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A general asymmetric access to the podocarpane diterpenoids

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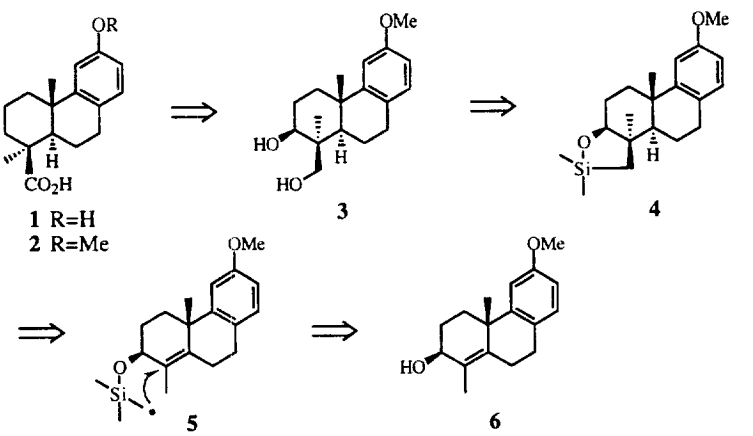
Abstract: An efficient and enantiocontrolled total synthesis of (+)-*O*-methylpodocarpic acid **2** has been accomplished by employing a combined strategy of the lipase-mediated kinetic resolution of the tricyclic allyl alcohol (±)-**7** and a highly diastereoselective silylmethyl radical cyclization of **5** leading to the tetracyclic silyl ether **4**. © 1997 Published by Elsevier Science Ltd

(+)-Podocarpic acid **1** is a representative member of the podocarpane diterpenoids[1] isolated from *Podocarpus cupressina* var. *imbricata*.[2] In view of the versatility of this natural product as a chiral pool[3] for the syntheses of several biologically important congeners, the development of a general and efficient synthetic route to enantiomerically pure **1** is of significant value. Although many reports on the synthesis of the racemic modification of **1** have appeared,[4] the enantioselective synthesis has so far been reported by only three groups.[3,5] As part of our efforts directed towards the asymmetric synthesis of biologically significant natural products, we recently reported the enantiocontrolled total syntheses of three diterpenoids possessing interleukin-1 inhibitory activity by employing the strategy for the construction of four contiguous asymmetric stereogenic centers, which consists of a combination of the lipase-mediated kinetic resolution of allyl alcohol and a highly diastereoselective silylmethyl radical cyclization.[6] We now report an efficient total synthesis of enantiomerically pure, naturally occurring *O*-methylpodocarpic acid **2**,[2] a penultimate intermediate[7] for **1**, as an application and extension of our strategy. The success of the synthesis relies on the chemoselective deoxygenation of the secondary hydroxyl moiety in **3** which can be derived from the tetracyclic silyl ether **4**. The stereochemically adjusted **4** should be prepared via a diastereoselective 5-exo-trigonal mode of radical cyclization[8] of **5**, which can, in turn, be derived from the corresponding enantiomerically pure tricyclic allyl alcohol **6** shown in Scheme 1.



Scheme 1.

