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A chiral pool approach for asymmetric syntheses of both antipodes of equol and sativan

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ABSTRACT

For the first time, both antipodes of the isoflavans, equol and sativan were synthesized in >98% *ee* with good overall yields starting from readily available starting materials. The chiral isoflavan, (−)-equol is produced from soy isoflavones, formonentin and daidzein by the action of intestinal bacteria in certain groups of population and other chiral isoflavans are reported from various phytochemical sources. To produce these chiral isoflavans in gram quantities, Evans' enantioselective aldol condensation was used as a chiral-inducing step to introduce the required chirality at the C-3 position. Addition of chiral boron-enolate to substituted benzaldehyde resulted in functionalized *syn*-aldol products with >90% yield and excellent diastereoselectivity. Functional group transformations followed by intramolecular Mitsunobu reaction and deprotection steps resulted the target compounds, *S*-(−)-equol and *S*-(+)-sativan, with high degree of enantiopurity. By simply switching the chiral auxiliary to (*S*)-4-benzyloxazolidin-2-one and following the same synthetic sequence the antipodes, *R*-(+)-equol and *R*-(−)-sativan were achieved. Both enantiomers are of interest from a clinical and pharmacological perspective and are currently being developed as nutraceutical and pharmacological agents. This flexible synthetic process lends itself quite readily to the enantioselective syntheses of other biologically active C-3 chiral isoflavans.

1. Introduction

Isoflavanes are a subclass of isoflavonoids,[1] characterized by a chirality at the C-3 position of the pyran ring and are thought to be derived from the corresponding isoflavonids *via* reductive processes (Fig. 1). In general, isoflavans of plant origin always have an oxygen at C2′ and they almost never have oxygenation at C5.[2] There are a number of isoflavans with some reported to possess unique, promising biological activities. Examples include: sativan and vestitol isolated from the leaves of *Medicago sativa*[3,4] and in *Lotus corniculatus*[5]; colutelol, isolated from the roots of *Colutea arborescens*[6]; lespedezol G_1, isolated from the stems of *Lespedeza homoloba*[7]; and lespecyrtin D_1 isolated from the root extracts of *Lespedza cyrtobotrya*.[8]

Equol, the first isoflavan discovered, is widely considered as a dietary phytoestrogen. It was first isolated unexpectedly from equine urine, in an attempt to isolate estrogen[9,10] and later from the urine of other animals[11] and humans.[12] Its absolute configuration as a *S*-isomer[13] was assigned after the identification of naturally occurring isoflavans *S*-(+)-vestitol, *S*-(−)-duartin, *S*-(−)-mucronulatol from *Dalbergia variabilis* and several *Macherium* species.[13] The *S*-equol is reported to bind with several receptors[14,15] including estrogen receptors (ER)[16] with 13 times more selectivity to ER subtype β compared to subtype α.[16–18] In addition to estrogenic activity, several biological activities such as anti-fungal,[19] anti-cancer,[20] anti-osteoporotic, anti-androgen,[14] anti-inflammatory, anti-oxidant and anti-aging properties[21] are reported and it is claimed to promote brain mitochondrial function[22] and inhibit prostate growth.[14]

The composition of colonic microbiota have been reported to influence the metabolic fate and biological effects of dietary intake of soy isoflavones. Indeed, the extent of at least some of the potential health benefits of soy intake are thought to depend on one's

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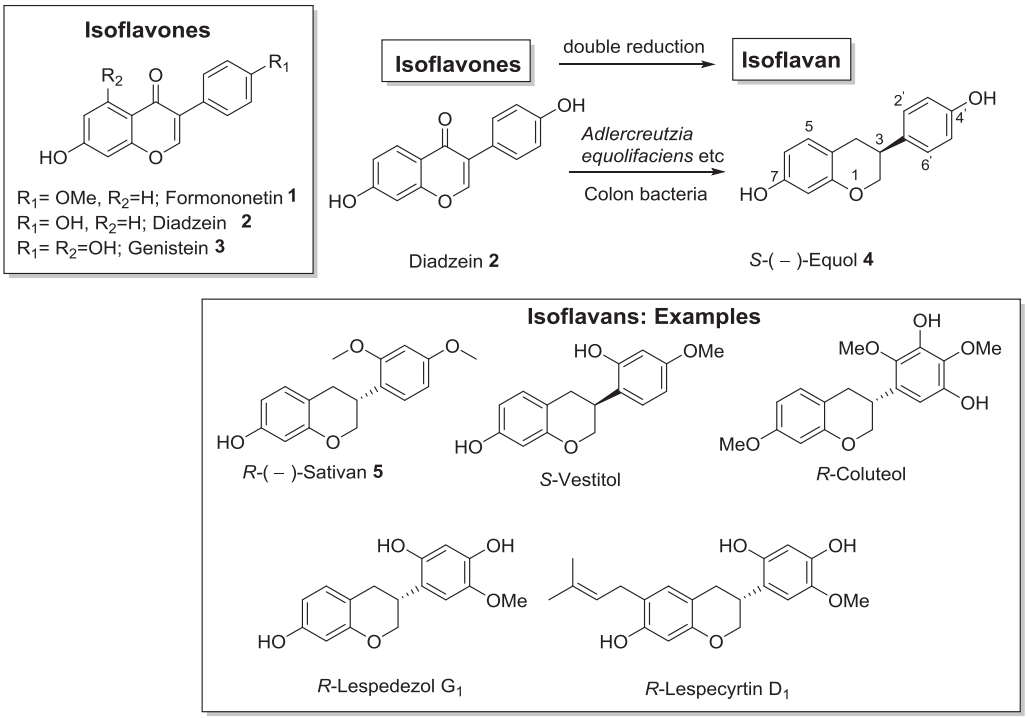

