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A New Synthesis of 4-Methoxy-6-valeryl-5,6-dihydro-2-pyrone*

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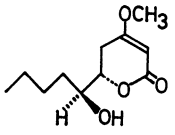
Synopsis. The reaction of ethyl 2-acetoxy-3-oxoheptanoate with γ-bromo-β-methoxy-*cis*-crotonate in the presence of sodium ethoxide afforded diethyl 3-methoxy-5-hydroxy-5-valeryl-2-hexenedioate (**7**) in 65% yield. Treatment of **7** with a dilute aqueous NaOH in acetone gave (±)-4-methoxy-6-valeryl-5,6-dihydro-2-pyrone, a key intermediate leading to pestalotin, in 41% yield.

Several reports have appeared on the synthesis of the pestalotin (**1**),[1-7] a gibberellin synergist isolated by Kimura and Tamura from the culture broth of *Pestalotia cryptomeriaecola* Sawada. First total synthesis of optically active pestalotin was accomplished by Seebach and Meyer[6] by the asymmetric reduction of (±)-4-methoxy-6-valeryl-5,6-dihydro-2-pyrone (**2**) in *ca.* 10% optical yield. They obtained dihydropyrone **2** *via* its 1,3-dithiane derivative. This paper deals with a convenient, alternative synthesis of dihydropyrone **2**.



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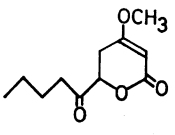

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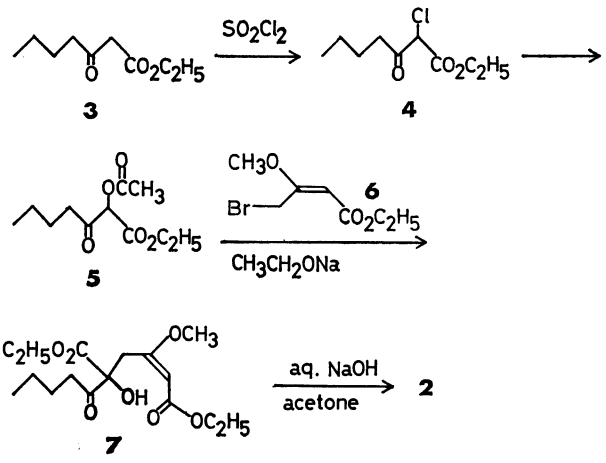
Chlorination of ethyl 3-oxoheptanoate (**3**) with sulfuryl chloride gave ethyl 2-chloro-3-oxoheptanoate (**4**) in 88% yield. This was converted into ethyl 2-acetoxy-3-oxoheptanoate (**5**)[9] by the action of potassium acetate in 61% yield. Reaction of the ester **5** with ethyl γ-bromo-β-methoxy-*cis*-crotonate (**6**) in the presence of sodium ethoxide afforded diester **7** in 65% yield. Treatment of **7** with a weak aqueous NaOH in acetone gave the desired dihydropyrone **2** in 41% yield. The spectral data (IR, NMR) of this product support its structure. Reduction of **2** with sodium borohydride in aqueous dioxane gave a mixture of (±)-pestalotin and (±)-epipestalotin in 90% yield.



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Experimental

Melting points and boiling points are uncorrected. UV spectra were taken with a Hitachi Model EPS-3T recording spectrophotometer, IR spectra with a Hitachi Model EPI-S2 spectrometer, NMR spectra (60 MHz) with a Hitachi Model R-24 spectrometer, and MS spectra with a Hitachi Model RMS-4 mass spectrometer (70 eV). Analytical and preparative TLC were carried out on silica gel PF_{254} (E. Merck AG, Darmstadt) with layers of 0.25 mm and 1.0 mm thickness, respectively. Compounds **3** and **6** were prepared according to the methods of Anderson *et al.*[10] and Ellestad *et al.*,[3] respectively.

Ethyl 2-Chloro-3-oxoheptanoate (4). To a solution of ethyl 3-oxoheptanoate (**3**) (80 g, 0.47 mol) in 90 ml of dichloromethane was added slowly 63.5 g (0.47 mol) of sulfuryl chloride at a temperature below 45 °C. After the addition was over the mixture was refluxed for 2 h. Removal of the solvent left a clean oil which, on distillation, gave 84.5 g (88%) of **4**; bp 130—135 °C/30 Torr; IR (neat) 1750—1710 (C=O), 1630 (C=C), and 1600 cm^{-1} (enolic C=O); NMR ($CDCl_3$) δ 0.90 (t, 3H, J=6 Hz, $C\underline{H}_3(CH_2)_3$–), 1.0—1.7 (m, 4H, $CH_3(C\underline{H}_2)_2CH_2$–), 1.30 (t, 3H, J=7.5 Hz, $CO_2CH_2C\underline{H}_3$), 2.61 (t, 2H, J=6 Hz, –$C\underline{H}_2CO$–), 4.25 (q, 2H, J=7.5 Hz, $CO_2C\underline{H}_2CH_3$), and 4.72 ppm (s, 1H, –C<u>H</u>Cl–).

