

Studies of Aromatic Sesquiterpenes. III. The Synthesis of 4-Methoxyisocadalene¹⁾

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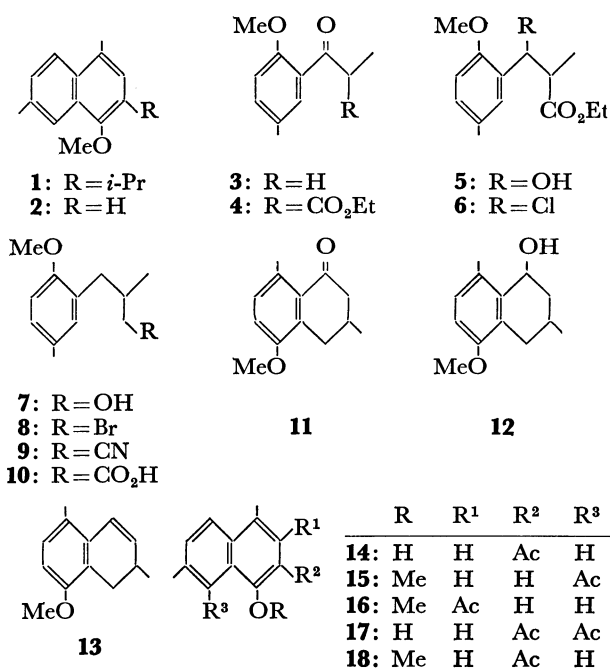
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Synopsis. Starting from *p*-cresol, the title sesquiterpene was synthesized through 4-methoxy-1,6-dimethylnaphthalene as a key intermediate.

The new aromatic sesquiterpene ether, 4-methoxyisocadalene, was recently isolated,²⁾ along with cadalene and other substances, from the aerial parts of Mexican *Heterotheca inuloides* Cass. (Compositae). 2-Isopropyl-1-methoxy-4,7-dimethylnaphthalene (**1**) was proposed as the structure of this sesquiterpene on the basis of comprehensive spectral studies.²⁾ In this paper the synthesis of **1** through the acetylation of 4-methoxy-1,6-dimethylnaphthalene (**2**) will be described.

2-Methoxy-5-methylpropiofenone (**3**) was converted to ethyl 2-(2-methoxy-5-methylbenzoyl)propionate (**4**), which, on reduction with NaBH₄ and subsequent chlorination, afforded ethyl 3-chloro-2-methyl-3-(2-methoxy-5-methylphenyl)propionate (**6**). The reduction of **6** with LiAlH₄ gave 2-methyl-3-(2-methoxy-5-methylphenyl)-1-propanol (**7**), from which 3,4-dihydro-5-methoxy-3,8-dimethyl-1(2*H*)-naphthalenone (**11**) was prepared in 4 steps. The aromatization of **11** produced a key intermediate (**2**), which, on acetylation, resulted in a mixture of 2-acetyl-4,7-dimethyl-1-naphthol (**14**) and other acetyl compounds (**15**—**17**). The title compound was synthesized from the reaction product of the methyl ether (**18**) with methylmagnesium iodide.

The structure of the synthesized product (**1**) was confirmed by a comparison of its NMR data with those reported in the literature.²⁾ The complexes of **1** with picric acid and 1,3,5-trinitrobenzene showed mp 90.5—91.5 °C and 104.5—105.5 °C respectively.



Experimental

2-Methoxy-5-methylpropiofenone (3). The condensation of *p*-methylanisole (122.2 g) and propionyl chloride (97.3 g) by AlCl₃ (140 g) in CS₂ (370 ml) gave **3** (173.8 g) in a 97.5% yield; bp 128—130 °C/10 mmHg (1 mmHg ≈ 133.322 Pa); IR: 1675, 810 cm⁻¹; NMR: δ 1.08 (t, 3H, CH₃), 2.23 (s, 3H, CH₃), 2.86 (q, 2H, CH₂), 3.78 (s, 3H, OCH₃), 6.71 (d, 1H, *J* = 9 Hz), 7.08 (dd, 1H, *J* = 9 and 2 Hz), 7.35 (d, 1H, *J* = 2 Hz).

2,4-Dinitrophenylhydrazone: Yellow needles; mp 112.0—112.5 °C. Found: C, 57.24; H, 5.03; N, 15.84%. Calcd for C₁₇H₁₈N₄O₅: C, 56.98; H, 5.06; N, 15.64%.

