Note

Synthesis of Elsholtzia Ketone

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Elsholtzia ketone [3-methyl-1-(3-methyl-2-furyl)-1-butanone, **5**] is a naturally occurring monoterpenoid¹⁾ which has previously been prepared by the reaction of 3-methyl-2-furancarboxitrile with isobutylmagnesium bromide,²⁾ by Friedel-Crafts acylation of 3-methylfuran,³⁾ or by sigmatropic rearrangement of 4-methyl-2-(3-furyl-methoxy)pentanenitrile.⁴⁾

In the preceding paper, the author reported a new route for synthesizing rosefuran from crotonaldehyde via γ -oxoaldehyde as an intermediate.⁵⁾ This new method is now applied to the synthesis of **5** with good results.

3,7-Dimethyl-4-oxooctanal (**1**), which had been prepared from 4-methylpentanal and crotonaldehyde by a radical addition reaction in a 57% yield, was treated with pyrophosphoric acid in benzene to obtain 3-methyl-2-(3-methylbutyl)furan (dihydorosefuran, **2**) in a 40% yield. Furan **2** was then converted to 3-methyl-1-(3-methyl-2-furyl)butyl acetate (**3**) by selectively acetoxylation with lead tetra-acetate in an acetic acid–ether (2:1) solution in a 76% yield. Acetate **3** was hydrolyzed in a 77% yield with aqueous sodium hydroxide to give 3-methyl-1-(3-methyl-2-furyl)-1-butanol (**4**), which was finally oxidized with activated manganese dioxide to **5** in an 81% yield. The infrared spectrum of **5** agreed with that of the naturally occurring elsholtzia ketone.⁶⁾

Experimental

Analytical determination by GLPC was performed on a Hitachi model 163 gas chromatograph fitted with an

FFAP column (3 mm o.d. $\times$ 2 m) on Chromosorb W. IR spectra were measured in films on a Hitachi 270-30 instrument. NMR spectra were recorded on a Hitachi R-24 B instrument at 60 MHz in CCl_4 with TMS as an internal standard, and GC-MS data were obtained with a Hitachi M-80 B spectrometer at 70 eV.

3,7-Dimethyl-4-oxooctanal (1). This compound (bp 82°C at 3 mmHg) was prepared from 4-methylpentanal and crotonaldehyde in a 57% yield according to the procedure described in the previous paper.⁵⁾ IR ν_{max} cm^{-1} : 2950, 2870, 2700, 1720, 1700, 1450, 1390, 1375, 1365, 1330, 1260, 1200, 1160, 1145, 1120, 1060, 1040, 1000, 680. NMR δ : 0.90 (6H, d, $J=6$ Hz, CH_3), 1.10 (3H, d, $J=7$ Hz, CH_3), 1.20–1.80 (3H, m, CH , CH_2), 2.20–3.20 (5H, m, CH_2CO , CHCO), 9.20 (1H, s, CHO). MS m/z : 170 (M^+ , 2), 128 (4), 78 (15), 99 (53), 86 (7), 81 (43), 72 (24), 71 (39), 57 (6), 55 (10), 43 (100), 42 (6), 41 (36), 29 (10), 27 (18).

3-Methyl-2-(3-methylbutyl)furan (dihydorosefuran, 2). A solution of **1** (17.0 g, 0.1 mol) and pyrophosphoric acid (0.05 g) in benzene (150 ml) was refluxed for 4 hr. with azeotropic removal of the water. The mixture was poured into a 5% NaHCO_3 solution (200 ml), and the organic layer was separated. This organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was distilled (bp 83–84°C at 30 mmHg) to give 6.1 g (40% yield) of 3-methyl-2-(3-methylbutyl)furan (**2**). IR ν_{max} cm^{-1} : 2950, 2920, 2860, 1550, 1500, 1450, 1380, 1360, 1220, 1190, 1140, 1050, 950, 885, 830. NMR δ : 0.95 (6H, d, $J=6$ Hz, CH_3), 1.30–1.80 (3H, m, CH_2 , CH), 1.95 (3H, s, CH_3), 2.55 (2H, t, $J=6$ Hz, CH_2), 6.10 (1H, d, $J=2$ Hz, β -H of furan), 7.15 (1H, d, $J=2$ Hz, α -H of furan). MS m/z : 152 (M^+ , 13), 96 (11), 95 (100), 41 (14), 39 (7).