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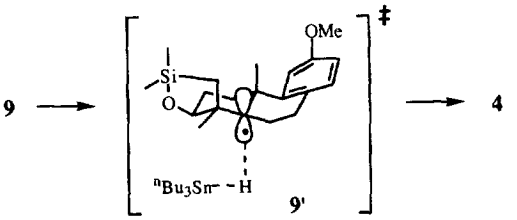
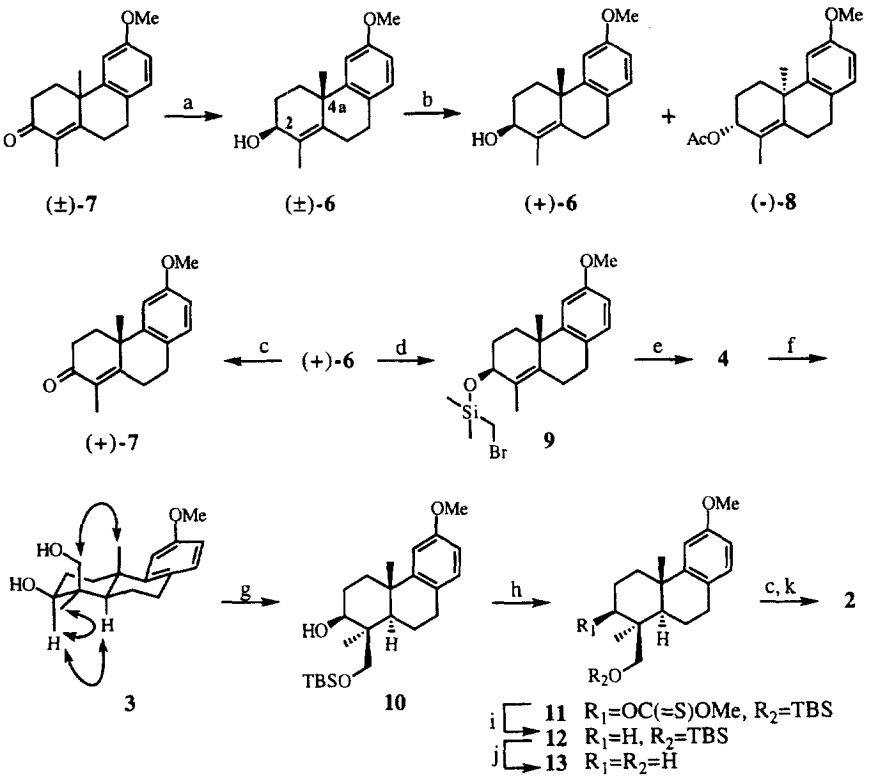
Chemo- and diastereoselective reduction of the carbonyl function in the racemic tricyclic enone **7**[9] was achieved by reduction with sodium borohydride and cerium trichloride[10] to give the racemic **6** in 80% yield. The stereochemistry of (±)-**6** was deduced to be 2*S** and 4a*S** based on the literature precedent[11] and the ^{1}H-NMR, in which the methine proton at the hydroxy-bearing carbon (C-2) appears at δ 4.06 as a triplet with J=8.1 Hz. We next turned to the search for optimum conditions for the lipase-mediated kinetic resolution[12] of (±)-**6** in organic solvent. Of these, NOVOZYM 435 (*Candida antarctica* lipase)-catalyzed acetylation[13] conditions using vinyl acetate as an acyl donor in benzene proved to be the best choice; only the (*R*)-alcohol was acetylated to give (−)-**8** in 40% yield, leaving behind the enantiomerically enriched alcohol (+)-**6** in 48% yield. The enantiomeric excesses of the alcohols (+)-**6** and (−)-**8** were determined to be 98% and 88%, respectively by HPLC analysis on a Chiralcel OD column. The absolute configuration of (+)-**6** was established upon transformation of (+)-**6** into the known optically active (+)-**7**,[14] $[\alpha]_D$+225 (see paper by Vandewalle and Nerinckx[14] for the material of 70% ee; $[\alpha]_D$+181) by Swern oxidation. The optically active (+)-**6** thus obtained was then converted into the bromomethyldimethylsilyl ether **9**, which was treated with a catalytic tri-*n*-butyltin chloride and sodium cyanoborohydride in the presence of AIBN[15] to provide the tetracyclic silyl ether **4** as a single diastereomer via the 5-exo-trigonal mode of radical cyclization.[8] It should be mentioned that examples for the creation of a quaternary stereogenic center by using such a radical cyclization are rarely found in the literature.[8c,16] Although the exact stereostructure of **4** could not be determined at this stage, the confirmation was made by the following conversion. Treatment of **4** with potassium hydrogen carbonate and 30% aqueous hydrogen peroxide[17] afforded the 1,3-diol **3** in 56% overall yield from (+)-**6**. The stereostructure of **3** was elucidated by the NOE experiments, in which signal enhancements are indicated by arrows as shown in Scheme 2. The high diastereoselectivity during the radical cyclization can be explained by taking into account the transition structure of tertiary radical **9'**, in which the hydrogen abstraction should occur preferentially on the sterically less hindered α-face of the molecule as shown below.