Ethyl 2-(2-Methoxy-5-methylbenzoyl)propionate (4). A reaction product of diethyl oxalate (76.7 g) and a sodio-derivative of **3** prepared from **3** (89.0 g) and Na (12.1 g) in ethanol (160 ml) was decarbonylated (2 h, 180 °C) to give **4** (113.1 g) in a 90.5% yield; bp 144—145 °C/3 mmHg; IR: 1735, 1675, 810 cm⁻¹; NMR: δ 1.15 (t, 3H, CH₃), 1.43 (d, 3H, CH₃), 2.25 (s, 3H, CH₃), 3.82 (s, 3H, OCH₃), 4.09 (q, 2H, CH₂), 4.33 (q, 1H, >CH—), 6.85 (d, 1H, *J* = 8 Hz), 7.27 (dd, 1H, *J* = 8 and 2 Hz), 7.57 (d, 1H, *J* = 2 Hz).

Ethyl 3-Hydroxy-2-methyl-3-(2-methoxy-5-methylphenyl)propionate (5). The reduction of **4** (25.0 g) with NaBH₄ (1.4 g) in methanol (100 ml) (3 h, 25 °C) furnished **5** (24.2 g) in a 96.0% yield; bp 143—144 °C/6 mmHg; IR: 3450, 1730, 805 cm⁻¹; NMR: δ 1.03 (d, 3H, CH₃), 1.20 (t, 3H, CH₃), 2.27 (s, 3H, CH₃), 2.78 (m, 1H, >CH—), 3.20 and 3.32 (1H, OH), 3.77 (s, 3H, OCH₃), 4.08 (q, 2H, CH₂), 4.87 (m, 1H, >CH—), 6.63 (d, 1H, *J* = 9 Hz), 6.85 (d, 1H, *J* = 2 Hz), 7.09 (dd, 1H, *J* = 9 and 2 Hz).

Ethyl 3-Chloro-2-methyl-3-(2-methoxy-5-methylphenyl)propionate (6). A mixture of **5** (77.2 g) and concd HCl (450 ml) was stirred for 1 h at 20 °C to give **6** (77.2 g) in a 93.2% yield as a mixture consisting of two diastereomers (1:1); bp 148—148.5 °C/7 mmHg.

dl-erythro-Isomer of 6: Prisms, mp 75—76 °C; IR 1735, 1040, 1035, 805 cm⁻¹; NMR: δ 0.94 (d, 3H, CH₃), 1.27 (t, 3H, CH₃), 2.27 (s, 3H, CH₃), 3.12 (dq, 1H, >CH—, *J* = 11 and 7 Hz), 3.77 (s, 3H, OCH₃), 4.16 (q, 2H, CH₂), 5.51 (d, 1H, >CH—, *J* = 11 Hz), 6.73 (d, 1H, *J* = 9 Hz), 7.03 (dd, 1H, *J* = 9 and 2 Hz), 7.20 (br, 1H). Found: C, 62.24; H, 6.83%. Calcd for C₁₄H₁₉ClO₃: C, 62.11; H, 7.07%.

dl-threo-Isomer of 6: Oil, bp 135—136 °C/5 mmHg; IR: 1735, 1030, 810 cm⁻¹; NMR: δ 1.05 (t, 3H, CH₃), 1.26 (d, 3H, CH₃), 2.27 (s, 3H, CH₃), 3.17 (qin, 1H, >CH—, *J* = 7 Hz), 3.77 (s, 3H, OCH₃), 3.98 (q, 2H, CH₂), 5.66 (d, 1H, >CH—, *J* = 7 Hz), 6.69 (d, 1H, *J* = 9 Hz), 7.03 (dd, 1H, *J* = 9 and 2 Hz), 7.27 (br, 1H). Found: C, 62.16; H, 7.22%. Calcd for C₁₄H₁₉ClO₃: C, 62.11; H, 7.07%.

3-Methyl-4-(2-methoxy-5-methylphenyl)butyric Acid (10). The reduction of **6** (9.2 g) with LiAlH₄ (4.0 g) in ether (60 ml) gave 2-methyl-3-(2-methoxy-5-methylphenyl)-1-propanol (**7**); yield, 5.7 g (86.4%); bp 124—126 °C/7 mmHg; IR: 3350, 800 cm⁻¹.

The reaction of **7** (19.4 g) with PBr₃ (11.7 g) in CCl₄ (60 ml) gave 2-methyl-3-(2-methoxy-5-methylphenyl)propyl bromide (**8**); yield, 12.1 g (47.1%); bp 118—119.5 °C/4

mmHg.

