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A General Asymmetric Route to Enantio-enriched Isoflavanes via an Organocatalytic Annulation of *o*-Quinone Methides and Aldehydes

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ABSTRACT

Reported herein is a general approach to optically active isoflavanes based on a chiral amine-catalyzed [4 + 2] asymmetric annulation of *o*-quinone methides and aldehydes. A number of naturally occurring isoflavanes, including equol, sativan, isosativan, vestitol and medicarpin, as well as isoflavane analogues were readily prepared with good to excellent enantioselectivities.

Isoflavanes, including equol,[1] vestitol,[2] and coluteol[3], are a small subgroup of isoflavonoids that widely found in leguminous plants (Fig. 1). These natural products have attracted considerable attention in the field of medicinal chemistry. For instance, medicarpin[4] are effective in the inhibition of a number of bacteria,[5] as well as pathogenic fungi.[6] Equol, initially isolated from fraction of pregnant mare urine, exhibits interesting phytoestrogenic activity[1c] and potency in menopausal hormone replacement therapy.[1b]

Structurally, isoflavanes feature with a chiral 3-phenylchroman backbone. Some of the isoflavanes naturally exist in both enantiomers, but in different sources: some (*S*)-enantiomers of isoflavanes were detected in *Machaerium* and *Dalbergia species* while the (*R*)-enantiomers usually can be found in *Leguminosae* and *Papilionoideae*.[7] And, more interestingly, these enantiomers typically exhibit different physiological activities, for example, the (*R*)-equol shows higher binding affinity to estrogen receptor α (ERα) than the naturally occurring (*S*)-equol whereas the (*S*)-enantiomer exhibits greater binding affinity to estrogen receptor β (ERβ).[8]

Given the importance of these class of molecules, a number of studies have been reported on the synthesis of these biologically intriguing compounds. Early studies have been focused on the synthesis of racemic form of isoflavanes. [8-9] In 1995, Versteeg *et al.* reported the first enantioselective synthesis of isoflavanes with the chiral auxiliary strategy.[10] The first enantioselective total synthesis of (*S*)-equol was documented in 2006 by the Boulanger laboratory,[11] where the chiral auxiliary strategy was also employed to construct the chiral center. Since then, several approaches have been developed for the preparation of optically active equol, such as allylic substitution,[12] asymmetric hydrogenation,[13] and flavan-isoflavan rearrangement.[14]

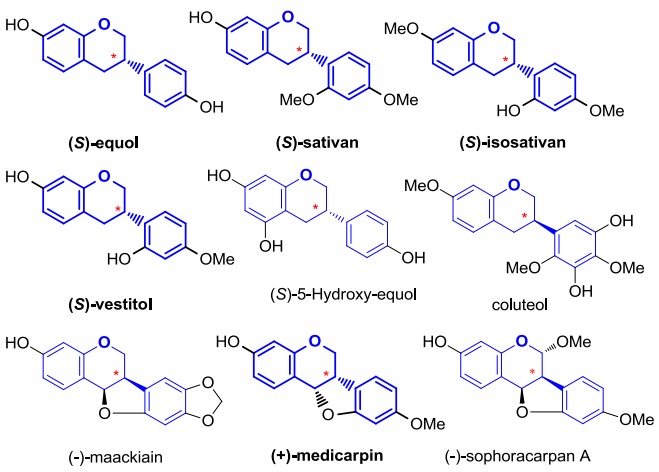

Fig. 1. Selected examples of isoflavanes

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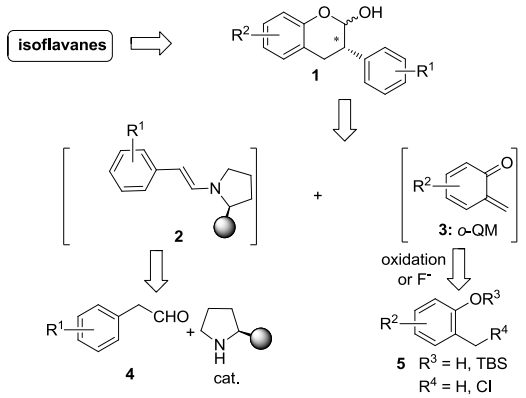


