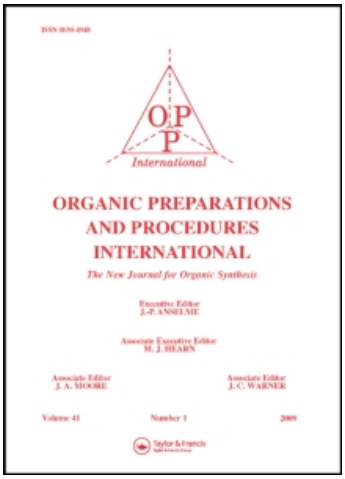

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(±)-3,4,4a,5,6,7-HEXAHYDRO-4a,7,7-TRIMETHYL-1(2*H*)-NAPHTHALENONE

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E. L. Weinberg and J. D. McCowan *J. Organomet. Chem.*, **170**, 51 (1979) and references therein.

7. The preparation of dimethyltitanocene from methylmagnesium iodide and dichlorotitanocene in diethyl ether has been reported in a German patent. Few details of the procedure are provided, and a yield of 58% is reported [German Patent #1,037,446 (March 12, 1959) to Farbwerke Hoechst (Chem. Abs., **54**:18546f) (1960)].

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(±)-3,4,4a,5,6,7-HEXAHYDRO-4a,7,7-TRIMETHYL-1(2*H*)-NAPHTHALENONE

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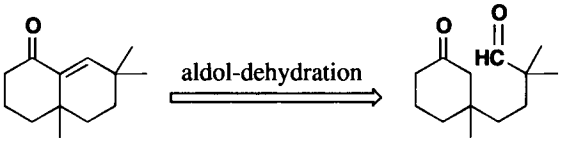
A recent photochemical study in this laboratory required the preparation of (±)-3,4,4a,5,6,7-hexahydro-4a,7,7-trimethyl-1(2*H*)-naphthalenone (**1**). Retrosynthetic analysis suggested that **1** should be readily available by intramolecular aldol condensation of (±)-2,2-dimethyl-4-(1-methyl-3-oxocyclohexyl)butanal (**2**). Precedent for this closure has appeared in earlier work describing annulations based on acid-mediated cyclization of keto acetals[1] and in a similar ring closure applied to the synthesis of a fused-ring heterocyclic natural product.[2]

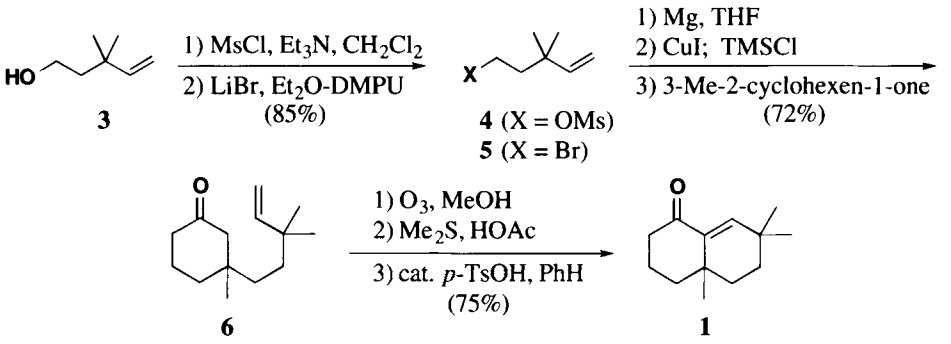


1 **2**

We anticipated that direct preparation of the aldehyde by alkylation of isobutyraldehyde would be complicated by competing aldol processes; other possible routes would require manipulation of protecting groups and would result in a longer synthesis. Thus, it was planned to generate the aldehyde functionality by ozone cleavage of a side-chain alkene group. By use of this strategy, the title compound was prepared in three steps from 5-bromo-3,3-dimethyl-1-pentene and 3-methyl-2-cyclohexen-1-one in an overall yield of 54%.

