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TOTAL SYNTHESIS OF (±)-SHONANYL METHYL ETHER AND (±)-FERRUGINYL METHYL ETHER

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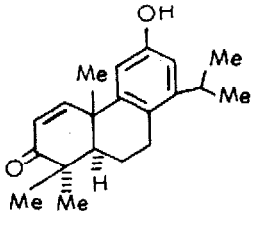
Summary : An efficient reductive methylation of the tricyclic ketone 12 in anhydrous ammonia provided the β,γ-unsaturated ketone 15 in high yield which was subsequently converted into (±)-shonanyl methyl ether (3) and (±)-ferruginyl methyl ether (6).

Shonanol, a tricyclic diterpene, was isolated from Libocedrus formosana by Lin and Liu[1]. On the basis of spectral studies, the structure 1 was tentatively proposed[1] for shonanol. This structure is unique among the naturally occurring tricyclic diterpenes in that it contains an α,β-unsaturated carbonyl group in ring A and a hydroxyl group at the position meta to an isopropyl group in ring C. Matsumoto et al[2]. synthesised 1 as well as several of its isomers and came to the conclusion that shonanol should be represented by the structure 2. A synthesis of (+)-shonanol (2) was also carried out by Matsumoto and his coworkers[3] utilising methyl (+)-12-methoxyabieta-8,11,13-trien-18-oate (4) as the starting material. In connection with our studies on the synthesis of hydrophenanthrenes related to diterpenes, we have accomplished a total synthesis of (±)-shonanyl methyl ether (3) starting from 2-isopropylanisole. The salient feature of our synthesis is very efficient and clean reductive methylation of the aromatic ketone 12 to provide the β,γ-unsaturated ketone 15 in high yield and subsequent utilisation of the double bond in the ring B of 15 to generate the required trans-stereochemistry of the A/B ring juncture. The diterpene ferruginol (5) served as the key intermediate in the synthesis[4] of several important natural products, e.g. taxodione, royleanone, taxoquinone, cryptojaponol etc. During the present study, a synthesis of ferruginyl methyl ether (6) from 15 has also been accomplished.



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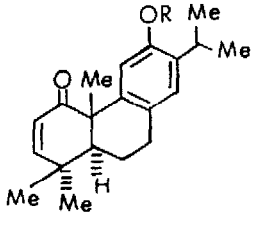
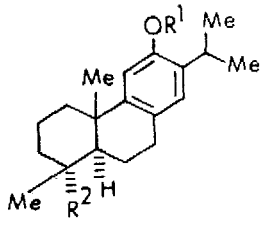
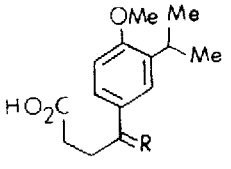


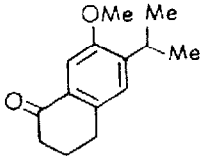
2, R = H
3, R = Me



4, R^1 = Me, R^2 = CO_2Me
5, R^1 = H, R^2 = Me
6, R^1 = R^2 = Me



7, R = O
8, R = H_2



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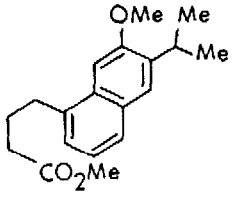

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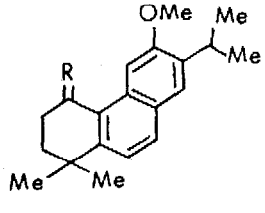
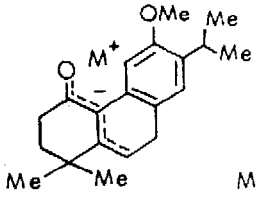
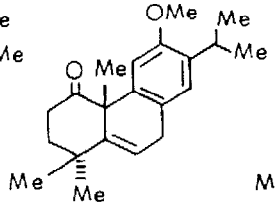


11, R = H_2
12, R = O



13, M = K
14, M = Li



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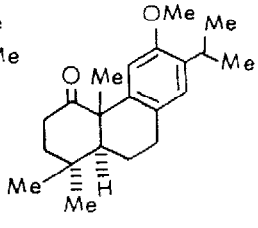

