A Concise Enantiodivergent Synthesis of Equol

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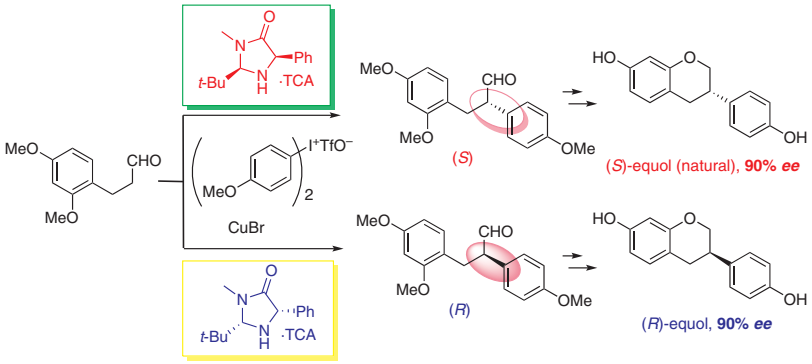

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Abstract Equol, a nonsteroidal estrogen produced from the metabolism of the isoflavonoid phytoestrogen daidzein, has been synthesized as both enantioenriched forms based on MacMillan's α-arylation of carbonyl compound mediated by amino acid derived indazolidinones and copper precatalysts. The natural form of (*S*)-equol and its enantiomer (*R*)-equol have been synthesized in 8 steps from 2,4-dimethoxybenzaldehyde with good enantiomeric purity (90% *ee* and 90% *ee*, respectively).

Key words equol, asymmetric synthesis, isoflavan, α-arylation, MacMillan's catalyst

Equol (**1**) is an isoflavandiol estrogen metabolized from daidzein, a type of isoflavone found in soybeans and other plant sources, by bacterial flora in the intestines (Figure 1).[1] A series of congeners for equol have also been elucidated (Figure 1).[2–4]

Equol (**1**) was first isolated from horse urine in 1932[5] and structurally elucidated to be (3*S*)-3-(4-hydroxyphenyl)-7-chromanol.[6] Since then, a variety of reports dealing with its biological functions have been documented,[1] which include the treatment of estrogen- or androgen-mediated diseases or disorders,[7] skin-health-improving and anti-aging substance,[8] the treatment of menopausal symptoms,[9] symptoms of menopausal vaginal atrophy,[10] and selective agonist of ERβ.[11]

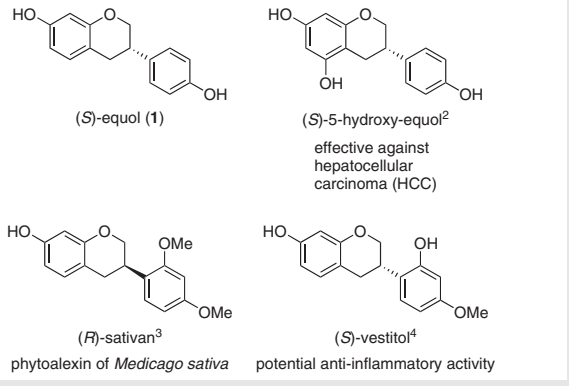
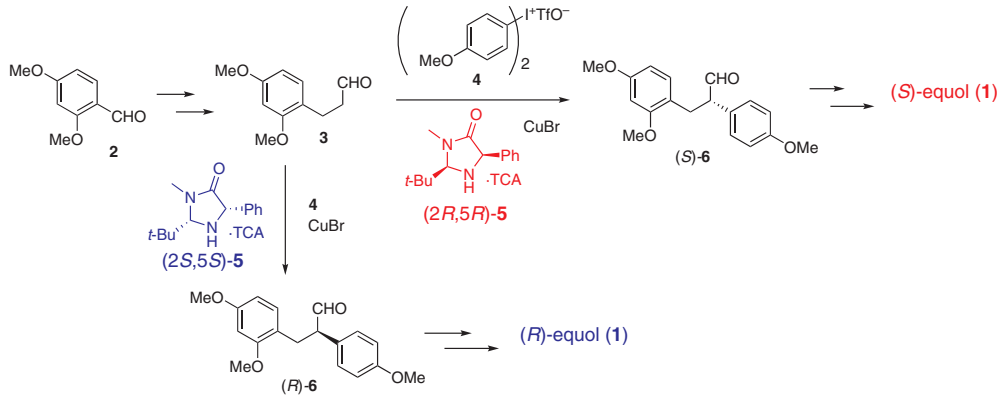


