOH and Bu^{t}OH were distilled after addition of Na. Work-up means extraction with CH_2Cl_2, washing the organic layer with brine, drying (Na_2SO_4) and evaporation under reduced pressure. (−)-Nitroalkene **1a** was prepared according to the literature procedure,[12] and its enantiomeric excess (ee) was determined to be 87% by ^1H NMR (400 MHz) with Eu(hfc)$_3$.

(3S)-3-[(1S *and* 1R)-3-(*p-Methoxyphenyl*)-1-(*nitromethyl*)-*propyl*]-3-*methyltetrahydropyran*-2-*one* **14a** *and* **b**.—To a solution of compound **13** (0.58 mol dm^{-3} in THF; 10 cm^3, 5.80 mmol) in dry THF (20 cm^3), was added dropwise a solution of (3*S*)-3-methyl-3-(2-nitrovinyl)tetrahydropyran-2-one **1a** (449 mg, 2.43 mmol) in dry THF (20 cm^3) under N_2 at −78 °C. The reaction mixture was stirred for 2 h and then poured into aqueous NH_4Cl. Work-up gave a mixture of **14a** and **14b** (596 mg, 77%), which was subjected to short column chromatography (Et_2O–hexane, 1:2) followed by preparative TLC (Et_2O–hexane, 6:1) to afford the title compounds **14a**, as needles (from Et_2O) (364 mg), m.p. 75–76 °C; $[\alpha]_D^{17}$ −24.3 (*c* 1.4, $CHCl_3$); ν_{max}/cm^{-1} 1725, 1618, 1560 and 1250; $\delta_H(CDCl_3)$ 1.33 (3 H, s), 1.55–2.05 (6 H, m), 2.65 (2 H, m), 2.95 (1 H, m), 3.79 (3 H, s), 4.18–4.60 (4 H, m), 6.87 (2 H, d, *J* 8) and 7.10 (2 H, d, *J* 8) (Found: C, 63.6; H, 7.2; N, 4.4. $C_{17}H_{23}NO_5$ requires C, 63.53; H, 7.21; N 4.36%); and **14b**, a colourless oil,



Scheme 2 Ar = *p*-$MeOC_6H_4$

Scheme 3



Scheme 4 Synthesis of (+)-lambetric acid. *Reagents and conditions:* i, $Cr(CO)_6$; ii, BuLi, Me_2CO; iii, pyridine, reflux; iv, Et_3SiH–CF_3CO_2H; v, $AlCl_3$–Et_2S

$[\alpha]_D^{21}$ +17.1 (*c* 1.64, $CHCl_3$); ν_{max}/cm^{-1} 1705, 1610, 1550 and 1240; $\delta_H(CDCl_3)$ 1.33 (3 H, s), 1.05–1.75 (5 H, m), 2.00 (1 H, m), 2.35–2.60 (2 H, m), 2.75 (1 H, m), 3.79 (3 H, s), 4.22 (1 H, dt, *J* 3, 11), 4.40 (1 H, dt, *J* 3, 11), 4.55 (1 H, dd, *J* 5, 13), 4.95 (1 H, dd, *J* 5, 13), 6.85 (2 H, d, *J* 8) and 7.10 (2 H, d, *J* 8) (Found: C, 63.4; H, 7.2; N, 4.3. $C_{17}H_{23}NO_5$ requires C, 63.53; H, 7.21; N, 4.36%).

Methyl (3S,4S) *and* (3R,4S)-7-*Hydroxy*-1-(p-*methoxyphenyl*)-4-*methyl*-3-*nitromethylheptane*-4-*carboxylate* **15a** *and* **b**.—To a solution of the tetrahydropyranone **14a** (373 mg, 1.16 mmol) in dry MeOH was added a solution of NaOMe (1 mol dm^3 in MeOH; 5.8 cm^3, 5.8 mmol). The reaction solution was stirred for 8 h at room temperature, and then cooled to 0 °C. After addition of AcOH (480 mm^3), the reaction mixture was concentrated under reduced pressure. Addition of HCl (0.5 mol dm^3; 20 cm^3) was followed by work-up. Short column chromatography of the crude product (Et_2O–hexane, 1:1) afforded the carboxylate **15a** (411 mg, 100%) as a colourless oil, $[\alpha]_D^{20}$ −21.0 (*c* 0.4, $CHCl_3$); ν_{max}/cm^{-1} 3450, 1720, 1600 and 1550; $\delta_H(CDCl_3)$ 1.12 (3 H, s), 1.20–1.90 (7 H, m), 2.40–2.70 (3 H, m), 3.59 (2 H, t, *J* 7), 3.66 (3 H, s), 3.79 (3 H, s), 4.36 (1 H, dd, *J* 7, 13), 4.60 (1 H, dd, *J* 5, 13), 6.84 (2 H, d, *J* 8) and 7.09 (2 H, d, *J* 8) (M + H^+, 354.192. *M* + H, 354.191).

