Total Synthesis of (±)-Veadeiroic Acid†

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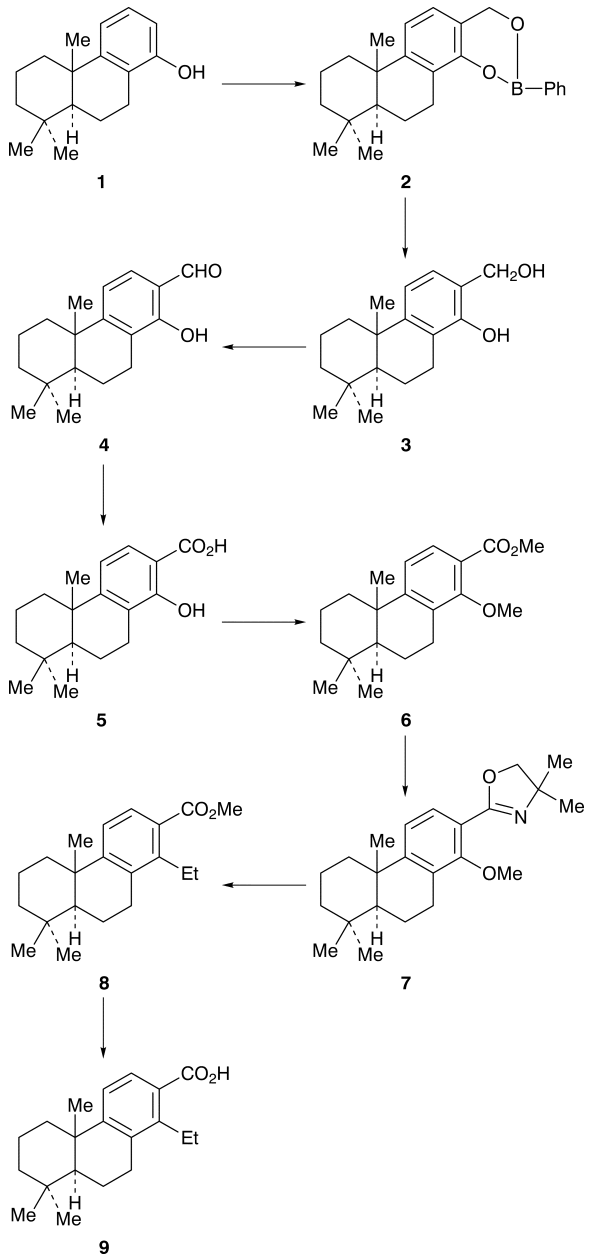
The synthesis of the diterpene veadeiroic acid (**9**) from the phenol **1** is described.

Nagata *et al.*[1] reported an interesting method for the introduction of the hydroxymethylene group at the *ortho* position of phenols which consisted in treatment of the phenol with phenylboronic acid and a catalytic amount of propionic acid followed by addition of paraformaldehyde and propane-1,3-diol. This observation encouraged us to study hydroxymethylation of the already reported[2] phenol **1** by the published procedure[1] to obtain the diol **3** aiming at its further transformation to veadeiroic acid **9**, a diterpene with the rare cleistanthane skeleton whose first total synthesis was reported by Saha and Nasipuri.[3] The present paper records the results of our efforts towards the synthesis of veadeiroic acid **9**.

The phenol **1** on treatment with phenylboronic acid (Aldrich) and paraformaldehyde in the presence of a catalytic amount of propionic acid yielded a boron complex **2** which exhibited almost total disappearance of the hydroxy group in the IR spectrum. In the mass spectrum it presented a peak at *m/z* 242 [M^+–$PhBH_2CO$]. The product **2** without purification was converted into the diol **3** by heating under reflux with benzene and propylene glycol. Its structure was confirmed by spectroscopic properties. The diol **3** on heating with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in 1,4-dioxane[4] afforded the aldehyde **4** in 74% yield. It had a strong peak at *m/z* 272 (M^+) in the mass spectrum and a signal at δ 9.02 (CHO) in the ^1H NMR spectrum. The aldehyde **4** on oxidation[5] with nickel peroxide in aqueous alkaline solution yielded the acid **5** in 60% yield. It exhibited strong IR absorptions, at 3240 and 1710 cm^{-1} and a peak at *m/z* in the mass spectrum. These absorptions at 3240 and 1710 cm^{-1} and a peak at *m/z* 243 in the mass spectrum. These spectroscopic data lent strong support to the structure of the acid **5** which was methylated with an excess of dimethyl sulfate in the presence of potassium carbonate to ester **6**. This exhibited a molecular ion at *m/z* 316 (M^+) and a peak at *m/z* 256 (M^+–MeCOOH) in the mass spectrum and absorption at 1720 cm^{-1} in the IR spectrum.

