

Studies on Aromatic Sesquiterpenes. XI.¹⁾ Synthesis of 7-Isopropyl-3,5-dimethyl-1-naphthol

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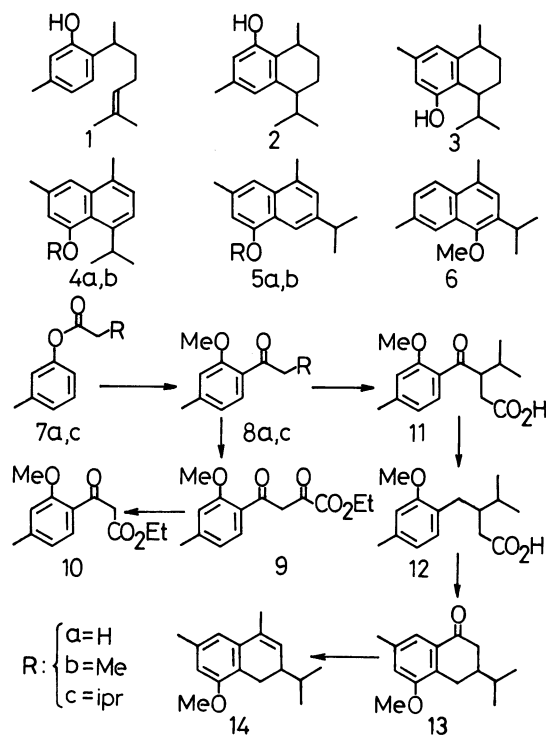
Synopsis. Starting from *m*-cresol, the title new naphthol was synthesized through 4-methyl-3-(2-methoxy-4-methylbenzoyl)pentanoic acid as a key intermediate.

Phenolic sesquiterpene curcuphenol²⁾ (**1**) was cyclized by treatment with acid catalysts to give 8-hydroxycalamenene (**2**) along with its structural isomer, 5-hydroxyisocalamenene (**3**).³⁾ The tetrahydronaphthol (**2**) and its methyl ether have been, respectively, isolated from *Dysoxylum* species (Meliaceae) and a horny coral as naturally occurring sesquiterpenes, and their absolute configuration were confirmed by chemical derivation.⁴⁾ 5-Methoxydaucalene (**4b**) derived from the methyl ether of **3** afforded 5-hydroxydaucalene (**4a**) by demethylation with BBr₃.¹⁾ However, **4b** was refluxed in a solution of acetic acid with HBr to furnish a new naphthol, which was apparently different from **4a**. 7-Isopropyl-3,5-dimethyl-1-naphthol (**5a**) was proposed as the structure of this new naphthol on the basis of comprehensive spectral studies.¹⁾ 4-Methoxyisocadalene (**6**) has been isolated from *Heterotheca* species (Compositae) and also synthesized.⁵⁾ However, the naphthol (**5**), having a related structure with **6**, is an unknown phenolic sesquiterpenoid as a natural product.

In this paper we report on an efficient synthesis of **5**, starting from *m*-cresol through 4-methyl-3-(2-methoxy-4-methylbenzoyl)pentanoic acid (**11**) as a key intermediate. This synthetic fashion is useful for the preparation of 7-isopropyl-1-naphthol derivatives, which are expected to occur as natural products or formation by the conversion of some sesquiterpenes.

In order to prepare the keto acid (**11**), at first the methoxyacetophenone (**8a**) obtained from *m*-tolyl acetate (**7a**) was derived to the diketo ester (**9**). Generally, the diketo esters prepared from a ketone with diethyl oxalate are readily converted into the β -keto esters by decarbonylation with heating,⁶⁾ but the pyrolysis of **9** gave a mixture of four components (**8a**, **10**, and the dimerized product including **9**), in which the desired β -keto ester (**10**) was found in low yield (32.8%). Therefore, we next attempted the bromination of isovalerophenone derivative (**8c**) obtained from *m*-tolyl isovalerate (**7c**) and successive condensation of the resulting α -bromo ketone with ethyl cyanoacetate. The crude reaction product was hydrolyzed to give a γ -keto acid (**11**), which showed in its NMR spectrum two methyl proton signals of an isopropyl group at $\delta=0.73$ and 0.97 as a pair of doublets ($J=7$ Hz) and methylene proton signals as a pair of double doublets at $\delta=2.35$ ($J=17$ and 4 Hz) and 2.91 ($J=17$ and 10 Hz). By a Clemmensen reduction the keto acid (**11**) was converted into 4-methyl-3-(2-methoxy-4-methylbenzyl)pentanoic acid (**12**), which was cyclized with phos-