16

Succinoylation of 2-isopropylanisole in the presence of anhydrous $AlCl_3$ afforded the keto-acid 7 (75%), m.p. 132-133°. Reduction of 7 with $NaBH_4$ in aqueous NaOH followed by catalytic hydrogenolysis (H_2, 10% Pd on carbon) of the crude proudct in AcOH provided the acid 8 in 84% overall yield. Intramolecular cyclisation of 8 with polyphosphoric acid furnished the 1-tetralone derivative 9 (76%) [^{1}H-NMR (CCl_4) : δ 1.19 (d,6H,J=7Hz), 1.80-2.97(m,6H),3.30(m,1H),3.87(s,3H),6.95(s,1H),7.35(s,1H)]. Reformatsky reaction of 9 with methyl γ-bromocrotonate and subsequent dehydrogenation of the crude product with sulphur in refluxing diphenyl ether provided the methyl ester 10 in 67% overall yield. Treatment of 10 with an excess of MeMgI in anhydrous Et_2O followed by cyclisation of the resulting crude carbinol with polyphosphoric acid afforded the hydrophenanthrene 11 (75%), m.p.84-85°. Oxidation of 11 with $Na_2Cr_2O_7$ in AcOH furnished the aromatic ketone 12 (60%), m.p. 88-89°; ^{1}H-NMR ($CDCl_3$): δ 1.30 (d,6H,J=7Hz) 1.43(s,6H),2.10(t,2H,J=7Hz),2.87(t,2H,J=7Hz),3.44(m,1H),4.03(s,3H),7.43(d,1H,J=8Hz),7.61(s,1H),7.95(d, 1H,J=8Hz),8.93(s,1H). To perform reductive methylation of the ketone 12, a solution of 12 in dry THF containing tert-butyl alcohol (3 equiv.) was added rapidly under nitrogen to a stirred solution of K(3 equiv.) in distilled liquid ammonia. After 6 min, the resulting potassium enolate 13 was converted in the reaction medium into lithium enolate 14 by treatment with dry LiBr in THF. After stirring for another 15 min, an excess of MeI was added followed immediately by aqueous THF. Evaporative distillation furnished the pure alkylated ketone 15 in 95% yield [^{1}H-NMR ($CDCl_3$): δ 1.18 (d,6H,J=7Hz),1.23(s,6H) 1.35(s,3H),1.80(t,2H,J=7Hz),2.49(t,2H,J=7Hz),3.29(m,1H),3.37(d,1H,J=4Hz),3.77(s,3H),6.08(t,1H,J=4Hz), 6.53(s,1H),7.08(s,1H)]. In order to generate trans-stereochemistry at the A/B ring juncture, the ketone 15 was reduced with $NaBH_4$ and the resulting crude product subjected to catalytic hydrogenation in AcOH in the presence of 10% palladium on carbon. Jones oxidation followed by crystallisation of the product afforded the trans-fused ketone 16 in 64% yield, m.p. 85°; ^{1}H-NMR ($CDCl_3$): δ 1.08(s,6H), 1.14(d,6H,J=7Hz),1.50(s,3H),1.67-2.87(m,9H),3.22(m,1H),3.82(s,3H),6.77(s,1H),7.31(s,1H). Huang-Minlon reduction of 16 provided (±)-ferruginyl methyl ether (6)[5](82%) [^{1}H-NMR (CCl_4): δ 0.94(s,6H),1.16(d,6H, J=7Hz),1.18(s,3H),1.33-2.90(m,11H),3.19(m,1H),3.75(s,3H),6.56(s,1H),6.68(s,1H)]. Bromination of the ketone 16 with Br_2 in AcOH at 15° and subsequent dehydrobromination of the resulting α-bromoketone with LiBr and Li_2CO_3 in dimethylformamide at 120° afforded (±)-shonanyl methyl ether (3) in 70% yield, m.p. 110°; IR (KBr): 1675 cm^{-1}; ^{1}H-NMR (CCl_4): δ 1.16(d,6H,J=7Hz),1.18(s,6H),1.47(s,3H),3.20(m,1H),3.82 (s,3H),5.77(d,1H,J=10Hz),6.38(d,1H,J=10Hz),6.65(s,1H),7.21(s,1H). The spectral data of 3 are in good agreement with those reported[3] in the literature.

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