Figure 1 Equol and congeners

Therefore, large amount of reports dealing with the chemical synthesis of equol have been demonstrated which include both racemic[12] and enantioselective syntheses.[13] The latter constitutes the methods based on asymmetric transfer hydrogenation/deoxygenation,[13a] rhodium-catalyzed asymmetric addition,[13b] enantioselective allylic alkylation,[13c] organocatalytic annulation of *o*-quinone methides and aldehydes,[13d] a chiral pool approach,[13e] iridium-catalyzed asymmetric hydrogenation,[13f] the flavan–isoflavan rearrangement,[13g] deracemization of α-aryl hydrocoumarins via catalytic asymmetric protonation,[13h] enantioselective iridium-catalyzed hydrogenation,[13i] allylic substitution,[13j] Evans alkylation,[13k] and catalytic dynamic kinetic resolution,[13l] However, few reports for the synthesis of the both antipodes of equol have been documented[13e,f] despite the biological importance of unnatural (*R*)-equol.[14]

In this report, we disclose the asymmetric synthesis of both enantiomers of equol based on enantioselective α-arylation of aldehyde **3** with diaryliodonium salt **4**[15] employing MacMillan's protocol in a concise and enantiodivergent manner with acceptable overall yield and good enantiopurity.[16]

Our synthetic plan for both antipodes of equol is illustrated in Scheme 1. α-Arylation of aldehyde **3**, derived from commercially available 2,4-dimethoxybenzaldehyde **2**, with diaryliodonium salt **4** in the presence of cuprous bromide and organocatalyst (2*R*,5*R*)-**5**[16] should afford aldehyde (*S*)-**6**, presumably.[16] Aldehyde (*S*)-**6** would afford natural (*S*)-equol (**1**) by the known transformations.[13i,j] On the other



Scheme 1 Synthetic strategy for (*R*)- and (*S*)-equols

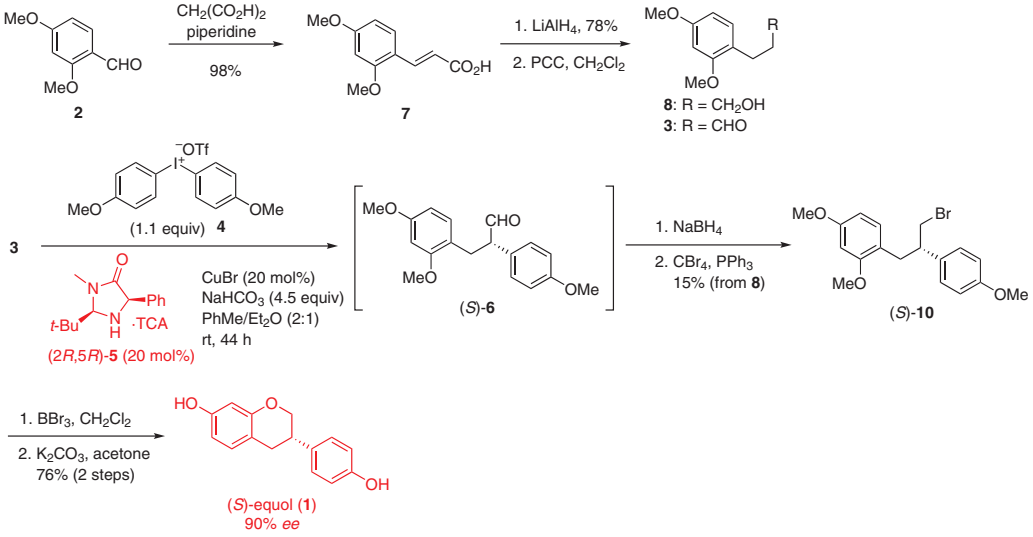
hand, by switching the chiral catalyst from (2*R*,5*R*)-**5** to its enantiomer (2*S*,5*S*)-**5**, (*R*)-equol (**1**) would be synthesized along the same sequences.