The tetrahydropyranone **14b** (1 g) was treated in the same way as compound **14a** to afford the carboxylate **15b** (1.1 g, 100%), colourless oil, $[\alpha]_D^{20}$ +8.5 (*c* 1.5, $CHCl_3$); ν_{max}/cm^{-1} 3450, 1720, 1550 and 1240; $\delta_H(CDCl_3)$ 1.11 (3 H, s), 1.15–1.70 (7 H, m), 2.40–2.80 (3 H, m), 3.57 (2 H, t, *J* 7), 3.61 (3 H, s), 3.78 (3 H, s), 4.29 (1 H, dd, *J* 5, 13), 4.60 (1 H, dd, *J* 5, 13), 6.83 (2 H, d, *J* 8) and 7.05 (2 H, d, *J* 8) (Found: C, 61.5: H, 7.5; N, 3.9. $C_{18}H_{25}NO_6$ requires C, 61.20; H, 7.70; N, 3.96%).

Methyl (3S,4S)- *and* (3R,4S)-7-*Iodo*-1-(p-*methoxyphenyl*)-4-*methyl*-3-*nitromethylheptane*-4-*carboxylate* **16a** *and* **b**.—To a solution of the carboxylate **15a** (411 mg, 1.16 mmol) in dry CH_2Cl_2 (20 cm^3) was added MsCl (180 mm^3, 2.32 mmol) followed by dropwise addition of Et_3N (323 mm^3, 2.32 mmol) at 0 °C. The reaction solution was stirred at 0 °C for 1 h, poured into CH_2Cl_2 (100 cm^3) and washed with brine. Evaporation of the solvent gave the crude mesylate which was dissolved in dry acetone (30 cm), NaI (1.74 g, 11.6 mmol) was added and stirred for 10 h at room temperature, followed by refluxing for 3 h. Work-up afforded a crude product which was purified by short column chromatography (CH_2Cl_2–hexane, 1:2) to provide the iodide **16a** (468 mg, 87%) as a colourless oil, $[\alpha]_D^{18}$ −15.0 (*c* 0.74, $CHCl_3$); ν_{max}/cm^{-1} 1725, 1560 and 1250; $\delta_H(CDCl_3)$ 1.10 (3 H, s), 1.40–1.90 (6 H, m), 2.40–2.75 (3 H, m), 3.10 (2 H, t, *J* 7),

3.65 (3 H, s), 3.80 (3 H, s), 4.35 (1 H, dd, *J* 7, 13), 4.57 (1 H, dd, *J* 5, 13), 6.84 (2 H, d, *J* 8) and 7.08 (2 H, d, *J* 8) (M^+, 463.089. *M*, 463.092).

The same reaction with carboxylate **15b** (851 mg) gave iodide **16b** (994 mg, 89%) as a colourless oil, $[\alpha]_D^{18}$ +15.5 (*c* 2.46, $CHCl_3$); ν_{max}/cm^{-1} 1720, 1550 and 1240; $\delta_H(CDCl_3)$ 1.11 (3 H, s), 1.50–1.80 (6 H, m), 2.40–2.75 (3 H, m), 3.10 (2 H, m), 3.64 (3 H, s), 3.79 (3 H, s), 4.30 (1 H, dd, *J* 6, 13), 4.61 (1 H, dd, *J* 5, 13), 6.84 (2 H, d, *J* 8) and 7.06 (2 H, d, *J* 8) (Found: C, 46.9; H, 5.6; N, 2.8. $C_{18}H_{26}INO_5$ requires C, 46.70; H, 5.66; N, 3.02%).

