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Facile Synthesis of 5,6-Dimethoxy-1-tetralone†

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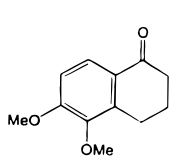
Abstract:
A facile synthesis of 5,6-dimethoxy-1-tetralone, a key intermediate in the synthesis of an antidepressant compound, ABT-200, was developed from the inexpensive starting material guaiacol.

5,6-Dimethoxy tetralone (**1**) is a key intermediate in the synthesis of some novel antidepressants which are α-2-antagonists and norepinephrine uptake inhibitors e.g., ABT-200 (**2**).[1] It can also be a synthon for certain 2-substituted



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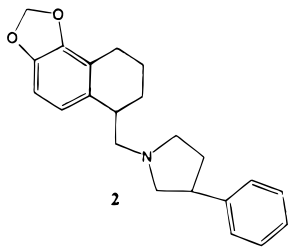

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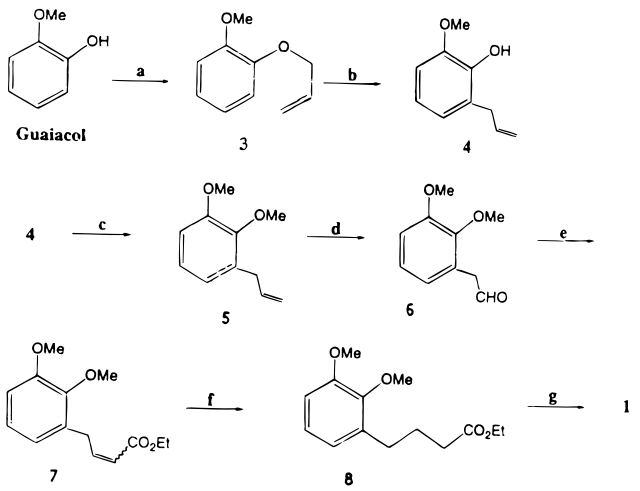
octabenzo(f)quinolines[2] which are dopamine agonists. An efficient, high-yielding route for the tetralone **1** will be of potential utility in large-scale synthesis of these bioactive compounds for the complete preclinical and clinical evaluation. Various approaches[2,3] have been used in the literature for the synthesis of **1**; these involve long reaction sequences or expensive starting materials, such as 2,3-dimethoxy benzaldehyde.[2] Herein we present an efficient and high-yielding route for the synthesis of **1** starting from guaiacol, an inexpensive and readily available material.

The key feature of the synthesis is the efficient preparation of 3-(2,3-dimethoxyphenyl) propionic ester (five steps), which can be converted to tetralone in one step with good yields.[3h]

Scheme 1[a]



[a] Conditions: (a) allyl bromide, K_2CO_3, acetone, reflux; (b) *N*,*N*-dimethylaniline, 200 °C; (c) DMS, K_2CO_3, acetone, reflux; (d) $NaIO_4$, $NaHCO_3$, OsO_4, CH_3OH (aq); (e) $Ph_3P{=}CHCOOEt$; (f) Pd-C/H_2; (g) (i) H_2SO_4 (85%), 85−90 °C, (ii) DMS, K_2CO_3.

Compound **1** was prepared as follows. Treatment of guaiacol with allyl bromide and K_2CO_3 in acetone under reflux gave *O*-allyl guaiacol (**3**, Scheme 1). Compound **3** was subjected to Claisen rearrangement by heating at 195−200 °C in *N*,*N*-dimethylaniline. *N*,*N*-Dimethylaniline was distilled out, and the crude compound **4** was carried to the next step without further purification. To obviate the hazardous condition (heating to high temperature) involved in the above reaction, the compound **3** was subjected to clay-mediated Claisen rearrangement.[4] Compound **3** was refluxed in dry benzene in the presence of montmorillonite K-10 for 4 h to get the desired compound **4** (81%). The crude Claisen rearrangement product was methylated by treating it with dimethylsulphate/K_2CO_3 and then distilled to get the pure compound **5** (60%). Oxidative cleavage of the double bond with OsO_4 (catalytic) and sodium metaperiodate in aqueous methanol furnished the aldehyde **6**, which on immediate treatment with carbethoxymethylene triphenylphosphorane gave the Wittig product **7** (combined yield is 50% for the last two steps). Hydrogenation of the compound **7** with Pd−C yielded 2,3-dimethoxyphenyl butyrate **8** (90%). Heating of **8** in 85% H_2SO_4 at 85−90 °C for 15 min provided compound **1** (75%) as white crystals. In conclusion, the above method helps in making the compound **1** in good overall yield and

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in optimal time. This approach also helps in making 5-hydroxy or -alkoxy tetralones from corresponding phenols.

Experimental Section

NMR spectra were recorded on a Varian Gemini (200 MHz) instrument. Tetramethylsilane was used as the internal standard. IR spectra were recorded on a Shimadzu IR-470 spectrometer. Mass spectra were obtained with a Finnigan Mat 1020B instrument.

2-Methoxy *O*-Allyl Benzene (3). To a mixture of guaiacol (12.5 g, 100.69 mmol) and allyl bromide (12.18 g, 100.69 mmol) in acetone (300 mL) was added potassium carbonate (41.75 g, 302.07 mmol), was added and the mixture was refluxed for 4 h. It was filtered and the filtrate concentrated under reduced pressure. The residue was disolved in dichloromethane and washed with 1 N NaOH, water, and brine, respectively. The organic portion was dried and concentrated in vacuo to get the compound **3** (15.39 g, 93%). ^{1}H NMR $(CDCl)_3$: δ 3.85 (s, 3 H), 4.58 (m, 2 H), 5.24 (m, 1 H), 5.38 (m, 1 H), 6.04 (m, 1 H), 6.84 (m, 4 H).

