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# An easy and straightforward approach to the asymmetric synthesis of isoflavanones

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**Abstract**—Isoflavanones **4a–d** have been prepared in a stereocontrolled fashion using (*S*,*S*)-(+)-pseudoephedrine as a chiral auxiliary. The employed synthetic pathway consists of only four steps and involves initial formation of the stereogenic centre via diastereoselective aldol reaction of pseudoephedrine arylacetamides **1a–c** with formaldehyde, followed by aryl ether formation under Mitsunobu conditions, removal of the chiral auxiliary by hydrolysis and final Friedel–Crafts intramolecular acylation.


## 1. Introduction

Isoflavanoids represent a relatively large group of naturally occurring secondary metabolites, displaying a wide array of physiological activities.[1] Among them, the isoflavanones are a small group of natural products (some examples are shown in Fig. 1)[2] which have shown interesting antifungal[3] and antibacterial[4] activities as well as behaving as potent phytoalexins.[5] Additionally, these compounds have been used as components of anovulatory pharmaceuticals[6] and their reduced derivatives, the isoflavanols, have shown promising antitumour activity.[7]

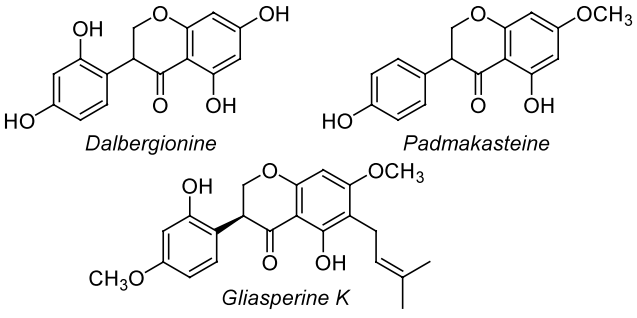


**Figure 1.**

A closer analysis of the structure of these compounds indicates that a stereogenic centre is present in their structure and therefore, the design of synthetic procedures that allow their synthesis in a stereocontrolled fashion becomes an extremely stimulating task for the synthetic organic chemist. However, to date only the asymmetric syntheses of structurally similar derivatives such as isoflavans,[8] isoflavone epoxides,[9] homoisoflavanones,[10] pterocarpans[11] or isoflavanols,[7,12] are known but no asymmetric synthesis of isoflavanones has yet been reported.

Surprisingly, it has to be mentioned that most of the natural isoflavanones isolated to date have been obtained in racemic form, which is interpreted in terms of an epimerization side-process during the isolation.[13] Therefore, the interest in designing efficient synthetic procedures for the preparation of these compounds in enantiopure form, in order to allow structure–activity relationship studies and to find analogues with improved biological activities should be emphasized.

In this context, and in connection with our efforts directed towards the stereocontrolled synthesis of natural products,[14] we wish to report herein a simple and efficient procedure for the asymmetric synthesis of isoflavanones.[15] The key step in the synthetic route, concerning the stereocontrolled installation of the stereogenic centre, relies upon an asymmetric aldol reaction using the inexpensive and commercially available amino alcohol (*S*,*S*)-(+)-pseudoephedrine as chiral auxiliary.[16] The reported procedure is particularly inter-

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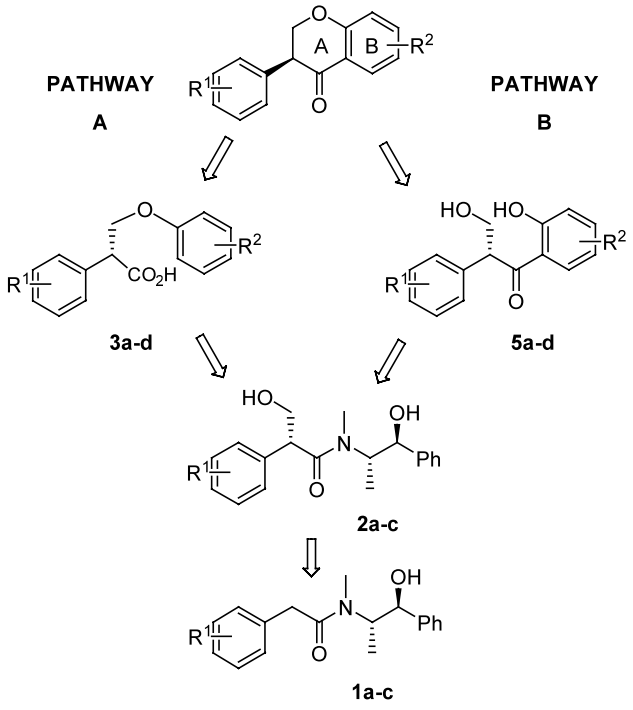
esting, owing to the fact that it allows the preparation of analogues with different substitution patterns at both aromatic rings. Additionally, the pathway is short and implies the use of easy and high yielding transformations.