phoryl chloride to give the tetralone (**13**). Ketone **13** was allowed to react with methylmagnesium iodide and the dehydration of the resulting alcohol with formic acid afforded 3,4-dihydro-3-isopropyl-5-methoxy-1,7-dimethylnaphthalene (**14**), which was dehydrogenated by heating with 5% Pd-C at 240–250 °C to give 7-isopropyl-1-methoxy-3,5-dimethylnaphthalene (**5b**). 7-Isopropyl-3,5-dimethyl-1-naphthol (**5a**) was obtained by the demethylation of **5b** with HBr in a refluxing acetic acid. The spectra (¹H and ¹³C NMR, IR and GC) of the synthesized naphthol **5a** were completely coincident with those of the naphthol obtained from the reaction of **4b** with HBr.¹⁾ The IR and NMR spectra of the acetate of **5a** were wholly different from those of the acetate of **4a**.¹⁾



Experimental

2-Methoxy-4-methylacetophenone (8a) and 2-Methoxy-4-methylisovalerophenone (8c). A mixture of *m*-cresol (0.1 mol), acyl chloride (0.12 mol), Mg (1.2 g), and benzene (25 ml) was refluxed for 1 h to give the corresponding *m*-tolyl esters.⁷⁾

m-Tolyl acetate (**7a**): 78.1%, bp 88 °C/11 mmHg (1 mmHg=133.322 Pa); IR (neat): 1770, 1375, 1210, and 1150 cm⁻¹.

m-Tolyl isovalerate (**7c**): 94.7%, bp 136 °C/22 mmHg; IR (neat): 1755, 1240, 1180, 1140, and 1100 cm⁻¹.

A mixture of the tolyl ester (0.1 mol), AlCl_3 (0.12 mol), and carbon disulfide (16 ml) was refluxed for 2 h with stirring. The solvent was removed and the residue heated at 145–150°C for 4 h. The reaction mixture was decomposed with dil. HCl to give the *o*-hydroxy ketone.

2-Hydroxy-4-methylacetophenone: 84.0%, bp 106–108°C/9 mmHg; IR (neat): 3600–2300, 1630, 1370, 1325, 1300, 1250, 1230, and 795 cm^{-1} ; ^1H NMR (CDCl_3): δ =2.30 (s, 3H, CH_3), 2.53 (s, 3H, COCH_3), 6.65 (d, 1H, J =8 Hz), 6.71 (broad s, 1H), 7.54 (d, 1H, J =8 Hz), and 12.27 (s, 1H, OH).

2-Hydroxy-4-methylisovalerophenone: 95.3%, bp 151–152°C/21 mmHg; IR (neat): 3500–2500, 1640, 1360, 1310, 1275, 1210, 1150, and 795 cm^{-1} ; ^1H NMR (CDCl_3): δ =0.99 (d, 6H, J =6.5 Hz, $\text{CH}_3\times 2$), 2.26 (m, 1H, J =6.5 Hz, >CH-), 2.31 (s, 3H, CH_3), 2.78 (d, 2H, J =6.5 Hz, CH_2), 6.66 (dd, 1H, J =8, 1.5 Hz), 6.74 (broad s, 1H), 7.60 (d, 1H, J =8 Hz), and 12.50 (s, 1H, OH).

To a mixture of the *o*-hydroxy ketone (0.04 mol) and K_2CO_3 (0.06 mol) in acetone (30 ml) was added dimethyl sulfate (0.05 mol) at room temperature; the mixture was refluxed for 10 h with stirring to yield the *o*-methoxy ketone.