HRMS: calculated for $C_{10}H_{12}O_2$, 164.0837; found, 164.0845.

2-Hydroxy-3-methoxy Allyl Benzene (4). Compound **4** (13.15 g, 80.18 mmol) was taken in *N*,*N*-dimethylaniline (50 mL) and heated under N_2 at 195−200 °C for 6 h. *N*,*N*-Dimethylaniline was distilled out, and the residue was dissolved in ethyl acetate. The organic portion was washed with dilute HCl (2 N) and water, dried, and concentrated to get compound **4**, which was carried to the next step without further purification.

Clay-Mediated Claisen Rearrangement. A mixture of **3** (1 g, 6.09 mmol) and montmorillonite K-10 (1.8 g, unactivated) in dry benzene was refluxed for 5 h. The reaction mixture was filtered and concentrated. The residue was column chromatographed to get the compound **4** (0.81 g, 81%). IR (neat): 3500, 1480 cm^{-1}. ^{1}H NMR $(CDCl)_3$: δ 3.41 (d, 2 H, J = 7.8 Hz), 3.88 (s, 3 H), 5.0−5.15 (m, 2 H), 5.64 (s, 1 H), 6.0 (m, 1 H), 6.75 (m, 3 H).

HRMS: calculated for $C_{10}H_{12}O_2$, 164.0837; found, 164.0845.

2,3-Dimethoxy Allyl Benzene (5). To a mixture of crude allyl benzene (10 g, 61 mmol) and dimethylsulphate (8.2 g, 65 mmol) in acetone (200 mL) was added potassium carbonate (25.2 g, 183 mmol), and the mixture was refluxed for 2 h. The reaction mixture was filtered and concentrated. The residue was dissolved in dichloromethane and washed with $NaHCO_3$ solution, water, and brine, respectively. The organic portion was concentrated and distilled under vaccum to get the compound **5** (6.5 g, 60%). ^{1}H NMR $(CDCl)_3$: δ 3.4 (d, 2 H, J = 6.0 Hz), 3.8 (s, 3 H), 3.86 (s, 3 H), 4.98−5.12 (m, 2 H), 5.95 (m, 1 H), 6.78 (m, 2 H), 6.97 (dd, 1 H, J = 7 Hz).

HRMS: calculated for $C_{11}H_{14}O_2$, 178.0993; found, 178.1000.

4-(2,3-Dimethoxyphenyl) Ethyl But-2-enate (7). To a solution of compound **5** (2 g, 11.23 mmol) in methanol and water (15 mL + 2 mL) were added sodium metaperiodate (7.2 g, 33.7 mmol) and sodium bicarbonate (0.94 g, 11.23 mmol), followed by OsO_4 (1.45 mL, 0.56 mmol; 10% solution in toluene). Stirring for 20 min at room temperature and filtering furnished a mixture which was carried to the next reaction.

Carbethoxymethylene triphenylphosphorane (6 g, 17.2 mmol) was added to the solution of compound **6,** and the solution was stirred for 2 h. It was concentrated, and the residue was triturated in a mixture of diisopropyl ether and hexane (7:3). It was filtered, and the filtrate was concentrated to get the compound **7**, which was carried to the next step without further purification.

2,3-Dimethoxyphenyl Butyrate (8). Compound **7** (1.1 g, 4.4 mmol) was taken in methanol, Pd−C (10 mg) was added, and the mixture was stirred under H_2 atmosphere (balloon) for 10 h. It was filtered and concentrated to yield the compound **8** (1 g, 90%) as an oil. ^{1}H NMR $(CDCl)_3$: δ 1.26 (t, 3 H, J = 7 Hz), 1.92 (m, 2 H), 2.32 (t, 2 H, J = 7.5 Hz), 2.65 (t, 2 H, J = 7.0 Hz), 3.8 (s, 3 H), 3.86 (s, 3 H), 4.12 (q, 2 H), 6.75 (m, 2 H), 6.95 (dd, 1 H, J = 7.5 Hz).

HRMS: calculated for $C_{14}H_{20}O_4$, 252.1361; found, 252.1374.

5,6-Dimethoxy Tetralone (1). Compound **8** (1 g, 3.96 mmol) was heated at 85−90 °C for 15 min with sulphuric acid (85%). The resulting dark red solution was poured on ice, and the precipitate was collected. It was dissolved in acetone and refluxed for 2 h with dimethylsulphate (0.5 g, 3.96 mmol) and potassium carbonate (1.63 g, 11.88 mmol). The reaction mixture was filtered and concentrated. The residue was crystallised to get compound **1** (0.612 g, 75%) as white crystals. IR (KBr): 1670, 1600 cm^{-1}. ^{1}H NMR $(CDCl)_3$: δ 2.0 (m, 2 H), 2.5 (t, 2 H, J = 7.5 Hz), 2.85 (t, 2 H, J = 6 Hz), 3.7 (s, 3 H), 3.82 (s, 3 H), 6.77 (d, 1 H, J = 8.0 Hz), 7.75 (d, 1 H, J = 8 Hz). Mp 102 °C (lit.[3h] mp 104−105 °C).

HRMS: calculated for $C_{12}H_{14}O_3$, 206.0942; found, 206.0947.

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