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The first stereocontrolled synthesis of isoflavanones

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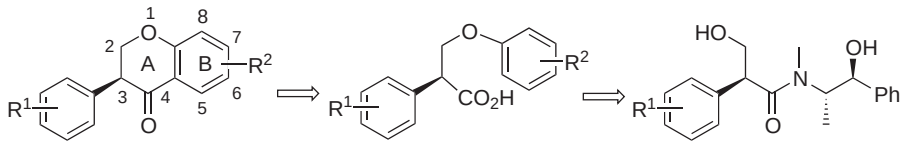
Abstract

The first asymmetric synthesis of isoflavanones has been performed employing a stereocontrolled aldol reaction between an (*S*,*S*)-(+)-pseudoephedrine arylacetamide and *para*-formaldehyde as the key step.

Keywords: asymmetric synthesis; flavanoids; isoflavanoids.

Isoflavanoids represent a large group of naturally occurring secondary metabolites displaying a wide array of physiological activities.[1] Among them, the isoflavanones are a relatively small group of compounds which have shown interesting antifungal[2] and antibacterial[3] activities and behave as potent phytoalexins.[4] A chiral centre is present in their structure, and therefore the design of synthetic procedures should allow their synthesis in a stereocontrolled way. To date, only the asymmetric syntheses of close derivatives like isoflavans,[5] pterocarpans[6] or isoflavanols[7] have been carried out but no asymmetric synthesis of isoflavanones have been reported.

In the context of our research in the field of asymmetric synthesis of natural products,[8] we have developed a procedure to obtain isoflavanone derivatives in a stereocontrolled way according to the *retro*-synthetic approach shown in Scheme 1. Following this sequence, the chiral centre present in the final molecule will be formed by an asymmetric aldol reaction between an (*S*,*S*)-(+)-pseudoephedrine-based arylacetamide derivative and formaldehyde under



Scheme 1.

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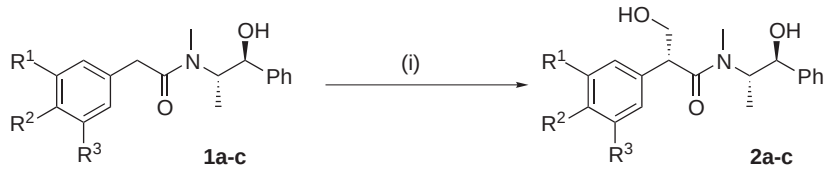
a protocol developed previously by us.[9] Later, the B ring will be introduced in the form of a phenol ether and finally, after the chiral auxiliary is removed, the A ring will be formed by an intramolecular acylation process building up the skeleton of the target heterocycle. This preparative approach to accessing this kind of heterocycle is novel in this group of substances.

The arylacetamides **1**, prepared by a previously reported procedure,[10] were submitted to deprotonation by 2 equiv. of LDA in THF at −78°C (Scheme 2) and the formed dianion was reacted with *para*-formaldehyde (4 equiv.) at −105°C yielding the corresponding β-hydroxy-amides in good yields and only one of the two possible diastereomers was formed, as indicated by HPLC analysis under the optimised conditions for a 1:1 mixture of both epimers (see Table 1). According to a previously reported mechanism for the asymmetric aldol reactions of (*S*,*S*)-(+)-pseudoephedrine amides,[9] the configuration of the newly created chiral centre was assigned as *S*.



Scheme 2. *Reagents and conditions*: (i) 1. LDA, THF, −78°C; 2. HCHO, THF, −105°C

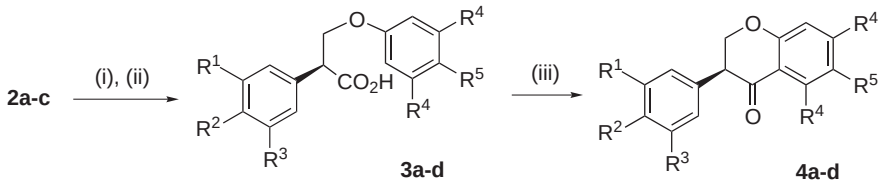
Table 1
Asymmetric aldol reaction between arylacetamides **1a**–**c** and HCHO

Product	R^1	R^2	R^3	d.e. (%)[a]	Yield
2a	OCH_3	OCH_3	H	>99	85
2b	OCH_3	OCH_3	OCH_3	>99	81
2c	OCH_2O	OCH_2O	H	>99	86

[a] Determined by HPLC (Chiralcel OD, hexane/*iso*-propanol 70:30, flow rate 1.00 mL/min).