2-Methoxy-4-methylacetophenone (**8a**): 87.9%, bp 125–126°C/10 mmHg; IR (neat): 1670, 1605, 1290, 1260, 1240, 1170, and 1035 cm^{-1} ; ^1H NMR (CDCl_3): δ =2.36 (s, 3H, CH_3), 2.57 (s, 3H, COCH_3), 3.87 (s, 3H, OCH_3), 6.74 (broad s, 1H), 6.78 (d, 1H, J =8 Hz), and 7.66 (d, 1H, J =8 Hz).

2-Methoxy-4-methylisovalerophenone (**8c**): 96.1%, bp 146°C/10 mmHg; IR (neat): 1670, 1610, 1470, 1410, 1300, 1280, 1255, 1170, and 1040 cm^{-1} ; ^1H NMR (CDCl_3): δ =0.94 (d, 6H, J =6.5 Hz, $\text{CH}_3\times 2$), 2.21 (m, 1H, J =6.5 Hz, >CH-), 2.35 (s, 3H, CH_3), 2.82 (d, 2H, J =6.5 Hz, CH_2), 3.85 (s, 3H, OCH_3), 6.73 (broad s, 1H), 6.77 (d, 1H, J =8 Hz), and 7.56 (d, 1H, J =8 Hz).

Ethyl 3-(2-Methoxy-4-methylphenyl)-3-oxopropionate (**10**). To a mixture of methoxy ketone **8a** (5.0 g) and Na (0.8 g) in ethanol (17 ml) was added diethyl oxalate (5.1 g) with cooling in an ice bath; the mixture was stirred for 3 h. The reaction mixture was decomposed by adding dil. H_2SO_4 under cooling. The precipitate was collected by filtration, (7.8 g, 97.5%) to give ethyl 4-(2-methoxy-4-methylphenyl)-2,4-dioxobutyrates (**9**) as yellow leaves (from petroleum ether), mp 73.0–74.0°C; IR (KBr): 1745, 1605, 1500, 1295, 1250, 1230, and 1025 cm^{-1} ; ^1H NMR (CDCl_3): δ =1.39 (t, 3H, J =7 Hz, CH_3), 2.40 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 4.37 (q, 2H, J =7 Hz, CH_2), 6.79 (s, 1H), 6.84 (d, 1H, J =8 Hz), 7.31 (s, 1H, $=\text{CH-}$), 7.81 (d, 1H, J =8 Hz), and 15.42 (broad s, 1H, enol-OH, disappeared with D_2O). Found: C, 63.63; H, 6.05%. Calcd for $\text{C}_{14}\text{H}_{18}\text{O}_5$: C, 63.62; H, 6.10%.

A mixture of the diketone ester **9** (3.0 g), ground glass (0.3 g), and iron borings (0.03 g) was heated at 150°C under reduced pressure (16 mmHg). A subsequent distillation of the reaction mixture gave an oily product, bp 157–158°C/6 mmHg (1.3 g), which was a mixture of **8a** (22.4%), **10** (68.2%), and an unreacted **9** (9.4%) on the basis of the ^1H NMR. The β -keto ester (**10**) was purified by redistillation: (0.8 g, 28.6%), bp 157–158°C/6 mmHg; IR (neat): 1740, 1670, 1610, 1325, 1260, 1195, and 1035 cm^{-1} ; ^1H NMR (CDCl_3): δ =1.23 (t, 3H, J =7 Hz, CH_3), 2.36 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 3.92 (s, 2H, CH_2), 4.17 (q, 2H, J =7 Hz, CH_2), 6.75 (s, 1H), 6.80 (d, 1H, J =8 Hz), and 7.78 (d, 1H, J =8 Hz).

The distillation residue was chromatographed on silica gel and eluted with CH_2Cl_2 to give an unidentified dimerized product (0.4 g) as yellow needles after recrystallization from benzene, mp 213.0–213.5°C. Found: C, 69.47; H, 5.54%. Calcd for $\text{C}_{22}\text{H}_{20}\text{O}_6$: C, 69.46; H, 5.30%.

