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SYNTHESIS OF (±)-MAYTENOQUINONE, (±)-DISPERMOL, AND (±)-DISPERMONE

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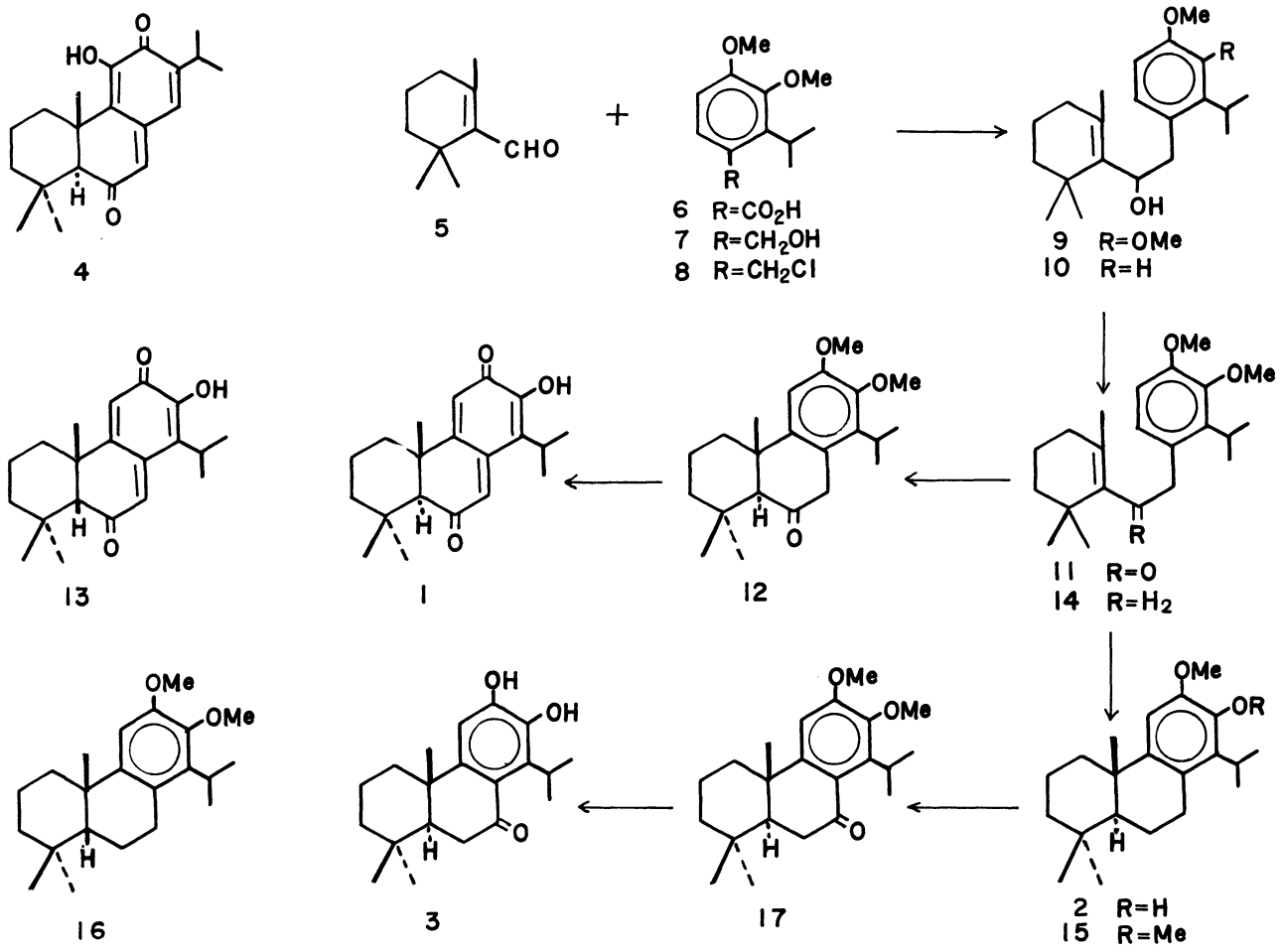
Three tricyclic diterpenes, maytenoquinone (1), dispermol (2), and dispermone (3), were synthesized as racemic forms starting from β-cyclocitral (5) by a simple route. Condensation of 5 with 3,4-dimethoxy-2-isopropylbenzyl chloride (8) afforded an alcohol (9) which was successively subjected to oxidation, intramolecular cyclization, demethylation, and oxidation to give (±)-1. Reductive cleavage of a hydroxyl group in 9 followed by cyclization gave (±)-2 which was further converted into (±)-3.