Scheme 1. Retro-synthesis analysis of isoflavanes.

ortho-Quinone methides (*o*-QMs) are a type of ephemeral molecules with exceptionally high reactivities.[15] Recently, this class of molecules have been intensively investigated in the asymmetric transformations[16] and a large number of enantioselective reactions have been developed, particularly with small organic molecules as catalysts.[17]

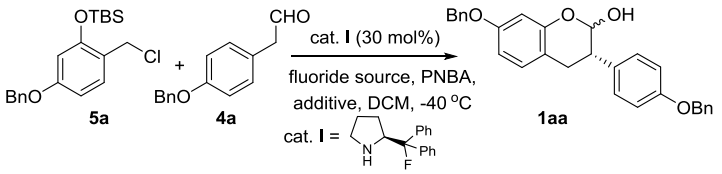
The [4 + 2] cycloaddition of *o*-QMs and electron-rich olefins has proven to be a reliable approach in the construction of chroman scaffolds,[18] for instance, equol and vestitol.[9] Furthermore, by incorporation chiral auxiliary on the olefins, this process has been applied in the enantioselective synthesis of a number of chroman-containing natural products.[19] Particularly, highly enantio-enriched (-)-medicarpin and (-)-sophoracarpan A were readily accessible with this enantioselective method.[20] Nevertheless, construction of this type of molecules in a catalytic asymmetric manner, avoiding pre-installation of chiral auxiliary on the olefins and subsequent removal of auxiliary, still remains as a more desirable approach. Herein, in our continuing research interest on the chemistry of quinone methide,[17t, 17y, 21] we report a general asymmetric route for the synthesis of enantiomerically enriched isoflavanes based on a chiral amine-catalyzed [4 + 2] annulation of *o*-quinone methides and aldehydes. With this approach, a range of optically active isoflavanes (e.g., equol, vestitol, sativan, isosativan and medicarpin) and isoflavane analogues were readily prepared in good to excellent enantioselectivities.

The key for the synthesis of optically active isoflavanes relies on the efficient construction of the 3-chiral center of chroman (Scheme 1). We recently disclosed a chiral amine-catalyzed enantioselective [4 + 2] annulation of aldehydes and *in situ* oxidation-generated QMs for the synthesis of enantio-enriched 3-substituted chromanols.[17y] We envisioned this asymmetric process may serve as a general approach for the efficient construction of 3-chiral center of isoflavanes.

We initialed our study with with substituted *o*-methylphenol as *o*-QM precursor but the strategy of oxidative generation of *o*-QM[17y] soon proved to be incompatible with this type of substrate. We then moved to the desilylation/elimination process for the *in situ* generation of the highly reactive *o*-QMs.[17e, 17j] Previous study has indicated that, due to the low stability, fluoro was not a suitable leaving group for the *o*-QM precursor with strong electron-donating groups (e.g. methoxyl),[17t] we thus adopted chloro-substituted **5a** as the *o*-QM precursor. However, this type of substrate requires stoichiometric amount of fluoride to generate *o*-QM, which poses a potential problem for the amine-catalyzed asymmetric process. A number of reaction conditions have been tested and the results are summarized in Table 1. This [4 + 2] annulation proceeded smoothly in the presence 1.1 equiv. of tetrabutyl ammonium fluoride (TBAF) and *p*-nitrobenzoic acid (PNBA), as well as chiral fluorinated pyrrolidine (cat. **I**) as catalyst, giving chromanol **1aa** in 44% yield and with 74% ee (entry 1). And the amount of PNBA has marked impact on this asymmetric reaction as the addition of 1.2 equivalent of PNBA significantly enhanced the enantioselectivity to 84% ee, but, unfortunately, only trace amount of product was obtained. As a result, more additives were then tested and the combination of NaH_2PO_4 and PNBA were found to be able to increase both yield and enantioselectivity, delivering **1aa** in 62% yield and with 85% ee (entry 6). It is worth noting that potassium fluoride was inefficient as fluoride source in this reaction, resulting in nearly no desired product formation, which is likely due to the low solubility of potassium fluoride in dichloromethane (DCM). Furthermore, the use of aldehyde **4a**, instead of **5a**, as the limiting reagent, led to much lower yield (16%, entry 8).

