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REDUCTIVE METHYLATION OF α-NAPHTHYL KETONES
STEREOCONTROLLED SYNTHESIS OF TRANS-OCTAHYDROPHENANTHRENES RELATED TO DITERPENES

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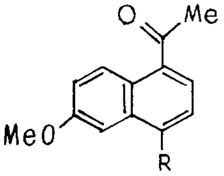
Summary: Reductive methylation of the tricyclic ketones 12 and 13 with lithium in liquid ammonia afforded the β,γ-unsaturated ketones 14 and 15 respectively which were stereoselectively converted into the corresponding A/B trans-fused ketones 16 and 17.

α-Naphthyl alkyl ketones undergo Birch reduction quite readily to give α,β-unsaturated ketones in good yield. We reported earlier[1] metal-ammonia reduction of the ketone 5 which contains a methoxy group at the para position. During the reduction complete loss of the p-methoxy group was observed and protonation of the intermediate enolate anion 6 furnished the α,β-unsaturated ketone 7 in 83% yield. A methoxy group at C-1 of the naphthalene nucleus is often useful for the incorporation of carbonyl substituents at C-4. For example, Friedel-Crafts acetylation of 1,7-dimethoxynaphthalene readily affords the ketone 1 but the corresponding desmethoxy ketone 2 is not so easily accessible. Metal-ammonia reduction of 1 and 2, however, under appropriate experimental conditions would give rise to the same enolate anion 3 since hydrogenolysis of a p-methoxy group is usually very facile during Birch reduction of α-naphthyl ketones. We reasoned that trapping of the enolate anion generated from an α-naphthyl alkyl ketone with a reactive alkyl halide should be practically feasible and such reductive alkylation of suitably constructed ketones might provide useful intermediates for terpenoids and other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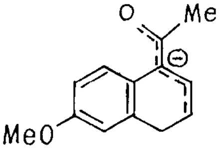
2, R = H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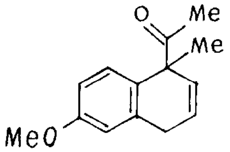
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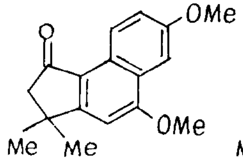
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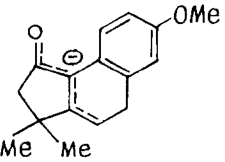
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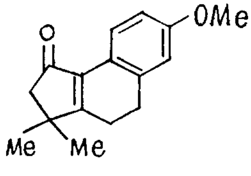
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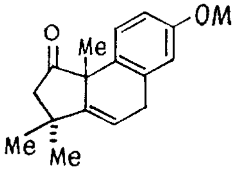
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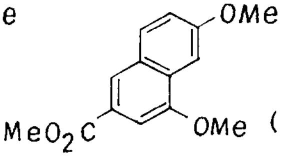
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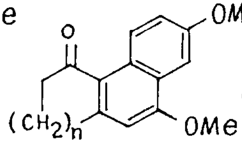
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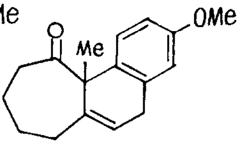
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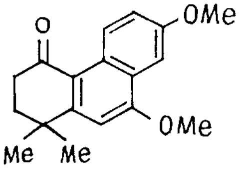
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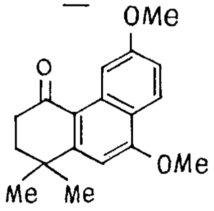
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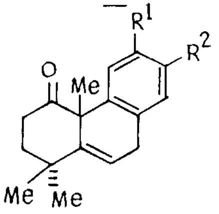
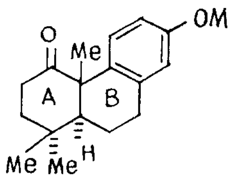