Recently, Martin[1] has reported the isolation and structural elucidation of three new diterpenes possessing a 12-oxygenated totarol skeleton; maytenoquinone (1), dispermol (2), and dispermone (3). Among natural diterpenes, maytenoquinone (1) is a novel tricyclic diterpene having an unique quinone-methide chromophore such as that in taxodione (4)[2] which has shown significant tumor-inhibiting activity. In view of the close structural similarity between maytenoquinone and taxodione, synthesis of 1 was deemed of interest. This communication[3] describes the total syntheses of (±)-1, (±)-2, and (±)-3 starting from β-cyclocitral (5).[4]

Esterification of 3,4-dimethoxy-2-isopropylbenzoic acid (6)[5] with diazomethane followed by reduction with lithium aluminum hydride afforded a benzyl alcohol derivative (7) which was then treated with thionyl chloride (r.t., 1.5 hr) to give 3,4-dimethoxy-2-isopropylbenzyl chloride (8)[5], NMR: 1.35 (d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.23 (m, J=7 Hz, $-C\underline{H}(CH_3)_2$), 3.81 (s, $2-OCH_3$), 4.51 (s, $-CH_2-$), 6.57 and 6.83 (each d and J=8 Hz, aromatic protons). Condensation of β-cyclocitral (5) with 8 in the presence of lithiun naphthalenide in tetrahydrofuran was carried out at 0-10°C for 2 hr in a stream of nitrogen. Since spectral data of the crude product showed the

presence of a small amount of phenolic compound, it was methylated with methyl iodide and anhydrous potassium carbonate in refluxing methyl ethyl ketone (6 hr). The product was then purified by column chromatography on silica gel to give the desired alcohol (9: 54%), mp 72-72.5°C, Mass: m/e 346 (M^+), IR: 3560 cm^{-1}, NMR: 0.94 and 1.08 (each s, $-\overset{|}{C}(CH_3)_2$), 1.32 (d, J=7 Hz, $-CH(\underline{CH}_3)_2$), 1.89 (s, $-\overset{|}{C}=\overset{|}{C}CH_3$), 3.77 and 3.79 (each s, 2-OCH_3), 4.24 (dd, J=4 and 9 Hz, $-\overset{|}{C}\underline{H}OH$), 6.60 and 6.72 (each d and J=9 Hz, aromatic protons), along with a demethoxylated alcohol (10: 3%), IR: 3560 cm^{-1}, NMR: 0.95 and 1.09 (each s, $-\overset{|}{C}(CH_3)_2$), 1.22 and 1.24 (each d and J=7 Hz, $-CH(\underline{CH}_3)_2$), 1.90 (s, $-\overset{|}{C}=\overset{|}{C}CH_3$), 3.73 (s, $-OCH_3$), 4.30 (dd, J=4 and 9 Hz, $-\overset{|}{C}\underline{H}OH$), 6.57 (dd, J=2 and 8 Hz), 6.68 (d, J=2 Hz), and 6.98 (d, J=8 Hz) (aromatic protons). Oxidation of 9 with a chromium trioxide-pyridine complex (5°C, 2 hr) gave the corresponding α,β-unsaturated ketone (11: 42%[6]), mp 81-82.5°C, IR: 1690 cm^{-1}, NMR: 3.72 (s, $-COCH_2-$), which was then submitted to intramolecular cyclization with anhydrous aluminium chloride in refluxing toluene (6 hr). Because of the presence of phenolic compound, the crude product was immediately methylated with methyl iodide and anhydrous potassium carbonate in refluxing methyl ethyl ketone (6 hr) to give (±)-12,13-dimethoxytotara-8,11,13-trien-6-one (12: 52%), mp 144-145°C, IR: 1710 cm^{-1}, NMR: 1.05 and 1.12 (each s, $-\overset{|}{C}(CH_3)_2$), 1.29 (s, $C_{10}-CH_3$), 1.29 (d, J=7 Hz, $-CH(\underline{CH}_3)_2$), 2.35 (s, C_5-H), 3.41 (s, $-COCH_2-$), 3.78 and 3.80 (each s, 2-OCH_3), 6.66 (s, $C_{11}-H$). Demethylation of 12 with boron tribromide in dichloromethane at 0-5°C for 1 hr and then at room temperature for 30 min followed by column chromatography of the resulting phenol on silica gel afforded (±)-maytenoquinone (1: 69%), mp 173-174°C, IR (KBr): 3320, 1670, 1620 cm^{-1}, NMR ($CDCl_3$): 1.17 and 1.26 (each s, $-\overset{|}{C}(CH_3)_2$), 1.26 (s, $C_{10}-CH_3$), 1.31 and 1.37 (each d and J=7 Hz, $-CH(\underline{CH}_3)_2$), 2.48 (s, C_5-H), 3.06 (m, J=7 Hz, $-\underline{CH}(CH_3)_2$), 6.37 and 6.59 (each d and J=2 Hz, C_7-H and $C_{11}-H$), 7.12 (s, $C_{13}-OH$). On the other hand, demethylation of 12 with hydrobromic acid in refluxing acetic acid (2.5 hr) and subsequent chromatographic purification on silica gel yielded (±)-cis-maytenoquinone (13: 82%), mp 184-187°C (sintered at ca. 160°C), IR: 3370, 1650, 1630 cm^{-1}, NMR ($CDCl_3$): 0.62 and 0.97 (each s, $-\overset{|}{C}(CH_3)_2$), 1.18 (s, $C_{10}-CH_3$), 1.31 and 1.37 (each d and J=7 Hz, $-CH(\underline{CH}_3)_2$), 2.26 (s, C_5-H), 6.45 and 6.64 (each d and J=2 Hz, C_7-H and $C_{11}-H$), 7.20 (s, $C_{13}-OH$).

