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Stereocontrolled Total Synthesis of (±)-Totaryl methyl ether and (±)-Semperviryl methyl ether

Swati Das, Sukanta Bhattacharyya, and Debabrata Mukherjee*

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta - 700 032, India.

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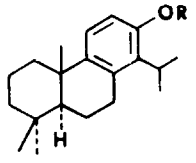
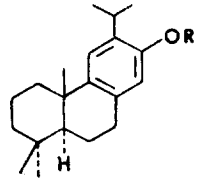
Abstract : Stereocontrolled synthesis in racemic form of the title diterpene ethers is described. Friedel-Crafts acylation of the naphthalene derivative **15** afforded the methyl ketone **16** in high yield. The compounds **5** and **16** were converted into the hydrophenanthrenones **6** and **7** respectively. Reductive methylation of **6** and **7** in anhydrous ammonia furnished the β , γ -unsaturated ketones **8** and **9** which were stereoselectively transformed into the trans-fused ketones **10** and **11**. Huang-Minlon reduction of **10** and **11** afforded the octahydrophenanthrene **27** and (±)-totaryl methyl ether **(2)** respectively. Friedel-Crafts acylation of **27** provided the methyl ketone **28** which was converted into (±)-semperviryl methyl ether **(4)**.

The tricyclic diterpenes totarol **(1)** and sempervirol **(3)** incorporate trans-fused octahydrophenanthrene nucleus as the basic carbocyclic framework. Totarol contains a modified abietane skeleton and was first isolated as a major constituent of the heartwood of Podocarpus totara by Easterfield and McDowell.[1] On the basis of chemical and spectroscopic studies, the structure **1** was proposed for totarol by Short and his co-workers.[2] The diterpene sempervirol **(3)** also possesses a rearranged abietane skeleton and was isolated by Mangoni and Caputo[3] from the resin from

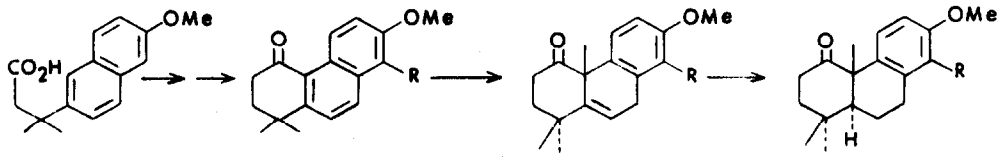


1, R = H
2, R = Me



3, R = H
4, R = Me

Cupressus sempervirens. The structures **1** and **3** for totarol and sempervirol respectively were confirmed by the synthesis[4,5] of these diterpenes. Earlier methodologies for the synthesis of **1** and **3** most commonly employed Robinson annulation or cation-arene cyclisation as the key reactions. We describe here stereocontrolled total synthesis of (±)-totaryl methyl ether **(2)** and (±)-semperviryl methyl ether **(4)** from a common starting material using a conceptually different approach. Our basic strategy for the construction of appropriately substituted octahydrophenanthrene ring systems



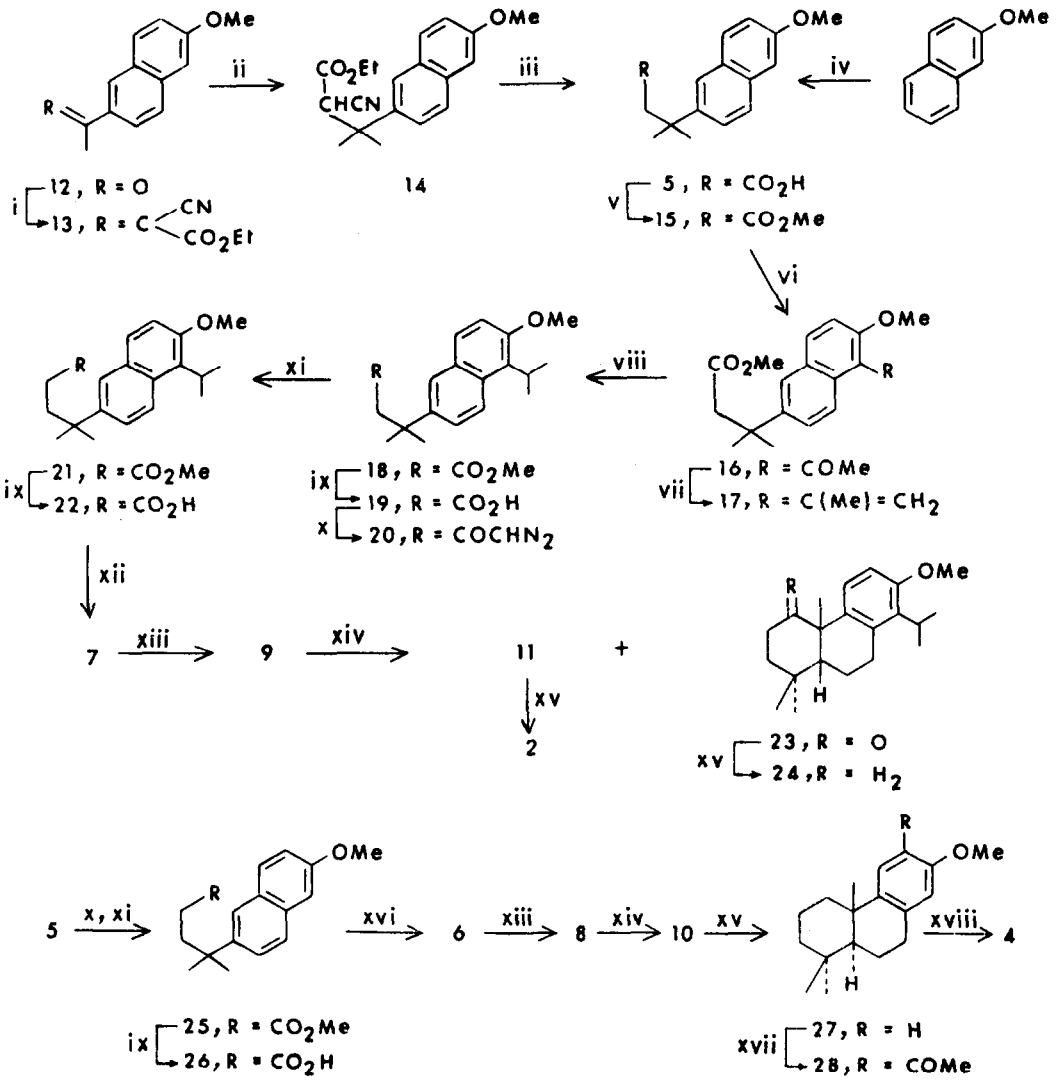
5 6, R = H 7, R = i-Pr 8, R = H 9, R = i-Pr 10, R = H 11, R = i-Pr

