Simple and Efficient Synthesis of (±)-Equol and Related Derivatives

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Abstract: A simple and efficient synthesis of (±)-equol and related derivatives in good yields from inexpensive starting materials has been described.

Key words: flavanone, flavone, benzopyran, equol, dehydroequol, estrogen, Grignard reaction, Friedel–Crafts reaction

Isoflavonoids are an important class of naturally occurring compounds that are present in vegetables, beans, peas, and other legumes. These are possible cancer preventing agents, particularly for hormone dependent cancers such as breast and prostate cancer.2–5 Due to their health-friendly behavior, soy foods, rich in isoflavonoids, have been recommended by the Federal Drug Administration, USA.6 Daidzein (1) and genistein (2) are the prominent isoflavones in the soy product, which can be used as an alternatives to the hormone replacement therapy (HRT) in the treatment of postmenopausal disorders (Figure 1).7,8 Detailed studies have shown that this class of compounds decreases the risk of cancer, osteoporosis, and coronary heart disease.9 The reductive metabolism of these compounds play a significant role in their biological action and leads to the compounds (reduced metabolite), which are often more active than the parent compounds.10–14 Owing to their superior activity, attention has been shifted to isoflavone metabolites recently. Equol (3) and dehydroequol (4), the active metabolites of phytoestrogen daidzein (1), have longer half-lives and greater biological activity profiles including superior antioxidant as well as antiandrogenic activity than daidzein (1).11,15–18 Compared with daidzein (1), equol (3) is more estrogenic and has relatively high relative binding affinity for estrogen receptors whereas dehydroequol (4) possesses significant anticancer as well as DNA topoisomerase II inhibitory activities.19,20 The two enantiomeric forms of the equol (3) (–),(S)-equol (5) and (+),(R)-equol (6) have selectivities for the estrogen receptors α and β (ER-α and -β).20 There are some reports in the literature describing the synthesis of equol (3) and related derivative from commercially available starting materials.21 Often, the overall yields in these multistep syntheses are low. Alternatively, these compounds were synthesized through catalytic reduction of their parent compounds (corresponding isoflavone or isoflavanone).22 The present communication describes a simple and efficient synthetic method for preparation of these compounds from inexpensive starting materials in good yields (Schemes 1 and 2).

The synthesis of the target compounds was started by a Friedel–Crafts acylation reaction of resorcinol (7) with 4-methoxyphenylacetic acid (8) in the presence of BF₃·OEt₂ at 100 °C for 7 hours using a known procedure, which gave 1-(2,4-dihydroxyphenyl)-2-(4-methoxyphenyl)ethane (9) in 62% yield (Scheme 1). We observed that the planned synthesis of 7-hydroxy-3-(4-methoxyphenyl)chroman-4-one (10), through crossed aldol condensation of 9 with paraformaldehyde followed by cyclization, was not successful (Scheme 1). An indirect pathway was therefore employed to synthesize the core flavanone nucleus (protected daidzein derivative), through Friedel–Crafts acylation reaction of 3-methoxyphenol (11), in the place of resorcinol (7), with 4-hydroxymethylacetic acid (12) under the same reaction conditions used for the synthesis of compound 9 (Scheme 2). Interestingly, this reaction gave 1-(4-methoxy-2-hydroxyphenyl)-2-(4-ethoxyphenyl)ethane (13) in 70% yield along with 1-(4-methoxy-2-hydroxyphenyl)-2-(4-hydroxyphenyl)ethane (14) as a minor product (Scheme 2). Crossed aldol condensation of 13 with
The newly synthesized compounds were characterized by 1H NMR spectroscopy, fast-atom bombardment (FAB) mass spectroscopy, infrared spectroscopy, and their elemental analyses.

Reagents and conditions: (a) BF₃·OEt₂, heat, 7 h; (b) HCHO, aq NaOH, heat.

The reported melting points were determined in open capillaries and are uncorrected. The 1H NMR was recorded on Bruker Avance DRX 200 (200 MHz) FT NMR spectrometer using TMS as internal standard. The chemical shifts are expressed in δ (ppm) as values and coupling constants in Hz. Mass spectra (FAB) were recorded on Jeol JMS-D-300 spectrometer. IR spectra were recorded in KBr pellets on a Perkin-Elmer model 881.

