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Short and Efficient Synthesis of the Antitumor Heptenes Melodienone and Isomelodienone

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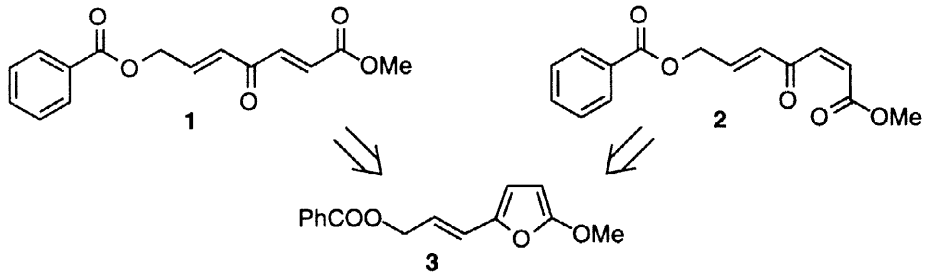
Abstract: The antitumor heptenes melodienone and isomelodienone were synthesized in 5 steps from 2-methoxyfuran (overall yield = 36 and 45% respectively) via oxidative ring-opening of a common methoxyfuran precursor.

Reported in 1990,[1] melodienone (**1**) and isomelodienone (**2**) are the archetypal members of a small group of heptene dienones isolated from the bark of the Thai shrub Lamduan (*Melodorum fruticosum* Lour.).[2] Notwithstanding their ostensibly simple structures, these molecules display an array of reactive functionality; every carbon atom in their C_7 skeleton is functionalized. In addition, isomelodienone exhibits significant activity against breast cancer and colon adenocarcinoma human cell lines (ED_{50} = 0.17 and 0.51 μg/ml, respectively).[1] To date, there has been no reported synthesis of isomelodienone, although its less potent congener **1** has been prepared by Barco *et al* in ten steps from dimethyl malate.[3] As a continuation of our interest in exploiting oxygenated furans as a source of masked functionality,[4,5] we describe here a particularly concise synthesis of **1** and **2** by a unified strategy based on oxidative opening of methoxyfuran **3** under the appropriate conditions.



The synthesis began with the formylation of commercial 2-methoxyfuran **4** (Scheme 1). Thus, sequential treatment of **4** with *n*-BuLi (2.5M in hexanes, 1 equiv) in THF at 0 °C for 2 h and DMF (2 equiv) at -78 °C for 1.5 h afforded 5-methoxyfurfural[6] **5** in 83% yield.[7,8] Horner-Emmons olefination of **5** with triethyl phosphonoacetate furnished the crystalline *E*-acrylate **6** with high efficiency. Subsequent DIBAL-H reduction (71%) and benzoylation (100%) provided the rather unstable relay furan **3** which was carried forward without purification. Oxidative opening of **3** using Kobayashi's modification (NBS/$NaHCO_3$/aq. acetone)[9] of the Clauson-Kaas reaction, delivered melodienone **1** as a single isomer (mp 68-70 °C, lit.[1] 69-70 °C) in 70% yield after silica gel chromatography. On the other hand, exposure of **3** to 1 equiv. of dimethyldioxirane[4] in acetone (-78 °C, 1 h) led uniquely to isomelodienone **2** (pale yellow oil, 86% yield). The spectral properties of **1** and **2** (IR, ^1H and ^{13}C NMR) were in full agreement with those reported for the corresponding natural products.[1]

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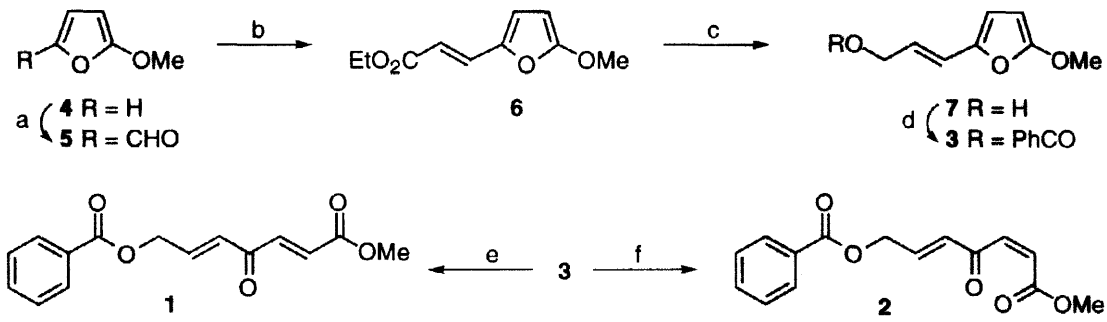
Scheme 1