Scheme 1

related to the diterpenes **1** and **3** is shown in Scheme 1. The bicyclic acid **5**, easily prepared from 2-methoxynaphthalene, was converted into the hydrophenanthrenones **6** and **7** which underwent reductive alkylation in anhydrous ammonia to afford the β,γ-unsaturated ketones **8** and **9** respectively in high yields. Reduction of the Δ^5-bonds of **8** and **9** under appropriate conditions provided stereoselectively the trans-fused ketones **10** and **11** which were subsequently transformed into the diterpene ethers **4** and **2** respectively. Total synthesis of naturally occurring tricyclic diterpenes involving reductive methylation of hydrophenanthrenones has been relatively unexplored.

Results and Discussion

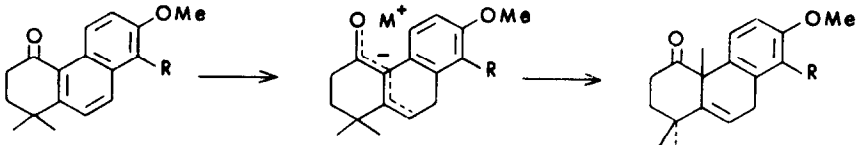
In the present study the hydrophenanthrenones **6** and **7** were chosen as the potential intermediates for **4** and **2** respectively. The tricyclic ketones **6** and **7** were conveniently prepared from a common starting material in the following manner (Scheme 2). 2-Acetyl-6-methoxynaphthalene **(12)**[6] was condensed with ethyl cyanoacetate in the presence of NH_4OAc to provide the unsaturated cyanoester **13** as a mixture of geometrical isomers. Conjugate addition of MeMgI to **13** in the presence of CuI furnished the gem-dimethylated product **14** contaminated with ca 25% of **13**. Separation of **14** from **13** was effected by a simple procedure. The mixture was treated with calculated quantity of the sodium salt of cyanoacetamide in EtOH at room temperature for several hours. On dilution with water, **13** was removed completely as a water-soluble salt[7] and the desired dimethyl compound **14** was recovered in a pure state in 62% overall yield. Hydrolysis of **14** with 20% KOH in refluxing ethylene glycol : water (5:1) followed by thermal decarboxylation of the crude product afforded the crystalline acid **5** in 82% yield. The acid **5** was also prepared from 2-methoxynaphthalene in one step in 42% yield. Thus, reaction of 2-methoxynaphthalene with 3-methylcrotonic acid in the presence of anhydrous $AlCl_3$ in carbon disulphide followed by crystallisation of the acidic product from benzene furnished pure **5**. The samples of the acid **5** prepared by the two routes were identical in all respects. The corresponding methyl ester **15** was treated with AcCl in the presence of anhydrous $AlCl_3$ to afford the 1-acetyl compound **16** in 84% yield. Friedel-Crafts acylation of 2-methoxynaphthalene usually yields[8] a mixture of 6-acyl and 1-acyl derivatives.



Scheme 2. Reagents and Conditions : i, $CH_2(CN)CO_2Et$, NH_4OAc, AcOH, C_6H_6, reflux; ii, MeMgI, CuI, Et_2O, 0-25°C then reflux; iii, KOH, $(CH_2OH)_2$, H_2O, reflux, H_3O^+; heat (200°C); iv, $(Me)_2C{=}CHCO_2H$, $AlCl_3$, CS_2, 0-25°C; v, CH_2N_2, Et_2O, 0-25°C; vi, AcCl, $AlCl_3$, CH_2Cl_2, 0-25°C; vii, $CH_3P(C_6H_5)_3I$, t-BuOK, 120°C; viii, H_2, EtOH, PtO_2; ix, KOH, MeOH, reflux, H_3O^+; x, $(COCl)_2$, CH_2Cl_2, reflux; CH_2N_2, Et_2O, 0-25°C; xi, $C_6H_5CO_2Ag$, MeOH, Et_3N, rt; xii, $(COCl)_2$, CH_2Cl_2, reflux; $AlCl_3$, $C_6H_5NO_2$, 0-25°C; xiii, K, liq. NH_3, THF, t-BuOH, LiBr, MeI; xiv, LAH, Et_2O, reflux; H_2, Pd-C, AcOH then Jones oxdn.; xv, N_2H_4, $N_2H_4.2HCl$, diethylene glycol, 130°C, KOH, 210°C; xvi, PPA, 80°C; xvii, AcCl, $SnCl_4$, CH_2Cl_2, 0°C; xviii, MeMgI, Et_2O, reflux; H_2, Pd-C, AcOH, $HClO_4$