4-Methyl-3-(2-methoxy-4-methylbenzoyl)pentanoic Acid (**11**). The ketone **8c** (8.0 g) in ether (10 ml) was brominated in the presence of AlCl_3 (10 mg) with bromine (3.2 g)⁸ to give 2-bromo-3-methyl-1-(2-methoxy-4-methylphenyl)-1-

butanone as an oil (11.0 g, 99.1%); IR (neat): 1675, 1610, 1460, 1405, 1295, 1280, 1255, 1165, and 1035 cm^{-1} ; ^1H NMR (CDCl_3): δ =1.05 (d, 3H, J =6.5 Hz, CH_3), 1.08 (d, 3H, J =6.5 Hz, CH_3), 2.3 (m, 1H, J =6.5 Hz, >CH-), 2.37 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 5.33 (d, 1H, J =6.5 Hz, >CH-), 6.76 (s, 1H), 6.80 (d, 1H, J =8 Hz), and 7.61 (d, 1H, J =8 Hz).

The α -bromo ketone (11.0 g) was added to sodio-cyanoacetate prepared from ethyl cyanoacetate (4.5 g) and Na (0.9 g) in ethanol (20 ml); the mixture was refluxed for 5 h with stirring. The reaction mixture was diluted with water and extracted with benzene to give a crude condensed product (11.0 g), which was refluxed with an aqueous solution of 5% NaOH for 5 h. The solution was acidified with HCl and extracted with benzene. The extract was evaporated and recrystallized from benzene to give **11** as prisms (3.6 g, 35.3%), mp 128.5–129.5°C; IR (KBr): 1700, 1660, 1610, 1465, 1410, 1290, 1260, 1200, 1035, and 820 cm^{-1} ; ^1H NMR (CDCl_3): δ =0.73 (d, 3H, J =7 Hz, CH_3), 0.97 (d, 3H, J =7 Hz, CH_3), 2.1 (m, 1H, >CH-), 2.35 (dd, 1H, J =17, 4 Hz, $\text{>C-CH}_2\text{H}$),

2.36 (s, 3H, CH_3), 2.91 (dd, 1H, J =17, 10 Hz, $\text{>C-CH}_2\text{H}$), 3.86 (s, 3H, OCH_3), 3.9 (m, 1H, >CH-), 6.74 (broad s, 1H), 6.78 (d, 1H, J =8 Hz), 7.59 (d, 1H, J =8 Hz), and 10.58 (broad s, 1H, CO_2H). Found: C, 67.76; H, 7.87%. Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_4$: C, 68.16; H, 7.63%.

When the above α -bromo ketone was condensed with diethyl malonate in place of ethyl cyanoacetate, the yield of keto acid **11** was only 17.6%.

4-Methyl-3-(2-methoxy-4-methylbenzyl)pentanoic Acid (**12**). The Clemmensen reduction of keto acid **11** (3.1 g) with amalgamated zinc prepared from Zn (7.6 g) and HgCl_2 (0.9 g) for 10 h gave **12** (1.7 g, 58.6%), bp 163–164°C/5 mmHg, mp 96.5–97.5°C (from petroleum ether); IR (KBr): 1700, 1610, 1505, 1460, 1450, 1410, 1320, 1300, 1290, 1260, 1155, and 1040 cm^{-1} ; ^1H NMR (CDCl_3): δ =0.90 (d, 3H, J =6.5 Hz, CH_3), 0.94 (d, 3H, J =6.5 Hz, CH_3), 1.7 (m, 1H, >CH-), 2.2 (m, 3H, CH_2 , >CH-), 2.29 (s, 3H, CH_3), 2.5 (m, 2H, CH_2), 3.76 (s, 3H, OCH_3), 6.61 (s, 1H), 6.64 (d, 1H, J =8 Hz), 6.97 (d, 1H, J =8 Hz), and 11.11 (broad s, 1H, CO_2H). Found: C, 71.54; H, 9.16%. Calcd for $\text{C}_{15}\text{H}_{22}\text{O}_3$: C, 71.97; H, 8.86%.