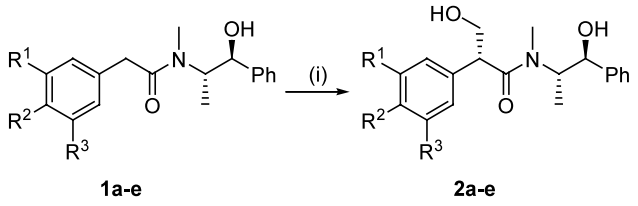
According to the retrosynthetic approach shown in Scheme 1, access to the isoflavanone skeleton could be achieved starting from the (*S*,*S*)-(+)-pseudoephedrine arylacetamides **1a**–**c** by performing a diastereoselective aldol reaction with formaldehyde. In this way the stereogenic centre present in the final compounds can be introduced. Next, the future A ring of the heterocyclic system would be built up via aryl ether formation and finally, a Friedel–Crafts intramolecular acylation should provide the target compounds (pathway A). An alternative approach can be envisaged (pathway B) in which the 1,2-addition reaction of a conveniently substituted aryllithium reagent to the amide functionality of the adduct obtained after the stereocontrolled aldol reaction **2a**–**c**, should provide the key aryl benzyl ketones **5a**–**d** directly, affording the desired compounds after formation of the phenol ether bond that closes the A ring.




**Scheme 1.**

## 2. Results and discussion

We proceeded to evaluate the two proposed synthetic approaches, dealing first with the stereocontrolled aldol reaction of amides **1a**–**c** with formaldehyde. Therefore, these amides (which were prepared by acylation of the commercially available chiral β-amino alcohol (*S*,*S*)-(+)-pseudoephedrine with different arylacetyl chlorides, as previously reported by us)[17] were deprotonated with 2 equiv. of LDA at −78°C and the dianion formed was allowed to react with *para*-formaldehyde at 0°C (Scheme 2), furnishing the corresponding β-hydroxy-amide adducts **2a**–**c** in good yields and as single diastereoisomers, as indicated by $^1$H NMR analysis of the crude reaction mixture (Table 1). The absolute configuration of the newly created stereogenic centre was assigned as *S* according to a previously proposed mechanism that accounts for the asymmetric aldol reactions with (*S*,*S*)-(+)-pseudoephedrine propionamide enolates.[16a]



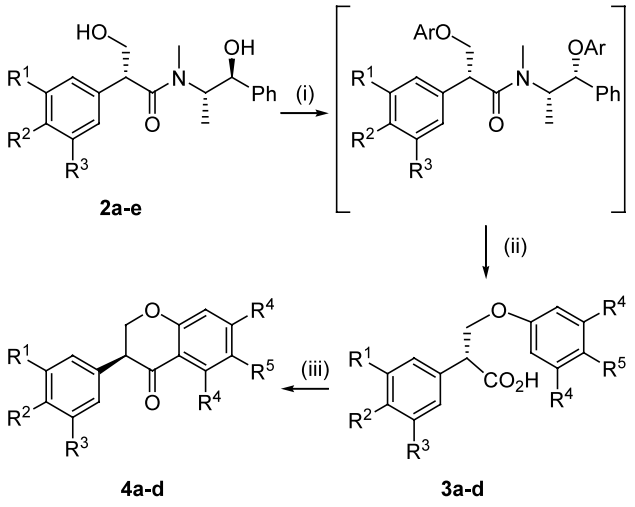

**Scheme 2.** *Reagents and conditions*: (i) 1. LDA, THF, −78°C; 2. HCHO, THF, 0°C.

**Table 1.** Stereocontrolled aldol reaction of amides **1a**–**c** with formaldehyde

| Prod. | $R^1$ | $R^2$ | $R^3$ | Yield (%)[a] | de (%)[b] |
|---|---|---|---|---|---|
| **2a** | OMe | OMe | H | 85 | >95 |
| **2b** | OMe | OMe | OMe | 81 | >95 |
| **2c** | $OCH_2O$ | | H | 86 | >95 |

[a] Yield of pure product isolated after column chromatography.
[b] Determined by $^1$H NMR analysis of the crude reaction mixture.

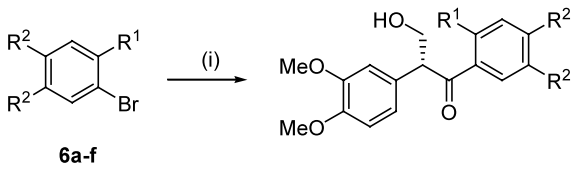
According to the route depicted in Scheme 1, we began evaluating synthetic pathway A. Therefore, we proceeded first to introduce the future B ring of the heterocyclic system, in the form of an aryl ether moiety. In this context, among the different methods described in the literature for the preparation of aryl ethers, the nucleophilic displacement of the hydroxyl function by an aromatic alcohol under Mitsunobu conditions seemed to be, a priori, a very promising approach.[18] Consequently, and taking into account that two hydroxylic functionalities are present in the starting amides **2a**–**c**, these were treated with 2 equiv. of the conveniently substituted phenol, in the presence of 2 equiv. of $PPh_3$ and excess di-isopropyl azodicarboxylate (DIAD) in THF at rt.[18d] The reaction was monitored by TLC and, after 12 h, the analysis of aliquots showed that all the starting material had disappeared. Disappointingly, all attempts to purify the reaction product were fruitless, due to the presence of bulk quantities of triphenylphosphine oxide. For that reason, we decided to perform the removal of the chiral auxiliary by direct hydrolysis of the crude reaction mixture obtained after the Mitsunobu reaction (Scheme 3). In this way, after refluxing this mixture in 9 M $H_2SO_4$/dioxane for 12 h, it was possible to isolate the desired acids **3a**–**d** in good yields after standard acid–base work-up, followed by flash column chromatography purification (Table 2).