Since the position 6 of the present compound **15** is already substituted, the formation of the 1-acyl derivative was anticipated. The structure of **16** was easily deduced from the ^{1}H NMR spectrum where the five aromatic protons displayed expected splitting patterns. Further confirmation followed from subsequent transformations leading to (±)-totaryl methyl ether (**2**). Wittig reaction[9] of the ketone **16** with methylenetriphenyl phosphorane afforded in 82% yield the olefin **17** which on catalytic hydrogenation provided the ester **18**. Homologation of **18** was carried out efficiently following a procedure reported by Hudlicky et al.[10] Hydrolysis of **18** yielded the acid **19** which was converted into the diazomethyl ketone **20**. Treatment of **20** with silver benzoate in methanol in the presence of Et_3N furnished the ester **21** in 76% overall yield. The corresponding acid **22** was treated with oxalyl chloride to yield an acid chloride which underwent intramolecular cyclisation in the presence of $AlCl_3$ in nitrobenzene to afford the tricyclic ketone **7** in 77% yield. Cyclisation of **22** with polyphosphoric acid (PPA) also provided **7** (58%). The ^{1}H NMR spectrum of the ketone revealed the presence of four ortho-coupled aromatic protons and was in full accord with structure **7**. Due to deshielding effect of the carbonyl group, the aromatic hydrogen at C-5 appeared in the spectrum at a very low field (δ 9.15). The hydrophenanthrenone **6** was prepared in a similar manner. Homologation of the ester **15** afforded **25** which was saponified to provide the acid **26**. Intramolecular cyclisation of **26** with PPA furnished **6** in 72% yield. The structure of **6** received support from analytical and spectral data.

With the hydrophenanthrenones **6** and **7** in hand, our next objective enroute to the natural products was to incorporate the required angular methyl substituents. In order to facilitate subsequent generation of trans-stereochemistry at the A/B ring



6, R = H
7, R = i-Pr

29, R = H
30, R = i-Pr

8, R = H
9, R = i-Pr

juncture, introduction of angular methyl groups through reductive alkylation[11] of the hydrophenanthrenones **6** and **7** in liquid ammonia was considered most expedient. To carry out reductive methylation, the aromatic ketones **6** and **7** were subjected to Birch reduction with potassium (2.5 equiv.) in liquid ammonia in the presence of t-BuOH (2 equiv.). The resulting potassium enolates **29** (M=K) and **30** (M=K) on treatment with LiBr were converted in the reaction medium into lithium enolates **29** (M=Li) and **30** (M=Li) which were alkylated with MeI to afford the β,γ-unsaturated ketones **8** and **9** respectively in excellent yields. Having thus an efficient route to **8** and **9**, we next turned our attention to generate trans-stereochemistry at the A/B ring juncture. This was smoothly achieved by reducing the ketones **8** and **9** with $LiAlH_4$ and subjecting

the crude products to catalytic hydrogenation in AcOH in the presence of 10% Pd on charcoal. Jones oxidation furnished the trans-fused ketones **10** and **11** respectively in 72% and 65% overall yields. The construction of the basic tricarbocyclic framework of sempervirol **(3)** and totarol **(1)** was thus accomplished in a stereocontrolled manner. The assignment of trans-stereochemistry to the ketones **10** and **11** was confirmed by subsequent transformation of **10** and **11** into known compounds possessing trans-streochemistry at the A/B ring juncture. Thus, Huang-Minlon reduction[12] of **11** afforded (±)-totaryl methyl ether **(2)** in 84% yield. A similar reduction of the ketone **10** furnished the known [13] octahydrophenanthrene **27**. Friedel-Crafts acylation of **27** with AcCl in the presence of $SnCl_4$ afforded the methyl ketone **28** as the only product in 80% yield. In the ^1H NMR spectrum of **28**, the two aromatic protons at C-11 and C-14 appeared as singlets at δ 7.68 and δ 6.60 respectively. Reaction of **28** with MeMgI followed by catalytic hydrogenolysis (H_2, 10% Pd-C) of the resultant carbinol in AcOH containing a few drops of perchloric acid afforded (±)-semperviryl methyl ether **(4)** in 80% yield. The identity of synthetic **2** and **4** was confirmed through comparison of ^1H NMR spectra with those of authentic samples. The conversion of **2**[4] and **4**[14] into the diterpenes totarol **(1)** and sempervirol **(3)** respectively by treatment with BBr_3 in dichloromethane was reported earlier by Matsumoto et al.