Ethyl 2-Acetoxy-3-oxoheptanoate (5). This compound was prepared according to the procedure given by Henecka.[8] To a mixture of potassium acetate (106 g, 1.08 mol), acetic acid (300 ml) and acetic anhydride (20 ml) was added 81.8 g (0.4 mol) of **4** at 110 °C. The mixture was stirred at 135 °C for 6 h. The solvent was removed *in vacuo*, and the residue was neutralized with dilute aqueous $NaHCO_3$. The organic layer was extracted with ether, washed with water, and dried over $MgSO_4$. After removal of the solvent the residue was distilled to give 56.3 g (61%) of **5**: bp 129—135 °C/8 Torr (lit,[9] bp 138—140 °C/17 Torr); IR (neat) 1750—1715 (C=O); NMR ($CDCl_3$) δ 0.91 (t, 3H, J=6 Hz, $C\underline{H}_3(CH_2)_3$–), 1.28 (t, 3H, J=7.5 Hz, $CO_2CH_2C\underline{H}_3$), 1.0—1.8 (m, 4H, $CH_3(C\underline{H}_2)_2CH_2$–), 2.14 (s, 3H, –OCOC<u>H</u>$_3$), 2.56 (br, t, 2H, J=6.5 Hz, $CH_3(CH_2)_2C\underline{H}_2$–), 4.18 (q, 2H, J=7.5 Hz, $CO_2C\underline{H}_2CH_3$), and 5.29 ppm (s, 1H, –C<u>H</u>$CO_2C_2H_5$); MS (70 eV) *m/e* (rel intensity) 188 (4), 185 (4), 146 (39), 104 (83), 85 (100), 76 (26), 57 (98).

Diethyl 3-Methoxy-5-hydroxy-5-valeryl-2-hexenedioate (7). Sodium (1.15 g, 0.05 mol) was dissolved in 75 ml of absolute ethanol, 11.5 g (0.05 mol) of the ester **5** being added dropwise at 0—5 °C. The mixture was stirred for 2.5 h at room temperature, and to this was added dropwise 11.2 g (0.05 mol) of ethyl γ-bromo-β-methoxy-*cis*-crotonate (**6**) at 5 °C. The resulting mixture was brought to room temperature, and then stirred for 1 h. After it was made weakly acidic, the solvent was removed. The residue was extracted with ether, and the ethereal layer was washded with water and dried over $MgSO_4$. Removal of the solvent left a clean oil which, on

distillation, gave 10.2 g (65%) of **7**: bp 168—170 °C/0.06 Torr: IR (neat) 3455 (OH), 1740 (ester C=O), 1720 (ketone C=O), 1680 (conjugated ester C=O), and 1630 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.90 (t, 3H, J=6 Hz, $C\underline{H}_3(CH_2)_3CO$–), 1.25 (t, 6H, J=7.5 Hz, 2 $CO_2CH_2C\underline{H}_3$), 1.00—1.90 (m, 4H, $CH_3(C\underline{H}_2)_2CH_2CO$–), 2.3—2.8 (m, 4H, $-C\underline{H}_2C(OCH_3)$=CH– and $CH_3(CH_2)_2C\underline{H}_2CO$–), 3.56 (s, 3H, $C\underline{H}_3O$–), 4.18 (q, 4H, 2 $CO_2C\underline{H}_2CH_3$), 4.90 (s, 1H, O<u>H</u>), and 5.19 ppm (s, –C<u>H</u>=C〈).

Found: C, 57.90; H, 7.92%. Calcd for $C_{16}H_{26}O_7$: C, 58.17; H, 7.93%.

4-Methoxy-6-valeryl-5,6-dihydro-2-pyrone (2). To a solution of 1.0 g, (3 mmol) of **7** in 90 ml of acetone was added 60 ml of 0.2 M aqueous NaOH at room temperature during a period of 3 min. After being stirred for 2 h, the mixture was poured into a large amount of water. Acetone was removed *in vacuo*. The residue was extracted with ether, washed with water, and then dried over $MgSO_4$. Removal of the solvent left 0.27 g (41%) of **2**: mp 82—83 °C (from hexane) (lit,[6] mp 83 °C): IR (KBr) 1705 (C=O), 1690 (shoulder, conjugate C=O), and 1620 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.90 [t, 3H, $C\underline{H}_3(CH_2)_3$–), 1.10—1.90 (m, 4H, $CH_3(C\underline{H}_2)_2$-CH_2CO–), 2.50—3.00 (m, 4H, $-C\underline{H}_2C(OCH_3)$=CH– and $CH_3(CH_2)_2C\underline{H}_2CO$–), 3.72 (s, 3H, $C\underline{H}_3O$–), 4.70 (t, 1H, –COC<u>H</u>–O–), and 5.13 ppm (s, 1H, –C<u>H</u>=C〈).

Reduction of **2** *with Sodium Borohydride.* To a solution of dihydro-2-pyrone **2** (88 mg, 0.42 mmol) in 0.3 ml of 75% aqueous dioxane was added dropwise a solution of $NaBH_4$ (17 mg, 0.42 mmol) in 0.3 ml of 75% aqueous dioxane with stirring at 25 °C. After being stirred for 3 h the mixture was acidified with dilute H_2SO_4, and extracted with chloroform. The chloroform extract was dried over $MgSO_4$, and evaporated to yield 80 mg (90%) of an oil which showed one spot at TLC (benzene: ethyl acetate=1: 1, R_f=0.35). This was subjected to preparative TLC for analysis and spectral determinations: IR (neat) 3430, 1710—1670, and 1630 cm^{-1}; NMR ($CDCl_3$) δ 0.9 (t, br, 3H), 1.1—1.7 (m, br, 6H,) 1.95—2.2 (s, br, 1H, OH), 2.20 (m, 1H, ring methylene), 2.81 (m, 1H, ring methylene), 3.72 (m, br, 1H, –C<u>H</u>(OH)–), 3.74 (s, 3H, CH_3O–), 4.28 (m, 1H, ring >H<u>C</u>–O–), and 5.14 ppm (d, 1H, =C<u>H</u>); MS (70 eV) *m/e* (rel intensity) 214 (M^+), 127 (base peak); UV λ_{max} 233 nm (ε=12000, 95% EtOH).

Found: C, 61.86; H, 8.22%. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47%.

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