Fig. 1. Soy isoflavonoids: Isoflavones (formonentin **1**, daidzein **2**, genistein **3**) and isoflavans including *S*-(−)-equol **4**.

capacity to convert isoflavones to key metabolites during digestion.[23,24] The gut bacteria, *Adlercreutzia equolifaciens* is reported produce *S*-equol from daidzein (**2**) and genistein (**3**).[25] Studies measuring urinary equol excretion after soy consumption indicated that equol was produced by about 25%–30% of the adult population in Western countries compared to 50%–60% of adults living in Asian countries and Western adult vegetarians.[26,27] This high variability in equol production was presumably attributed to inter-individual differences in the composition of the intestinal microflora, such as *A. equolifaciens*.[28] Moreover, it was reported that the racemic equol may not show the same activities as that of pure enantiomers, as demonstrated in the pharmacokinetic studies on this compound.[26] Further studies of the biological and clinical properties of equol, including our own,[29,30] attest to the immense interest in this is an area of research. Given the desirable biological properties of isoflavans, it is important to have enantiopure, gram quantities of these isoflavans to enable further study of their biological, metabolic and pharmacokinetic properties.

The majority of reported syntheses were for the synthesis of a racemic form of isoflavans which are purified by chiral separation.[31–33] Examples of racemic synthesis include, catalytic hydrogenation of isoflavans using Pd catalysts at different solvent and pH conditions.[34–37] Multistep total syntheses of racemic mixtures of 5-*O*-methyllicoricidin,[38,39] halogen-substituted isoflavans and isoflavenes[40] were also reported.[41] Equol **4** was synthesized from formononetin **1** and daidzein **2** in racemic form using Pearlman's catalyst (20% $Pd(OH)_2$ on carbon),[17] by bacterial flora[42] and from resorcinol *via* an isoflavene intermediate.[43] Ferreira and co-workers have demonstrated the enantioselective synthesis of the dimethoxy analogue of *S*-equol *via* α-benzylation of *N*-acyl imidazolidinones.[44,45] In a similar approach for introduction of the required C–3 stereocenter, Heemstra et al. reported the enantioselective total synthesis of *S*-equol *via* Evans' alkylation followed by Buchwald intramolecular etherification.[46] However, the key transformations, such as Evans' alkylation of oxazolidinone with a regiomeric mixture of bromobenzyl bromide and palladium-catalyzed Buchwald etherification, produced less than 50% conversion with an overall yield <10%. *S*-equol **4** and other chiral isoflavans, *R*-sativan **5** and *R*-vestitol **9**, were synthesized utilizing allylic substitution[47] as the chirality transfer step with the copper reagent derived from PhMgBr and $CuBr \cdot Me_2S$. Yang et al., reported an enantioselective iridium-catalyzed hydrogenation[48] of α-aryl-cinnamic acids and applied the same methodology for the synthesis of *S*-equol **4** with an overall yield of 48%. Recently, Jingzhao Xia et al., reported the asymmetric hydrogenation of 2H-chromenes using Ir/In-BiphPHOX catalyst to produce to isoflavan derivatives, including *S*-equol in 82% yield with >95% ee.[49]

In continuation of our work on phytoestrogens for women's health, several grams of enantiomerically pure *S*-equol **4** and other chiral isoflavans were required. To address this need, we report herein a scalable enantioselective synthesis of four isoflavans: equol enantiomers, (−)-**4**, (+)-**4**, and sativan isomers (+)-**5**, (−)-**5**,

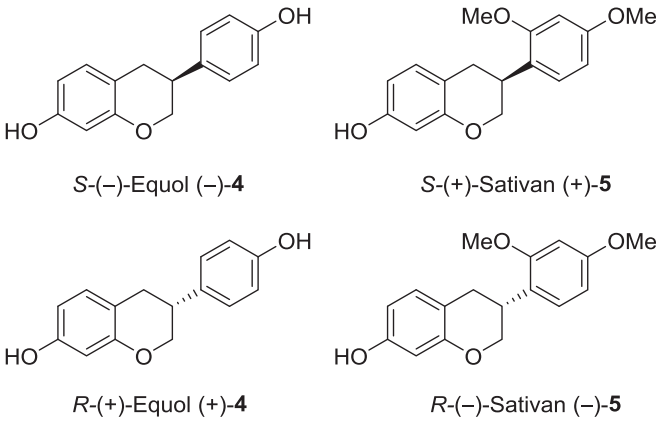

Fig. 2. Structures of the synthesized chiral isoflavans.