It must be mentioned here that although the trans-fused ketone **10** was the only isolable product in the aforementioned transformation of the β,γ-unsaturated ketone **8**, the cis-fused ketone **23** was isolated in 16% yield from the mother liquor of crystallisation of **11** through chromatography. Conclusive evidence for the cis-stereochemistry of the A/B ring fusion of **23** was achieved by the conversion of **23** through Huang-Minlon reduction into the octahydrophenanthrene **24**. In the ^1H NMR spectrum of **24**, three-proton singlets appeared at δ 0.43 and δ 0.96 for the gem-dimethyl group at C-4 which is a diagnostic feature[15,16] for cis-fused octahydrophenanthrenes.

To conclude, we have described stereocontrolled synthesis of the diterpene ethers **2** and **4** from a common starting material using reductive methylation of hydrophenanthrenones as the key reaction. Application of the present method is currently being pursued for the synthesis of the tricyclic diterpenes taxodione and royleanone which possess antitumor cytotoxicity.

Experimental Section

The compounds described are all racemates. Melting points and boiling points are uncorrected. Melting points were taken in open capillaries in a sulphuric acid bath. IR spectra were recorded on a Perkin-Elmer 298 infrared spectrophotometer. ^{1}H NMR spectra were recorded on Varian EM-360 and Varian XL-200 spectrometers. Peak positions are indicated in ppm downfield from internal TMS in δ units. Product purities were routinely checked by TLC. Organic extracts were dried over anhydrous Na_2SO_4. Light petroleum refers to the fraction of b.p. 60-80°C and ether refers to diethyl ether.

Ethyl 2-cyano-3-(6-methoxy-2-naphthyl)crotonate (13). A mixture of 2-acetyl-6-methoxynaphthalene **(12)**[6] (15 g, 0.075 mol), ethyl cyanoacetate (16 g, 0.14 mol), AcOH (5 ml), NH_4OAc (3 g), and benzene (40 ml) was refluxed for 30 h using a Dean-Stark water separator. It was then cooled, washed with aqueous $NaHCO_3$ and water, dried and concentrated. The residue was distilled to afford the unsaturated cyano-ester **13** as a viscous liquid (16.6 g, 75%), b.p. 178-180°C/0.2 mm; IR (film) : 2220, 1725, 1627, 1600 cm^{-1}. ^{1}H NMR spectrum showed **13** as a mixture of geometrical isomers [δ(CCl_4) : 1.03, 1.37 (2t, 3H, J = 7 Hz), 2.53, 2.70 (2s, 3H), 3.87 (s, 3H), 3.99, 4.27 (2q, 2H, J = 7 Hz), 6.93-7.85 (m, 6H)]. Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found : C, 73.25; H, 5.96; N, 4.83.

Ethyl 2-cyano-3-methyl-3-(6-methoxy-2-naphthyl)butanoate (14). To a stirred solution of **13** (16 g, 0.054 mol) in dry ether (60 ml) under N_2 was added CuI (0.76 g, 4 mmol). The mixture was cooled to 0°C and a solution of MeMgI [prepared from Mg (2 g) and MeI (11.5 g, 0.081 mol)] in ether (100 ml) was added dropwise with vigorous stirring. After stirring at 0°C for 1 h and at 25°C for 2 h, the mixture was refluxed for 2 h and then cooled, decomposed with cold dil. HCl, and extracted with ether. The ethereal extract was washed with water, dried and concentrated. The residue was distilled at 182-185°C/0.2 mm to afford a colourless oil (15.4 g). From integration of ^{1}H NMR signals the oil was estimated to contain **14** and **13** in a ratio of ca. 3:1. A solution of the oil in EtOH (20 ml) was added under N_2 to a stirred suspension of sodium salt of cyanoacetamide [prepared from EtONa (1 g)[2] and cyanoacetamide (1.3 g)] in EtOH (15 ml). After 12 h at 25°C, the reaction mixture was diluted with water and extracted with ether. The ethereal extract was washed with water, dried and concentrated. Distillation of the residue furnished the saturated cyano-ester **14** (10.5 g, 62%), b.p. 182-184°C/0.2 mm; IR (film) : 2250, 1740, 1630, 1605 cm^{-1}; ^{1}H NMR (CCl_4) : δ 0.88 (t, 3H, J = 7 Hz), 1.67 (s, 6H), 3.65 (s, 1H), 3.85 (s, 3H), 3.86 (q, 2H, J = 7 Hz), 6.92-7.73 (m, 6H). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found : C, 73.20; H, 6.97; N, 4.45.

3-Methyl-3-(6-methoxy-2-naphthyl)butanoic acid (5). (a) The cyano-ester **14** (10 g) was hydrolysed by refluxing under N_2 for 24 h with a solution of KOH (30 g) in ethylene glycol (125 ml) and water (25 ml). Usual work-up afforded an acidic material which was decarboxylated by heating it at 200°C for 20 min. The product was crystallised from benzene to furnish the acid **5** (6.8 g, 82%), m.p. 140-141°C; IR (KBr) : 1710, 1630, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 1.51 (s, 6H), 2.68 (s, 2H), 3.88 (s, 3H), 7.00-7.76 (m, 6H). Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found : C, 74.49; H, 7.25. (b) A solution of 3-methylcrotonic acid (2 g, 0.02 mol) in CS_2 (15 ml) was added during 40 min to a vigorously stirred mixture of 2-methoxynaphthalene (6.3 g, 0.04 mol) and anhydrous $AlCl_3$ (2.7 g, 0.02 mol) in CS_2 (30 ml) at 0°C. $AlCl_3$ (2.7 g, 0.02 mol) was again added followed by dropwise addition of a solution of 3-methylcrotonic acid (2 g, 0.02 mol) in CS_2 (15 ml) maintaining the temperature at 0°C. After stirring at 0°C for 2 h and at 25°C for 6 h, the reaction mixture was decomposed with cold diluted HCl and extracted with ether. The organic layer was then extracted with 4% NaOH solution. The alkaline extract was acidified with cold concentrated HCl and extracted with ether. The ethereal extract was washed with brine and water, dried and concentrated. The residue was purified through evaporative distillation followed by crystallisation

(from benzene) to afford 5 (4.3 g, 42%), m.p. 140-141°C. The samples of the acid 5 prepared by the methods (a) and (b) were identical (m.p., IR, ^{1}H NMR).

