Hydrogen-Atom Abstraction/Cyclization in Synthesis. Direct Syntheses of Coumestan and Coumestrol

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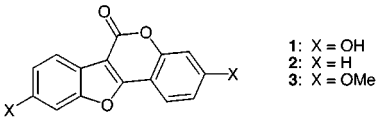
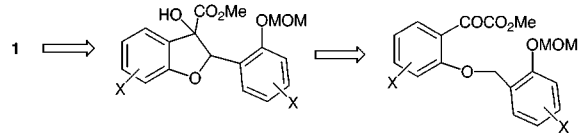
The synthesis of coumestrol has been achieved in five steps from 1,3-dimethoxybenzene. The key step is a photochemical cyclization of a glyoxylate ester.

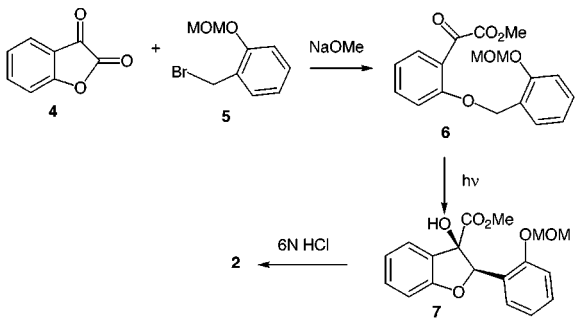
Coumestrol (**1**) is a phytoestrogen which is found in plants.[1] Although it is one of the most potent phytoestrogens, its estrogenic activity is approximately 77 times less potent than estradiol, the primary human estrogen and the standard by which activity is measured.[2] Coumestrol is present in alfalfa, cabbage, and, to a lesser extent, soybeans. It is the subject of recent concern in animal reproductive physiology because it lowers the amount of natural estrogen in animals.[3] A few syntheses of this compound have been reported.[4] In these syntheses, the compound is constructed by an annulation onto a functionalized coumarin, forming the furan ring in the last step.



Our approach to the synthesis of **1** was based on the rationale that a flexible synthetic route that could easily prepare both **1** and **2** plus selected oxygenated analogues was needed to support the toxicology studies. In view of the ready availability of hydroxylated analogues of phenyl glyoxylic acid and the commercial availability of hydroxylated benzylic alcohols, we developed our synthesis of **1** along the retrosynthetic analysis shown below. The hydroxy ester would be derived from a photochemically mediated hydrogen atom abstraction/cyclization reaction.[5]

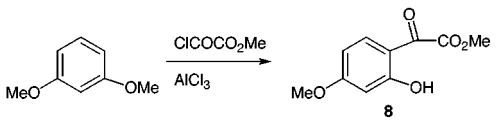


The synthesis of coumestan (**2**) is illustrated below. The reaction of benzofuran dione **4** with sodium methoxide generated a phenoxide that reacted with **5** to afford compound **6** in 65% yield.[6] Irradiation of **6** for 48 h,



according to the conditions of Neckers,[7] produced hydroxy ester **7** as what appeared to be one stereoisomer on the basis of the proton NMR spectrum. Pappas studied the solvent dependence of photocyclizations of *o*-benzyloxyphenyl glyoxylate and found that, with benzene as the solvent, over 95% of the product was the stereoisomer with the phenyl group cis to the hydroxyl group.[5] Therefore, the stereochemistry is tentatively assigned as shown. These stereogenic centers are eliminated in the subsequent step. Treatment of **7** with 6 N HCl in THF for 36 h generated coumestan **2** in 45% yield from **6**. This compound exhibited a melting point of 179−180 °C. The UV and NMR spectra of our compound were identical to the spectra reported in the literature.[8]

The synthesis of **1** begins with the acylation of 1,3-dimethoxybenzene with methyl chlorooxalate and aluminum chloride in dichloroethane at ambient temperature.[9] Keto ester **8** was produced in 50% yield. The



phenol subunit of this compound was then coupled with alcohol **9**[10] using a variant of the Mitsunobu reaction. The