1-(2-Hydroxy-4-methoxyphenyl)-2-(4-ethoxyphenyl)ethane (13)
A mixture of 3-methoxynaphthalene (11: 18.6 g, 0.15 mol) and 4-hydroxyphenylacetic acid (12: 22.8 g, 0.15 mol) dissolved in BF₃·OEt₂ (100 mL) was heated at 100 °C for 7 h. On completion of the reaction, the mixture was poured onto ice cold H₂O (500 mL) and extracted with EtOAc (5 × 150 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The crude material on chromatography afforded the pure compound 13; yield: 30.74 g (70%); mp 107–109 °C.
IR (KBr): 3469, 1602, 1513, 1384, 1354, 1228, 1122, 791 cm⁻¹.
1H NMR (CDCl₃): δ = 1.40 (t, J = 6.95 Hz, 3 H, CH₃), 3.82 (s, 3 H, OCH₃), 4.00 (q, J = 7.60 Hz, 2 H, CH₂), 4.14 (s, 3 H, CH₃), 6.41–6.46 (m, 2 H, ArH), 6.86 (d, J = 8.44 Hz, 2 H, ArH), 7.17 (d, J = 8.43 Hz, 2 H, ArH), 7.75 (d, J = 9.45 Hz, 1 H, ArH).
FAB-MS: m/z = 286, 287 (M + 1).
Anal. Calcd for C₁₇H₁₈O₄: C, 71.31; H, 6.34. Found: C, 71.52; H, 6.21.

3-(4-Ethoxyphenyl)-7-methoxychroman-4-one (15)
Compound 13 (2.0 g, 0.006 mol) was dissolved in 50% aq NaOH (30 mL), diluted with distilled H₂O (120 mL), and the mixture was heated at 60 °C with stirring. To this mixture, a solution of paraformaldehyde (0.30 g, 0.01 mol) dissolved in 50% aq NaOH (2 mL) and diluted with distilled H₂O (4 mL) was added. The reaction mixture was stirred for 2 h. On cooling, the solid material was filtered and purified by column chromatography on silica gel using EtOAc–hexane as eluent to give the pure compound 15; yield: 1.35 g (65%); mp 115–117 °C.
IR (KBr): 1686, 1607, 1243, 1188, 1115, 1014, 839 cm⁻¹.
1H NMR (CDCl₃): δ = 1.31 (t, J = 6.92 Hz, 3 H, CH₃), 3.74 (s, 3 H, OCH₃), 3.88 (q, J = 6.50 Hz, 2 H, CH₂), 4.52 (d, J = 6.21 Hz, 2 H, CH₂), 6.35 (d, J = 1.60 Hz, 1 H, ArH), 6.53 (d, J = 1.60 Hz, 2 H, ArH), 6.77 (d, J = 8.38 Hz, 2 H, ArH), 7.09 (d, J = 8.46 Hz, 2 H, ArH), 7.80 (d, J = 8.80 Hz, 1 H, ArH).
FAB-MS: m/z = 298, 299 (M + 1).

Anhydrous reactions were performed under an inert atmosphere, the set-up being assembled and cooled under dry N₂. Unless otherwise noted, starting material, reactant, and solvents were obtained commercially and used as such, or purified and dried by standard means. The reported melting points are determined in open capillaries and are uncorrected. The 1H NMR was recorded on Bruker Avance DRX 200 (200 MHz, FT NMR) spectrometer using TMS as internal standard. The chemical shifts are expressed in δ (ppm) as values and coupling constants in Hz. Mass spectra (FAB) were recorded on Jeol JMS-D-300 spectrometer. IR spectra were recorded in KBr pellets on a Perkin-Elmer model 881. Elemental analyses were carried out on a Carlo-Erba EA 1108 instrument and results were within ±0.4% of theoretical values.

Scheme 1
Reagents and conditions: (a) BF₃·OEt₂, heat, 7 h; (b) HCHO, aq NaOH, heat.
Synthesis of (±)-Equol

3-(4-Ethoxyphenyl)-7-methoxychroman (16)

A mixture of chromanone 15 (0.50 g, 0.0014 mol) in MeOH (25 mL) was hydrogenated in the presence of 10% Pd/C (50 mg) at 40–50 psi pressure for 6–8 h. The catalyst was filtered off and the solvent was evaporated to dryness. The crude product was purified by column chromatography on silica gel using 5% EtOAc–hexane as eluent to yield the pure compound 16; yield: 0.33 g (70%); mp 102–104 °C.

IR (KBr): 1611, 1510, 1249, 1199, 1159, 1114, 1034, 830 cm⁻¹.