Methyl (1R,2S,3S) *and* (1R,2S,3R)-2-[2-(p-*Methoxyphenyl*)-*ethyl*]-1-*methyl*-3-*nitrocyclohexanecarboxylate* **17a** *and* **b**.—Sodium hydride (60%; 194 mg, 4.85 mmol) was suspended in dry DMF (80 cm^3) at 0 °C under N_2 followed by dropwise addition of a solution of the iodide **16a** (900 mg, 1.94 mmol) in dry DMF. The mixture was stirred for 14 h at 0 °C. After addition of AcOH (0.8 cm^3) DMF was removed under reduced pressure at 50 °C. To the residue was added HCl (1 mol dm^{-3}; 100 cm^3) and work-up afforded a residue, short column chromatography (hexane–Et_2O, 3:1) of which gave the title carboxylate **17a** (363 mg, 56%) as a colourless oil, $[\alpha]_D^{18}$ −3.2 (*c* 2.34, $CHCl_3$); ν_{max}/cm^{-1} 1720, 1550, 1510 and 1245; $\delta_H(CDCl_3)$ 1.21 (3 H, s), 1.25–2.00 (8 H, m), 2.18–2.60 (3 H, m), 3.65 (3 H, s), 3.77 (3 H, s), 5.13 (1 H, dt, *J* 5, 10), 6.79 (2 H, d, *J* 8) and 7.04 (2 H, d, *J* 8) (M^+, 335.176. *M*, 335.173).

The same reaction of the iodide **16b** (458 mg) afforded the carboxylate **17b** (144 mg, 44%) as a 1 : 1 mixture epimeric at C-3.

Methyl (1S,2S)- *and* (1S,2R)-2-[2-(p-*methoxyphenyl*)*ethyl*]-1-*methyl*-3-*oxocyclohexanecarboxylate* **18a** *and* **b**.—To a solution of the carboxylate **17a** (126 mg, 0.37 mmol) in dry MeOH (5 cm^3) was added a solution of NaOMe (1 mol dm^{-3} in MeOH; 0.49 cm^3, 0.49 mmol). The mixture was stirred for 1 h under N_2 at room temperature and to this solution were added aqueous $TiCl_3$ (20%; 1.25 cm^3) and ammonium acetate (682 mg) in water (2 cm^3) under N_2 at 0 °C. The mixture was stirred for 2 h at room temperature. After addition of HCl (0.5%; 20 cm^3), work-up afforded the ketone **18a** (114 mg, 100%) after short column chromatography (Et_2O–hexane, 1:1), as a colourless oil, $[\alpha]_D^{18}$ +1.7 (*c* 2.43, $CHCl_3$); ν_{max}/cm^{-1} 1730, 1618, 1515 and 1250; $\delta_H(CDCl_3)$ 1.24 (3 H, s), 1.50 (1 H, m), 1.65–1.95 (3 H, m), 2.00–2.70 (7 H, m), 3.63 (3 H, s), 3.79 (3 H, s), 6.82 (2 H, d, *J* 8) and 7.08 (2 H, d, *J* 8) (M^+, 304.164. *M*, 304.167).

The carboxylate **17b** (72 mg, 0.21 mmol) was allowed to react under the same conditions as **17a**. Preparative TLC (Et_2O–hexane, 1:2) of the crude product afforded the ketones **18a** (42 mg, 64.4%) and **18b** (20 mg, 30.6%) as a colourless oil, $[\alpha]_D^{20}$ −5.0 (*c* 0.75, $CHCl_3$); ν_{max}/cm^{-1} 1725, 1710, 1610, 1510 and 1240; $\delta_H(CDCl_3)$ 1.02 (3 H, s), 1.05–1.30 (2 H, m), 1.70–2.45 (7 H, m), 2.66 (1 H, hept, *J* 4, 10), 2.88 (1 H, d, *J* 10), 3.64 (3 H, s), 3.79 (3 H, s), 6.82 (2 H, d, *J* 8) and 7.08 (2 H, d, *J* 8) (M^+ + H, 305.175. *M* + H, 305.175).

