An Expeditious Synthetic Route to Furolignans having Two Different Aryl Groups†

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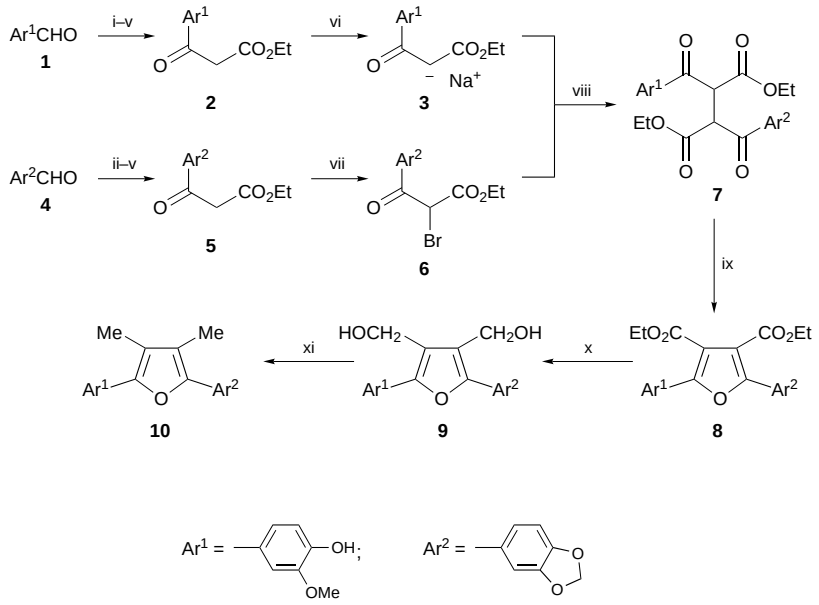
3,4-Dimethyl-2-piperonyl-5-veratrylfuran has been synthesized starting from vanillin and piperonal by employing as the key steps cross-coupling of a bromo β-oxo ester and the sodium salt of another β-oxo ester, affording a 1,4-diketone, and selective reductive removal of an allylic hydroxy group by palladium oxide.

The furolignans are a class of naturally occurring lignans,[1–3] and can be used as intermediates in the synthesis of other lignans such as tetrahydrofuran or aryltetralin derivatives.[4] Some elegant synthetic methods for furanoids have previously been reported[5,6] and we now present a simple and effective synthetic route to furolignans having two different aryl groups. 3,4-Dimethyl-2-piperonyl-5-veratrylfuran **10**[7] was chosen as the target molecule, and we have successfully completed a synthesis of compound **10** using this strategy (outlined in Scheme 1).



Scheme 1 *Reagents:* i, Me_2SO_4–NaOH; ii, $KMnO_4$; iii, $SOCl_2$; iv, $MeCOCH_2CO_2Et$–EtONa; v, NH_3–NH_4Cl; vi, EtONa; vii, Br_2; viii, CH_2Cl_2; ix, *p*-$MeC_6H_4SO_3H$–PhH; x, $LiAlH_4$–THF; xi, PdO–H_2

As shown in Scheme 1, the starting materials were vanillin **1** and piperonal **4** from which, based on an earlier report,[8] were conveniently prepared the sodium salt **3** and bromo derivative **6** of the corresponding β-oxo esters. By a cross-coupling reaction, compounds **3** and **6** were converted into the diester **7**.

Acid-catalysed cyclization of **7** led to the furan **8** which was then reduced with $LiAlH_4$ to produce **9**, both steps being easily achieved in good yield. Conversion of compound **9** into the target compound **10** was achieved completion in a mixed solvent (THF–$CHCl_3$, 10:1, v/v) under hydrogen with palladium oxide as catalyst, when a high yield was obtained.

Experimental

IR spectra (KBr) were recorded on a Nicolet 170 SXFT-IR spectrometer and ^{1}H NMR spectra on a Bruker AM400 spectrometer using Me_4Si as internal standard. Mass spectra were recorded on a ZAB-HS spectrometer. Microanalyses were performed on a MOD-1106 elemental analyser. Standard flash column techniques were employed to purify the crude reaction mixture using 300–400 mesh silica gel under positive nitrogen pressure. Light petroleum used for chromatography was the fraction of bp range 60–90 °C.