Methyl 3-methyl-3-(6-methoxy-2-naphthyl)butanoate (15). The acid 5 (10 g) was treated with an ethereal solution of diazomethane (excess) at 0°C to provide the methyl ester **15** (9.7 g, 92%), m.p. 67-68°C; IR (KBr) : 1735, 1635, 1600 cm^{-1}; ^{1}H NMR (CCl_4) : δ 1.50 (s, 6H), 2.60 (s, 2H), 3.45 (s, 3H), 3.85 (s, 3H), 6.88-7.70 (m, 6H). Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found : C, 74.85; H, 7.56.

Methyl 3-methyl-3-(5-acetyl-6-methoxy-2-naphthyl)butanoate (16). To a stirred solution of **15** (3.8 g, 0.014 mol) and $AlCl_3$ (3.2 g, 0.024 mol) in CH_2Cl_2 (30 ml) at 0°C was added AcCl (1.8 ml, 0.025 mol) during 30 min. After stirring at 0°C for 2 h and at 25°C for 12 h, the mixture was decomposed with cold diluted HCl and extracted with ether. The ethereal extract was washed with aqueous $NaHCO_3$ and water, dried and concentrated. The residue was chromatographed on neutral alumina (100 g). Elution with benzene-light petroleum (3:7) afforded the methyl ketone **16** (3.7 g, 84%), m.p. 63-64°C; IR (KBr) : 1735, 1690, 1590 cm^{-1}; ^{1}H NMR (CCl_4) : δ 1.48 (s, 6H), 2.51 (s, 3H), 2.61 (s, 2H), 3.43 (s, 3H), 3.88 (s, 3H), 7.09 (d, 1H, J = 9 Hz), 7.35 (dd, 1H, J = 9,2 Hz), 7.55 (d, 1H, J = 2 Hz), 7.65 (d, 1H, J = 9 Hz), 7.68 (d, 1H, J = 9 Hz). Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found : C, 72.74; H, 7.21.

Methyl 3-methyl-3-(5-isopropenyl -6-methoxy-2-naphthyl)butanoate (17). To a stirred suspension of potassium tert-butoxide (1.57 g, 0.014 mol) in dry benzene (25 ml) under N_2 was added methyltriphenylphosphonium iodide (5.67 g, 0.014 mol) and the mixture was refluxed for 1 h. The solvent was then distilled off under N_2 until the temperature of the remaining slurry reached 120°C. The ketone **16** (3.3 g, 10.5 mmol) was added and the temperature of the mixture was maintained at 120°C for 40 h. The mixture was then cooled, light petroleum (80 ml) and water (20 ml) were added with vigorous stirring and the organic layer was decanted. The heterogeneous residue was extracted with light petroleum. The combined organic extract was washed with water, dried and concentrated. The residue was chromatographed on neutral alumina (70 g). Elution with benzene-light petroleum (1:5) afforded the ester **17** (2.7 g, 82%), m.p. 52-53°C; IR (KBr) : 1740, 1640, 1590 cm^{-1}; ^{1}H NMR (CCl_4) : δ 1.50 (s, 6H), 2.08 (d, 3H, J = 1 Hz), 2.62 (s, 2H), 3.50 (s, 3H), 3.90 (s, 3H), 4.88 (m, 1H), 5.42 (m, 1H), 7.13 (d, 1H, J = 9 Hz), 7.37 (dd, 1H, J = 9,2 Hz), 7.59 (d, 1H, J = 2 Hz), 7.65 (d, 1H, J = 9 Hz), 7.83 (d, 1H, J = 9 Hz). Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found : C, 76.79; H, 7.93.

Methyl 3-methyl-3-(5-isopropyl-6-methoxy-2-naphthyl)butanoate (18). A solution of **17** (2.6 g) in EtOH (20 ml) was hydrogenated using platium oxide (100 mg) as catalyst. Uptake of H_2 ceased after 30 min. Usual work-up afforded the ester **18** (2.6 g, 96%), b.p. 160-162°C/0.2 mm; IR (film) : 1737, 1600 cm^{-1}; ^{1}H NMR (CCl_4) : δ 1.44 (d, 6H, J = 7 Hz), 1.50 (s, 6H), 2.62 (s, 2H), 3.47 (s, 3H), 3.88 (m, 1H), 3.88 (s, 3H), 7.11 (d, 1H, J = 9 Hz), 7.27-7.67 (m, 3H), 8.01 (d, 1H, J = 9 Hz). Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33. Found : C, 76.58; H, 8.49.