14, $R^1 = H, R^2 = OMe$
15, $R^1 = OMe, R^2 = H$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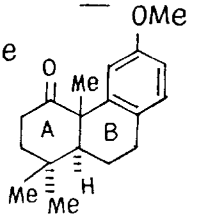
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natural products. We have now successfully carried out reductive methylation of several α-naphthyl ketones having methoxy substituents at the para position to furnish β,γ-unsaturated ketones in good yield. Furthermore, during the present studies the β,γ-unsaturated ketones 14 and 15, prepared from the α-naphthyl ketones 12 and 13 respectively, have been stereoselectively converted into the corresponding A/B trans-fused 4-oxooctahydrophenanthrenes 16 and 17 which promise to be useful intermediates for the synthesis of several tricyclic diterpenes.

The ketones 1[2] and 5 were prepared from 1,7-dimethoxynaphthalene involving Friedel-Crafts reaction with AcCl and β,β-dimethylacryloyl chloride respectively. To perform reductive methylation of the ketone 1, a solution of 1 in dry THF was added rapidly under nitrogen to a stirred solution of Li (5 equiv.) in distilled liquid ammonia. After 15 min. an excess of MeI was added followed immediately by aqueous THF. Evaporative distillation furnished the pure alkylated ketone 4 in 82% yield /‾^{1}H-NMR (CCl_4): δ 1.40 (s,3H), 1.83 (s,3H), 3.43 (t,2H,J=3 Hz), 3.73 (s,3H), 5.45 (t of d, 1H,J=10,2 Hz), 5.92 (t of d, 1H,J=10,3 Hz), 6.47-6.90 (m, 3H)_7. Similarly, reductive methylation of 5 yielded the β,γ-unsaturated ketone 8 (75%). The naphthoic ester 9[3] was utilised to synthesise the ketones 10 (n=1,2 and 3)[4]. Reductive methylation of 10 (n=3) afforded the unsaturated ketone 11 in 78% yield /‾^{1}H-NMR (CCl_4): δ 1.22 (s,3H), 1.33-2.67 (m,8H), 3.34 (d,2H,J=4 Hz), 3.70 (s,3H), 5.75 (t, 1H,J=4 Hz), 6.38-6.77 (m,3H) _7. The tricyclic ketones 12, m.p. 132-133° and 13, m.p. 107-108° were prepared[4] utilising 1,7- and 1,6-dimethoxynaphthalenes respectively as starting materials. Reductive methylation of 12 and 13 provided the β,γ-unsaturated ketones 14 (72%) and 15 (70%) respectively. Reduction of 14 with $NaBH_4$ followed by catalytic hydrogenation (H_2, 10% Pd-C) and Jones oxidation furnished the trans-fused ketone 16 in 72% overall yield, m.p. 131-132° /‾^{1}H-NMR ($CDCl_3$): δ 1.08 (s,3H), 1.12 (s,3H), 1.54 (s,3H), 1.68-2.90 (m,9H), 3.78 (s,3H), 6.61 (d,1H,J=3 Hz), 6.80 (d of d,1H,J=9,3 Hz), 7.66 (d,1H,J=9 Hz) _7. Similar treatment of 15 afforded 17 (72%) /‾ ^{1}H-NMR ($CDCl_3$): δ 1.07 (s,3H), 1.09 (s,3H), 1.54 (s,3H), 1.68-2.95 (m,9H), 3.77 (s,3H), 6.68 (d of d, 1H,J=8.5,3 Hz), 6.92 (d,1H,J=8.5 Hz), 7.30 (d,1H,J=3Hz)_7. ^{1}H-NMR spectra of the crude products in the aforementioned synthesis of the ketones 16 and 17 showed no methyl signals due to the A/B cis-fused isomers[5]. The present study thus provides a stereocontrolled route to A/B trans-fused 4-oxooctahydrophenanthrenes which are otherwise difficult to obtain. The possibility of application of this method to the synthesis of natural products is now being explored.

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References and Notes

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4 The details of the preparation of the ketones will be reported elsewhere.

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