In order to achieve the total synthesis of veadeiroic acid **9**, the ester **6** was hydrolysed with potassium *tert*-butoxide and dimethyl sulfoxide[6] to obtain the acidic material. Its acid chloride, prepared by treatment with thionyl chloride, on treatment[3] with 2-amino-2-methylpropanol followed by preparative chromatographic purification yielded oxazole derivative **7** as a thick liquid yellow material which though not homogeneous in TLC was almost free from the reference material. The crude product was treated with ethyllithium, prepared by the published procedure,[3] at –40 °C, hydrolysed with 10% methanolic hydrochloric acid to obtain the acidic material and esterified with diazomethane to obtain the already reported[3] methyl veadeiroate **8** whose mp and spectrosciopic data were identical with those reported.[3] This was converted by heating with dimethyl sulfoxide and potassium *tert*-butoxide[6] into the already reported veadeiroic acid **9** whose mp and spectroscopic properties were identical with those reported.



Scheme 1

Experimental

For general methods see Ref. 7.

1-*Hydroxy*-2-*hydroxymethyl*-4b,8,8-*trimethyl*-trans-4b,5,6,7,8,8a,9,10-*octahydrophenanthrene* **3**.—A solution of phenol **1** (2.46 g), phenylboronic acid (2.61 g) and propionic acid (408 mg) in dry benzene (150 ml) was refluxed with azeotropic removal of water. During refluxing paraformaldehyde (4 g) was added over 1.5 h and after 3 h phenylboronic acid (2.04 g) was added and the refluxing continued for 6 h. The usual work-up afforded product **2**, mp 48–53 °C, *m/z* 242 [M^+–$PhBH_2CO$].

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To crude product **2** (3.82 g) dissolved in dry benzene (60 ml) was added propylene glycol (35.25 g) and refluxed for 12 h. The usual work-up followed by chromatographic purification on silica gel (eluent diethyl ether–hexane 8:2) yielded the oily diol **3** (1.92 g, 70%), *m*/*z* 256 (M^+-H_2O) and 241 (M^+-H_2O-Me), $\tilde{\nu}_{max}/cm^{-1}$ 3450 (OH); δ 0.92 (3 H, s), 1.03 (3 H, s), 1.16 (3 H, s), 4b,8,8-Me) 4.62 (2 H, s, CH_2OH), 5.85 (s, 1 H, OH) (very weak), 6.68 (1 H, s) and 6.82 (1 H, s) (aromatic protons) (Found: C, 78.84; H, 9.58. $C_{18}H_{26}O_2$ requires C, 78.79; H, 9.55%).

2-*Formyl*-1-*hydroxy*-4b,8,8-*trimethyl*-trans-4b,5,6,7,8,8a,9,10-*octahydrophenanthrene* **4**.—To a solution of the diol **3** (1.82 g) in dry 1,4-dioxane (50 ml) was added DDQ (2.32 g) and stirred at room temperature for 16 h. The work-up afforded a brown solid which on crystallization afforded the aldehyde **4** (1.33 g, 74%), mp 119–120 °C, *m*/*z* 272 (M^+) and 2.57 (M^+–Me), $\tilde{\nu}_{max}/cm^{-1}$ 1720 (CO); δ 0.94 (3 H, s), 1.08 (3 H, s), 1.18 (3 H, s, 4b,8,8-Me), 5.82 (s, 1 H, OH) (very weak), 6.64 (1 H, s), 6.68 (1 H, s) (aromatic protons), 9.02 (CHO) (Found: C, 79.41; H, 8.91. $C_{18}H_{24}O_2$ requires C, 79.37; H, 8.88%).

2-*Carboxyl*-1-*hydroxy*-4b,8,8-*trimethyl*-trans-4b,5,6,7,8,8a,9,10-*octahydrophenanthrene* **5**.—To a solution of the aldehyde **4** (1.31 g) and sodium hydroxide (2.2 g) in water (50 ml) was added nickel peroxide (7.22 g) and stirred for 2 h at room temperature under nitrogen. The work-up yielded a gummy material which on crystallization with ether afforded the acid **5** (828 mg, 60%), mp 210–212 °C (From Et_2O), *m*/*z* 243 (M^+–COOH) and 228 (M^+–COOH-Me), $\tilde{\nu}_{max}/cm^{-1}$ 3425 (OH) 1710 (CO); δ 0.98 (3 H, s), 1.03 (3 H, s), 1.12 (3 H, s, 4b,8,8-Me), 5.48 (1 H, s, OH) (very weak), 7.48 (1 H, s), 7.68 (1 H, s) (aromatic protons) (Found: C, 75.02; H, 8.43. $C_{18}H_{24}O_3$ requires C, 74.97; H, 8.39%).