The ester **18** (2.4 g) was hydrolysed by refluxing for 6 h with a solution of KOH (2.4 g) in MeOH (22 ml) and water (2 ml). Usual work-up furnished the crystalline acid **19** (2.1 g, 92%), m.p. 91-92°C; IR (KBr) : 1710, 1590 cm^{-1}; ^{1}H NMR (CCl_4) : δ 1.44 (d, 6H, J = 7 Hz), 1.50 (s, 6H), 2.65 (s, 2H), 3.87 (m, 1H), 3.90 (s, 3H), 7.12 (d, 1H, J = 9 Hz), 7.43 (dd, 1H, J = 9,2 Hz), 7.57 (d, 1H, J = 9 Hz), 7.58 (d, 1H, J = 2 Hz), 8.00 (d, 1H, J = 9 Hz). Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found : C, 75.92; H, 8.26.

Methyl 4-methyl-4-(5-isopropyl-6-methoxy-2-naphthyl)pentanoate (21). A solution of **19** (1.8 g, 6 mmol) in CH_2Cl_2 (15 ml) was refluxed with oxalyl chloride (2.3 g, 18 mmol) for 4 h. Removal of the solvent and excess oxalyl chloride furnished the acid chloride as a pale yellow liquid (1.8 g). The crude acid chloride dissolved in ether

(25 ml) was added dropwise with stirring to a solution of diazomethane (large excess) in ether at 0°C and the resulting solution was left at room temperature for 10 h. It was then concentrated to afford the diazoketone **20** as a viscous liquid (1.8 g) [IR ($CHCl_3$) : 2110, 1640, 1600 cm^{-1}].

To a magnetically stirred solution of the above crude diazoketone in dry MeOH (30 ml) was added a solution of silver benzoate (150 mg) in Et_3N (4.5 ml) during 30 min. After stirring at 25°C for 1 h, the reaction mixture was filtered and concentrated. The residue was diluted with water and extracted with ether. The extract was washed with diluted HCl and water, dried and concentrated. The residue was evaporatively distilled at 168-170°C (bath temp.)/0.2 mm to furnish the ester **21** (1.5 g, 76%); ^1H NMR (CCl_4) : δ 1.40 (s, 6H), 1.46 (d, 6H, J = 7 Hz), 2.02 (s, 4H), 3.50 (s, 3H), 3.88 (m, 1H), 3.92 (s, 3H), 7.13 (d, 1H, J = 9 Hz), 7.30-7.67 (m, 3H), 8.03 (d, 1H, J = 9 Hz). Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found : C, 76.58; H, 8.67.

A mixture of **21** (1.4 g), KOH (2 g), MeOH (18 ml) and water (2 ml) was refluxed for 4 h. Usual work-up furnished the acid **22** (1.2 g, 90%), m.p. 116-117°C; IR (KBr) : 1700, 1590 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.43 (s, 6H), 1.49 (d, 6H, J = 7 Hz), 2.10 (s, 4H), 3.92 (m, 1H), 3.95 (s, 3H), 7.28 (d, 1H, J = 9 Hz), 7.48 (dd, 1H, J = 9,2 Hz), 7.67 (d, 1H, J = 2 Hz), 7.73 (d, 1H, J = 9 Hz), 8.16 (d, 1H, J = 9 Hz). Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33. Found : C, 76.34; H, 8.22.

1,2,3,4-Tetrahydro-1,1-dimethyl-7-methoxy-8-isopropylphenanthren-4-one (7). Oxalyl chloride (1.3 g, 0.01 mol) was added to a solution of the acid **22** (1.1 g, 3.5 mmol) in CH_2Cl_2 (10 ml) and the mixture was refluxed for 4 h. The solvent and excess oxalyl chloride were then distilled off to furnish the acid chloride (1.1 g) as an oil. To a magnetically stirred solution of the crude acid chloride in nitrobenzene (15 ml) at 0°C was added anhydrous $AlCl_3$ (0.93 g, 7 mmol) in small portions during 20 min. After stirring at 0°C for 2 h and at 25°C for 8 h, the reaction mixture was decomposed with cold diluted HCl. Nitrobenzene was removed by steam distillation and the product was extracted with ether. The ethereal extract was washed with aqueous $NaHCO_3$ and water, dried and concentrated. The residue was evaporatively distilled at 166-168°C (bath temp.)/0.2 mm to afford the ketone **7** as a solid compound (780 mg, 77%), m.p. 151-152°C; IR (KBr) : 1670, 1610, 1590 cm^{-1}; ^1H NMR (CCl_4) : δ 1.42 (s, 6H), 1.43 (d, 6H, J = 7 Hz), 2.03 (t, 2H, J = 6 Hz), 2.75 (t, 2H, J = 7 Hz), 3.90 (m, 1H), 3.93 (s, 3H), 7.27 (d, 1H, J = 9 Hz), 7.39 (d, 1H, J = 9 Hz), 8.26 (d, 1H, J = 9 Hz), 9.15 (d, 1H, J = 9 Hz). Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found : C, 81.18; H, 8.26.

Methyl 4-methyl-4-(6-methoxy-2-naphthyl)pentanoate (25). The conversion of the acid **5** (2 g, 7.7 mmol) into the ester **25** was carried out in the same way as described for **21**. The ester **25** was obtained as an oil (1.66 g, 75%), b.p. 155-157°C (bath temp.)/0.1 mm; IR ($CHCl_3$) : 1730, 1630, 1600 cm^{-1}; ^1H NMR (CCl_4) : δ 1.37 (s, 6H), 3.47 (s, 3H), 3.82 (s, 3H), 6.90-7.70 (m, 6H). Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found : C, 75.70; H, 7.91.