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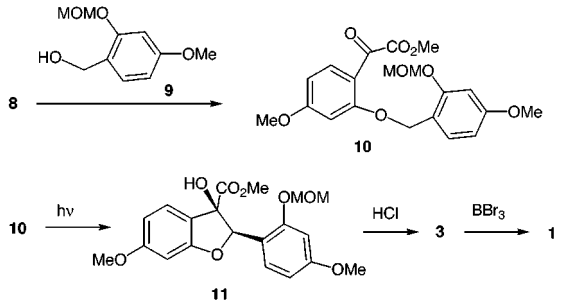
yield of this reaction was 32%. Irradiation of keto ester **10** using conditions developed in the synthesis of **2** furnished a dihydrobenzofuran as a mixture of isomers which could be converted into the dimethyl ether of coumestrol (**3**) in 38% overall yield using aqueous hydrochloric acid. Its melting point was 202−203 °C. The



transformation of **3** into coumestrol was achieved in 75% yield using 10 equiv of BBr_3 in methylene chloride from −78 °C to 25 °C for 12 h.[11] The proton NMR spectrum of this compound was identical to the NMR of an authentic sample.[12]

The synthetic route to **1** and **2** is readily adaptable to scale-up. The synthetic pathway is flexible with regard to substitution on the both the glyoxylate and the benzyl alcohol subunits. This route will permit the ready synthesis of analogues.

Experimental Section

H:EA refers to hexanes:ethyl acetate solvent mixtures for thin-layer chromatography and silica gel flash chromatography (sgc). Infrared spectra (IR) were recorded on a FTS-7 spectrophotometer. Proton NMR spectra were measured at 300 or 400 MHz with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded in $CDCl_3$ at 75 MHz. High-resolution mass spectra (HRMS) were EI spectra obtained by a Kratos MS50 magnetic sector mass spectrometer.

2-Methoxymethoxybenzyl Bromide (5). To a suspension of NaH (0.96 g, 40 mmol) in 50 mL of dry DMF was added a solution of *o*-cresol (2.16 g, 20 mmol) in 5 mL of DMF dropwise. After the release of hydrogen ceased, a solution of MOMCl (1.77 g, 22 mmol) in 5 mL of DMF was added slowly. After the resulting reaction mixture was stirred at room temperature for 1 h, ice and 1 N HCl were added and the product was extracted with ether 3 times. The combined ether layer was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. After removal of ether in vacuo, 2-methoxymethoxytoluene was obtained in quantitative yield that was used for the bromination without purification. ^1H NMR ($CDCl_3$): δ 7.17−7.10 (t, 2H, J = 7.1 Hz), 7.06−7.02 (d, 1H, J = 7.5 Hz), 6.94−6.88 (t, 1H, J = 7.8 Hz), 5.21 (s, 2H), 3.49 (s, 3H), 2.25 (s, 3H).

A mixture of 2-methoxymethoxytoluene, NBS (3.92 g, 22 mmol) and benzoyl peroxide (0.48 g, 2 mmol), in 40 mL of dry CCl_4 was boiled for 30 min and cooled. The white solid was filtered, and CCl_4 was removed to give **5** in over 80% yield as a light yellow oil that turned into a white solid when stored in freezer. Compound **5** can be used for the alkylation without purification. Pure **5** can be obtained by recrystallization from hexane. ^1H NMR ($CDCl_3$): δ 7.36−7.32 (dd, 1H, J = 7.5, 1.8 Hz), 7.30−7.24 (m, 1H), 7.12−7.07 (dd, 1H, J = 8.4, 0.9 Hz), 7.00−6.94 (m, 1H), 5.28 (s, 2H), 4.58 (s, 2H), 3.52 (s, 3H).

Methyl-2-(2-methoxymethoxybenzyloxy)phenyl Glyoxylate (6). To a freshly prepared NaOMe/MeOH solution (prepared by dissolving Na (92.0 mg, 4 mmol) in 16 mL of MeOH) was added benzofuran-2,3-dione[13,9] (296.2 mg, 2 mmol) in 2 mL of MeOH dropwise. After 1 h, a solution of **5** (568.4 mg, 2.2 mmol) in 2 mL MeOH was added, and the reaction mixture was allowed to react for 24 h at room temperature. It then was quenched with saturated NH_4Cl containing a small amount of HCl and extracted with ether 3 times. The ether layer was washed with saturated $NaHCO_3$ solution and brine and dried over $MgSO_4$. After removal of ether, the crude product was purified by sgc (H:EA 10:1) to produce **6** as a light yellow oil (428 mg, 65%). ^1H NMR ($CDCl_3$): δ 7.92−7.88 (dd, 1H, J = 8.1, 1.5 Hz), 7.62−7.56 (td, 1H, J = 8.0, 1.8 Hz), 7.41−7.38 (dd, 1H, J = 7.5, 1.5 Hz), 7.33−7.29 (td, 1H, J = 7.2, 1.8 Hz), 7.19−7.15 (d, 1H, J = 8.4 Hz), 7.12−7.02 (m, 3H, 5.22 (s, 2H), 5.16 (s, 2H), 3.47 (s, 3H), 3.34 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 186.8, 165.7, 160.0, 155.6, 136.5, 131.0, 130.5, 130.2, 124.5, 122.9, 122.0, 121.5, 114.4, 113.1, 94.8, 66.6, 56.2, 52.0. IR (neat): 1742, 1673 cm^{-1}. UV: λ_{max} (benzene) 279, 323 nm.