Thus, the crucial construction of the contiguous asymmetric stereogenic centers including two quaternary carbons was realized and we next addressed our attention to the selective removal of the secondary hydroxyl moiety in **3**. Selective protection of the primary hydroxyl group was conveniently achieved by reaction of **3** with *tert*-butyldimethylchlorosilane, imidazole and 4-dimethlyaminopyridine to give the *tert*-butyldimethylsilyl(TBS) ether **10** in 92% yield. Sequential treatment of **10** with thiocarbonyldiimidazole and methanol[18] afforded the thiocarbonate **11** which was then reduced with tri-*n*-butyltin hydride in the presence of AIBN to afford the deoxygenated TBS ether **12** in 52% yield for the two steps. Transformation of this material to *O*-methlylpodocarpic acid **2** was completed by the following three-step sequence of reactions. On exposure of **12** to tetra-*n*-butylammonium fluoride (+)-*O*-methlylpodocarpinol **13**[19] was obtained quantitatively. The ^{1}H-NMR, melting point, mp 89–90°C (mp 90.5–91.5°C)[19] and specific rotation, $[\alpha]_D$+75 ($[\alpha]_D$+67)[19], of **13** were identical with those reported. Finally, according to the procedure reported by Snider[5b] the alcohol **12** was treated with the conditions of Swern and the resultng aldehyde was further oxidized with sodium chlorite in the presence of 2-methyl-2-butene to produce *O*-methlylpodocarpic acid **2**. The identity of our synthetic **2** was established by careful comparison of the ^{1}H-NMR, melting point, mp 157°C (mp 158°C)[19] and specific rotation, $[\alpha]_D$+133 ($[\alpha]_D$+132)[19] with those reported. Since *O*-methylpodocarpic acid **2** has easily been converted into podocarpic acid **1**, the present synthesis means the formal synthesis of **1**.



Scheme 2. *Reagents and conditions*: a, $CeCl_3$, $NaBH_4$, MeOH, 0°C → rt, 80%; b, Novozym 435, vinyl acetate, benzene, rt, 40% for (+)-**6**, 48% for (−)-**8**; c, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C → rt, 44%; d, $BrCH_2Si(Me)_2Cl$, Et_3N, 4-DMAP, CH_2Cl_2, 0°C → rt; e, $^nBu_3SnCl$, $NaBH_3CN$, AIBN, ^{t}BuOH, reflux; f, $KHCO_3$, 30% H_2O_2, MeOH–THF (1:1), reflux, 56% from (+)-**6**; g, ^{t}BuSi(Me)$_2$Cl, imidazole, 4-DMAP, DMF, rt, 92%; h, $(Im)_2C{=}S$, toluene, reflux, 78% then MeOH, 60°C, 80%; i, $^nBu_3SnH$, AIBN, toluene, reflux, 65%; j, $^nBu_4NF$, THF, rt, 100%; k, 2-methyl-2-butene, $NaClO_2$, $NaH_2PO_4 \cdot 2H_2O$, ^{t}BuOH–H_2O (3:1), 11% from **13**.

In conclusion, we have completed a new and efficient total synthesis of enantiomerically pure *O*-methylpodocarpic acid **2** by employing our originally developed methodology for the construction of three contiguous asymmetric stereogenic centers presented in the target molecule. The synthetic route developed here would be general and accordingly be applicable to the total synthesis of a variety of biologically important podocarpane- and abietane-type of diterpenoids.

Experimental

Melting points were determined by a Yanagimoto MP-S2 apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1720FT-IR and a Hitachi 215 spectrophotometers. ^1H and ^{13}C NMR spectra were recorded at 200 MHz on a JEOL JMS FX-200 spectrometer and at 400 MHz (100 MHz for ^{13}C) on GSX-400 spectrometer in deuteriochloroform solutions with tetramethylsilane as an internal standard. Chemical shifts are reported in ppm (from TMS). When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened. Ordinary mass spectra and high resolution mass spectra were measured with a JEOL JMS-D300 mass spectrometer. Optical rotations were determined on a Union Giken PM-201 polarimeter. TLC was carried out with E. Merck Silica gel GOF-254 (0.25 mm thickness) precoated TLC plates. Column chromatography was carried out with silica gel (Kieselgel 60, 70–230 mesh, E. Merck). All reactions were performed under an atmosphere of argon. Solvents were freshly distilled

prior to use: tetrahydrofuran (THF), toluene and diethyl ether (Et_2O) were distilled from sodium: dichloromethane (CH_2Cl_2) and chloroform ($CHCl_3$) were distilled from phosphorus pentoxide and kept over 4 Å molecular sieves. Unless otherwise noted, all reaction mixtures were dried, after workup, over anhydrous magnesium sulfate.