Bromide **5** was prepared from the known 3,3-dimethyl-4-penten-1-ol (**3**)[3] via mesylate **4**[4] in an overall yield of 85%. The bromide was converted to the corresponding Grignard reagent and added to 3-methyl-2-cyclohexen-1-one at -78° in the presence of copper(I) iodide and chloro-

trimethylsilane.[5] This procedure resulted in conjugate addition of the organocopper species to the



3 4 (X = OMs) 5 (X = Br) 6 1

unsaturated ketone to afford (±)-3-(3,3-dimethyl-4-pentenyl)-3-methylcyclohexanone (**6**) in 72% yield. Ozonolysis of **6** in methanol, followed by reductive workup with dimethyl sulfide and acetic acid generated aldehyde **2**[6] which was treated directly with catalytic *p*-toluenesulfonic acid in benzene to give (±)-3,4,4a,5,6,7-hexahydro-4a,7,7-trimethyl-1(2*H*)-naphthalenone (**1**) in 75% yield. Interestingly, the product was formed with no detectable alkyl migration from the geminal dimethyl moiety. Thus, this synthetic approach likely represents a general method for the production of structurally related hexahydronaphthalenones[7] and should prove especially valuable for targets derived from sterically hindered aldehydes.

EXPERIMENTAL SECTION

THF was distilled from $LiAlH_4$; triethylamine was distilled from CaH_2 and stored over 4Å molecular sieves; DMPU (*N,N'*-dimethylpropyleneurea or 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) was stored over 4Å molecular sieves. Copper(I) iodide (CuI) was purified using a combination of the procedures reported by Dieter[8] and Kauffman.[9] CuI (13.0 g, 68.3 mmol) was dissolved in boiling, saturated KI (130 g KI / 100 mL of H_2O), then cooled, diluted with H_2O to precipitate the salt, and filtered. The solid was washed sequentially with H_2O, EtOH, EtOAc, Et_2O, and pentane, and then dried under vacuum for 24 hrs. Other reagents were used as received. All reactions were run under dry N_2 in oven-dried glassware. Reactions were monitored using capillary GC with FI detection (SE-30 column, 6 m x 0.25 mm i.d., 0.25 mm film thickness) programmed between 50-300°. The saturated NH_4Cl, 25% H_2SO_4, 10% HCl, saturated $NaHCO_3$, 5% $Na_2S_2O_3$, and saturated NaCl used in workup procedures refer to aqueous solutions. Preparative separations were performed using either short-path distillation or chromatography on silica gel (Grace, grade 62, 60-200 mesh) containing UV-active phosphor (Sylvania no. 2282); for the latter, band elution was monitored using a hand-held UV lamp. IR spectra are referenced to polystyrene. ^1H NMR and ^{13}C NMR were measured in $CDCl_3$ at 400 and 100 MHz, respectively, and are referenced to internal Me_4Si. High resolution mass spectra (HRMS, EI/DP) were obtained at 70 eV.

5-Bromo-3,3-dimethyl-1-pentene (**5**).- This bromide was prepared from 3,3-dimethyl-4-penten-1-ol (**3**)[3] by conversion to its mesylate (**4**) and nucleophilic displacement by bromide ion. The mesylate was prepared by the general procedure of Crossland and Servis.[4] A solution of 25.6 g (0.22 mol) of **3**

and 33.4 g (46.0 mL, 0.33 mol) of triethylamine in 600 mL of CH_2Cl_2 was stirred at -5° while a solution of 27.7 g (18.7 mL, 0.24 mol) of methanesulfonyl chloride in 25 mL of CH_2Cl_2 was added during 45 min. The reaction was stirred for 15 min and transferred to a separatory funnel containing a mixture of H_2O and crushed ice. The layers were separated, and the CH_2Cl_2 layer was washed with ice cold H_2O (2x), 10% HCl (1x), $NaHCO_3$ (1x), and NaCl (1x) and then dried (Na_2SO_4). Concentration under vacuum at 30-35° afforded 42.3 g (0.22 mol, 100%) of the crude mesylate **4** which was used without further purification.

