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THE REVISED STRUCTURE OF DISPERMOL AND TOTAL SYNTHESIS OF (-)-DISPERMONE, (+)-DISPERMOL, AND (+)-MAYTENOQUINONE

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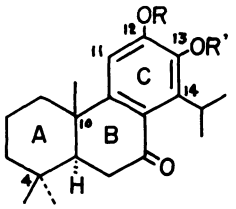
The total syntheses of natural tricyclic diterpenes, (-)-dispermone (1), (+)-dispermol (5), and (+)-maytenoquinone (3), were successfully achieved starting from (R)-(-)-α-cyclocitral (6) and the proposed structure (2) for dispermol was revised to 12-hydroxy-13-methoxytotara-8,11,13-triene (5).

Recently, three new tricyclic diterpenes possessing a totarane skeleton, dispermone, dispermol, and maytenoquinone, were isolated from Maytenus dispermus by Martin[1] and the structures of these natural products were assigned respectively to be 1, 2, and 3, on the basis of the chemical and spectroscopic studies. Among these natural diterpenes, maytenoquinone (3) was especially of interest, because it has a unique quinone-methide chromophore such as that in taxodione (4)[2] which has shown significant tumor-inhibiting activity.

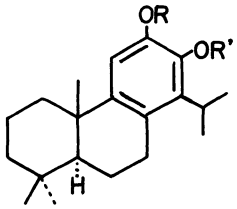
We first investigated the syntheses of these natural diterpenes as the racemic forms and the result has been reported in a previous communication.[3] Subsequently, we attempted the syntheses of the optically-active compounds in order to obtain further confirmation of the proposed structures and to elaborate the general synthetic route for the optically-active tricyclic diterpenes. This communication describes the simple total syntheses of natural (-)-dispermone (1), (+)-dispermol (5), and (+)-maytenoquinone (3) starting from (R)-(-)-α-cyclocitral (6), $[\alpha]_D$ - 712° (EtOH). From the present study, it is suggested that the proposed structure (2) for dispermol should now be revised to 12-hydroxy-13-methoxytotara-8,11,13-triene (5).

The Wittig reaction of 6 with 2-isopropyl-3,4-dimethoxybenzyltriphenylphosphonium chloride (7)[4] in hexane in the presence of butyllithium was carried out (7-10°C, 4 h)