(2S,4aS*)-2-Hydroxy-6-methoxy-1,4a-dimethyl-2,3,4,4a,9,10-hexahydrophenanthrene (±)-6*

A solution of the enone (±)-**7**[9] (2.0 g, 7.8 mmol) in MeOH (5 ml) was added to a stirred solution of $CeCl_3$, which was prepared on heating $CeCl_3 \cdot 7H_2O$ (1.16 g, 3.1 mmol) at 140°C, in MeOH (25 ml) at 0°C. To the mixture was added $NaBH_4$ (0.36 g, 9.4 mmol) and the resulting mixture was stirred at room temperature for 0.5 h. After removal of the solvent, a residue was extracted with CH_2Cl_2 and the extracts were washed with brine and dried. Evaporation of the solvent followed by chromatography on silica gel (hexane–ethyl acetate, 8:2, v/v) gave the alcohol (±)-**6** (1.6 g, 80%) as a pale yellow oil: IR (neat) cm^{-1} 3402; ^1H NMR ($CDCl_3$) δ 1.43 (3H, s), 1.53 (1H, br s, D_2O exchangeable), 1.66–1.83 (2H, m), 1.78 (3H, s), 2.11 (2H, dt, J=4.3 and 10.5 Hz), 2.24 (1H, m), 2.70 (2H, m), 2.83 (1H, m), 3.78 (3H, s), 4.05 (1H, dd, J=5.9 and 8.2 Hz), 6.66 (1H, dd, J=2.7 and 8.2 Hz), 6.79 (1H, d, J=2.7 Hz), 6.97 (1H, d, J=8.2 Hz); MS (EI) m/z 258 (M^+); HRMS Calcd for $C_{17}H_{22}O_2$: 258.1620. Found: 258.1602.

(+)-(2S,4aS)-2-Hydroxy-6-methoxy-1,4a-dimethyl-2,3,4,4a,9,10-hexahydrophenanthrene (+)-6 and (−)-(2R,4aR)-2-acetoxy-6-methoxy-1,4a-dimethyl-2,3,4,4a,9,10-hexahydrophenanthrene (−)-8

NOVOZYM 435 (0.83 g) was added to a solution of (±)-**6** (0.42 g, 1.61 mmol) and vinyl acetate (0.62 g, 7.25 mmol) in benzene (32 ml) and the mixture was stirred at room temperature for 48 h. After filtration, the filtrate was evaporated to give a residue which was chromatographed on silica gel (hexane–ethyl acetate, 8:2, v/v) to afford (+)-**6** (0.17 g, 40%) as a pale yellow oil. $[\alpha]_D$+220 (c=0.41, $CHCl_3$), whose spectral properties were identical with those of the racemate. From the later fractions, the acetate (−)-**8** (0.23 g, 48%) was obtained as a colorless oil; $[\alpha]_D$ −141 (c=0.37, $CHCl_3$); IR (neat) cm^{-1} 1732; ^1H NMR ($CDCl_3$) δ 1.44 (3H, s), 1.64 (3H, s), 2.10 (3H, s), 1.53–2.38 (5H, m), 2.56–2.95 (3H, m), 3.79 (3H, m), 5.30 (1H, t, J=7.6 Hz), 6.68 (1H, dd, J=2.4 and 8.3 Hz), 6.79 (1H, d, J=2.4 Hz), 6.98 (1H, d, J=8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.7, 21.3, 25.1, 25.6, 29.4, 30.0, 35.1, 38.9, 55.3, 73.7, 110.8, 111.6, 123.9, 128.3, 129.3, 140.5, 147.8, 158.2, 171.2; MS (EI) m/z 300 (M^+); HRMS Calcd for $C_{19}H_{24}O_3$: 300.1726. Found: 300.1741.