**Scheme 3.** *Reagents and conditions*: (i) ArOH, $PPh_3$, DIAD, THF, rt. (ii) $H_2SO_4$/dioxane, refl. (iii) 1. $SOCl_2$, toluene, refl.; 2. $AlCl_3$ or $SnCl_4$, $CH_2Cl_2$, −20°C.

It is notable that the chiral auxiliary (*S*,*S*)-(+)-pseudoephedrine was recovered during work-up from the basic extracts as its phenol ether derivative, which also indicated that both hydroxylic functions of the amides **2a–c** were converted to the respective phenol ethers during the Mitsunobu reaction. When we tried the formation of the aryl ether with only 1 equiv. of phenol and DIAD, expecting that the primary alcohol moiety would react faster than the secondary alcohol present in the structure of the chiral auxiliary, only complicated mixtures of products were isolated both at the Mitsunobu reaction and after performing the hydrolysis step. This indicates that the formation of both aryl ethers is necessary for the reaction to proceed in synthetically useful yields.

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 and as only one detectable enantiomer, as chiral HPLC analysis under conditions optimized for a racemic standard indicated. It has to be mentioned that, in the case of isoflavanone **4c**, in which a methylenedioxy bridge is present in the starting acid **3c**, $SnCl_4$ had to be employed as a Lewis acid in the Friedel–Crafts acylation, in order to avoid the formation of complicated mixtures of products in which the already mentioned methylenedioxy moiety was broken.[19] The commonly used $AlCl_3$ worked perfectly in the other substrates **3a–b** and **3d**.




**Scheme 4.** *Reagents and conditions*: (i) 1. *tert*-BuLi, THF, −78°C; 2. **2a**, THF, −78 to 0°C; 3. *i*-$Pr_2NH$, 0°C; 4. AcOH/$Et_2O$.

**Table 3.** Addition reaction of the organolithium reagents derived from **6a–f** and amide **2a**

| Entry | Aryl bromide **6a–e** | $R^1$ | $R^2$ | Yield (%)[a] |
|---|---|---|---|---|
| 1 | **6a** | OBn | H | –[b] |
| 2 | **6b** | OBn | OMe | –[b] |
| 3 | **6c** | OTBS | H | –[b] |
| 4 | **6d** | OTBS | OMe | –[b] |
| 5 | **6e** | H | H | 78 |
| 6 | **6f** | H | OMe | 81 |

[a] Yield of pure product isolated after column chromatography.
[b] Only starting material was recovered.

The proposed alternative approach to the isoflavanone skeleton (pathway B in Scheme 1) involved the formation of the 2-hydroxymethyl substituted aryl benzyl ketones **5a–d** directly from amides **2a–c** via 1,2-addition of an appropriately functionalised aryllithium reagent to the amide functionality, as we have already reported for similar β-hydroxyamide derivatives.[16a,20] This aryllithium reagent should bear a properly protected *ortho*-hydroxy moiety in order to facilitate the final A ring closure. Consequently, several aryl bromides **6a–d** were prepared as compounds which are suitable to undergo halogen-metal exchange with *tert*-butyllithium and therefore as suitable sources of the required functionalised aryllithium reagent.[21] Disappointingly, when amide **2a** was treated with 3 or more equivalents of these aryllithium reagents (Scheme 4), we did not observe any reaction and the starting amide was recovered unchanged even after prolonged reaction times (Table 3, entries 1–4).

This lack of reactivity of the aryllithium reagent towards the amide functionality should be interpreted

**Table 2.** Synthesis of the isoflavanones **4a–d** from the β-hydroxyamides **2a–d**

| Prod. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Yield (%)[a] | Prod. | Yield (%)[b] |
|---|---|---|---|---|---|---|---|---|
| **3a** | OMe | OMe | H | H | OMe | 69 | **4a** | 84 |
| **3b** | OMe | OMe | OMe | H | OMe | 71 | **4b** | 86 |
| **3c** | $OCH_2O$ | | H | H | OMe | 68 | **4c** | 81 |
| **3d** | OMe | OMe | H | OMe | H | 69 | **4d** | 88 |