IR (thin film): 3084, 1643, 1354, 1181 cm^{-1}; ^1H NMR: δ 5.76 (dd, 1 H, J = 17.4, 10.8 Hz), 5.00 (d, 1 H, J = 10.8 Hz), 4.97 (d, 1 H, J = 17.4 Hz), 4.20 (t, 2 H, J = 7.5 Hz), 2.99 (s, 3 H), 1.79 (t, 2 H, J = 7.5 Hz), 1.06 (s, 6 H); ^{13}C NMR: δ 146.4, 111.7, 67.6, 40.6, 37.3, 35.5, 36.8.

To a stirred suspension of 94.5 g (1.10 mol) of lithium bromide in 400 mL of anhydrous ether was added 100 mL of dry DMPU dropwise with stirring followed by 42.3 g (0.22 mol) of **4**. The reaction was stirred at reflux for 24 hrs, then cooled to 0°, cautiously treated with 100 mL of H_2O, and transferred to a separatory funnel. The layers were separated and the ether layer was washed with H_2O (2x), 10% HCl (2x), $NaHCO_3$ (1x), and NaCl (1x) and then dried ($MgSO_4$) and concentrated under vacuum. The crude product was distilled through a 15-cm Vigreux column to afford 32.9 g (85% from **1**) of **5** as a colorless oil, bp 53-56° (25 mm Hg).

IR (thin film): 3084, 1643, 1372, 1361, 1001, 915 cm^{-1}; ^1H NMR: δ 5.73 (dd, 1 H, J = 17.5, 10.8 Hz), 4.98 (d, 1 H, J = 10.8 Hz), 4.94 (d, 1 H, J = 17.5 Hz), 3.29 (m, 2 H), 1.91 (m, 2 H), 1.02 (s, 6 H); ^{13}C NMR: δ 146.5, 111.7, 45.9, 37.8, 29.3, 26.5; HRMS: *m/e* Calcd for $C_7H_{13}{}^{79}Br$: 176.0201. Found: 176.0188.

Anal. Calcd for $C_7H_{13}Br$: C, 47.45; H, 7.34. Found: C, 47.29; H, 7.32

(±)-3-(3,3-Dimethyl-4-pentenyl)-3-methylcyclohexanone (6).- This compound was prepared using an adaptation of the procedure reported by Paquette and Poupart.[5] To a vigorously stirred suspension of 1.40 g (58.3 mmol) of magnesium turnings in 2 mL of dry THF was added 5 mL of a solution consisting of 9.00 g (50.8 mmol) of **5** in 15 mL of THF. Once the reaction started, the remainder of the bromide was added over a 25 min period at a rate which maintained a gentle reflux. The reaction was heated at reflux for an additional 2 hrs. The resulting gray solution was diluted with 10 mL of dry THF, cooled to -5°, and treated with 4.59 g (24.1 mmol) of purified CuI. The deep blue solution was stirred for 10 min and then cooled to -78°. A solution of 2.52 g (2.94 mL, 23.2 mmol) of chlorotrimethylsilane in 5 mL of THF was added dropwise during 20 min followed, in a like manner, by a solution of 2.42 g (2.49 mL, 22.0 mmol) of 3-methyl-2-cyclohexen-1-one in 5 mL of THF. The resulting green solution was stirred for 1.5 hr during which time the reaction became blue again. The reaction was quenched by sequential addition of 5 mL of MeOH and 3 mL of 25% H_2SO_4, warmed to 22°, stirred for 2 hrs, then filtered through Celite® and concentrated under vacuum. The residue was diluted with 100 mL of ether and 50 mL of water and filtered through Celite® a second time. The layers were separated and the ether layer was washed with H_2O (3x), $Na_2S_2O_3$ (1x), and NaCl (1x) and then dried ($MgSO_4$) and concentrated under vacuum. The product from two runs was combined

and purified by short path distillation to give 6.60 g (72%) of **6** as a colorless liquid, bp. 69-74° (0.5 mm Hg).