3,4-Dihydro-3-isopropyl-5-methoxy-7-methyl-1(2H)-naphthalenone (**13**). A solution of the carboxylic acid **12** (1.7 g) and POCl_3 (0.7 g) in 1,1,2,2-tetrachloroethane (25 ml) was refluxed for 2 h with stirring; the mixture was poured into an ice water. The organic layer was separated and concentrated to afford **13** (1.5 g, 93.8%), bp 165–167°C/7 mmHg; IR (neat): 1685, 1610, 1465, 1340, 1320, 1300, 1250, 1130, and 1060 cm^{-1} ; ^1H NMR (CDCl_3): δ =0.98 (d, 6H, J =6 Hz, $\text{CH}_3\times 2$), 1.7 (m, 1H, J =6 Hz, >CH-), 1.8–2.5 (m, 3H, CH_2 , >CH-), 2.35 (s, 3H, CH_3), 2.9 (m, 2H, CH_2), 3.85 (s, 3H, OCH_3), 6.83 (d, 1H, J =1.5 Hz), and 7.44 (broad s, 1H), 2,4-Dinitrophenylhydrazones: Red microcrystals (from benzene), mp 216.0–217.0°C. Found: C, 61.00; H, 5.70; N, 13.33%. Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_5$: C, 61.15; H, 5.87; N, 13.59%.

3,4-Dihydro-3-isopropyl-5-methoxy-1,7-dimethylnaphthalene (**14**). A solution of tetralone **13** (1.2 g) in ether (15 ml) was added to a Grignard reagent prepared from methyl iodide (2.3 g) and Mg (0.4 g) in ether (20 ml) with cooling in an ice bath. The reaction mixture was refluxed for 10 h with stirring; the mixture was then decomposed by adding ice and NH_4Cl . The resulting crude alcohol (1.3 g, IR: 3380 cm^{-1}) was dehydrated by stirring with formic acid (2.5 ml) at 80°C for 2 h. After extraction with benzene, the resulting products were chromatographed on silica gel and eluted with CCl_4 to give **14** as an oil (1.0 g, 83.3%); IR (neat): 1605, 1570, 1460, 1280, 1140, 1060, and 830 cm^{-1} ; ^1H NMR (CDCl_3): δ =0.93 (d, 6H, J =6 Hz, $\text{CH}_3\times 2$), 1.69 (m, 1H, J =6 Hz, >CH-), 2.04 (broad s, 3H, >CH_3), 2.32 (s, 3H, CH_3), 2.5

(m, 2H, CH₂), 2.9 (m, 1H, >CH-), 3.79 (s, 3H, OCH₃), 5.73 (broad, 1H, =CH-), 6.59 (broad s, 1H), and 6.70 (broad s, 1H).

7-Isopropyl-3,5-dimethyl-1-naphthol (5a). The dihydronaphthalene **14** (1.0 g) was dehydrogenated by heating with 5% Pd-C (0.2 g) at 240–250°C for 5 h. The resulting products were chromatographed on silica gel and eluted with CCl₄ to give the methoxynaphthalene **5b** as an oil (0.8 g, 80.8%), which was identical in all respects with the specimen¹⁾ derived from **4b**. Picrate: Brown needles (from ethanol), mp 165.0–166.0°C (lit.¹⁾ mp 165.0–166.0°C).

A mixture of **5b** (0.7 g) and 48% HBr (7 ml) in glacial acetic acid (7 ml) was refluxed for 2 h. The reaction mixture was diluted with water (20 ml) and extracted with benzene. The extract was evaporated and the residue recrystallized from petroleum ether to give 7-isopropyl-3,5-dimethyl-1-naphthol **5a** (0.6 g, 90.9%) as woolly crystals, mp 86.0–87.0°C (lit.¹⁾ mp 86.0–87.0°C). The IR and NMR spectra of this naphthol **5a** were superimposable with those of the specimen¹⁾ obtained from **4b** by refluxing in acetic acid with HBr. Acetate: Prisms (from petroleum ether), mp 67.5–68.5°C; IR (KBr): 1760, 1610, 1400, 1365, 1200, 1120, 1025, and 870 cm⁻¹; ¹H NMR (CDCl₃): δ=1.29 (d, 6H, J=7 Hz, CH₃×2), 2.41 (s, 3H, COCH₃), 2.49 (s, 3H, CH₃), 2.62 (s, 3H, CH₃), 2.95 (m, 1H, J=7 Hz, >CH-), 7.04 (d, 1H, J=1.5 Hz), 7.20 (broad s, 1H), 7.43 (broad s, 1H), and 7.58 (broad s, 1H). Found: C, 79.58; H, 7.91%. Calcd for C₁₇H₂₀O₂: C, 79.65; H, 7.86%.

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