[a] Yield of pure product isolated after acid–base work-up followed by column chromatography.
[b] Yield of pure product isolated after column chromatography purification and showed to be >99% ee as determined by chiral HPLC analysis (Chiralcel OD column, UV detector, hexanes/*iso*-propanol 93:7, flow rate 1.00 mL/min).

in terms of a chelation effect exerted by the *ortho*-benzyloxy or *tert*-butyldimethylsilyloxy moieties that stabilize the carbon–metal bond, thus lowering the reactivity of the organometallic reagent. This chelation effect was confirmed by the fact that simple phenyllithium and 3,4-dimethoxyphenyllithium did in fact react with the amide **2a** (Table 3, entries 5 and 6), affording the corresponding ketones in moderate yield. Trying to increase the reactivity of the aforementioned *ortho*-functionalised aryllithium reagents by adding TMDA or HMPA did not lead to any positive result. For that reason, this second synthetic approach to the target isoflavanones **4a**–**d** was discarded and consequently pathway A was considered as the most convenient one for the stereocontrolled synthesis of these heterocycles.

## 3. Conclusions

A very easy and straightforward procedure has been developed for the asymmetric synthesis of several isoflavanones, employing the asymmetric aldol reaction of (*S*,*S*)-(+)-pseudoephedrine arylacetamides with formaldehyde as the key step with respect to the formation of the stereogenic centre. Subsequent transformations (aryl ether formation, hydrolysis and intramolecular acylation) furnished the target heterocycles in good yields and excellent enantiomeric purities. The alternative approach, starting from β-hydroxyamides **2a**–**c** (1,2-addition of a conveniently functionalised aryllithium reagent followed by aryl ether formation) proved to be inoperative due to the low reactivity of the aryllithium reagents towards amide **2a**.

## 4. Experimental

### 4.1. General procedures

Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained on KBr pellets (solids) or $CHCl_3$ solution (oils). NMR spectra were recorded at 20–25°C, running at 250 MHz for $^1H$ and 62.8 MHz for $^{13}C$ in $CDCl_3$ solution and resonances are reported in ppm relative to tetramethylsilane unless otherwise stated. Assignment of individual $^{13}C$ resonances are supported by DEPT experiments. $^1H\{^1H\}$ NOE experiments were carried out in the difference mode by irradiation of all the lines of a multiplet.[22] Mass spectra were recorded under electron impact at 70 eV. TLC was carried out with 0.2 mm thick silica gel plates (Merck Kiesegel $GF_{254}$). Visualization was accomplished by UV light or by spraying with Dragendorff's reagent.[23] Flash column chromatography[24] on silica gel was performed with Merck Kiesegel 60 (230–400 mesh). Determination of enantiomeric excesses was performed by chiral HPLC analysis of non crystallized samples using a Chiracel OD® column with a UV detector with the eluents and flow rates as indicated in each case. All solvents used in reactions were dried and purified according to standard procedures.[25] All air- or moisture-sensitive reactions were performed under argon. The glassware was over dried (140°C) overnight and purged with argon. Amides **1a**–**c** were prepared according to literature procedures.[17]

### 4.2. General procedure for the diastereoselective aldol reaction with formaldehyde. Synthesis of β-hydroxyamides, 2a–c

A solution of the amide **1a**–**c** (1 equiv.) in dry THF was added over a cooled (−78°C) solution of LDA (2.1 equiv.) in dry THF, the mixture was stirred for 1 h at this temperature and was allowed to reach to rt. The mixture was then cooled to 0°C, at which temperature *para*-formaldehyde (4 equiv.) was added at once. The mixture was stirred for 5 h at 0°C, after which it was quenched with a saturated $NH_4Cl$ solution and extracted with $CH_2Cl_2$. The combined organic fractions were collected, dried over $Na_2SO_4$, filtered and the solvent was removed under reduced pressure. The resulting residue was purified by flash column chromatography (hexanes/ethyl acetate, 2:8) to afford β-hydroxyamides **2a**–**c** as white solids.

**4.2.1. [2*S*,1′*S*,2′*S*]-(+)-2-(3,4-Dimethoxyphenyl)-3-hydroxy-*N*-methyl-*N*-(2′-phenyl-2′-hydroxy-1′-methylethyl)propanamide, 2a**. The reaction of amide **1a** (1.00 g, 2.92 mmol) with LDA (5.83 mmol) and *para*-formaldehyde (0.35 g, 9.68 mmol) following the general procedure afforded amide **2a** (0.93 g, 2.48 mmol) as a white solid. Yield: 85%. Mp 170–172°C ($Et_2O$). $[\alpha]_D^{20}$: +31.2 (*c* 0.7, $CH_2Cl_2$). IR (KBr): 3350 (OH); 1620 (C=O). $^1H$ NMR ($\delta$, ppm) (3:1 rotamer ratio; *indicates minor rotamer resonances): 0.35* (d, 3H, $J=6.7$ Hz); 0.69 (d, 3H, $J=6.7$ Hz); 2.69 (s, 3H); 2.74* (s, 3H); 3.49 (m, 1H); 3.69* (s, 3H); 3.71 (s, 3H); 3.72 (s, 3H); 3.74* (s, 3H); 3.81–4.51 (m, 5H); 4.58–5.06 (m, 1H); 6.66–6.78 (m, 3H); 7.11–7.30 (m, 5H). $^{13}C$ NMR: 13.6*; 14.0; 26.7*; 29.1; 51.1; 55.4; 57.8; 65.2; 65.4*; 74.5*; 74.9; 110.4; 110.5*; 111.0; 111.1*; 119.5; 120.1*; 125.8; 126.2*; 126.5; 126.7*; 127.3; 127.5*; 141.2; 141.4*; 141.6*; 142.5; 147.7*; 148.2; 148.8*; 149.1; 173.4*; 173.5. MS (EI) *m*/*z* (rel. int.): 373 ($M^+$, 1), 248 (39), 178 (7), 163 (100), 148 (6), 105 (9), 91 (9), 79 (8), 77 (17), 58 (30), 56 (11), 51 (10). Anal. calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.50; H, 7.33; N, 3.71%.