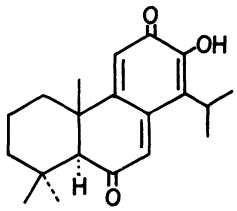
under nitrogen atmosphere and the product was purified by column chromatography on silica gel to afford the desired styrene derivative (8: 77%), $[\alpha]_D$[5] - 258°, NMR:[5] 0.91 and 0.96 (each 3H and s, $-\overset{|}{C}(CH_3)_2$), 1.32 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.67 (3H, bs, $=\overset{|}{C}CH_3$), 3.37 (1H, m, $-C\underline{H}(CH_3)_2$), 3.77 and 3.80 (each 3H and s, $2\text{-}OCH_3$), 5.42 (1H, m, $-CH=\overset{|}{C}-$), 5.55 (1H, dd, J=9 and 15 Hz, $-\overset{|}{C}H-C\underline{H}=CH-$), 6.61 (1H, d, J=15 Hz, $-\overset{|}{C}H-CH=C\underline{H}-$), 6.58 and 6.90 (each 1H, d, and J=9 Hz, aromatic protons). In the NMR spectrum of 8 the vicinal coupling constant (J=15 Hz) of vinyl protons suggested the presence of a trans disubstituted double bond. The ethanol solution of 8 was submitted to partial catalytic-hydrogenation over 5% Pd-C to give the corresponding dihydro derivative (9: 84%), $[\alpha]_D$ - 90.3°, which was then cyclized with anhydrous aluminium chloride in benzene (25-30°C, 30 min) to yield the cis- (10: 34%), $[\alpha]_D$ - 36.4°, and trans-isomer (11: 43%), $[\alpha]_D$ + 32.4°. 10; NMR: 0.43 and 0.94 (each 3H, and s, $-\overset{|}{C}(CH_3)_2$), 1.14 (3H, s, $C_{10}\text{-}CH_3$), 1.21 and 1.30 (each 3H, d, and J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.79 and 3.81 (each 3H and s, $2\text{-}OCH_3$), 6.66 (1H, s, C_{11}-H). 11; NMR: 0.93 and 0.97 (each 3H and s, $-\overset{|}{C}(CH_3)_2$), 1.20 (3H, s, $C_{10}\text{-}CH_3$), 1.28 (6H, bd, J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.76 (6H, s, $2\text{-}OCH_3$), 6.59 (1H, s, C_{11}-H). The cis-configuration of the A/B ring junction in 10 was supported by its NMR spectrum, which showed signal due to the $C_{4\beta}$ methyl group at very high field (δ 0.43 ppm) owing to the shielding effect of aromatic C-ring. The crystallization of the trans-isomer (11) from methanol gave the optically pure compound, mp 89-91°C, $[\alpha]_D$ + 50.2°, and this was then oxidized with Jones reagent (16°C, 30 min) to afford the 7-oxo compound (12: 74%), $[\alpha]_D$ - 19.2°, IR: 1660 cm^{-1}. The demethylation of 12 with boron tribromide in dichloromethane (0°C, 2 h) gave (-)-dispermone (1: 92%), mp 262-267°C, $[\alpha]_D$ - 47.3° (EtOH), NMR (acetone-d_6): 0.94 and 1.02 (each 3H and s, $-\overset{|}{C}(CH_3)_2$), 1.09 (3H, s, $C_{10}\text{-}CH_3$), 1.33 and 1.42 (each 3H, d, and J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.92 (1H, m, $-C\underline{H}(CH_3)_2$), 6.78 (1H, bs, C_{11}-H). In order to obtain (+)-dispermol, 11 was partially demethylated[3] with anhydrous aluminium chloride in refluxing benzene (3 h) to give the monomethyl ether (2: 77%),[6] mp 87-88.5°C, $[\alpha]_D$ + 50.2°, IR: 3540 cm^{-1}, NMR ($CDCl_3$): 0.93 and 0.95 (each 3H and s, $-\overset{|}{C}(CH_3)_2$), 1.20 (3H, s, $C_{10}\text{-}CH_3$), 1.35 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.25 (1H, m, $-C\underline{H}(CH_3)_2$), 3.84 (3H, s, $-OCH_3$), 5.62 (1H, s, -OH), 6.68 (1H, s, C_{11}-H). The mp of the synthetic 2 is largely different from the reported value for natural dispermol (mp 164-166°C, $[\alpha]_D$ + 37°). However, since the NMR spectra of the synthetic 2 and dispermol were very similar, the structure of the natural product might be expected to be 12-hydroxy-13-methoxytotara-8,11,13-triene (5). Therefore, the



1 R=R'=H
12 R=R'=Me
13 R=$CH_2C_6H_5$, R'=H
14 R=$CH_2C_6H_5$, R'=Me



2 R=Me, R'=H
5 R=H, R'=Me
11 R=R'=Me



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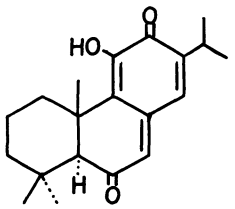

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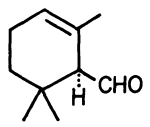

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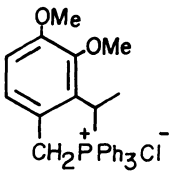

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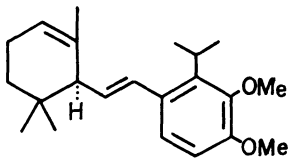

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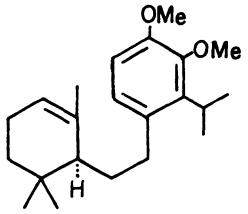

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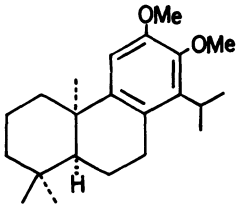

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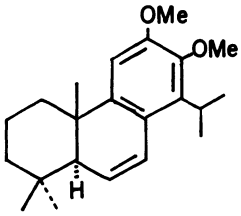

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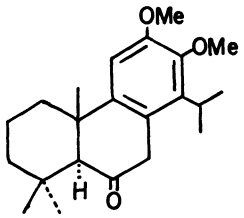

