

A SHORT SYNTHESIS OF 4-(3-FURYL)-4-OXOBUTANOIC ACID AND SYNTHESIS OF EGOMAKETONE

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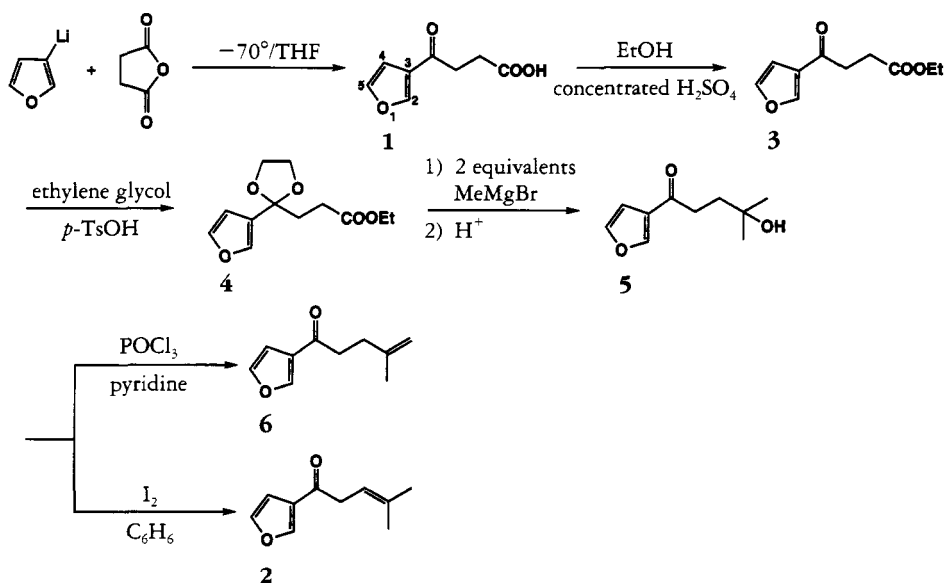
ABSTRACT.—3-Lithiofuran in THF was added to succinic anhydride in THF to yield 4-(3-furyl)-4-oxobutanoic acid [**1**]. Egomaketone [**2**], isolated from *Perilla frutescens* was synthesized from **1** in four steps. The isomer of **2**, 5-(3-furyl)-2-methyl-5-oxo-1-pentene [**6**], was also prepared from **1**.

Oxygenated perillens (perilla ketone, egomaketone, and isoegomaketone), isolated from *Perilla frutescens* Birt. (1–3), are a major cause of bovine respiratory toxicity (4). The syntheses of compounds belonging to this group of furan monoterpenoids have been accomplished by various methods. Egomaketone [**2**] has been prepared via 3-cyanofuran (5, 6), 3-furoyl chloride (7), 3-furancarbaldehyde (8), 2-(3-furyl)-1,3-dithiane (9), and 3-furyltrimethyltin (10), using 3-bromofuran as starting material. However, some of these syntheses involve many steps and others use expensive reagents to introduce a side-chain onto the 3-position of furan.

The preparation of 2-(3-furanoyl)-

benzoic acid from 3-lithiofuran has been effected by our group in only one step (11). In the present paper, we report a one-step synthesis of 4-(3-furyl)-4-oxobutanoic acid [**1**], an intermediate in the preparation of oxygenated perillens, from 3-lithiofuran. The previously reported synthesis of **1** requires five steps from diethyl 3,4-furandicarboxylate (12). Further, we report a new synthetic route from **1** to egomaketone [**2**] (Scheme 1).

The intermediate **1** was obtained by the reaction of succinic anhydride with 3-lithiofuran in one step. Acid **1** was esterified to give ethyl 4-(3-furyl)-4-oxobutanoate [**3**], and the ketone was protected as the ketal, ethyl 4-(3-furyl)-4-(1,3-dioxolan-2-yl)butanoate [**4**]. Re-



SCHEME 1. Syntheses of 5-(3-furyl)-2-methyl-5-oxo-1-pentene [**6**] and egomaketone [**2**] from 3-lithiofuran.

action of **4** with two equivalents of methylmagnesium bromide, followed by treatment with iced 10% HCl, yielded the tertiary alcohol, 5-(3-furyl)-2-methyl-5-oxo-2-pentanol [**5**]. The heat-sensitive alcohol **5** was used for the next reaction without further purification.

The alcohol **5** was allowed to react with phosphorus oxychloride (13) in pyridine. The reaction mixture was analyzed by gc-ms which detected the starting material and two dehydrated compounds. The mixture was purified by cc to afford white needles of 5-(3-furyl)-2-methyl-5-oxo-1-pentene [**6**] (mp 34–36°) in poor yield. The ¹H-nmr spectrum of **6** showed characteristic signals for the exomethylene group at δ 4.70 (s) and a methyl group at δ 1.77 (s).

The alcohol **5** was then reacted with iodine in C₆H₆ (14). The reaction mixture was analyzed by gc-ms, which detected the starting material and two dehydrated compounds. The mixture was purified by cc to give egomaketone [**2**] in low yield; spectral data for **2** were in accord with those of an authentic sample (6).