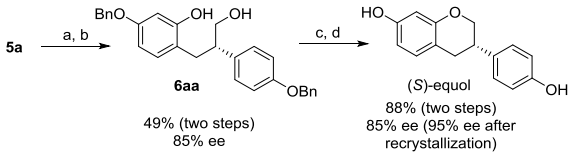
With enantio-enriched chromanol **1aa** in hand, we turned our attention to reduction of the hydroxyl group. The TMSOTf/Et_3SiH-mediated reduction was first tested for **1aa**. But, to our surprise, this reaction turned out to be less efficient,

Table 1 Optimization of reaction conditions[a]

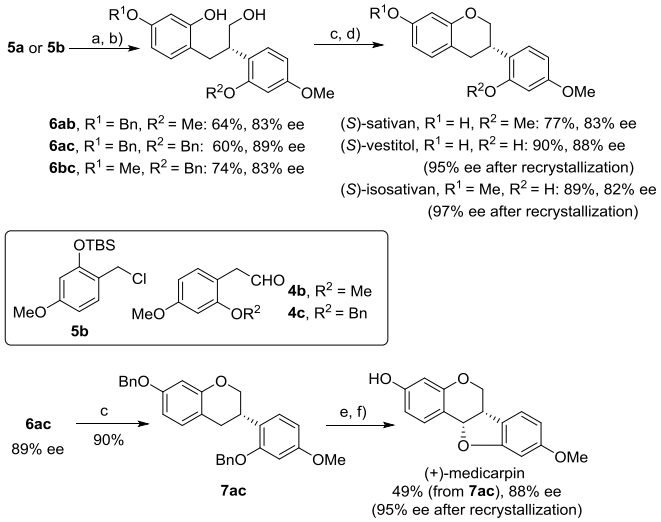


Entry	Fluoride source (equiv.)	Additive	Yield (%)[b]	Ee(%)[c]
1[d]	TBAF (1.1)	-	44	74
2[e]	TBAF (1.1)	-	<5[f]	84
3	TBAF (1.1)	-	36	77
4[g]	TBAF (1.1)	NaH_2PO_4	51	71
5	TBAF (1.5)	NaH_2PO_4	58	71
6	TBAF (1.1)	NaH_2PO_4	62	85
7	KF (1.0)	NaH_2PO_4	<5[f]	--
8[h]	TBAF (1.1)	NaH_2PO_4	16	79

[a] Unless otherwise specified, the reaction was conducted with **5a** (0.10 mmol) and **4a** (0.3 mmol) in DCM (2.0 mL) in the presence of catalyst (0.03 mmol), fluorine source (0.11 mmol), PNBA (0.03 mmol), additive (0.10 mmol) at -40 °C. [b] Isolated yields. [c] Ee was determined by chiral HPLC analysis of the corresponding diols after reduction of **1aa** with $NaBH_4$. [d] 0.2 equiv of PNBA and 20 mol% of catalyst were used. [e] 1.2 equiv of PNBA and 20 mol% of catalyst were used. [f] Based on TLC analysis. [g] At 0 °C. [h] 1.1 equiv of **5a** and 1 equiv of **4a** were used.