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conversion of (-)-dispermone (1) into 5 was carried out as follows. The synthetic 1 was partially benzylated with benzyl chloride in refluxing methyl ethyl ketone (5.5 h) in the presence of potassium iodide and potassium carbonate to afford the corresponding 12-benzyl ether (13: 99%). The presence of a phenolic hydroxyl group at C-13 position in 13 was supported by pyridine-induced solvent shift ($\Delta = \delta_{CDCl_3} - \delta_{C_5D_5N}$)[7] of isopropyl methyls (Δ =-0.42 ppm) in its NMR spectrum.[8] The methylation of 13 with methyl iodide gave the methyl ether (14: 94%), which on catalytic hydrogenation over platinium oxide in ethanol containing a small amount of perchloric acid afforded (+)-dispermol (5: 66%),[9] mp 166.5-167.5°C, $[\alpha]_D$ + 43.5°, IR: 3550, 3360 cm^{-1}; NMR ($CDCl_3$):[10] 0.95 (6H, bs, $-\overset{1}{C}(CH_3)_2$), 1.19 (3H, s, $C_{10}-CH_3$), 1.34 (6H, d, J=7 Hz, $-CH(\underline{CH_3})_2$), 3.37 (1H, m, $-\underline{CH}(CH_3)_2$), 3.79 (3H, s, $-OCH_3$), 5.2 (1H, bs, -OH), 6.80 (1H, s, $C_{11}-H$). Subsequently, our attention was directed toward the synthesis of (+)-maytenoquinone (3). For this purpose, 12 was reduced with lithium aluminium hydride in ether (2 h) and the resulting alcohol was dehydrated with dilute hydrochloric acid to give the dehydro derivative (15: 85%), mp 96-97°C, $[\alpha]_D$ - 100°, NMR:

5.83 and 6.76 (each 1H, dd, and J=3 and 10 Hz, C_6-H and C_7-H). This was oxidized with m-chloroperbenzoic acid in dichloromethane (5°C, 1.5 h) and then treated with dilute hydrochloric acid in refluxing methanol (30 min) under nitrogen atmosphere to afford the 6-oxo compound (16: 69%), $[\alpha]_D$ + 117°, IR: 1707 cm^{-1}. The demethylation of 16 with boron tribromide in dichloromethane (0°C, 1 h) followed by oxidation with silver oxide in refluxing chloroform (1 h) gave (+)-maytenoquinone (3: 54%), mp 156-158°C, $[\alpha]_D$ + 407°, IR: 3395, 1665, 1625 cm^{-1}, NMR ($CDCl_3$): 1.19 and 1.27 (each 3H and s, $-\overset{|}{C}(CH_3)_2$), 1.27 (3H, s, C_{10}-CH_3), 1.33 and 1.38 (each 3H, d, and J=7 Hz, $-CH(\underline{C}H_3)_2$), 2.51 (1H, s, C_5-H), 3.10 (1H, m, $-C\underline{H}(CH_3)_2$), 6.41 and 6.64 (each 1H, d, and J=2 Hz, 2-$COCH=\overset{|}{C}-$), 7.25 (1H, s, -OH).

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1) J. D. Martin, Tetrahedron, 29, 2553 (1973).

2) S. M. Kupchan, A. Karim, and C. Marcks, J. Am. Chem. Soc., 90, 5923 (1968); J. Org. Chem., 34, 3912 (1969).

3) T. Matsumoto and T. Ohmura, Chem. Lett., 1977, 335.

4) The Wittig reagent (7), mp 243-245°C, was prepared from 2-isopropyl-3,4-dimethoxybenzyl chloride[3] and triphenylphosphine in refluxing benzene (6 h).

5) The IR spectra and optical rotations were measured in chloroform. The NMR spectra were taken in carbon tetrachloride, unless otherwise stated. The chemical shifts are presented in the δ values; s: singlet, bs: broad singlet, d: doublet, bd: broad doublet, dd: double doublet, m: multiplet.

6) The IR and NMR spectra of 2 were identical in every respect with those of the authentic racemate.[3]

7) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, J. Am. Chem. Soc., 90, 5480 (1968).

8) The NMR spectrum of 13 in pyridine-d_5: 0.81 and 0.90 (each 3H and s, $-\overset{|}{C}(CH_3)_2$), 1.07 (3H, s, C_{10}-CH_3), 1.74 and 1.87 (each 3H, d, and J=7 Hz, $-CH(\underline{C}H_3)_2$), 4.44 (1H, m, $-C\underline{H}(CH_3)_2$), 5.25 (2H, s, $-OCH_2-$), 6.93 (1H, s, C_{11}-H).

9) The physical and spectral data of the synthetic 5 were consistent with those reported for dispermol.[1]

10) The pyridine-induced solvent shifts of an aromatic proton (Δ=-0.33 ppm) and isopropyl methyls (Δ=-0.15 ppm) and methine (Δ=-0.06 ppm) suggested the presence of a hydroxyl group at C-12 position.

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