**4.2.2. [2*S*,1′*S*,2′*S*]-(+)-3-Hydroxy-*N*-methyl-*N*-(2′-phenyl-2′-hydroxy-1′-methylethyl)-2-(3,4,5-trimethoxyphenyl)propanamide, 2b**. The reaction of amide **1b** (1.00 g, 2.68 mmol) with LDA (5.63 mmol) and *para*-formaldehyde (0.32 g, 9.72 mmol) following the general procedure afforded amide **2b** (0.87 g, 2.17 mmol) as a white solid. Yield: 81%. Mp 188–190°C ($Et_2O$). $[\alpha]_D^{20}$: +69.4 (*c* 0.3, $CH_2Cl_2$). IR (KBr): 3340 (OH); 1615 (C=O). $^1H$ NMR ($\delta$, ppm) (3:2 rotamer ratio; *indicates minor rotamer resonances): 0.33* (d, 3H, $J=6.7$ Hz); 0.71 (d, 3H, $J=6.7$ Hz); 2.71 (s, 3H); 2.76* (s, 3H); 3.36 (m, 1H); 3.71 (s, 6H); 3.76 (s, 3H); 3.79* (s, 3H); 3.86–4.39 (m, 5H); 4.48–5.06 (m, 1H); 6.54 (s, 2H); 6.68* (s, 2H); 7.03–7.27 (m, 5H). $^{13}C$ NMR ($\delta$, ppm) 13.5*; 14.2; 26.4*; 29.2; 51.1; 51.3; 55.5;

57.6; 65.4; 65.7*; 76.7*; 77.1; 110.7; 111.4*; 119.7; 120.3*; 126.4; 126.9*; 127.8; 128.6*; 141.4; 141.6*; 141.8*; 142.5; 147.5*; 147.9; 148.9*; 149.3; 173.4*; 173.7. MS (EI) $m/z$ (rel. int.): 403 ($M^+$, 1), 255 (27), 178 (12), 163 (100), 148 (15), 105 (10), 91 (14), 77 (8), 58 (28), 56 (17), 51 (22). Anal. calcd for $C_{22}H_{29}NO_6$: C, 65.49; H, 7.24; N, 3.47. Found: C, 65.57; H, 7.36; N, 3.38%.

**4.2.3. [2*S*,1′*S*,2′*S*]-(+)-3-Hydroxy-*N*-methyl-2-(3,4-methylenedioxyphenyl) - *N* - (2′ - phenyl - 2′ - hydroxy - 1′-methylethyl)propanamide, 2c**. The reaction of amide **1c** (1.00 g, 3.06 mmol) with LDA (6.43 mmol) and *para*-formaldehyde (0.33 g, 12.24 mmol) following the general procedure afforded amide **2c** (0.94 g, 2.63 mmol) as a white solid. Yield: 86%. Mp 175–177°C ($Et_2O$). $[\alpha]_D^{20}$: +55.6 ($c$ 0.3, $CH_2Cl_2$). IR (KBr): 3342 (OH); 1620 (C=O). $^1$H NMR ($\delta$, ppm) (3:1 rotamer ratio; *indicates minor rotamer resonances): 0.44* (d, 3H, $J=6.7$ Hz); 0.88 (d, 3H, $J=6.7$ Hz); 2.76 (s, 3H); 2.79* (s, 3H); 3.45 (m, 1H); 3.79–4.42 (m, 5H); 4.51–5.11 (m, 1H); 5.66 (s, 2H); 5.78* (s, 2H); 6.68–6.81 (m, 3H); 7.03–7.27 (m, 5H). $^{13}$C NMR ($\delta$, ppm): 13.4*; 14.6; 26.7*; 29.5; 51.3; 58.4; 65.6; 66.4*; 77.7*; 77.9; 100.5; 100.8*; 111.4*; 115.7; 126.2*; 127.5; 127.8*; 128.3; 141.1; 141.7*; 142.3*; 142.8; 147.1*; 147.9; 149.2*; 150.4; 173.6*; 173.9. MS (EI) $m/z$ (rel. int.): 357 ($M^+$, 1), 243 (15), 178 (21), 163 (100), 148 (9), 91 (29), 77 (21), 58 (7), 56 (23), 51 (35). Anal. calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 65.11; H, 6.56; N, 3.84%.