Methyl-(2-hydroxy-4-methoxyphenyl) Glyoxylate (8). A finely powered anhydrous $AlCl_3$ (666.7 mg, 5 mmol) was added at 0 °C to a solution of 1,3-dimethoxybenzene (345 mg, 2.50 mmol) and methyloxalyl chloride[14] (306.3 mg, 2.5 mmol) in 5 mL of dry 1,2-dichloroethane under N_2 atmosphere. The resulting dark red mixture was stirred at room temperature for 24 h, poured into 100 mL of ice water, and extracted with CH_2Cl_2 four times. The combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by sgc (H:EA 10:1) to give **8** as a yellow solid (260.7 mg, 50%). ^1H NMR ($CDCl_3$): δ 11.75 (s, 1 H), 7.69−7.66 (d, 1H, J = 8.8 Hz), 6.51−6.46 (m, 2H), 3.98 (s, 3H), 3.88 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 188.1, 168.1, 167.4, 163.3, 134.1, 110.6, 109.3, 101.2, 56.0, 53.1. IR (Nujol): 1734, 1635 cm^{-1}. MS *m*/*z*: 151, 210. HRMS: found 210.0541; calcd 210.0542.

Methyl 2-(2-methoxymethoxy-4-methoxybenzyloxy)-4-methoxy Phenylglyoxylate (10).[15] To a solution of **8** (105.1 mg, 0.5 mmol), alcohol **9**[10] (99.1 mg, 0.5 mmol), and PPh_3 (157.4 mg, 0.6 mmol) in 5 mL of dry DMF was added diethyl azodicarboxylate (104.5 mg, 94.5 μL, 0.6 mmol) dropwise at 0 °C under N_2 atmosphere. The solution was then stirred at room temperature for 24 h. The solution was concentrated in vacuo and diluted with a small amount of ether. The precipitate was filtered, the filtrate was concentrated, and the residue was purified by sgc (H:EA 10:1) to give **10** as a light yellow solid (125 mg, 32%). ^1H NMR ($CDCl_3$): δ 7.94−7.90 (d, 1H, J = 8.4 Hz), 7.31−7.27 (d, 1H, J = 8.7 Hz), 6.77−6.75 (d, 1H, J = 2.4 Hz), 6.61−6.56 (m, 3H), 5.20 (s, 2H), 5.04 (s, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 3.47 (s, 3H), 3.30 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 185.4, 166.9, 166.3, 162.1, 161.6, 157.0, 133.0, 131.9, 116.7, 116.0, 106.8, 106.5, 101.7, 99.1, 95.0, 66.4, 56.4, 55.9, 55.7, 51.8. IR (Nujol): 1732, 1663 cm^{-1}. UV: λ_{max} (benzene) = 280, 316 nm, λ_{max} (CH_2Cl_2) = 239, 281, 318 nm. MS *m*/*z*: 181, 331, 390. HRMS: found 390.1320; calcd 390.1315.

General Procedure for the Irradiation, Dehydration, and Lactonization. The precursor of the photochemical reaction (20 mg) was dissolved in 2 mL of dry benzene in a sealed Pyrex tube. The solution was flushed with argon for 30 min. The irradiation was conducted in a photochemical reactor (manufactured by Southern New England Ultraviolet Company, model no. RPR-100) loaded with a circle of UV lamps (λ_{max} = 300 nm). The deoxygenated solution was irradiated for 48 h at room temperature. TLC showed that there was no starting material present. Benzene was removed in vacuo, and the crude product was used directly for next step without purification.

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The unpurified product of the photoreaction was dissolved in small amount of THF. After the addition of 6 N HCl (20 equiv), the solution was stirred at 50 °C for 36 h, cooled, poured into water, and extracted with EtOAc 3 times. The combined organic layers were washed with brine and dried over $MgSO_4$. After removal of solvent, the crude product was purified to give the resulting lactone.