Substrate **3** for the asymmetric α-arylation reaction was synthesized from 2,4-dimethoxybenzaldehyde (**2**) through the Doebner modification of the Knoevenagel reaction followed by reduction of both carboxyl group and double bond, and then oxidation by PCC in 63% (3 steps) via carboxylic acid **7** and primary alcohol **8** (Scheme 2).[17]

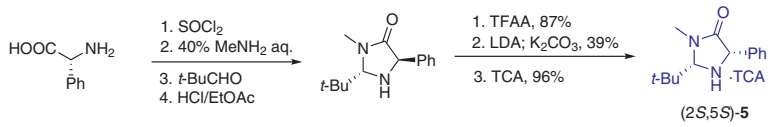
Then, aldehyde **3** was subjected to α-arylation reaction with the use of MacMillan's catalyst (2*R*,5*R*)-**5**[16] (20 mol%) and diaryliodonium salt **4**[15] in the presence of copper(I) bromide (20 mol%) to afford product (*S*)-**6**. The aldehyde (*S*)-**6** was directly converted into bromide (*S*)-**10** through the reduction of aldehyde (*S*)-**6** to primary alcohol (*S*)-**9** (not shown) followed by bromination with CBr_4/PPh_3 system.[13i] Then, the bromide (*S*)-**10** was transformed to (*S*)-equol (**1**) by the literature procedure with degradation of methyl ether using boron tribromide followed by base-mediated intramolecular alkylation via triol (*S*)-**11** (not shown).[13i,j] The optical purity of (*S*)-equol (**1**) have been determined by chiral HPLC column to be 90% *ee* (see the Supporting Information).

As the natural enantiomer of equol has been successfully synthesized with an acceptable enantioselectivity and yield, we next focused on the synthesis of (*R*)-equol due to its potential biological activity.[14] First, catalyst (2*S*,5*S*)-**5**, required for the access to antipode of natural (*S*)-equol (**1**), was newly prepared starting from D-phenylglycine as shown in Scheme 3.[16b,17]

Along the same reaction sequences for the synthesis of (*S*)-equol (**1**), (*R*)-equol (**1**) was synthesized through α-arylation protocol with the use of enantiomeric (2*S*,5*S*)-**5** catalyst in a similar manner (Scheme 4). The optical purity of obtained (*R*)-equol (**1**) was 90% *ee* (see the Supporting Information).



Scheme 2 Synthesis of (*S*)-equol (**1**)



Scheme 3 Synthesis of organocatalyst (2*S*,5*S*)-**5**

The mechanism for the reaction pathway and enantiodiscrimination step for the α-arylation reaction is assumed as shown in Scheme 5.[16] The *re*-face attack of copper species **12** formed from diaryliodonium salt **4** and copper(I) bromide to β-carbon of enamine **13** would be preferable due to the steric effect to afford the desired enantiomer **6**, selectively.

In conclusion, we have developed a simple protocol for the enantioselective synthesis of equol through MacMillan's α-arylation method. The (*S*)- and (*R*)-equols have been synthesized by simply applying the enantiomeric organocatalysts (2*R*,5*R*)-**5** and (2*S*,5*S*)-**5**, respectively. This method would serve as the synthesis of isoflvan and related compounds with chiral center at C-3 position. Synthesis of other isoflavans related to equol (Figure 1) by applying the present protocol is now in progress.