Hydrolysis of **25** (1.6 g) with 10% methanolic KOH (20 ml) afforded the acid **26** as a crystalline compound (1.4 g, 92%), m.p. 136-137°C; IR ($CHCl_3$) : 1708, 1630, 1604 cm^{-1}. Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found : C, 74.81; H, 7.59.

1,2,3,4-Tetrahydro-1,1-dimethyl-7-methoxyphenanthren-4-one (6). The acid **26** (1.3 g, 4.8 mmol) was added to polyphosphoric acid (PPA) [prepared from P_2O_5 (10 g) and H_3PO_4 (6 ml, 85%)] at 80°C. The mixture was stirred at 80°C for 20 min and then cooled, decomposed with crushed acid, and extracted with ether. The ethereal extract was washed with aq. $NaHCO_3$ and water, dried and concentrated. The residue was evaporatively distilled at 160-162°C (bath temp.)/0.2 mm to afford the ketone **6** as a colourless oil (0.87 g, 72%); IR (film) : 1672, 1620, 1600 cm^{-1}; ^1H NMR (CCl_4) : δ 1.40 (s, 6H), 1.99 (t, 2H, J = 7 Hz), 2.72 (t, 2H, J = 7 Hz), 3.83 (s, 3H), 6.90-7.47 (m, 3H), 7.73 (d, 1H, J = 8 Hz), 9.10 (d, 1H, J = 9 Hz). Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found : C, 80.40; H, 7.19.

13-Methoxy-14-isopropylpodocarpa-5,8,11,13-tetraen-1-one (9). A solution of the ketone **7** (750 mg, 2.5 mmol) in dry THF (15 ml) and t-BuOH (370 mg, 5 mmol) was added under N_2 to distilled liquid ammonia (70 ml). To this mixture was added potassium (244 mg, 6.25 mmol) with stirring during 2 min. After 10 min, a solution of LiBr (650 mg, 7.5 mmol) in THF (5 ml) was added. Stirring was continued for another 15 min and then MeI (1 ml, 16 mmol) was added followed immediately by aqueous THF (1:1, 5 ml). The ammonia was allowed to evaporate. The residue was diluted with water and extracted with ether. The ethereal extract was washed with water, dried and concentrated. The residue was evaporatively distilled to afford the β,γ-unsaturated ketone **9** (750 mg, 95%) as a colourless oil, b.p. (bath temp.) 160-162°C/0.1 mm; IR (film) : 1710, 1600 cm^{-1}; ^1H NMR (CCl_4) : δ 1.13 (s, 3H), 1.20 (s, 3H), 1.22 (s, 3H), 1.33 (d, 6H, J = 7 Hz), 1.57-2.63 (m, 4H), 3.13-3.60 (m, 3H), 3.78 (s, 3H), 5.94 (m, 1H), 6.61 (d, 1H, J = 9 Hz), 6.76 (d, 1H, J = 9 Hz). Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found : C, 80.55; H, 9.26.

13-Methoxy-14-isopropylpodocarpa-8,11,13-trien-1-one (11). The ketone **9** (700 mg, 2.2 mmol) was reduced with LAH (100 mg, 2.6 mmol) in ether (20 ml). The crude product (700 mg) was hydrogenated in AcOH (10 ml) in the presence of 10% palladium on charcoal (500 mg). Uptake of hydrogen ceased after 10 h. The mixture was filtered and the solvent evaporated off under reduced pressure. The residue was dissolved in acetone (20 ml) and oxidised with Jones reagent at 0°C. Work-up with ether afforded a solid compound which was crystallised from methanol to furnish the trans-fused ketone **11** (460 mg, 65%), m.p. 135-136°C; IR (KBr) : 1710, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.07 (s, 3H), 1.12 (s, 3H), 1.29 (d, 6H, J = 7 Hz), 1.58 (s, 3H), 1.67-3.00 (m, 9H), 3.25 (m, 1H), 3.80 (s, 3H), 6.83 (d, 1H, J = 9 Hz), 7.53 (d, 1H, J = 9 Hz). Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found : C, 80.30; H, 9.67.

The mother liquor from crystallisation of **11** was concentrated and the residue chromatographed on neutral alumina (10 g). Elution with benzene-light petroleum (1:9) afforded the cis-fused ketone **23** (115 mg, 16%), m.p. 121-122°C; IR (KBr) : 1700, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 0.97 (s, 3H), 1.03 (s, 3H), 1.31 (d, 3H, J = 7 Hz), 1.36 (d, 3H, J = 7 Hz), 1.43 (s, 3H), 1.50-3.00 (m, 9H), 3.32 (m, 1H), 3.85 (s, 3H), 6.73 (s, 2H). Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.02; H, 9.83.

(±)-Totaryl methyl ether (2). Huang-Minlon reduction[12] of the ketone **11** (200 mg) afforded a solid product which was crystallised from methanol to furnish (±)-totaryl methyl ether (**2**) (160 mg, 84%), m.p. 99-100°C (lit.[17] m.p. 95-98°C), ^1H NMR ($CDCl_3$) : δ 0.96 (s, 6H), 1.22 (s, 3H), 1.33 (d, 6H, J = 7 Hz), 1.50-3.00 (m, 11H), 3.28 (m, 1H), 3.80 (s, 3H), 6.73 (d, 1H, J = 9 Hz), 7.15 (d, 1H, J = 9 Hz). Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found : C, 83.87; H, 10.90.