In conclusion, the key intermediate **1** was obtained from 3-lithiofuran in one step. Egomaketone **2**, isolated from *Perrilla frutescens* Birt., and the isomer **6** were prepared from **1**. It has been demonstrated that this method affords a new route to 3-acylfurans.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All mps (open capillaries) were determined using a Yamato MP-21 apparatus and are reported uncorrected. All boiling points are also reported uncorrected. The ¹H-nmr spectra were determined at 60 MHz on a Nippon Denshi JNM PMR-60SI nmr spectrometer with TMS as internal reference. The ir spectra were measured using a Jasco IR-810 spectrometer and the mass spectra were obtained on a Nippon Denshi DX-300 spectrometer at 70 eV. THF was distilled over LiAlH₄ prior to use. Chromatography was carried out using Si gel (Wakogel C-200, Wako Pure Chemical Industries, Ltd.). Methylmagnesium bromide (ca. 3 M in Et₂O, Tokyo Chemical Industry Co., Ltd.) and

n-butyllithium (1.68 M in hexane, Kanto Chemical Co., Inc.) were obtained commercially.

4-(3-Furyl)-4-oxobutanoic acid [**1**].—3-Bromofuran (21.6 g, 147 mmol) in THF (180 ml) was added to *n*-butyllithium (110 ml of 1.68 M in hexane, 185 mmol) with stirring at -70° under an atmosphere of N₂. The mixture was allowed to react for 10 min. The mixture was then added to succinic anhydride (16.2 g, 162 mmol) in THF (240 ml) at -70° under an atmosphere of N₂ for 1 h. The mixture was warmed to room temperature for 30 min and poured into ice-cold H₂O. The solution was made acidic with 10% HCl and extracted with Et₂O. The desired compound **1** was extracted with 5% NaHCO₃ from the Et₂O layer. The aqueous solution was made acidic with 10% HCl and extracted with Et₂O. The Et₂O layer was washed with brine and dried over anhydrous Na₂SO₄. The solution was evaporated, and the residue was recrystallized from H₂O to yield **1** as white scales (11.7 g, 70 mmol, 47% yield): mp 146–147° [mp 148–150° (15)]; ir ν max (KBr) 1720 (COOH), 1660 (C=O) cm⁻¹; ¹H nmr (DMSO-*d*₆) δ 12.17 (1H, s, OH, exchangeable proton), 8.53 (1H, d), 7.73 (1H, t), 6.75 (1H, d), 3.05 (2H, t, *J*=7 Hz, COCH₂), 2.55 (2H, t, *J*=7 Hz, CH₂COOH); ms *m/z* [M]⁺ 168 (10), 150 (14), 95 (100); *anal.*, calcd for C₈H₈O₄, C, 57.14, H, 4.80; found C, 57.10, H, 4.74.

Ethyl 4-(3-furyl)-4-oxobutanoate [**3**].—To compound **1** (10.0 g, 60 mmol) in absolute EtOH (35 ml), concentrated H₂SO₄ (0.7 ml) was added slowly, and the mixture was refluxed for 4 h. Excess EtOH was evaporated, and the resulting mixture was poured into ice-cold H₂O. The solution was extracted with Et₂O. The Et₂O layer was washed with 5% NaHCO₃, then brine, and dried over anhydrous Na₂SO₄. The solvent was evaporated, and the residue was recrystallized from EtOH/H₂O to yield **3** as white needles (9.0 g, 46 mmol, 77% yield): mp 53–55°; ir ν max (KBr) 1720 (COOEt), 1670 (C=O) cm⁻¹; ¹H nmr (CDCl₃) δ 8.03 (1H, d), 7.73 (1H, t), 6.73 (1H, d), 4.11 (2H, q, *J*=7 Hz, CH₂CH₃), 3.07 (2H, t, *J*=7 Hz, COCH₂), 2.72 (2H, t, *J*=7 Hz, CH₂COOEt), 1.23 (3H, t, *J*=7 Hz, CH₂CH₃), ms *m/z* [M]⁺ 196 (5.1), 151 (15), 95 (100); *anal.*, calcd for C₁₀H₁₂O₄, C, 61.22, H, 6.16; found, C, 61.06, H, 6.16.

Ethyl 4-(3-furyl)-4-(1,3-dioxolan-2-yl)butanoate [**4**].—Ethylene glycol (18.0 ml) and *p*-toluenesulfonic acid (0.4 g) were added to compound **3** (10.0 g, 51 mmol) in ethyl orthoformate (34.0 ml), then the mixture was heated at 165° for 12 h. The mixture was cooled to room temperature and diluted with Et₂O. The Et₂O layer was washed with brine and dried over anhydrous Na₂SO₄, then the solvent was evaporated. The residue was distilled to yield **4** as a colorless liquid (10.5 g, 44

mmol, 86% yield); bp 126° (3 mm Hg); ν max (neat) 1735 (COOEt) cm^{-1} ; ^1H nmr (CDCl_3) δ 7.30 (2H, d), 6.30 (1H, d), 4.12 (2H, q, $J=7$ Hz, CH_2CH_3), 3.90 (4H, m, dioxolane), 2.32 (4H, m, CH_2CH_3), 1.21 (3H, t, $J=7$ Hz, CH_2CH_3); ms m/z [$\text{M}]^+$ 240 (0.4), 195 (15), 139 (100); *anal.*, calcd for $\text{C}_{12}\text{H}_{16}\text{O}_5$, C, 59.99, H, 6.71; found, C, 59.71, H, 6.61.