IR (thin film): 3080, 1720, 1643, 1382, 1362, 1001, 911 cm^{-1}; ^1H NMR: δ 5.70 (dd, 1 H, J = 17.4, 10.8 Hz), 4.91 (d, 1 H, J = 10.8 Hz), 4.88 (d, 1 H, J = 17.4 Hz), 2.26 (t, 2 H, J = 6.7 Hz), 2.16 (A of ABq, 1 H, J = 13.4 Hz), 2.09 (B of ABq, 1 H, J = 13.4 Hz), 1.84 (quintet, 2 H, J = 6.5 Hz), 1.60 (m, 1 H), 1.53 (m, 1 H), 1.28-1.12 (complex, 4 H), 0.97 (s, 6 H), 0.89 (s, 3 H); ^{13}C NMR: δ 212.1, 148.1, 110.6, 53.8, 40.9, 38.2, 36.1, 35.8, 37.7, 35.6, 26.6 (2), 24.9, 22.0; HRMS: *m/e* Calcd for $C_{14}H_{24}O$: 208.1828. Found: 208.1826.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.77; H, 11.53. Found: C, 80.56; H, 11.48

(±)-3,4,4a,5,6,7-Hexahydro-4a,7,7-trimethyl-1(2*H*)-naphthalenone (**1**).- A solution of 5.50 g (26.4 mmol) of **6** in 150 mL of MeOH at -78° was treated with ozone until the solution turned a light blue color. The reaction was quenched at -78° with a solution of 7.62 g (9.00 mL, 122.5 mmol) of dimethyl sulfide and 1 mL of acetic acid, warmed to 22°, and stirred for 12 hrs. The solvent was removed under vacuum and the crude product was dissolved in ether and washed with H_2O (4x) and NaCl (1x). The ether layer was dried ($MgSO_4$) and concentrated under vacuum to give the crude aldehyde which was used without further purification.[6]

The aldehyde was dissolved in 125 mL of benzene, 50 mg of *p*-toluenesulfonic acid was added, and the solution was heated under reflux using a Dean-Stark apparatus to separate water from the reaction. GC analysis indicated that the reaction was complete after 4 hrs. The cooled reaction mixture was washed with $NaHCO_3$ (1x) and NaCl (1x) and then dried ($MgSO_4$) and concentrated under vacuum to afford a yellow oil. The product was purified by chromatography on a 50 cm x 3 cm silica gel column eluted with 5% ether in hexane. Band 2 afforded 3.82 g (75%) of **1** as a pale yellow oil which slowly crystallized on standing, mp. 24-26°.

IR (thin film): 1693, 1628 cm^{-1}; ^1H NMR: δ 6.14 (s, 1 H), 2.55 (ddt, 1 H, J = 16.9, 5.1, 2.0 Hz), 2.28 (ddd, 1 H, J = 16.9, 12.6, 7.6 Hz), 1.99 (m, 1 H), 1.88 (m, 1 H), 1.78-1.40 (complex, 6 H), 1.07 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H); ^{13}C NMR: δ 203.4, 142.5, 141.9, 40.4, 38.8, 35.8, 35.4, 32.8, 32.5, 29.9, 28.3, 25.2, 19.2; HRMS: *m/e* Calcd for $C_{13}H_{20}O$: 192,1514. Found: 192.1513.

Anal. Calcd for $C_{13}H_{20}O$: C, 81.25; H, 10.42. Found: C, 80.99; H, 10.40

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7. The substitution pattern in the title compound matches that found in the DE rings of several triterpenes, see J. W. ApSimon, K. E. Fyfe and A. M. Greaves in *"The Total Synthesis of Natural Products,"* J. W. ApSimon, Ed., Vol. 6, p. 85, Wiley-Interscience, New York, N.Y., 1984.

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