Diethyl 2-(3,4-*Dimethoxybenzoyl*)-3-(3,4-*methylenedioxybenzoyl*)-*butane*-1,4-*dioate* (**7**).—Sodium hydride (0.4 g; 80%) was washed with dry pentane and then suspended in dry dichloromethane (10 ml). To this was added a solution of ethyl (3,4-dimethoxybenzoyl)acetate (**2**) (3 g, 12 mmol) in dry dichloromethane (15 ml). This mixture was refluxed for 15 min and then a solution of ethyl bromo(3,4-methylenedioxybenzoyl)acetate (**6**) (3.8 g, 12 mmol) in dry dichloromethane (15 ml) was added. The product was then refluxed with stirring for 3 h. The suspension was cooled, washed with water (2 × 10 ml), and dried (Na_2SO_4). After removal of the solvent, the residue was purified through column chromatography using light petroleum–ethyl acetate (3:2, v/v) as eluant, to give compound **7** (4.7 g, 9.7 mmol), yield 80%. Recrystallization from ethanol gave a white *crystalline solid*, mp 114–116 °C; ν_{max}/cm^{-1} (KBr) 2980–2880, 1730, 1665, 1610; δ_H ($CDCl_3$) 1.10 (6 H, t, *J* 7.1 Hz), 3.86 (6 H, s), 4.01 (4 H, q, *J* 7.1 Hz), 5.16 (2 H, s), 5.90 (2 H, s), 6.65–7.67 (6 H, m), δ_C ($CDCl_3$) 13.64, 13.83, 52.96, 53.88, 55.90, 61.88, 61.90, 101.92, 107.88, 108.78, 110.00, 110.99, 124.7, 126.36, 128.66, 130.62, 148.12, 148.84, 152.42, 153.97, 167.13, 167.73, 191.19, 191.80; *m*/*z* (EI) 486 (M^+), 395, 291, 263, 165 (base), 149 (Found: C, 61.56; H, 5.24. $C_{25}H_{26}O_{10}$ requires C; 61.73; H, 5.35%).

Diethyl 2-(3,4-*Dimethoxyphenyl*)-5-(3,4-*methylenedioxyphenyl*)-*furan*-3,4-*dicarboxylate* (**8**).—Toluene-*p*-sulfonic acid (0.5 g) was added to a solution of compound **7** (2.5 g, 5.1 mmol) in dry benzene

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(50 ml). The mixture was refluxed for 8 h, and then concentrated. The residue was chromatographed on silica gel (light petroleum–ethyl acetate; 8:1, v/v) to give the *furan* **8** (1.9 g, 79%) as a white solid, mp 117–118 °C; ν_{max}/cm^{-1} (KBr) 1725, 1706, 1505; δ_H ($CDCl_3$) 1.30 (6 H, t, *J* 7.09 Hz), 3.83 (6 H, s,), 4.26 (4 H, q, *J* 7.09 Hz), 5.87 (2 H, s), 6.6–7.5 (6 H, m); *m*/*z* (EI) 468 (M^+, base), 423, 234, 149 (Found: C, 63.92; H, 5.24. $C_{25}H_{24}O_9$ requires C, 64.10; H 5.16%).

2-(3,4-*Dimethoxyphenyl*)-2-(3,4-*methylenedioxyphenyl*)-3,4-*bis*(*hydroxymethyl*)*furan* (**9**).—$LiAlH_4$ (0.5 g) was suspended in dry THF (50 ml), and a solution of compound **8** (1.0 g, 2.1 mmol) in THF (30 ml) was added dropwise with stirring. The mixture was refluxed for 8 h, stirred overnight at room temperature and then carefully decomposed with ethyl acetate (10 ml) and hydrochloric acid (5 ml; 6 M). Removal of solvent under reduced pressure and subsequent purification by flash chromatography (acetone as eluent) afforded the *furan* **9** (780 mg, 95%) as a white solid, mp 148–149 °C; ν_{max}/cm^{-1} (KBr) 3431, 1510; δ_H ($CDCl_3$) 3.67 (2 H, s, disappeared on D_2O exchange), 3.86 and 3.70 (6 H, 2 s), 4.56 (4 H, s), 5.80 (2 H, s) 6.7–7.44 (6 H, M); *m*/*z* (EI) 384 (M^+ base), 366, 352, 165, 149 (note: this product is not stable).

3,4-*Dimethyl*-2-*piperonyl*-5-*veratrylfuran* (**10**).—In an autoclave, PdO (150 mg) was added to a solution of the furan **9** (500 mg, 1.3 mmol) in THF–$CHCl_3$ (10:1 v/v; 50 ml). The mixture was stirred under hydrogen (6 MPa) at 80 °C for 24 h and at room temperature for 24 h, then filtered to remove the solid residue. Evaporation and chromatography of the residue on silica gel H using light petroleum–ethyl acetate (8.1, v/v) as eluant gave the *furan*, **10** (394 mg, 86%) as a white solid, mp 123–124 °C (lit,[7] 166–169 °C); ν_{max}/cm^{-1} (KBr) 2924, 1603, 1501, 1445, 1251; δ_H ($CDCl_3$) 2.22 (6 H, s), 3.94, 3.97 (6 H, 2 s), 6.02 (2 H, s), 6.6–7.3 (6 H, m); *m*/*z* (EI) 352 (M^+, base), 337, 165, 149, 135 (Found: C, 71.33; H, 5.60. $C_{21}H_{20}O_5$ requires C, 71.57; H, 5.72%). All the spectral data were in good agreement with those reported.[7]

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