3-Methyl-1-(3-methyl-2-furyl)butyl acetate (3). To a solution of **2** (15.2 g, 0.1 mol) in acetic acid–ether (2:1, 250 ml), lead tetra-acetate (44.3 g, 0.1 mol) was added while stirring at 5°C, the mixture being further stirred for 8 hr. The reaction mixture was poured into water (500 ml) and extracted with ether (300 ml). The combined extracts were washed with 5% NaHCO_3 and brine in turn, and dried over Na_2SO_4 . After evaporating the solvent, the residue

was distilled (bp 78°C at 4 mmHg) to give 16.0 g (76% yield) of 3-methyl-1-(3-methyl-2-furyl)butyl acetate (**3**). IR $\nu_{\max}$ cm^{-1} : 2960, 2940, 2890, 1722, 1520, 1480, 1460, 1440, 1420, 1380, 1245, 1180, 1160, 1135, 1080, 1055, 1020, 950, 930, 895, 750. NMR δ : 0.75–1.10 (6H, m, CH_2), 1.15–1.80 (3H, m, CH_2 , CH), 1.90 (3H, s, CH_3), 2.00 (3H, s, CH_3CO), 5.75 (1H, t, $J=8$ Hz, CH), 6.00 (1H, d, $J=2$ Hz, β -H of furan), 7.10 (1H, d, $J=2$ Hz, α -H of furan). MS m/z : 210 (M^+ , 10), 153 (10), 151 (12), 150 (7), 135 (16), 112 (7), 111 (100), 109 (13), 108 (42), 107 (8), 95 (38), 79 (7), 77 (6), 53 (6), 43 (40), 41 (12), 39 (9), 27 (7).

3-Methyl-1-(3-methyl-2-furyl)-1-butanol (4). A mixture of **3** (10.5 g, 0.05 mol) and 20% aqueous NaOH (100 ml) was refluxed for 2 hr. The mixture was then extracted with ether, and the combined extracts were washed with brine, and dried over Na_2SO_4 . After removing the solvent, the product was distilled (bp 76°C at 4 mmHg) to give 6.5 g (77% yield) of 3-methyl-1-(3-methyl-2-furyl)-1-butanol (**4**). IR $\nu_{\max}$ cm^{-1} : 3350, 2950, 2940, 1520, 1475, 1460, 1415, 1384, 1362, 1300, 1270, 1230, 1215, 1155, 1120, 1070, 1040, 1000, 900, 890, 840, 780, 740. NMR δ : 0.70–1.15 (6H, m, CH_3), 1.30–1.90 (3H, m, CH_2 , CH), 2.00 (3H, s, CH_3), 2.55 (1H, br. s, OH), 4.65 (t, 1H, $J=8$ Hz, CH), 6.10 (1H, d, $J=2$ Hz, β -H of furan), 7.18 (1H, d, $J=2$ Hz, α -H of furan). MS m/z : 168 (M^+ , 6), 112 (6), 111 (100), 55 (7), 41 (7), 39 (6), 27 (6).

Elsholtzia ketone (5). Activated manganese dioxide (Aldrich Chemical Co., 30.0 g) was added to a stirred solution of **4** (5.0 g, 0.0179 mol) in hexane (150 ml), and

stirring at room temperature was continued for 48 hr. The solution containing the manganese dioxide was filtered, and the filtrate was concentrated under reduced pressure. The residue was distilled (bp 93–99°C at 15 mmHg) to give 4.0 g (81% yield) of 3-methyl-1-(3-methyl-2-furyl)-1-butanone (**5**). IR $\nu_{\max}$ cm^{-1} : 2950, 2930, 2860, 1680, 1594, 1494, 1487, 1408, 1380, 1362, 1318, 1300, 1260, 1240, 1182, 1108, 1050, 1000, 940, 892, 890, 775. NMR δ : 0.98 (6H, d, $J=6$ Hz, CH_3), 2.00–2.30 (1H, m, CH), 2.38 (3H, s, CH_3), 2.60–3.00 (2H, m, CH_2), 6.35 (1H, d, $J=2$ Hz, β -H of furan), 7.35 (1H, d, $J=2$ Hz, α -H of furan). MS m/z : 166 (M^+ , 7), 151 (12), 124 (49), 110 (7), 109 (100), 82 (8), 53 (11), 51 (5), 41 (10), 39 (9), 27 (10).

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