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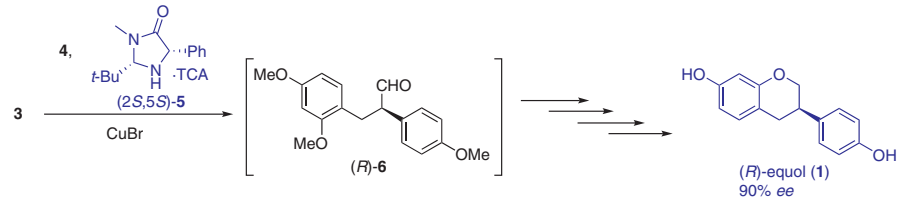
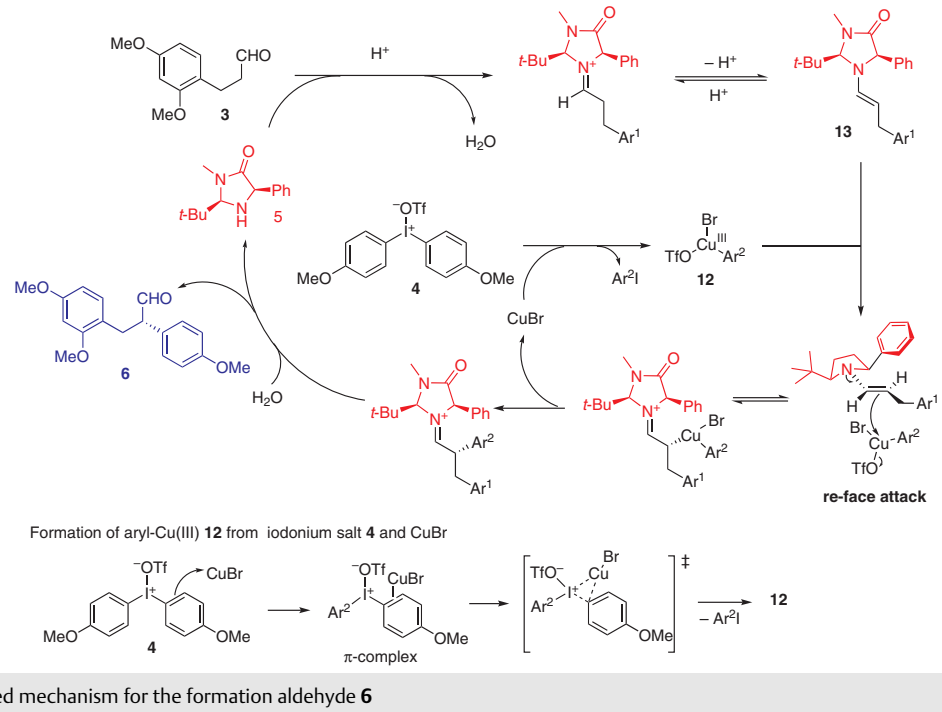


Scheme 4 Synthesis of (*R*)-equol **1**



Scheme 5 Proposed mechanism for the formation aldehyde **6**

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1303-9935.

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(17) **General Procedure for the Synthesis of (*S*)-3-(2,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)propan-1-ol (9)[16a]**

To an oven-dried round-bottom flask was added crude diaryliodonium salt **4** (65–70% purity determined by ^{1}H NMR; 3.24 g, 4.34 mmol) and CuBr (122 mg, 0.85 mmol), and then toluene (6.4 mL) and Et_2O (3.2 mL) were added. Afterwards, (2*R*,5*R*)-**5** (334 mg, 0.844 mmol) and $NaHCO_3$ (1.62 g, 19.3 mmol) were added to the suspension. Under argon atmosphere, a solution of aldehyde **3** (823 mg) in toluene/Et_2O (2:1, 4.8 mL) was added. The reaction mixture was stirred at room temperature for 44 h. The resulting mixture was diluted with CH_2Cl_2 (10 mL) and cooled to –23 °C. After adding $NaBH_4$ (1.64 g, 43.3 mmol), cold MeOH (8 mL) was gradually added to the solution, and the mixture was stirred for 1 h at –23 °C. The reaction mixture was quenched with water (8 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with sat. NH_4Cl aq. (2 × 30 mL), dried over Na_2SO_4, and the solvent was removed in vacuo. The resulting yellow oil was purified by silica gel column chromatography using hexane/EtOAc (7:3) as an eluent to give (*S*)-3-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)propan-1-ol (**9**) including inseparable 3-(2,4-dimethoxyphenyl)propyl alcohol (**8**) as a pale yellow oil (630 mg, (*S*)-**9**/**8** = 71:29 estimated by ^{1}H NMR analysis).