Subsequently, our attention was directed toward the syntheses of dispermol (2) and dispermone (3). For reductive cleavage of a hydroxyl group, the alcohol 9 was treated with dichloroaluminium hydride[7] in dry ether (r.t., 3 hr) and the resulting crude product[8] was further reduced by catalytic hydrogenation using Pd-C in acetic



acid to give the corresponding phenethyl derivative (14: 60%). Intramolecular cyclization of 14 with anhydrous aluminium chloride in refluxing benzene (4 hr) gave three products (2, 15, and 16): (±)-dispermol (2: 34%), mp 125-126°C, IR: 3538 cm^{-1}, NMR ($CDCl_3$): 0.92 and 0.95 (each s, $-\dot{C}(CH_3)_2$), 1.20 (s, C_{10}-CH_3), 1.34 (d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.84 (s, $-OCH_3$), 5.62 (s, C_{13}-OH), 6.70 (s, C_{11}-H), (pyridine-d_5): 0.90 and 0.93 (each s, $-\dot{C}(CH_3)_2$), 1.21 (s, C_{10}-CH_3), 1.61 and 1.63 (each d and J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.72 (s, $-OCH_3$), 6.82 (s, C_{11}-H); (±)-12,13-dimethoxytotara-8,11,13-triene (15: 36%), mp 133.5-134°C, NMR: 0.92 and 0.94 (each s, $-\dot{C}(CH_3)_2$), 1.19 (s, C_{10}-CH_3), 1.24 and 1.26 (each d and J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.73 (s, 2-OCH_3), 6.58 (s, C_{11}-H); (±)-12,13-dimethoxy-5βH-totara-8,11,13-triene (16: 9%), NMR: 0.43 and 0.94 (each s, $-\dot{C}(CH_3)_2$), 1.15 (s, C_{10}-CH_3), 1.22 and 1.30 (each d and J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.80 (s, 2-OCH_3), 6.66 (s, C_{11}-H). By a similar treatment with anhydrous aluminium chloride, the dimethyl ether 15 was partially demethylated to (±)-2. The presence of a phenolic hydroxyl group at C-13 position in (±)-2 was supported by pyridine-induced solvent shifts ($\Delta = \delta_{CDCl_3} - \delta_{C_5D_5N}$)[9] of isopropyl methyls ($\Delta \fallingdotseq -0.28$ ppm) and an aromatic

proton (Δ = - 0.12 ppm) in the NMR spectrum. Methylation of (±)-2 with methyl iodide in methyl ethyl ketone in the presence of potassium carbonate (reflux, 14 hr) gave 15 (82%) which was then oxidized with chromium trioxide in acetic acid (r.t., 6 hr) to afford the corresponding 7-oxo compound (17: 52%), mp 129-130°C, IR: 1660 cm^{-1}, NMR (90 MHz): 0.93 and 1.02 (each s, $-\overset{|}{C}(CH_3)_2$), 1.12 (s, C_{10}-CH_3), 1.23 and 1.31 (each d and J=7 Hz, $-CH(\underline{CH}_3)_2$), 3.76 and 3.83 (each s, 2-OCH_3), 6.58 (s, C_{11}-H). The ketone 17 was finally demethylated with boron tribromide in dichloromethane (r.t., 4 hr) to give (±)-dispermone (3: 88%), mp 242-245°C (sintered at ca. 230°C), IR: 3595, 3540, 3200, 1655 cm^{-1}, NMR (acetone-d_6): 0.92, 1.01, and 1.08 (each s, $-\overset{|}{C}(CH_3)_2$ and C_{10}-CH_3), 1.30 and 1.38 (each d and J=7 Hz, $-CH(\underline{CH}_3)_2$), 3.86 (m, J=7 Hz, $-\underline{CH}(CH_3)_2$), 6.73 (s, C_{11}-H). The spectra of the synthetic (±)-1, (±)-2, and (±)-3 were respectively identical with those published[1] for natural maytenoquinone, dispermol, and dispermone.

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3) Although the formulas depicted represent only one enantiomer, they are taken to indicate racemates. IR spectra were taken in $CHCl_3$ and NMR spectra in CCl_4 at 60 MHz unless otherwise specified. Their chemical shifts are presented in terms of δ values.

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8) The product contained significant amounts of diene compound which was produced by dehydration of the hydroxyl group in 9.

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