1H NMR (CDCl₃): \(\delta = 1.41 \) (t, \(J = 6.52\) Hz, 3 H, CH₃), 2.93 (d, \(J = 8.02\) Hz, 2 H, CH₂), 3.30–3.20 (m, 1 H, CH), 3.77 (s, 3 H, OCH₃), 4.01 (q, \(J = 6.50\) Hz, 2 H, CH₂), 4.28 (dd, \(J = 2.30\) Hz, 1 H, CH), 6.46 (m, 2 H, ArH), 6.87 (d, \(J = 8.45\) Hz, 2 H, ArH), 6.97 (d, \(J = 8.21\) Hz, 1 H, ArH), 7.14 (d, \(J = 8.40\) Hz, 2 H, ArH).

FAB-MS: \(m/z = 283\) (M – 1), 284, 285 (M + 1).


4,4¢-Dihydroxy-3-phenylchroman (3)

In a flask, compound 16 (0.50 g) was heated at 220 °C with excess of pyridinium hydrochloride for 1.5 h under dry reaction conditions. Ice cold H₂O (150 mL) was then added and the mixture was extracted with EtOAc (4 × 50 mL). The combined organic layers were dried (Na₂SO₄) and concentrated and the residue was purified on silica gel column using EtOAc–hexane as eluent; yield: 0.29 g (70%); mp 155–157 °C.

IR (KBr): 3427, 1599, 1511, 1249, 1156, 1028, 825 cm⁻¹.

1H NMR (CDCl₃): \(\delta = 2.79 \) (d, \(J = 10.50\) Hz, 2 H, CH₂), 3.01 (br s, 1 H, CH), 3.89 (t, \(J = 10.30\) Hz, 1 H, CH), 6.19 (s, 1 H, ArH), 6.29 (d, \(J = 2.30\) Hz, 1 H, CH), 6.46 (m, 2 H, ArH), 6.87 (d, \(J = 8.45\) Hz, 2 H, ArH), 6.97 (d, \(J = 8.21\) Hz, 1 H, ArH), 7.14 (d, \(J = 8.40\) Hz, 2 H, ArH).

FAB-MS: \(m/z = 241\) (M – 1), 242.

Anal. Calcd for C₁₅H₁₂O₃: C, 74.36; H, 5.82. Found: C, 74.63; H, 5.52.

Scheme 2  Reagents and conditions: (a) BF₃·OEt₂, heat, 7 h; (b) HCHO, aq NaOH, heat; (c) Pd/C, H₂, MeOH, (d) pyridinium hydrochloride, heat; (e) NaBH₄, MeOH, r.t.; (f) HCl, EtOH, reflux.

3-(4-Ethoxyphenyl)-7-methoxychroman (16)

4,4¢-Dihydroxy-3-phenylchroman (3)
3-(Ethoxyphenyl)-7-methoxy-3,4-dehydrochroman (18)
To a solution of 15 (1.49 g, 5.0 mmol) in MeOH (50 mL) was added NaBH4 (76 mg) in portions at 0 °C. After 30 min at 0 °C, the mixture was stirred at r.t. for 5 h. On completion of the reaction, the solvent was evaporated andaq sat. NH4Cl (50 mL) was added to the mixture followed by its extraction with EtOAc (5 × 50 mL). The combined organic layers were dried (Na2SO4) and concentrated to give an oily residue. The crude residue was dissolved in EtOH (25 mL) and few drops of concd HCl was added to this solution. The mixture was then refluxed for 1.3 h. The solvent was evaporated and the residue was dissolved in EtOAc (50 mL) and washed with H2O (100 mL). The organic layer was dried (Na2SO4) and concentrated to give an oily residue. The crude material was purified on silica gel column using EtOAc–hexane as eluent; yield: 1.13 g (80%); mp 153–155 °C.

IR (KBr): 1607, 1510, 1388, 1351, 1279, 1159, 1034, 825 cm–1.

1H NMR (CDCl3): δ = 1.32 (t, J = 6.90 Hz, 3 H, CH3), 3.68 (s, 3 H, OCH3), 3.93 (q, J = 6.60 Hz, 2 H, CH2), 6.39–6.35 (m, 2 H, CH2), 6.56 (s, 1 H, CH), 6.79 (d, J = 8.70 Hz, 2 H, ArH), 6.87 (d, J = 8.70 Hz, 2 H, ArH), 6.41 (dd, J = 8.45 Hz, 2 H, ArH), 6.94 (d, J = 8.00 Hz, 1 H, ArH), 7.23 (d, J = 8.70 Hz, 2 H, ArH).

FAB-MS: m/z = 281 (M – 1), 282.

Anal. Calcd for C15H12O3: C, 74.99; H, 5.03. Found: C, 75.05; H, 5.01.

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References
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