a) *n*-BuLi (1 equiv), THF, 0 °C, 2h, then DMF (2 equiv), -78°C, 1.5 h, 83%; b) $(EtO)_2P(O)CH_2CO_2Et$ (1.1 equiv), *n*-BuLi, THF, - 78 → 25 °C, 88%; c) DIBAL-H (2 equiv), CH_2Cl_2, - 78 °C,1 h, 71%; d) PhCOCl (1.1 equiv), Et_3N (4 equiv), CH_2Cl_2, 30 min, 0 °C, 100%; e) NBS (1.1 equiv), $NaHCO_3$ (2 equiv), acetone/H_2O (10:1), -20 °C, 20 min, then furan (4 equiv), pyridine (4 equiv), 25 °C, 1 h, 70%; f) dimethyldioxirane (1 equiv), acetone, -78 °C, 1 h, 86%.

In conclusion, the first synthesis of isomelodienone and a new synthesis of melodienone have been accomplished in a highly concise and efficient fashion (5 steps, overall yield = 45 and 36%, respectively) by an inherently flexible pathway that is well-suited to the preparation of analogues for SAR studies.

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References and Notes

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7. This transformation has been previously mentioned in the literature without details (see note 12 in ref. 6); we found that the use of THF as a solvent is crucial for optimal results.
8. Yields refer to chromatographically and spectroscopically homogeneous products (except for **3**). The acid-sensitive compounds **6** and **7** were purified by flash chromatography on silica gel pre-treated with a 5% solution of Et_3N in hexanes and by using Et_3N (1%) as co-eluent. New compounds **3**, **6** and **7** gave satisfactory NMR (^1H and ^{13}C; 300 and 75 MHz respectively, $CDCl_3$), IR and HRMS data. **3**: ^1H δ 8.05 (dd, J = 8.2, 1.4 Hz, 2H), 7.58 (tt, J = 8.2, 1.4 Hz, 1H), 7.45 (tt, J = 8.2, 1.4 Hz, 2H), 6.26 (d, J = 15.5 Hz, 1H), 6.07 (d, J = 3.1 Hz, 1H), 6.05 (dt, J = 15.5, 6.6 Hz, 1H), 5.11 (d, J = 3.1 Hz, 1H), 4.81 (d, J = 6.6 Hz, 2H), 3.73 (s, 3H); ^{13}C δ 166.2, 162.2, 142.4, 133.3, 129.6, 129.3, 128.4, 122.3, 118.1, 111.0, 81.5, 65.3, 57.5. **6** (mp 39-40 °C): ^1H δ 7.19 (d, J = 15.6 Hz, 1H), 6.45 (d, J = 3.4 Hz, 1H), 6.01 (d, J = 15.6 Hz, 1H), 5.21 (d, J = 3.4 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C δ 167.4, 163.2, 141.7, 130.6, 117.9, 111.8, 83.3, 60.0, 57.6, 14.2. **7**: ^1H δ 6.26 (d, J = 15.5 Hz, 1H), 6.07 (d, J = 3.1 Hz, 1H), 6.05 (dt, J = 15.5, 6.1 Hz, 1H), 5.11 (d, J = 3.1 Hz, 1H), 4.22 (d, J = 6.1 Hz, 2H), 3.83 (s, 3H), 1.80 (br. s, 1H); ^{13}C δ 161.3, 142.8, 123.7, 119.2, 109.8, 81.2, 63.3, 57.5.
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