1-*Methoxy*-2-*methoxycarbonyl*-4b,8,8-*trimethyl*-trans-4b,5,6,7,8,8a,9,10-*octahydrophenanthrene* **6**.—To a solution of the acid **5** (800 mg) in acetone (10 ml) was added anhydrous potassium carbonate (208 mg) and dimethyl sulfate (1.12 g) and then refluxed for 12 h. Work-up followed by chromatographic purification (diethyl ether–hexane 6:4) afforded the ester **6** (614 mg, 70%), mp 165–166 °C (from Et_2O), *m*/*z* 316 (M^+) and 256 (M^+–MeCOOH), $\tilde{\nu}_{max}/cm^{-1}$ 1730 (CO), δ 0.96 (3 H, s), 1.05 (3 H, s), 1.14 (3 H, s, 4b,8,8-Me), 3.58 (3 H, s), 3.62 (s, 3 H) (1,2-OMe), 7.02 (1 H, d), 7.08 (1 H, d) (each $J = 8$ Hz) (aromatic protons) (Found: C, 75.95; H, 8.95. $C_{20}H_{28}O_3$ requires C, 75.91; H, 8.92%).

(±)-*Methyl Veadeiroate* **8**.—To a solution of the ester **6** (602 mg) in dimethyl sulfoxide (5 ml) was added freshly prepared potassium *tert*-butoxide (300 mg) and heated in an oil-bath (90 °C) for 40 min. Work-up afforded an acidic material (550 mg), mp 158–164 °C, $\tilde{\nu}_{max}/cm^{-1}$ 3260 (OH) and 1710 (CO). To the crude acid material dissolves in chloroform (20 ml) was added thionyl chloride (5 ml) and stirred for 17 h. Work-up afforded the chloride derivative which was dissolved in dichloromethane (10 ml), added to 2-amino-2-methylpropan-1-ol (5 ml) in dichloromethane (10 ml) in an ice-bath and then stirred at room temperature for 5 h. Work-up afforded a dark oily material which was treated with thionyl chloride (3 ml), stirred for 30 min and ether (50 ml), added and stirred. After decantation of the ether, the gummy material was treated with aqueous sodium hydroxide solution (10%, 30 ml). The usual work-up afforded a viscous oil which was placed on a silica gel plate (2 mm, PF_{254}, Merck) and eluted with 45% ethyl acetate–hexane to afford the oxazolinone derivative **7** (457 mg), *m*/*z* 343 (M^+), $\tilde{\nu}_{max}/cm^{-1}$ 1650. To the derivative **7** (455 mg) in tetrahydrofuran (15 ml) was added an excess of ethyllithium in hexane (4 ml) under nitrogen. The mixture was stirred at −45 °C for 3 h and then at room temperature for 18 h. Work-up afforded an oily material which showed a very weak ^1H NMR signal of the methoxy group.

The crude compound was hydrolysed with hydrochloric acid (10%, 25 ml) by heating for 1 h and then further refluxing with methanolic hydroxide (10%, 40 ml) for 1 h. Work-up, esterification with diazomethane followed by chromatographic purification (hexane: 1:1) afforded methyl vadeiroate **8** (179 mg, 30%), mp 78–81 °C (from aqueous acetone) (lit.,[3] 78–80 °C), *m*/*z* 314 (M^+), $\tilde{\nu}_{max}/cm^{-1}$ 1720 (CO), δ 0.96 (3 H, s), 0.98 (3 H, s), 1.21 (3 H, s), 4b,8,8-Me), 1.22 (3 H, t, $J = 6$, $ArCH_2Me$), 2.84–3.08 (4 H, m, $2 \times ArCH_2$), 3.68 (3 H, s, OMe), 7.23 (1 H, d, $J = 8$) and 7.60 (1 H, d, $J = 9$ Hz) (aromatic protons) (Found: C, 80.04; H, 9.74. $C_{21}H_{30}O_2$ requires C, 80.21; H, 9.62%).

(±)-*Veadeiroic Acid* **9**.—The ester **8** (150 mg) in dimethyl sulfoxide (4 ml) was treated with potassium *tert*-butoxide (100 mg) and heated for 40 min at 90 °C. Work-up followed by crystallization afforded veadeiroic acid **9** (80 mg, 56%), mp 204–206 °C (aqueous acetone), (lit.,[3] 204–205 °C), *m*/*z* 300 (M^+) and 285 (M^+–Me); $\tilde{\nu}_{max}/cm^{-1}$ 3442–2845 (br); δ 0.94 (3 H, s), 0.98 (3 H, s), 1.21 (3 H, s), 1.24 (1 H, t, $J = 8$, $ArCH_2Me$), 286–3.02 (4 H, m, $2 \times ArCH_2$), 3.56 (3 H, s, OMe), 7.23 (1 H, d, $J = 8$) and 7.60 (1 d, d, $J = 8$ Hz) (aromatic protons) (Found: C, 79.82; H, 9.52. $C_{20}H_{28}O_2$ requires C, 79.95; II, 9.39%).

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