Scheme 2. Enantioselective synthesis of (*S*)-equol. a) **4a**, cat. **I**, TBAF, PNBA, NaH_2PO_4, DCM, -40 °C; b) $NaBH_4$, MeOH, 0 °C; c) DEAD, PPh_3, THF, 0 °C to rt; d) $Pd(OH)_2/C$, H_2, MeOH/THF/H_2O, rt. DEAD: diethylazodicarboxylate



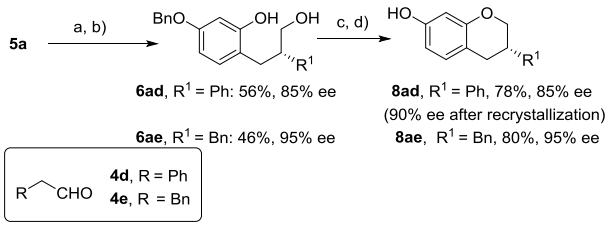
Scheme 3. Enantioselective synthesis of (*S*)-sativan, (*S*)-vestitol, (*S*)-isosativan and (+)-medicarpin. a) **4b** or **4c**, cat. **I**, TBAF, PNBA, NaH_2PO_4, DCM, -40 °C; b) $NaBH_4$, MeOH, 0 °C; c) DEAD, PPh_3, THF, 0 °C to rt; d) $Pd(OH)_2/C$, H_2, MeOH/THF/H_2O, rt; e) Pb_3O_4, AcOH, benzene, reflux; f) $Pd(OH)_2/C$, H_2, EtOH/THF; K_2CO_3, EtOAc, rt.

resulting in the reduced product **6aa** in only 40% yield, which may associate with the presence of benzyl-protecting group. Further optimizations of this reaction, for instance, with $BF_3{\cdot}Et_2O$ as Lewis acid, failed to yield satisfactory results.

We then switched to the reduction-Mitsunobu process for the reduction of hydroxyl.[7] As depicted in Scheme 2, the $NaBH_4$-mediated reduction of **1aa** went smoothly, and the combination of [4 + 2] annulation and reduction afforded diol **6aa** in 49% yield for two steps and with 85% ee after one column chromatography purification.

A Mitsunobu reaction of **6aa** followed by a $Pd(OH)_2$-mediated hydrogenation furnished equol with 85% ee and in 88% yield for two steps (Scheme 2). No erosion of enantioselectivity was observed over these processes. It is worth noting that the optical purity of equol can be further boosted to 95% ee after one recrystallization. The ^1H NMR spectrum of this compound is fully consistent with reported data (Table S1) and the absolute configuration of the synthetic equol was determined to be *S* by comparing its optical rotation with reported data (Table S6). The stereo-chemical outcome of this asymmetric catalytic process is in agreement with our previous observation.[17y]

Encouraged by these results, we further capitalized with this strategy in the synthesis other natural occurring isoflavanes. As exhibited in Scheme 3, under standard [4 + 2] asymmetric annulation protocol followed by subsequent reduction by $NaBH_4$, diols **6ab** and **6ac** were prepared in 64% and 60% yield (two steps) and with 83% ee and 89% ee, respectively. Similarly, enantio-enriched (*S*)-sativan and (*S*)-vestitol can be efficiently synthesized with 83% ee, 88% ee (95% ee after one recrystallization) after the Mitsunobu-hydrogenation process.



Scheme 4. Enantioselective synthesis of isoflavane analogues. a) **4d** or **4e**, cat. **I**, TBAF, PNBA, NaH_2PO_4, DCM, -40 °C; b) $NaBH_4$, MeOH, 0 °C; c) DEAD, PPh_3, THF, 0 °C to rt; d) $Pd(OH)_2/C$, H_2, MeOH/THF/H_2O, rt.