### 4.3. General procedure for the Mitsunobu reaction/hydrolysis sequence. Synthesis of arylacetic acids, 3a–d

DIAD (3.0 equiv.) was carefully added over a cooled (0°C) solution of the amide **2a**–**c** (1 equiv.), $PPh_3$ (2.2 equiv.) and the corresponding phenol (2 equiv.) in dry THF. The mixture was stirred for 12 h at rt, after which it was quenched with a saturated $Na_2CO_3$ solution and extracted with $CH_2Cl_2$. The combined organic fractions were collected, dried over $Na_2SO_4$, filtered and the solvent was removed under reduced pressure. The resulting oil was dissolved in dioxane (20 mL), a 9 M $H_2SO_4$ solution (20 mL) was added at once and it was refluxed for 24 h. After cooling to rt, the mixture was basified to pH 10, washed with $Et_2O$ and carefully acidified to pH 3. The mixture was then extracted with $CH_2Cl_2$ and the combined organic fractions were collected, dried over $Na_2SO_4$, filtered and the solvent was removed under reduced pressure, affording arylacetic acids **3a**–**d** after flash column chromatography purification (hexanes/ethyl acetate, 1:1).

**4.3.1. [2*S*]-(+)-2-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyloxy)propanoic acid, 3a**. The reaction of amide **2a** (1.23 g, 5.76 mmol) with $PPh_3$ (3.02 g, 11.52 mmol), DIAD (3.40 mL, 17.28 mmol) and 4-methoxyphenol (1.43 g, 11.52 mmol) following the general procedure afforded acid **3a** (1.32 g, 3.97 mmol) as a reddish oil. Yield: 69%. $[\alpha]_D^{20}$: +23.5 ($c$ 0.1, $CH_2Cl_2$). IR ($CHCl_3$): 3354 (OH); 1718 (C=O). $^1$H NMR ($\delta$, ppm): 2.84 (dd, 1H, $J=3.6$, 13.8 Hz); 3.18 (dd, 1H, $J=9.6$, 13.8 Hz); 3.44 (dd, 1H, $J=3.6$, 9.6 Hz); 3.71 (s, 3H); 3.75 (s, 3H); 3.81 (s, 3H); 6.48 (dd, 2H, $J=1.7$, 7.1 Hz); 6.75–7.03 (m, 5H). $^{13}$C NMR ($\delta$, ppm): 25.4; 48.6; 55.1; 55.3; 55.5; 101.5; 106.3; 111.9; 113.6; 121.4; 131.9; 148.2; 149.3; 154.2; 161.4; 180.9. MS (EI) $m/z$ (rel. int.): 332 ($M^+$, 14), 314 ($M^+$-18, 63), 283 (35), 178 (100), 163 (21), 135 (9), 107 (15), 91 (12), 77 (9), 51 (18).

**4.3.2. [2*S*]-(+)-3-(4-Methoxyphenyloxy)-2-(3,4,5-trimethoxyphenyl)propanoic acid, 3b**. The reaction of amide **2b** (2.19 g, 5.44 mmol) with $PPh_3$ (2.85 g, 10.88 mmol), DIAD (3.21 mL, 16.33 mmol) and 4-methoxyphenol (1.35 g, 10.88 mmol) following the general procedure afforded acid **3b** (1.40 g, 3.86 mmol) as a reddish oil. Yield: 71%. $[\alpha]_D^{20}$: +21.8 ($c$ 0.1, $CH_2Cl_2$). IR ($CHCl_3$): 3350 (OH); 1723 (C=O). $^1$H NMR ($\delta$, ppm): 2.94 (dd, 1H, $J=3.7$, 14.1 Hz); 3.25 (dd, 1H, $J=9.5$, 14.1 Hz); 3.53 (dd, 1H, $J=3.7$, 9.5 Hz); 3.68 (s, 3H); 3.58 (s, 6H); 3.74 (s, 3H); 6.53 (dd, 2H, $J=1.8$, 7.2 Hz); 6.77 (s, 2H); 7.13 (dd, 2H, $J=1.8$, 7.2 Hz). $^{13}$C NMR ($\delta$, ppm): 28.6; 47.5; 55.3; 55.7; 56.4; 101.1; 107.4; 113.4; 132.4; 148.4; 149.5; 154.3; 159.2; 180.5. MS (EI) $m/z$ (rel. int.): 362 ($M^+$, 14), 344 ($M^+$–18, 28), 313 (41), 178 (100), 163 (15), 135 (8), 107 (21), 91 (11), 77 (15), 75 (24), 51 (10).

