PTC Synthesis of the Isoflavanoid S-Equol
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Introduction
S-Equol is an isoflavanoid metabolized from the isoflavone daidzein by intestinal bacteria. Only 30-50 percent of all individuals possess bacteria that produce S-Equol. Recent data supports the compound's pharmaceutical potential for treating prostate cancer and post-menopausal estrogen deficiency (ref. 1). Because the compound is only minutely available from natural sources, an affordable asymmetric total synthesis would be necessary to generate sufficient quantities for expanded research. Only one asymmetric total synthesis of S-Equol has been reported to date, using a chiral auxiliary to give product in a 10 percent yield over 6 steps (ref. 2). It is our goal to develop an improved asymmetric synthesis of S-Equol, and thereby obtain sufficient quantities for biological testing.

Applying Phase-Transfer Catalysis (PTC) to Asymmetric Alkylation
Asymmetric PTC can be used to generate asymmetric products of type 3 (ref. 3). Treatment of 1 with a metal-hydroxide base under biphasic conditions gives Z-enolate 2, which complexes electrostatically with the charged, chiral phase-transfer catalyst R*N*. Electrophilic attack gives products with high enantioselectivity, and the catalyst repeats the reaction cycle.

Takeoff Reaction
While developing a total synthesis of (S)-Naproxen\textsuperscript{TM}, the Andrus group converted 4 to 5 with high selectivity (93% ee) and good yield (77%) using phase-transfer catalyst A (next panel).

Proposed Total Synthesis
(Electrophile 6c shown)

Asymmetric Alkylation Model Studies

Catalyst 7
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Synthesizing Electrophiles 6

Conclusions
• A new asymmetric total synthesis of the soy flavanoid (S)-equol is proposed, requiring only nine linear steps.
• The key model step, an asymmetric phase-transfer-catalyzed benzylation of 7, still only gives a 48% ee using the best conditions studied thus far. This will be improved by exploring various substrates, catalysts, bases, solvents, and temperatures.
• The syntheses of electrophiles 6 still need to be finished.
• It is anticipated that this work will help expand the scope of asymmetric phase-transfer-catalyzed alkylation.

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References