13-Methoxy-14-isopropyl-5-epi-podocarpa-8,11,13-triene (24). Huang-Minlon reduction[12] of **23** (100 mg) afforded the cis-fused compound **24** (72 mg, 75%), m.p. 86-87°C; ^1H NMR ($CDCl_3$) : δ 0.43 (s, 3H), 0.96 (s, 3H), 1.17 (s, 3H), 1.26 (d, 3H, J = 7 Hz), 1.34 (d, 3H, J = 7 Hz), 3.30 (m, 1H), 3.81 (s, 3H), 6.74 (d, 1H, J = 9 Hz), 7.16 (d, 1H, J = 9 Hz). Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found : C, 83.74; H, 10.62.

13-Methoxypodocarpa-5,8,11,13-tetraen-1-one (8). Reductive methylation of the ketone **6** (800 mg, 3.2 mmol) in liquid ammonia was carried out in the same way as described for **9** to afford the β,γ-unsaturated ketone **8** (800 mg, 93%) as a colourless oil, b.p. (bath temp.) 156-158°C/0.1 mm; IR (film) : 1710, 1608 cm^{-1}; ^1H NMR (CCl_4) : δ 1.13 (s, 3H), 1.20 (s, 3H), 1.25 (s, 3H), 1.51-2.85 (m, 4H), 3.25 (d, 2H, J = 4.5 Hz), 3.70 (s, 3H), 5.85 (t, 1H, J = 4.5 Hz), 6.33-6.87 (m, 3H) . Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found : C, 80.10; H, 8.41.

13-Methoxypodocarpa-8,11,13-trien-1-one (10). Starting from **8** (760 mg), the steps of reduction (LAH, Et_2O), catalytic hydrogenation (H_2, AcOH, 10% Pd-C) and Jones oxidation were carried out as for **11** to furnish a solid product. This was crystallised from methanol to afford the trans-fused ketone **10** (560 mg, 72%), m.p. 132°C; ^1H NMR ($CDCl_3$) : δ 1.08 (s, 3H), 1.12 (s, 3H), 1.54 (s, 3H), 1.68-2.90 (m, 9H), 3.78 (s, 3H), 6.61 (d, 1H, J = 3 H), 6.80 (d of d, 1H, J = 9,3 Hz), 7.66 (d, 1H, J = 9 Hz).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found : C, 79.22; H, 8.79.

12-Acetyl-13-methoxypodocarpa-8,11,13-triene (28). Huang-Minlon reduction[12] of the ketone **10** (500 mg) afforded the octahydrophenanthrene **27** (380 mg, 80%), m.p. 86-87°C (lit.[18] m.p. 82-86°C); ^{1}H NMR (CCl_4): δ 0.94 (s, 6H), 1.16 (s, 3H), 1.30-3.00 (m, 11H), 3.72 (s, 3H), 6.47 (d, 1H, J = 2 Hz), 6.58 (dd, 1H, J = 8,2 Hz), 7.07 (d, 1H, J = 8 Hz). Anal. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14. Found : C, 83.75; H. 10.33.

To a stirred solution of **27** (360 mg, 1.4 mmol) and AcCl (0.25 ml, 3.5 mmol) in CH_2Cl_2 (2 ml) at 0°C was added a solution of $SnCl_4$ (0.4 ml, 3.4 mmol) in CH_2Cl_2 (2 ml) during 20 min. After stirring at 0°C for 3 h, the reaction mixture was decomposed with cold diluted HCl. Work-up with ether afforded a solid product which was purified by chromatography over neutral alumina (12 g). Elution with benzene-light petroleum (1:3) furnished the methyl ketone **28** (335 mg, 80%), m.p. 102-103°C; IR (KBr) 1660, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 0.92 (s, 3H), 0.94 (s, 3H), 1.15 (s, 3H), 1.20-3.00 (m, 11H), 2.57 (s, 3H), 3.84 (s, 3H), 6.60 (s, 1H), 7.68 (s, 1H). Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found : C, 79.80; H, 9.28.

(±)-Sempervirvl methyl ether (4). A solution of **28** (200 mg, 0.67 mmol) in dry ether (5 ml) was added dropwise at 25°C to a stirred solution of MeMgI [prepared from Mg (40 mg) and MeI (0.1 ml, 1.6 mmol)] in ether (10 ml). After stirring at 25°C for 4 h, the mixture was refluxed for 1 h, cooled and quenched with aqueous NH_4Cl. After usual work-up, the product was hydrogenated in the presence of 10% Pd-C (100 mg) in AcOH (10 ml) containing perchloric acid (a few drops). Uptake of H_2 ceased after 30 min. The mixture was filtered, diluted with water and extracted with ether. The ethereal extract was washed with aqueous $NaHCO_3$ and water, dried and concentrated. The residue was chromatographed on neutral alumina (10 g). Elution with light petroleum afforded (±)-sempervirvl methyl ether (160 mg, 80%), m.p. 62-63°C; ^{1}H NMR (CCl_4) : δ 0.95 (s, 6H), 1.15 (s, 3H), 1.16 (d, 6H, J = 7 Hz), 1.32-2.97 (m, 11H), 3.20 (m, 1H), 3.77 (s, 3H), 6.37 (s, 1H), 6.97 (s, 1H). Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found : C, 83.77; H, 10.50.

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