(+)-(4aS)-1,4a-Dimethyl-6-methoxy-2,3,4,4a,9,10-hexahydro-2-phenanthrone (+)-7

DMSO (16 mg, 0.21 mmol) and a solution of the alcohol (+)-**6** (28 mg, 0.09 mmol) in CH_2Cl_2 (1 ml) were added successively to a stirred solution of oxalyl chloride (13 mg, 0.10 mmol) in CH_2Cl_2 (2 ml) at −78°C. After being stirred at the same temperature for 20 min, Et_3N (44 mg, 0.43 mmol) was added and the mixture was stirred at −78°C for 10 min and at room temperature for 10 min. Water was added to the mixture, which was extracted with CH_2Cl_2 and the extracts were washed with brine and dried. Removal of the solvent gave a residue which was chromatographed on silica gel (hexane–ethyl acetate, 7:3, v/v) to give (+)-**7**[14] (12 mg, 44%) as a pale yellow oil; $[\alpha]_D$+225 (c=0.41, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.53 (3H, s), 1.84 (3H, s), 1.97–3.10 (8H, m), 3.80 (3H, s), 6.72 (1H, dd, J=2.4 and 8.3 Hz), 6.84 (1H, d, J=2.4 Hz), 7.05 (1H, d, J=8.3 Hz).

(+)-(1S,2S,4aS,10aR)-2-Hydroxy-1-hydroxymethyl-6-methoxy-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene 3

Et_3N (0.38 g, 3.72 mmol) and bromomethyldimethylchlorosilane (0.7 g, 3.72 mmol) was added successively to an ice-cooled solution of the alcohol (+)-**6** (0.64 g, 2.48 mmol) and 4-DMAP (catalytic amount) in CH_2Cl_2 (35 ml) under stirring. After being stirred at room temperature for 0.5 h, water was added to the mixture and the resulting two phases were separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were washed with brine, dried and evaporated to leave the silyl ether **9** (1.03 g, 100%) as a colorless oil which was used for the next reaction without further purification: ^1H NMR ($CDCl_3$) δ 0.33 (6H, s), 1.43 (3H, s), 1.63–2.27 (5H, m), 1.71 (3H, s), 2.53

(2H, s), 2.69 (2H, m), 2.82 (1H, m), 3.79 (3H, s), 4.18 (1H, dd, J=6.4 and 9.1 Hz), 6.65 (1H, dd, J=2.6 and 8.3 Hz), 6.77 (1H, d, J=2.6 Hz), 6.98 (1H, d, J=8.3 Hz); MS (EI) m/z 408 (M^+); HRMS Calcd for $C_{20}H_{29}O_2BrSi$: 408.1121. Found: 408.1095. $NaCNBH_3$ (0.33 g, 4.96 mmol), AIBN (42 mg, 0.25 mmol) and tri-*n*-butyltin chloride (0.08 g, 0.25 mmol) were added successively to a solution of **9** (1.03 g, 2.48 mmol) in ^{t}BuOH (150 ml) and the resulting solution was refluxed for 3 h. After cooling down, removal of the solvent left a residue which was extracted with CH_2Cl_2. The extracts were washed with brine, dried and evaporated to give the cyclic silyl ether **4** (0.9 g, 100%) as an oil, which was submitted to the next reaction without further purification; ^{1}H NMR ($CDCl_3$) δ 0.29 (6H, s), 0.50 (1H, d, J=15.0 Hz), 1.07 (1H, d, J=15.0 Hz), 1.14 (3H, s), 1.23 (3H, s), 0.91–2.00 (6H, m), 2.21 (1H, m), 2.89 (2H, m), 3.64 (1H, dd, J=5.5 and 11.0 Hz), 3.78 (3H, s), 6.68 (1H, dd, J=2.7 and 8.2 Hz), 6.78 (1H, d, J=2.7 Hz), 6.99 (1H, d, J=8.2 Hz); MS (EI) m/z 330 (M^+); HRMS Calcd for $C_{20}H_{30}O_2Si$: 330.2015. Found: 330.2005. $KHCO_3$ (0.49 g, 4.96 mmol) and 30% aqueous H_2O_2 (8.4 g, 74.4 mmol) were added to a solution of **4** (0.9 g, 2.48 mmol) in a mixture of MeOH (15 ml) and THF (15 ml) and the resulting mixture was refluxed for 5 h. After being cooled, the solvent was evaporated to give a residue which was taken up into CH_2Cl_2. The organic phase was washed with brine, dried and evaporated to leave a residue which was chromatographed on silica gel (hexane–ethyl acetate, 1:1, v/v) to give the diol **3** (0.4 g, 56% for the three steps) as a colorless prisms after recrystallization from benzene: mp 182°C; $[\alpha]_D$+108 (c=0.12, $CHCl_3$); IR (neat) cm^{-1} 3327; ^{1}H NMR ($CDCl_3$) δ 1.16 (3H, s), 1.31 (3H, s), 1.41–1.69 (3H, m), 1.88–2.03 (3H, m), 2.30 (1H, dt, J=3.4 and 13.2 Hz), 2.70–2.96 (4H, m), 3.42 (1H, brd, J=11.2 Hz), 3.52 (1H, dd, J=4.6 and 11.2 Hz), 3.77 (3H, s), 4.31 (1H, dd, 1.9 and 11.2 Hz), 6.67 (1H, dd, J=2.4 and 8.3 Hz), 6.77 (1H, d, J=2.4 Hz), 6.96 (1H, d, J=8.3 Hz); MS (EI) m/z 290 (M^+); Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.43; H, 9.03. Found: C, 74.15; H, 9.03.