Preparation of the Ketone **18a** *from* **18b**.—To a solution of **18b** (20 mg, 0.07 mmol) in dry MeOH (10 cm^3) was added *p*-TsOH (12 mg. 0.07 mmol). The reaction solution was refluxed for 1 h. After removal of solvent, the residue was separated by preparative TLC (Et_2O–hexane, 1 : 2) to give **18a** (10 mg) and **18b** (10 mg).

8-[2-(p-*Methoxyphenyl*)*ethyl*]-1,5-*dimethyl*-6-*oxabicyclo*-[3.2.1]*octan*-7-*one* **21**.—To a solution of (±)-**18a** *,[1] (18 mg, 0.06 mmol) in dry THF (6 cm^3) was added a solution of MeMgI (2 mol dm^{-3} in hexane; 0.12 cm^3, 0.24 mmol) under N_2. The reaction mixture was stirred for 6 h at room temperature and then poured into aqueous NH_4Cl (15 cm^3). Preparative TLC (Et_2O–hexane, 1:1) of the crude product obtained upon work-up afforded the ketone (±)-**21** (10 mg, 59%) as a colourless oil, ν_{max}/cm^{-1} 1760, 1610, 1510 and 1240; $\delta_H(CDCl_3)$ 1.24 (3 H, s), 1.47 (3 H, s), 1.53–1.90 (9 H, m), 2.60 (2 H, m), 3.79 (3 H, s), 6.84 (2 H, d, *J* 8) and 7.07 (2 H, d, *J* 8) (M^+, 288.172. *M*, 288.172).

Methyl 3-*Hydroxy*-2-[2-(p-*methoxyphenylethyl*)]-1,3-*dimethylcyclohexanecarboxylate* **22**.—To a solution of (±)-**18b** (143 mg, 0.47 mmol) in dry THF (15 cm^3) was added a solution of MeMgI (2 mol dm^{-3} in hexane; 0.52 cm^3, 1.04 mmol). The reaction mixture was stirred for 2 h under N_2 at 0 °C, and treated as for **18a**. Short column chromatography (CH_2Cl_2) afforded the title compound **22** (138 mg, 92%) as a colourless oil, ν_{max}/cm^{-1} 3500br, 1720, 1610, 1510 and 1240; $\delta_H(CDCl_3)$ 1.26 (3 H, s), 1.33 (3 H, s), 1.37–1.95 (9 H, m), 2.53 (2 H, m), 3.67 (3 H, s), 3.78 (3 H, s), 6.82 (2 H, d, *J* 8) and 7.07 (2 H, d, *J* 8) (M^+, 320.198. *M*, 320.198).

Methyl (1S,2R)-2-[2-(p-*Methoxyphenyl*)*ethyl*]-3-*methylene*-1-*methylcyclohexanecarboxylate* **19a**.—To dry THF (50 cm^3) a zinc powder suspension (5.75 g, 88 mmol) in CH_2Br_2 (2.02 cm^3, 28.8 mmol) was added. After dropwise addition $TiCl_4$ (2.3 cm^3, 21 mmol) at −40 °C under nitrogen, the mixture was stirred for 3 days at 0 °C to form the Nozaki reagent.[18]

To a solution of **18a** (41 mg, 0.14 mmol) in dry CH_2Cl_2 was added the Nozaki reagent (3 cm^3). The mixture was stirred for 1 h under N_2 at room temperature and then poured into HCl (0.5 mol dm^{-3}; 15 cm^3). Work-up followed by preparative TLC (EtO–hexane, 1:2) afforded the carboxylate **19a** (35 mg, 85%), as a colourless oil, $[\alpha]_D^{20}$ +57.5 (*c* 0.55, $CHCl_3$); ν_{max}/cm^{-1} 2940, 1710, 1655 and 1240; $\delta_H(CDCl_3)$ 1.18 (3 H, s), 1.25–2.05 (6 H, m), 2.10 (2 H, m), 2.30 (2 H, m), 2.50 (1 H, m), 3.64 (3 H, s), 3.78 (3 H, s), 4.72 (1 H, d, *J* 2), 4.89 (1 H, br s), 6.81 (2 H, d, *J* 8) and 7.05 (2 H, d, *J* 8) (Found: C, 75.4; H, 8.8. $C_{19}H_{26}O_3$ requires C, 75.45; H, 8.67).