We then proceeded to introduce the isoflavanone B ring via phenol ether formation, which was performed by nucleophilic displacement of the hydroxylic function by a phenolic alcohol under Mitsunobu conditions.[11] Thus after 12 h of reaction of amides **2a**–**c** with 2 equiv. of phenol and di-isopropyl azodicarboxylate (DIAD) in THF at rt, in the presence of excess PPh_3, the starting material was completely consumed. However, attempts to isolate the reaction product were unsuccessful due to the presence of large amounts of PPh_3=O. Therefore, the crude reaction mixture was subjected to acid hydrolysis (4 M H_2SO_4/dioxane, reflux) and, after a previous standard acid–base work-up treatment followed by flash column chromatography purification, the corresponding acids **3a**–**d** were obtained in moderate overall yield. The chiral auxiliary (*S*,*S*)-(+)-pseudoephedrine was recovered from the work-up of the basic extracts but as its phenol ether derivative, which indicated that both hydroxylic functions of the amides **2a**–**c** were converted to the respective phenol ethers during the Mitsunobu reaction.

Finally, in the last step of the synthesis, these acids were converted into the final heterocycles by intramolecular Friedel–Crafts acylation (see Scheme 3) yielding the isoflavanones **4a**–**d** in good yields (see Table 2) and only as one detectable enantiomer, as indicated by chiral HPLC analysis under optimised conditions for a racemic standard.[12]



Scheme 3. *Reagents and conditions*: (i) PPh_3, ArOH, DIAD; (ii) 4 M H_2SO_4/dioxane, reflux; (iii) 1. $SOCl_2$, toluene, reflux, 2. $SnCl_4$, CH_2Cl_2, rt

Table 2
The prepared isoflavanones **4a–d**

Prod.	R^1	R^2	R^3	R^4	R^5	Yield	Prod.	e.e. (%)[a]	Yield
3a	OCH_3	OCH_3	H	H	OCH_3	69	**4a**	>99	84
3b	OCH_3	OCH_3	OCH_3	H	OCH_3	71	**4b**	>99	86
3c	OCH_2O	OCH_2O	H	H	OCH_3	68	**4c**	>99	81
3d	OCH_3	OCH_3	H	OCH_3	H	69	**4d**	>99	88

[a] Determined by HPLC (Chiralcel OD, hexane/*iso*-propanol 93:7, flow rate 1.00 mL/min).

In summary, stereoselective synthesis of several isoflavanones has been achieved by employing the asymmetric aldol reaction of (*S*,*S*)-(+)-pseudoephedrine arylacetamides with formaldehyde as the key step with respect to the formation of the chiral centre. Subsequent transformation (aryl ether formation, hydrolysis and intramolecular acylation) furnished the target heterocycles in good yields and excellent optical purities.

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12. **4a**: Mp 168–170°C (EtOH); $[\alpha]_D^{20}$ +51.8 (*c* 0.1, CH_2Cl_2); ^1H NMR (δ, ppm): 3.03 (dd, 1H, $J=10.3$, 16.4 Hz); 3.19 (dd, 1H, $J=6.8$, 16.4 Hz); 3.83 (s, 3H); 3.85 (s, 3H); 3.88 (s, 3H); 4.03 (dd, 1H, $J=6.8$, 10.3 Hz); 6.45–6.79 (m, 5H); 7.18 (s, 1H); ^{13}C NMR (δ, ppm): 44.9, 55.5, 55.8, 56.3, 72.4, 103.5, 111.0, 110.4, 111.3, 115.1, 119.6, 130.2, 147.6, 148.4, 152.7, 161.3, 192.4. Relevant data for the rest of isoflavanones **4**: **4b**: Mp 177–180°C (EtOH), $[\alpha]_D^{20}$ +64.4 (*c* 0.2, CH_2Cl_2). **4c**: Mp 159–162°C (EtOH), $[\alpha]_D^{20}$ +58.3 (*c* 0.2, CH_2Cl_2). **4d**: Mp 163–165°C (EtOH), $[\alpha]_D^{20}$ +54.6 (*c* 0.2, CH_2Cl_2).