A solution of **8** (42.9 g), KCN (32.2 g) and water (60 ml) in ethanol (386 ml) was refluxed for 20 h to give 3-methyl-4-(2-methoxy-5-methylphenyl)butanenitrile (**9**); yield, 29.8 g (87.9%); bp 130–132 °C/7 mmHg; IR: 2240, 805 cm^{-1} .

A mixture of **9** (29.8 g), concd H_2SO_4 (60 ml), acetic acid (60 ml), and water (60 ml) was refluxed for 5 h to give **10**; yield, 23.4 g (71.8%); bp 164–167 °C/8 mmHg, mp 53.5–54.5 °C; IR: 1690, 805 cm^{-1} . Found: C, 70.21; H, 8.37%. Calcd for $\text{C}_{13}\text{H}_{18}\text{O}_3$: C, 70.24; H, 8.16%.

3,4-Dihydro-5-methoxy-3,8-dimethyl-1(2H)-naphthalenone (11). The reaction of **10** (19.2 g) and thionyl chloride (30.9 g) in benzene (50 ml) gave the acid chloride of **10**; yield, 19.7 g (94.7%); bp 137 °C/5 mmHg. The cyclization of this acid chloride (11.2 g) by SnCl_4 (36.5 g) in benzene (50 ml) gave 9.0 g (94.7%) of **11**; bp 140–142 °C/8 mmHg, mp 38–39 °C; IR: 1670, 810 cm^{-1} ; NMR: δ 1.10 (m, 3H, CH_3), 2.03–3.25 (m, 5H), 2.48 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.74 (d, 1H, $J=9$ Hz), 6.94 (d, 1H, $J=9$ Hz). Found: C, 76.41; H, 8.03%. Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$: C, 76.44; H, 7.90%.

2,4-Dinitrophenylhydrazones: Red needles, mp 196.5–197.0 °C. Found: C, 59.37; H, 5.19; N, 14.71%. Calcd for $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_5$: C, 59.37; H, 5.24; N, 14.58%.

4-Methoxy-1,6-dimethylnaphthalene (2) and Its Acetylation. The reduction of **11** (15.6 g) with NaBH_4 (1.5 g) in methanol (60 ml) produced 15.7 g (99.3%) of 1,2,3,4-tetrahydro-5-methoxy-3,8-dimethyl-1-naphthol (**12**), needles; mp 107.0–107.5 °C; IR: 3350, 800, 790 cm^{-1} . Found: C, 75.46; H, 8.93%. Calcd for $\text{C}_{13}\text{H}_{18}\text{O}_2$: C, 75.69; H, 8.80%.

The dehydration of **12** (15.0 g) with KHSO_4 (3.0 g) gave 12.3 g (89.9%) of 1,2-dihydro-8-methoxy-2,5-dimethylnaphthalene (**13**); bp 103–105 °C/4 mmHg; NMR: δ 1.09 (d, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.4–3.0 (m, 3H, CH_2 and $>\text{CH}-$), 3.70 (s, 3H, OCH_3), 5.82 (dd, 1H, $J=9$ and 3 Hz), 6.48 (d, 1H, $J=9$ Hz), 6.49 (d, 1H, $J=9$ Hz), 6.81 (d, 1H, $J=9$ Hz).

A dehydrogenation product of **13** (12.3 g) upon heating with 5% Pd–C (2.5 g) (5 h, 230 °C) was distilled to give two fractions. The fore-run (3.1 g) was a mixture of 1,6-dimethylnaphthalene (48.3%), **2** (36.8%) and other substances. The main fraction was 7.9 g (64.9%) of **2**; bp 123–125 °C/5 mmHg; IR: 1600, 1580, 1380, 1355, 1270, 1090, 815 cm^{-1} ; NMR: δ 2.48 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 6.58 (d, 1H, $J=8$ Hz), 7.08 (d, 1H, $J=8$ Hz), 7.29 (dd, 1H, $J=9$ and 2 Hz), 7.78 (d, 1H, $J=9$ Hz), 8.08 (br, 1H). *Picrate*: Red needles; mp 158.0–158.5 °C. Found: C, 55.00; H, 3.93; N, 10.02%. Calcd for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_8$: C, 54.94; H, 4.13; N, 10.12%.

The reaction of **2** (3.0 g) and acetyl chloride (2.3 g) with AlCl_3 (4.8 g) in CS_2 (40 ml) gave acetyl compounds (3.4 g), a mixture of **14** (45.5%), **15** (8.9%), **16** (23.4%), and

17 (18.2%). Each component was isolated by elution with CH_2Cl_2 through a silica-gel column.

