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

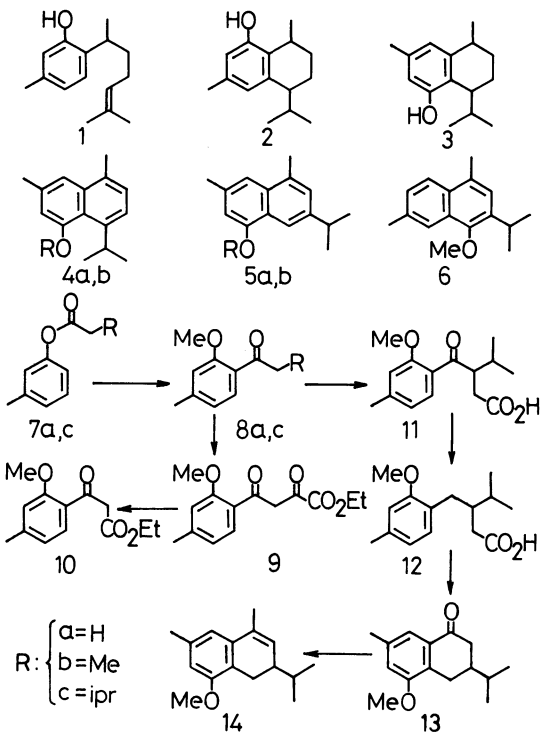
Juichi TANAKA and Kazuo ADACHI*
Osaka Institute of Technology, Omiya, Asahi-ku, Osaka 535
(Received December 7, 1988)

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 curcuphenol[2] (**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 BBr_3.[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 sesquiterpenoide 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 δ=0.73 and 0.97 as a pair of doublets (J=7 Hz) and methylene proton signals as a pair of double doublets at δ=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 phosphoryl 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 ^{13}C 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, CH_3×2), 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, CH_3×2), 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 (0.8g) 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-dioxobutyrate (**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, =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 $C_{14}H_{16}O_5$: C, 63.62; H, 6.10%.

A mixture of the diketo 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 recrystalization from benzene, mp 213.0—213.5 °C. Found: C, 69.47; H, 5.54%. Calcd for $C_{22}H_{20}O_6$: 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, $>C<^{H}_{H}$), 2.36 (s, 3H, CH_3), 2.91 (dd, 1H, J=17, 10 Hz, $>C<^{H}_{H}$), 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 $C_{15}H_{20}O_4$: 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 $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%.

3,4-Dihydro-3-isopropyl-5-methoxy-7-methyl-1(2*H*)-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, CH_3×2), 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-Dinitrophenylhydrazone: Red microcrystals (from benzene), mp 216.0—217.0 °C. Found: C, 61.00; H, 5.70; N, 13.33%. Calcd for $C_{21}H_{24}N_4O_5$: 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, CH_3×2), 1.69 (m, 1H, J=6 Hz, >CH-), 2.04 (broad s, 3H, $\geqslant$-CH_3), 2.32 (s, 3H, CH_3), 2.5

(m, 2H, CH_2), 2.9 (m, 1H, $\succ$CH-), 3.79 (s, 3H, OCH_3), 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 CCl_4 to give the methoxynaphthalene **5b** as an oil (0.8 g, 80.8%), which was identical in all respects with the specimene[1] 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 specimene[1] 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 ($CDCl_3$): δ=1.29 (d, 6H, J=7 Hz, CH_3×2), 2.41 (s, 3H, $COCH_3$), 2.49 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 2.95 (m, 1H, J=7 Hz, $\succ$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 $C_{17}H_{20}O_2$: C, 79.65; H, 7.86%.

References

1) Preceeding paper: J. Tanaka and K. Adachi, *Nippon Kagaku Kaishi*, **1989**, 268.

2) F. Bohlmann and M. Lonitz, *Chem. Ber.*, **111**, 843 (1978); F. J. McEnroe and W. Fenical, *Tetrahedron*, **34**, 1661 (1978); E. L. Ghisalberti, P. R. Jefferies, and A. D. Stuart, *Aust. J. Chem.*, **32**, 1627 (1979).

3) J. Tanaka, K. Nobutani, and K. Adachi, *Nippon Kagaku Kaishi*, **1988**, 1065.

4) Y. Kashman, *Tetrahedron*, **35**, 263 (1979); J. D. Bunko, E. L. Ghisalberti, and P. R. Jefferies, *Aust. J. Chem.*, **34**, 2237 (1981); M. Nishizawa, A. Inoue, S. Sastrapradja, and Y. Hayashi, *Phytochemistry*, **22**, 2083 (1983); M. Uemura, K. Isobe, and Y. Hayashi, *Chem. Lett.*, **1985**, 91.

5) F. Bohlmann and C. Zdero, *Chem. Ber.*, **109**, 2021 (1976); F. Bohlmann and W. Mailahn, *ibid.*, **114**, 1091 (1981); K. Adachi and N. Taniguchi, *Bull. Chem. Soc. Jpn.*, **55**, 1655 (1982); K. Adachi and M. Mori, *ibid.*, **56**, 651 (1983).

6) J. Tanaka and K. Adachi, *Yuki Gosei Kagaku Kyokaishi*, **32**, 1006 (1974); K. Adachi, J. Tanaka, Y. Imai, and T. Okazaki, *Nippon Kagaku Kaishi*, **1980**, 62.

7) A. Spasov, *Ann. Univ. Sofia. II Faculté Phy-math.*, Livre 2, **35**, 289 (1938—1939); *Chem. Abstr.*, **34**, 2343 (1940).

8) R. M. Cowper and L. H. Davidson, *Org. Synth.*, Coll. Vol. II, 480 (1943).