Methyl 12-*Methoxypodocarpa*-8,11,13-*trien*-19-*oate* **3**.—To a mixture of P_2O_5 (100 mg) and $MeSO_3H$ (1 g) was added the carboxylate **19a** (39 mg, 0.13 mmol). The mixture was stirred for 15 min at room temperature and then poured into ice. Work-up followed by preparative TLC (Et_2O–hexane, 1:1) afforded the title compound **3** (36 mg, 92%), as colourless needles (MeOH), m.p. 129–130.5 °C; optical rotation {$[\alpha]_D^{18}$ +128 (*c* 0.3, $CHCl_3$)}, IR and ^1H NMR data identical with those of an authentic specimen.

Methyl (+)-15-*Hydroxy*-12-*methoxyabieta*-8,11,13-*trien*-19-*oate* **27**.—To a solution of the chromium complex **26** (328 mg, 0.75 mmol) in dry THF (30 cm^3) was added a solution of BuLi (1.3 mol dm^{-3} in hexane; 0.69 cm^3, 0.9 mmol) and the mixture was stirred for 3 h under N_2 at −78 °C. Anhydrous acetone (165 mm^3, 2.25 mmol) was added and the mixture stirred for a further 2 h at same temperature. The solution was poured into HCl (0.5 mol dm^{-3}; 20 cm^3) and the mixture then worked up. The residue was dissolved in pyridine (15 cm^3) and heated under reflux for 2 h. The reaction mixture was filtered through Celite and pyridine was removed under reduced pressure. Short column chromatography (Et_2O–hexane, 1:3) afforded crude product which was recrystalized from Et_2O to give the abietoate **27** (144 mg, 55%), colourless prisms, m.p. 150–151.5 °C (lit.,[28] 148–150 °C); $[\alpha]_D^{21}$ +115.0 (*c* 2.22, $CHCl_3$), [lit.,[30] +119 (EtOH)]; ν_{max}/cm^{-1} 3550, 1715, 1500 and 1240; $\delta_H(CDCl_3)$ 1.03 (3 H, s), 1.27 (3 H, s), 1.58 (6 H, s), 3.66 (3 H, s), 3.87 (3 H, s), 6.78 (1 H, s) and 6.94 (1 H, s) (Found: C, 73.1; H, 8.95. Calc. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95).

* This compound was prepared from racemic **1a**[29] through a similar sequence to that for optically active series.

Methyl (+)-12-*Methoxyabieta*-8,11,13-*trien*-19-oate **28**.—To a solution of the abietoate **27** (80 mg, 0.22 mmol) in dry CH_2Cl_2 (10 cm^3) was added first triethylsilane (43 mm^3, 0.27 mmol) and then trifluoroacetic acid (120 mm^3, 1.54 mmol). The mixture was then stirred for 8 h under N_2 at room temperature, after which Na_2CO_3 (200 mg, 1.89 mmol) was added. The mixture was filtered and the filtrate was evaporated to dryness to afford a residue which was recrystalized from hexane to give **28** (70 mg, 92%) as colourless needles, m.p. 107–109 °C (lit.,[28] 105–107 °C); $[\alpha]_D^{21}$ +120 (*c* 1.2, $CHCl_3$) [lit.,[29] +124 (EtOH)]. ^1H NMR data were identical with those of ref. 29.

Methyl (+)-12-*Hydroxyabieta*-8,11,13-*trien*-19-*oate* **4**.—To a mixture of **28** (70 mg, 0.20 mmol) and EtSH (2 cm^3) was added $AlCl_3$ (500 mg, 3.76 mmol). The mixture was stirred for 24 h under N_2 at room temperature, and then poured into HCl (5%; 10 cm^3). Work-up followed by short column chromatography (hexane–EtOAc, 2:1) afforded pure product **4** (52 mg, 82%) as colourless needles, m.p. 252–254 °C (lit.,[26] 252–254 °C); $[\alpha]_D^{22}$ +127 (*c* 0.6, $CHCl_3$) [lit.,[23] $[\alpha]_D^{24}$ +121.5 (EtOH)]. ^1H NMR and IR data of product **4** were identical with those of ref. 23.

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