2-Acetyl-4,7-dimethyl-1-naphthol (14): Yellow needles; mp 124.0–124.5 °C; IR: 1615, 815 cm^{-1} ; NMR: δ 2.48 (br, 6H, two CH_3), 2.58 (s, 3H, CH_3), 7.27 (br, 1H), 7.41 (dd, 1H, $J=9$ and 2 Hz), 7.71 (d, 1H, $J=9$ Hz), 8.22 (br, 1H), 13.77 (s, 1H, OH). Found: C, 78.67; H, 6.43%. Calcd for $\text{C}_{14}\text{H}_{14}\text{O}_2$: C, 78.48; H, 6.59%.

1-Acetyl-8-methoxy-2,5-dimethylnaphthalene (15): Needles; mp 65.0–66.5 °C; IR: 1695, 820, 780 cm^{-1} . Found: C, 78.86; H, 7.19%. Calcd for $\text{C}_{15}\text{H}_{16}\text{O}_2$: C, 78.92; H, 7.06%.

2-Acetyl-4-methoxy-1,6-dimethylnaphthalene (16): Micro crystals; mp 71.5–72.5 °C; IR: 1675, 810 cm^{-1} . Found: C, 78.84; H, 7.19%. Calcd for $\text{C}_{15}\text{H}_{16}\text{O}_2$: C, 78.92; H, 7.06%.

2,8-Diacetyl-4,7-dimethyl-1-naphthol (17): Yellow micro crystals; mp 172.0–173.5 °C; IR: 1695, 1615, 870 cm^{-1} . Found: C, 75.02; H, 6.29%. Calcd for $\text{C}_{16}\text{H}_{16}\text{O}_3$: C, 74.98; H, 6.29%.

2-Acetyl-1-methoxy-4,7-dimethylnaphthalene (18). The methylation of **14** (0.4 g) with dimethyl sulfate (0.3 g) and K_2CO_3 (0.4 g) in acetone (20 ml) gave 0.4 g of **18**; IR: 1670, 815 cm^{-1} ; NMR: δ 2.50 (s, 6H, two CH_3), 2.60 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.26 (dd, 1H, $J=9$ and 2 Hz), 7.37 (br, 1H), 7.71 (d, 1H, $J=9$ Hz), 7.90 (br, 1H). **2,4-Dinitrophenylhydrazones**: Yellow needles; mp 230–231 °C (dec). Found: C, 61.84; H, 4.91; N, 13.55%. Calcd for $\text{C}_{21}\text{H}_{20}\text{N}_4\text{O}_5$: C, 61.76; H, 4.94; N, 13.72%.

4-Methoxyisocadalene (1). The reaction product of **18** (0.5 g) and the Grignard reagent prepared from Mg (0.5 g) and methyl iodide (2.2 g) in ether (40 ml) were stirred with concd HCl (10 ml) for 30 min. Then the reaction product was stirred with LiAlH_4 (1.0 g) in ether (20 ml) at 40 °C for 4 h. The resulting product was hydrogenated in ethanol (50 ml) over Pd–C (5%, 0.5 g) and then chromatographed over silica-gel, eluting with CH_2Cl_2 , to give 0.4 g (75.0%) of **1**; IR: 1625, 1605, 1380, 1350, 1095, 995, 875, 810 cm^{-1} ; NMR: δ 1.28 (d, 6H, CH_3), 2.52 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 3.52 (m, 1H, $>\text{CH}-$), 3.83 (s, 3H, OCH_3), 7.03 (br, 1H), 7.16 (dd, 1H, $J=9$ and 2 Hz), 7.71 (d, 1H, $J=9$ Hz), 7.80 (br, 1H). *Picrate*: Orange brown needles; mp 90.5–91.5 °C. Found: C, 58.00; H, 5.21; N, 8.92%. Calcd for $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_8$: C, 57.76; H, 5.07; N, 9.19%. **1,3,5-Trinitrobenzene complex**: Yellow orange needles; mp 104.5–105.5 °C. Found: C, 60.05; H, 5.40; N, 9.35%. Calcd for $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_7$: C, 59.86; H, 5.25; N, 9.52%.

References

- 1) Preceding paper: J. Tanaka and K. Adachi, *Nippon Kagaku Kaishi*, **1981**, 994.
- 2) F. Bohlmann and C. Zdero, *Chem. Ber.*, **109**, 2021 (1976).