*(+)-(1S,2S,4aS,10aR)-1-*tert*-Butyldimethylsilyloxymethyl-2-hydroxy-6-methoxy-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene* ***10***

tert-Butyldimethylchlorosilane (0.31 g, 2.76 mmol), imidazole (0.28 g, 5.52 mmol) and 4-DMAP (catalytic amount) were added to a stirred solution of **3** (0.4 g, 1.38 mmol) in DMF (20 ml) at room temperature and the mixture was stirred at the same temperature for 1 h. The solvent was evaporated and the residual mixture was extracted with CH_2Cl_2; the extracts were washed, dried and evaporated to leave a residue which was chromatographed on silica gel (hexane–ethyl acetate, 9:1, v/v) to give **10** (0.51 g, 92%) as a colorless prisms after recrystallization from benzene: mp 101°C; $[\alpha]_D$+66 (c=0.21, $CHCl_3$); IR (neat) cm^{-1} 3483; ^{1}H NMR ($CDCl_3$) δ 0.10 (6H, s), 0.92 (9H, s), 1.18 (3H, s), 1.28 (3H, s), 1.36–2.10 (6H, m), 2.30 (1H, dt, J=3.2 and 13.6 Hz), 2.66–2.79 (2H, m), 3.36 (1H, d, J=5.7 Hz), 3.50 (1H, d, J=10.1 Hz), 3.76 (3H, s), 4.28 (1H, d, J=6.8 Hz, D_2O exchangeable), 4.31 (1H, dd, J=1.5 and 10.3 Hz), 6.66 (1H, dd, J=2.6 and 8.4 Hz), 6.79 (1H, d, J=2.6 Hz), 6.95 (1H, d, J=8.4 Hz); MS (EI) m/z 404 (M^+); Anal. Calcd for $C_{24}H_{40}O_3Si$: C, 71.24; H, 9.97. Found: C, 71.09; H, 9.90.

*(+)-(1S,2S,4aS,10aR)-2-Methoxythiocarbonyloxy-1-*tert*-butyldimethylsilyloxymethyl-6-methoxy-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene* ***11***

A solution of **10** (31 mg, 0.077 mmol) and 1,1-thiocarbonyldiimidazole (82 mg, 0.46 mmol) in toluene (5 ml) was refluxed for 21 h. Removal of the solvent left a residue which was chromatographed on silica gel (hexane–ethyl acetate, 7:3, v/v) to give the corresponding imidazolylthiocarbonyl derivative (27 mg, 78%) as a colorless oil: $[\alpha]_D$+80 (c=0.21, $CHCl_3$); IR (neat) cm^{-1} 1100; ^{1}H NMR ($CDCl_3$) δ 0.11 (6H, s), 0.93 (9H, s), 1.13 (3H, s), 1.30 (3H, s), 1.51–2.57 (7H, m), 2.65–3.02 (2H, m), 3.78 (3H, s), 3.92 (1H, d, J=10.6 Hz), 4.00 (1H, d, J=10.6 Hz), 5.22–5.49 (1H, m), 6.69 (1H, dd, J=2.4 and 8.3 Hz), 6.79 (1H, d, J=2.4 Hz), 6.98 (1H, d, J=8.3 Hz), 7.04 (1H, s), 7.70 (1H, s), 8.40 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.3, 18.5, 20.3, 20.3, 23.2, 25.0, 26.0, 30.8, 37.0, 37.8, 43.6, 51.3, 55.3, 64.0, 90.5, 110.6, 111.4, 118.2, 127.0, 129.9, 130.5, 136.9, 148.0, 149.4, 157.9, 184.0; MS (EI) m/z 514 (M^+); HRMS Calcd for $C_{28}H_{42}O_3N_2SiS$: 514.2685. Found: 514.2706. A solution of the thiocarbonate (30 mg, 0.059 mmol) in MeOH (5 ml) was heated at 60°C for 2 h. Removal of