5-(3-Furyl)-2-methyl-5-oxo-2-pentanol [**5**].—Methylmagnesium bromide (6.1 ml of 3 M in Et_2O , 18.3 mmol) was diluted with absolute Et_2O (2 ml). To the solution, compound **4** (2.0 g, 8.3 mmol) in absolute Et_2O (6 ml) was added below 5° under an atmosphere of N_2 . The mixture was stirred at 0° for 2 h, then at room temperature for 2 h. The resulting mixture was poured into iced 10% HCl. The solution was extracted with Et_2O . The Et_2O layer was washed with brine and dried over anhydrous Na_2SO_4 ; then the solvent was evaporated to yield **5** as a colorless liquid (1.4 g, 7.7 mmol, 93% yield). Because alcohol **5** was sensitive to heat, it was used without further purification: ν max 3440 (OH), 1675 (C=O) cm^{-1} ; ^1H nmr (CDCl_3) δ 8.10 (1H, d), 7.42 (1H, t), 6.73 (1H, d), 2.90 (2H, t, $J=7$ Hz, COCH_2), 2.83 (1H, s, OH, exchangeable proton), 1.85 (2H, t, $J=7$ Hz, $\text{CH}_2\text{C}(\text{Me})_2\text{OH}$), 1.22 (6H, s, $\text{Me}\times 2$); hrms m/z calcd for $\text{C}_{10}\text{H}_{14}\text{O}_3$ 182.0943 ($[\text{M}]^+$, 5.1), observed 182.0930, 167 (26), 124 (64), 95 (100).

5-(3-Furyl)-2-methyl-5-oxo-1-pentene [**6**].—To compound **5** (1.4 g, 7.7 mmol) in absolute pyridine (66 ml), POCl_3 (6.6 ml, 72 mmol) in absolute pyridine (20 ml) was added at -15 – -20° ; the mixture was stirred at this temperature for 30 min and then at room temperature for 24 h. The mixture was poured into ice-cold H_2O and the solution was extracted with Et_2O . The Et_2O layer was washed with 10% HCl, H_2O , and brine. The Et_2O layer was dried over anhydrous Na_2SO_4 , then the solvent was evaporated. The residue was purified by cc over Si gel with hexane- EtOAc (9:1) as eluent to yield **6** as white needles (0.1 g, 0.6 mmol, 8% yield, R_f 0.34); mp 34–36°; ν max (KBr) 1665 (C=O) cm^{-1} ; ^1H nmr (CDCl_3) δ 8.02 (1H, d), 7.40 (1H, t), 6.73 (1H, d), 4.70 (2H, s, $\text{CH}_2=$), 2.90 (2H, t, $J=7$ Hz, COCH_2), 2.38 (2H, t, $J=7$ Hz, $\text{CH}_2\text{C}(\text{Me})=\text{CH}_2$), 1.77 (3H, s, Me); hrms m/z calcd for $\text{C}_{10}\text{H}_{12}\text{O}_2$ 164.0837 ($[\text{M}]^+$ 8.2), observed 164.0860, 95 (100).

Egomaketone [**2**].—To compound **5** (1.1 g,

6.0 mmol) in C_6H_6 (20 ml), iodine (0.2 g) was added and the mixture was refluxed for 1 h. The resulting mixture was poured into 10% $\text{Na}_2\text{S}_2\text{O}_3$. The solution was extracted with Et_2O . The Et_2O layer was washed with 10% $\text{Na}_2\text{S}_2\text{O}_3$ and brine. The Et_2O layer was dried over anhydrous Na_2SO_4 , and the solvent was evaporated. The residue was purified by cc over Si gel with hexane- EtOAc (19:1) as eluent to yield **2** as a colorless liquid (0.2 g, 1.2 mmol, 20% yield, R_f 0.18); ν max 1675 (C=O) cm^{-1} ; ^1H nmr (CDCl_3) δ 8.05 (1H, s), 7.41 (1H, t), 6.75 (1H, d), 5.38 (1H, dt, $J=2$ and 7 Hz, $\text{CH}=\text{}$), 3.45 (2H, d, $J=7$ Hz, COCH_2), 1.77 (3H, s, Me), 1.68 (3H, s, Me); hrms m/z calcd for $\text{C}_{10}\text{H}_{12}\text{O}_2$ 164.0837 ($[\text{M}]^+$, 12), observed 164.0858, 95 (100).

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