Coumestan (2). Data for 2,3-Dihydro-3-hydroxy-2-(2-methoxymethoxyphenyl)benzofuran-3-carboxylic acid methyl ester. ^{1}H NMR ($CDCl_3$): δ 7.61−7.58 (d, 1H, J = 6.9 Hz), 7.37−7.29 (m, 1H), 7.27−7.20 (m, 1H,), 7.14−6.94 (m, 5H), 6.27 (s, 1H), 5.16−5.08 (dd, 2H, J = 17.1, 6.6 Hz), 3.91 (s, 3H), 3.46 (s, 3H), 3.41 (s, 1H).

This product was taken directly on to the hydrolysis step.

Compound **2** was obtained as a white solid after purification by TLC (45% yield from **6**). Its melting point was 179−180 °C. ^{1}H NMR ($CDCl_3$): δ 8.17−8.14 (m, 1H), 8.07−8.03 (dd, 1H, J = 7.8, 1.5 Hz), 7.70−7.59 (m, 2H), 7.53−7.39 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 160.2, 158.3, 155.8, 153.9, 132.2, 127.0, 125.5, 124.9, 123.7, 122.11, 122.10, 117.7, 112.9, 112.0, 106.1. IR (Nujol): 1736 cm^{-1}. UV: λ_{max} (EtOH) 297, 310, 342 nm. MS m/z: 236 (M^+, base peak). HRMS: found 236.047662; calcd 236.047344.

Data for Coumestrol Dimethyl Ether (3). 2,3-Dihydro-3-hydroxy-6-methoxy-2-(4-methoxy-2-methoxymethoxyphenyl)benzofuran-3-carboxylic acid methyl ester (**11**). ^{1}H NMR ($CDCl_3$): δ 7.48−7.46 (d, 1H, J = 6.3 Hz), 7.12−7.10 (d, 1H, J = 6.3 Hz), 6.73−6.72 (d, 1H, J = 1.8 Hz), 6.62−6.51 (m, 3H), 6.23 (s, 1H), 5.13−5.07 (dd, 2H, J = 11.1, 5.1 Hz), 3.89 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.45 (s, 3H), 3.30 (s, 1H).

This compound was taken on to the hydrolysis step.

Compound **3** was obtained as a white solid after purification by TLC (38% yield from **10**). Its melting point was 202−203 °C. ^{1}H NMR (DMSO-d_6): δ 7.95−7.93 (d, 1H, J = 8.8 Hz), 7.81−7.79 (d, 1H, J = 8.4 Hz), 7.51−7.50 (d, 1H, J = 2.0 Hz), 7.22−7.21 (d, 1H, J = 2.4 Hz), 7.12−7.09 (m, 2H), 3.90 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 162.5, 159.6, 159.0, 157.4, 156.0, 154.7, 122.5, 120.7, 115.8, 113.6, 113.2, 105.3, 102.6, 101.6, 97.3, 56.1, 55.9. IR (Nujol): 1639 cm^{-1}. UV: λ_{max} (MeOH/CH_2Cl_2 1:1) 244, 303, 341 nm. MS m/z: 296 (M^+), 281 ([M − CH_3]$^+$, base peak). HRMS: found 296.0689386; calcd 296.068473.

Coumestrol (1). Compound **3** (4 mg, 0.0135 mmol) was dissolved in 50 μL of dry CH_2Cl_2, and the solution was cooled to −78 °C. A solution of BBr_3 in CH_2Cl_2 (1.0 M, 135 μL) was added via syringe. The reaction mixture was allowed to attain room temperature overnight, then hydrolyzed by ice water, extracted with CH_2Cl_2 3 times, and dried over $MgSO_4$. After removal of solvent, the residue was purified by TLC to produce coumestrol **1** as a white solid (2.7 mg, 75%). ^{1}H NMR (DMSO-d_6): δ 7.87−7.84 (d, 1H, J = 8.4 Hz), 7.71−7.68 (d, 1H, J = 8.4 Hz), 7.17−7.16 (d, 1H, J = 1.8 Hz), 6.96−6.90 (m, 3H). ^{13}C NMR (DMSO-d_6): δ 161.2, 159.5, 157.6, 157.0, 155.9, 154.6, 122.7, 120.6, 114.6, 114.0, 113.7, 104.2, 103.0, 102.0, 98.7. UV: λ_{max} (MeOH) 213, 278, 310, 379 nm. IR (Nujol): 3500−2800, 1703 cm^{-1}. MS m/z: 268 (M^+), 269 ([M + H]$^+$, base peak), 286 ([M + H_2O]$^+$). HRMS: found 268.037491; calcd 268.037173.

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Supporting Information Available: Spectra for compounds **1**−**3**, **6**, **8**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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