the solvent left a residue which was extracted with CH_2Cl_2 and the extracts were washed, dried and evaporated. Chromatographic purification of the residue on silica gel (hexane–ethyl acetate, 7:3, v/v) afforded **11** (30 mg, 80%) as a colorless oil: $[\alpha]_D$+54 (c=0.33, $CHCl_3$); IR (neat) cm^{-1} 3483; ^1H NMR ($CDCl_3$) δ 0.06 (6H, s), 0.90 (9H, s), 1.10 (3H, s), 1.34 (3H, s), 1.17–2.18 (6H, m), 2.34 (1H, d, J=12.9 Hz), 2.57–2.96 (4H, m), 3.66 (1H, d, J=10.5 Hz), 3.77 (3H, s), 4.05 (3H, s), 4.00–4.12 (1H, m), 5.09 (1H, dd, J=5.1 and 11.2 Hz), 6.67 (1H, dd, J=2.3 and 8.3 Hz), 6.78 (1H, d, J=2.3 Hz), 6.96 (1H, d, J=8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 5.6, 23.8, 26.7, 28.8, 29.0, 30.4, 31.5, 36.9, 42.9, 43.6, 48.6, 57.0, 60.9, 64.8, 70.2, 95.7, 116.3, 116.8, 133.0, 135.4, 155.7, 163.4, 202.1; MS (EI) m/z 478 (M^+); HRMS Calcd for $C_{26}H_{42}O_4SiS$: 478.2573. Found: 478.2584.

*(+)-(1S,4aS,10aR)-1-*tert*-Butyldimethylsilyloxymethyl-6-methoxy-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene* ***12***

AIBN (1.0 mg, 0.006 mmol) and $^nBu_3SnH$ (35 mg, 0.12 mmol) were added successively to a stirred solution of **11** (27 mg, 0.056 mmol) in toluene (40 ml) and the resulting solution was refluxed for 3 h. After removal of the solvent, the residue was extracted with CH_2Cl_2 and the extracts were washed, dried and evaporated to leave a residue which was chromatographed on silica gel (hexane–ethyl acetate, 9:1, v/v) to give **12** (15 mg, 65%) as colorless prisms: mp 40–41°C; $[\alpha]_D$+42 (c=0.71, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.05 (6H, s), 0.92 (9H, s), 1.00 (3H, s), 1.20 (3H, s), 1.41–1.76 (6H, m), 1.86 (1H, br d, J=13.2 Hz), 1.98 (1H, dd, J=7.2 and 13.2 Hz), 2.27 (1H, br d, J=12.7 Hz), 2.75 (1H, ddd, J=7.1, 11.6 and 16.7 Hz), 2.86 (1H, dd, J=6.2 and 16.7 Hz), 3.52 (1H, d, J=9.8 Hz), 3.71 (1H, d, J=9.8 Hz), 3.78 (3H, s), 6.67 (1H, dd, J=2.3 and 8.7 Hz), 6.82 (1H, d, J=2.3 Hz), 6.95 (1H, d, J=8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 18.3, 19.1, 19.5, 25.6, 25.9, 27.5, 30.3, 35.6, 38.0, 38.8, 39.1, 51.0, 55.2, 65.3, 110.4, 110.8, 127.4, 129.8, 151.3, 157.7; MS (EI) m/z 388 (M^+); HRMS Calcd for $C_{24}H_{40}O_2Si$: 388.2798. Found: 388.2807.

