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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. © 1998 Elsevier Science Ltd. All rights reserved.

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 C₇ skeleton is functionalized. In addition, isomelodienone exhibits significant activity against breast cancer and colon adenocarcinoma human cell lines ($ED_{50} = 0.17$ and $0.51 \mu g/ml$, 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-methoxyfurfural⁶ 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/NaHCO₃/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 dimethyldioxirane⁴ 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 ¹³C NMR) were in full agreement with those reported for the corresponding natural products.¹

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)CH₂CO₂Et (1.1 equiv), *n*-BuLi, THF, -78 \rightarrow 25 °C, 88%; c) DIBAL-H (2 equiv), CH₂Cl₂, -78 °C, 1 h, 71%; d) PhCOCI (1.1 equiv), Et₃N (4 equiv), CH₂Cl₂, 30 min, 0 °C, 100%; e) NBS (1.1 equiv), NaHCO₃ (2 equiv), acetone/H₂O (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 acidsensitive compounds **6** and **7** were purified by flash chromatography on silica gel pre-treated with a 5% solution of Et₃N in hexanes and by using Et₃N (1%) as co-eluent. New compounds **3**, **6** and **7** gave satisfactory NMR (¹H and ¹³C; 300 and 75 MHz respectively, CDCl₃), 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); ¹³C 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); ¹³C 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), 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); ¹³C δ 161.3, 142.8, 123.7, 119.2, 109.8, 81.2, 63.3, 57.5.
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