Table 2. Minimum inhibitory concentration (μg/mL) of isoflavanes and analogues against selected bacteria.[a]

Compound	Gram-positive		Gram-negative	
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*
rac-sativan	>128	>128	>128	>128
(*S*)-sativan	64	64	>128	>128
rac-vestitol	128	128	>128	>128
(*S*)-vestitol	64	128	>128	>128
rac-**8ad**	>128	>128	>128	>128
(*S*)-**8ad**	>128	>128	>128	>128
rac-**8ae**	64	64	>128	>128
(*R*)-**8ae**	64	64	>128	>128
(*S*)-equol	64	>128	>128	>128
Meropenem	0.125	0.125	0.0625	0.125

[a] *B. subtilis:* BR 151; *S. aureus:* ATCC 6538; *E. coli*: ATCC 25922; *P. aeruginosa:* ATCC 15442. All experiments were triplicated.

Similarly, (*S*)-isosativan was readily prepared with 82% ee (97% ee after recrystallization).

Moreover, starting from diol **6ac**, (+)-medicarpin can be efficiently constructed in 44% total yield and with 88% ee (95% ee after recrystallization) via the Mitsunobu-oxidation-hydrogenation-cyclization process.[20]

Besides naturally occurring molecules, this synthetic route is also feasible in the synthesis of other isoflavane analogues. For instance, compound **8ad** (R^1 = Ph) was readily prepared with 85% ee (90% ee after recrystallization) after similar process (Scheme 4). It is worth noting that the enantioselectivity of the product (**8ae**) can be as high as 95% ee when 3-phenylpropanal (R^1 = Bn, **4e**) was employed as substrate. These data further demonstrate this approach as a general route for the synthesis of optically active isoflavanes.

Some isoflavanes (e.g., medicarpin) have proven to have intriguing antimicrobial activities against a number of bacterial pathogens.[5] With these naturally occurring isoflavanes and their analogues prepared, we further investigated the antimicrobial activities of these compounds. We incubated these molecules, along with Meropenem[22] (as positive control), in a serial of concentrations with a number of clinically important Gram-negative bacteria (*E. coli* and *P. aeruginosa*) and Gram-positive bacteria (*B. subtilis* and *S. aureus*) to determine their minimum inhibitory concentrations (MICs). As shown in Table 2, these compounds seem to be less effective against Gram-negative bacterial pathogens. However, to our delight, some of these chromans displayed intriguing activities against Gram-positive bacterial. For example, (*S*)-sativan and (*R*)-**8ae** exhibited MIC of 64 μg/mL against *B. subtilis* and *S. aureus*.

It is interesting to observe that the racemic form of sativan seems to be much less effective against these bacteria.

In summary, we have disclosed a general asymmetric route to enantio-enriched isoflavanes with a chiral amine-catalyzed asymmetric formal [4 + 2] annulation of *o*-quinone methides and aldehydes as the key step. With this approach, a number of isoflavanes, including equol, sativan, isosativan, vestitol, and medicarpin, as well as isoflavane analogues, have been prepared with good to excellent enantioselectivities. Furthermore, the antimicrobial activities of these molecules have been assessed by measuring the minimum inhibitory concentrations against selected Gram-positive and Gram-negative bacteria.

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Supplementary data

Experimental procedures, characterizations, ^{1}H NMR and ^{13}C NMR spectra, HPLC traces are available in the online version.

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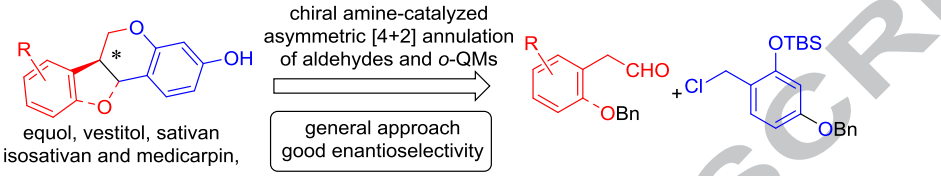

Research highlights

- A general asymmetric route to isoflavanes was developed.
- Five optically active natural isoflavanes were prepared.
- High synthetic efficiency