**4.3.3. [2*S*]-(+)-3-(4-Methoxyphenyloxy)-2-(3,4-methylenedioxyphenyl)propanoic acid, 3c**. The reaction of amide **2c** (1.28 g, 3.58 mmol) with $PPh_3$ (1.88 g, 7.16 mmol), DIAD (2.12 mL, 10.76 mmol) and 4-methoxyphenol (0.89 g, 7.16 mmol) following the general procedure afforded acid **3c** (0.77 g, 2.43 mmol) as a reddish oil. Yield: 68%. $[\alpha]_D^{20}$: +33.4 ($c$ 0.1, $CH_2Cl_2$). IR ($CHCl_3$): 3348 (OH); 1719 (C=O). $^1$H NMR ($\delta$, ppm): 2.88 (dd, 1H, $J=3.7$, 14.0 Hz); 3.22 (dd, 1H, $J=9.5$, 14.0 Hz); 3.49 (dd, 1H, $J=3.7$, 9.5 Hz); 3.77 (s, 3H); 5.71 (s, 2H); 6.62 (dd, 2H, $J=1.8$, 7.2 Hz); 6.84-7.22 (m, 5H). $^{13}$C NMR ($\delta$, ppm): 28.9; 45.5; 55.3; 100.2; 110.0; 111.3; 111.9; 114.5; 118.3; 133.2; 147.2; 149.1; 154.7; 156.1; 181.1. MS (EI) $m/z$ (rel. int.): 316 ($M^+$, 8), 298 ($M^+$–18, 16), 267 (20), 178 (100), 165 (41), 135 (10), 105 (11), 91 (16), 77 (8), 75 (31), 51 (12).

**4.3.4. [2*S*]-(+)-2-(3,4-Dimethoxyphenyl-3-(3,5-dimethoxyphenyloxy)propanoic acid, 3d**. The reaction of amide **2d** (2.15 g, 5.76 mmol) with $PPh_3$ (3.02 g, 11.52 mmol), DIAD (3.40 mL, 17.29 mmol) and 3,5-dimethoxyphenol (1.78 g, 11.52 mmol) following the general procedure afforded acid **3d** (1.65 g, 4.55 mmol) as a reddish oil. Yield: 69%. $[\alpha]_D^{20}$: +41.3 ($c$ 0.1, $CH_2Cl_2$). IR ($CHCl_3$): 3360 (OH); 1712 (C=O). $^1$H NMR ($\delta$, ppm): 2.93 (dd, 1H, $J=3.6$, 14.0 Hz); 3.25 (dd, 1H, $J=10.0$, 14.0 Hz); 3.53 (dd, 1H, $J=3.6$, 10.0 Hz); 3.69 (s, 3H); 3.73 (s, 3H); 3.82 (s, 6H); 6.10 (s, 2H); 6.78–6.95 (m, 4H). $^{13}$C NMR ($\delta$, ppm): 27.2; 50.5; 55.0; 55.3; 55.6; 106.4, 111.0, 115.4, 119.7, 121.3; 131.6; 148.0, 148.7, 155.4, 159.2; 180.5. MS (EI) $m/z$ (rel. int.): 344 ($M^+$–18, 63), 316 (16), 301 (17), 178 (100), 163 (13), 135 (5), 107 (5), 91 (3), 77 (7).

### 4.4. General procedure for the Friedel–Crafts cyclization. Synthesis of isoflavanones, 4a–d

A solution of the arylacetic acid **3a–d** (1 equiv.) and $SOCl_2$ (2.4 equiv.) in dry toluene was refluxed for 4 h. The volatiles were removed under reduced pressure and the resulting red oil was dissolved in dry $CH_2Cl_2$. This solution was dropwise added over a cooled (−20°C) solution of the Lewis acid (2.4 equiv.) in dry $CH_2Cl_2$. The reaction was stirred until TLC analysis of aliquots indicated full conversion and it was quenched with a 4 M HCl solution. The mixture was then extracted with $CH_2Cl_2$ and the combined organic fractions were collected, dried over $Na_2SO_4$, filtered and the solvent was removed under reduced pressure, affording isoflavanones **4a–d** after flash column chromatography purification (hexanes/ethyl acetate, 7:3).

**4.4.1. [2*S*]-(+)-3′,4′,6-Trimethoxyisoflavanone, 4a**. The reaction of arylacetic acid **3a** (0.53 g, 1.65 mmol) with $SOCl_2$ (0.39 mL, 3.95 mmol) and $AlCl_3$ (0.53 g, 3.95 mmol) following the general procedure afforded isoflavanone **4a** (0.43 g, 1.39 mmol) as a yellowish solid. Yield: 84%. Mp 168–170°C (EtOH). $[\alpha]_D^{20}$: +51.8 (*c* 0.1, $CH_2Cl_2$). $^1$H NMR ($\delta$, 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 ($\delta$, 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. MS (EI) *m*/*z* (rel. int.): 314 ($M^+$, 19), 313 (14), 312 (15), 301 (13), 278 (5), 164 (28), 150 (100), 137 (9), 121 (15), 77 (21). Anal. calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.80; H, 5.66%.