*(+)-*O*-Methylpodocarpinol* ***13***

Tetra-*n*-butylammonium fluoride (0.18 ml of 1.0 M solution in THF solution, 0.18 mmol) was added dropwise to a stirred solution of **12** (35 mg, 0.09 mmol) in THF (5 ml) at room temperature and the resulting solution was further stirred at the same temperature for 8 h. After removal of the solvent, the residue was extracted with CH_2Cl_2 and the extracts were washed, dried and evaporated to leave a residue which was chromatographed on silica gel (hexane–ethyl acetate, 7:3, v/v) to give **13** (15 mg, 65%) as colorless prisms after recrystallization from benzene: mp 89–90°C (mp 90.5–91.5°C)[19]; $[\alpha]_D$+75 (c=0.08, $CHCl_3$) [$[\alpha]_D$+67 ($CHCl_3$)][19]; ^1H NMR ($CDCl_3$) δ 1.05 (3H, s), 1.18 (3H, s), 1.41–1.73 (6H, m), 1.89 (1H, d, J=13.7 Hz), 1.97 (1H, dd, J=7.1 and 13.0 Hz), 2.28 (1H, d, J=12.7 Hz), 2.76 (1H, ddd, J=8.0, 13.0 and 16.4 Hz), 2.87 (1H, dd, J=6.1 and 16.4 Hz), 3.55 (1H, d, J=10.7 Hz), 3.77 (3H, s), 3.85 (1H, d, J=10.8 Hz), 6.59 (1H, dd, J=2.4 and 8.5 Hz), 6.80 (1H, d, J=2.4 Hz), 6.95 (1H, d, J=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 19.0, 19.3, 25.7, 26.8, 30.1, 35.2, 38.0, 38.8, 38.9, 51.2, 55.3, 65.3, 110.3, 110.9, 127.1, 129.8, 151.0, 157.7; MS (EI) m/z 274 (M^+); HRMS Calcd for $C_{18}H_{26}O_2$: 274.1933. Found: 274.1944.

*(+)-*O*-Methylpodocarpic acid* ***2***

DMSO (7 mg, 0.09 mmol) and a solution of the alcohol **13** (12 mg, 0.044 mmol) in CH_2Cl_2 (0.5 ml) were added successively to a stirred solution of oxalyl chloride (13 mg, 0.10 mmol) in CH_2Cl_2 (2 ml) at −78°C. After being stirred at the same temperature for 20 min, Et_3N (15 mg, 0.15 mmol) was added and the mixture was stirred at −78°C for 30 min and at room temperature for 20 min. Water was added to the mixture, which was extracted with CH_2Cl_2 and the extracts were washed with brine and dried. Removal of the solvent provided the corresponding aldehyde (9 mg, 84%) as a colorless oil, which was submitted to the next reaction without further purification; ^1H NMR ($CDCl_3$) δ 1.07 (3H, s), 1.11 (3H, s), 1.15–3.23 (11H, m), 3.77 (3H, s), 6.69 (1H, dd, J=2.5 and 8.3 Hz), 6.87 (1H, d, J=2.5 Hz), 6.99 (1H, d, J=8.3 Hz), 9.83 (1H, s). $NaClO_2$ (4.7 mg, 0.037 mmol) and a buffer solution (3.7 mg of $NaH_2PO_4 \cdot 2H_2O$ in 0.11 ml of water) were added to a solution of the above aldehyde (9

mg, 0.037 mmol) and 2-methyl-2-butene (83 mg, 1.19 mmol) in ^{t}BuOH (0.3 ml) at room temperature and the mixture was stirred for 37 h. The mixture was diluted with water, extracted with CH_2Cl_2 and the extracts were washed, dried and evaporated to leave a residue which was chromatographed on silica gel (hexane–ethyl acetate, 3:7, v/v) to give **2** (1 mg, 11% for the two steps) as colorless prisms after recrystallization from benzene: mp 157°C (mp 158°C)[19]; $[\alpha]_D$+133 (c=0.06, $CHCl_3$) [$[\alpha]_D$+132 ($CHCl_3$)][19]; ^{1}H NMR ($CDCl_3$) δ 1.13 (3H, s), 1.34 (3H, s), 1.39–2.33 (9H, m), 2.60–3.00 (2H, m), 3.77 (3H, s), 6.67 (1H, dd, J=2.4 and 8.3 Hz), 6.80 (1H, d, J=2.4 Hz), 6.96 (1H, d, J=8.3 Hz).

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