**4.4.2. [2*S*]-(+)-3′,4′,5′,6-Tetramethoxyisoflavanone, 4b**. The reaction of arylacetic acid **3b** (0.38 g, 1.05 mmol) with $SOCl_2$ (0.18 mL, 2.52 mmol) and $AlCl_3$ (0.33 g, 2.52 mmol) following the general procedure afforded isoflavanone **4b** (0.90 g, 2.07 mmol) as a yellowish solid. Yield: 86%. Mp 177–180°C (EtOH). $[\alpha]_D^{20}$: +64.4 (*c* 0.2, $CH_2Cl_2$). IR (KBr): 1680 (C=O). $^1$H NMR ($\delta$, ppm): 3.11 (dd, 1H, $J=10.3$, 16.3 Hz); 3.21 (dd, 1H, $J=6.8$, 16.3 Hz); 3.71 (s, 3H); 3.83 (s, 6H); 3.84 (s, 3H); 4.01 (dd, 1H, $J=6.8$, 10.3 Hz); 6.33 (s, 1H); 6.64 (s, 1H); 7.12 (m, 2H); 7.31 (s, 1H). $^{13}$C NMR ($\delta$, ppm): 46.4; 55.8; 55.9; 56.4; 71.3; 103.5; 111.4; 116.6; 121.4; 129.7; 148.6; 150.2; 156.9; 160.5; 192.2. MS (EI) *m*/*z* (rel. int.): 344 ($M^+$, 34), 343 (14), 342 (57), 316 (15), 301 (6), 164 (10), 150 (100), 137 (7), 121 (21), 77 (33). Anal. calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.18; H, 5.78%.

**4.4.3. [2*S*]-(+)-6-Methoxy-3′,4′-methylenedioxyisoflavanone, 4c**. The reaction of arylacetic acid **3c** (0.44 g, 1.39 mmol) with $SOCl_2$ (0.24 mL, 3.34 mmol) and $SnCl_4$ (0.39 mL, 3.34 mmol) following the general procedure afforded isoflavanone **4c** (0.33 g, 1.12 mmol) as a yellowish solid. Yield: 81%. Mp 159–162°C (EtOH). $[\alpha]_D^{20}$: +58.3 (*c* 0.2, $CH_2Cl_2$). IR (KBr): 1680 (C=O). $^1$H NMR ($\delta$, ppm): 3.02 (dd, 1H, $J=10.3$, 16.3 Hz); 3.14 (dd, 1H, $J=6.8$, 16.3 Hz); 3.80 (s, 3H); 4.12 (dd, 1H, $J=6.8$, 10.3 Hz); 5.66 (s, 2H); 6.68–7.21 (m, 5H); 7.36 (s, 1H). $^{13}$C NMR ($\delta$, ppm): 45.5; 56.6; 69.9; 100.2; 103.3; 110.9; 111.5; 115.8; 119.4; 121.2; 128.8; 148.7; 150.5; 151.9; 159.6; 192.3. MS (EI) *m*/*z* (rel. int.): 298 ($M^+$, 23), 297 (9), 296 (13), 254 (21), 164 (11), 150 (100), 137 (17), 121 (36), 77 (9). Anal. calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.56; H, 4.84%.

**4.4.4. [2*S*]-(+)-3′,4′,5,7-Tetramethoxyisoflavanone, 4d**. The reaction of arylacetic acid **3d** (0.85 g, 2.35 mmol) with $SOCl_2$ (0.41 mL, 5.64 mmol) and $AlCl_3$ (0.75 g, 5.64 mmol) following the general procedure afforded isoflavanone **4d** (0.71 g, 2.07 mmol) as a yellowish solid. Yield: 88%. Mp 163–165°C (EtOH). $[\alpha]_D^{20}$: +54.6 (*c* 0.2, $CH_2Cl_2$). IR (KBr): 1685 (C=O). $^1$H NMR ($\delta$, ppm): 3.06 (dd, 1H, $J=10.3$, 16.3 Hz); 3.26 (dd, 1H, $J=6.8$, 16.3 Hz); 3.78 (s, 3H); 3.81 (s, 3H); 3.84 (s, 3H); 3.86 (s, 3H); 3.95 (dd, 1H, $J=6.8$, 10.3 Hz); 6.25 (s, 1H); 6.77–6.81 (m, 3H); 7.26 (s, 1H). $^{13}$C NMR ($\delta$, ppm): 44.7; 55.5; 55.7; 55.8; 56.1; 71.7; 103.3; 111.0; 111.1; 115.4; 120.1; 129.0; 148.4; 148.9; 152.8; 157.2; 160.1; 192.6. MS (EI) *m*/*z* (rel. int.): 344 ($M^+$, 34), 343 (14), 342 (57), 316 (11), 301 (13), 299 (5), 180 (100), 164 (51), 152 (13), 149 (8), 137 (6), 121 (7). Anal. calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.34; H, 5.73%.

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