The First Enantioselective Synthesis of Isoflavonoids: (*R*)- and (*S*)-Isoflavans

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α-Benzylation of (+)- and (−)-*N*-phenylacetyl imidazolidinones with 2-*O*-methoxymethylbenzyl bromide, followed by reductive removal of the chiral auxiliary and cyclization, leads to isoflavans in excellent enantiomeric excess and yield.

Although the isoflavonoids exhibit a diverse range of physiological activity[1] and a surprisingly large structural diversity,[2] chirality in the non-planar analogues, *i.e.* isoflavanones, isoflavan-4-ols, isoflavans, rotenoids and pterocarpans, is limited to only three carbon atoms. Among the plethora of synthetic routes to these compounds, none has addressed the issue of stereocontrol at any of the stereogenic centres. Attempts at selectivity during the synthesis of these compounds are hence limited to a single example based on the resolution of isoflavan 4-ols during the preparation of pterocarpans.[3] Since the absolute configuration at C-2 or C-4 of the 3-phenylchroman system could be dictated by the configuration at C-3, a strategy of controlling the latter stereocentre would facilitate the stereoselective synthesis of all these compounds.

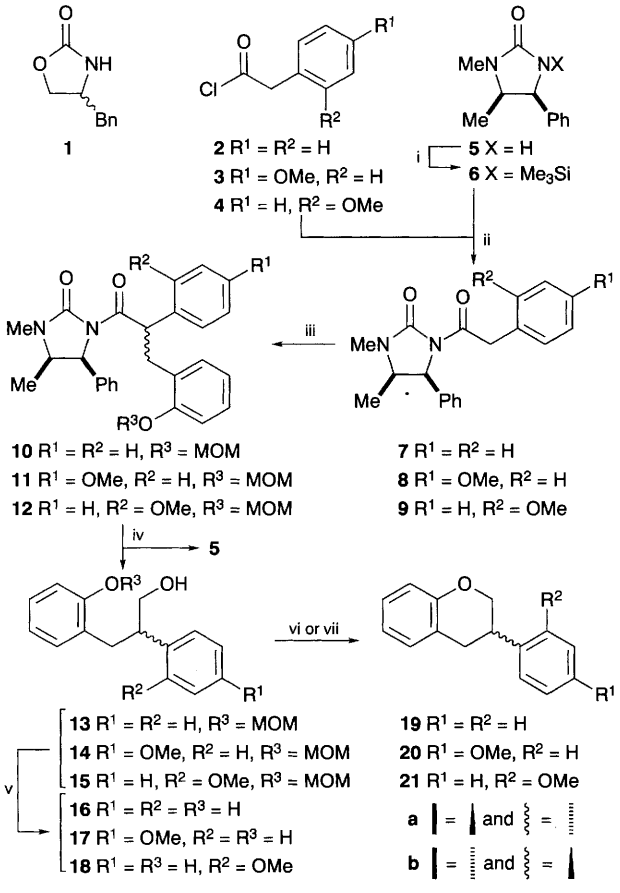
We therefore selected isoflavans as target molecules and opted for a protocol of stereoselective α-benzylation of phenylacetic acid derivatives followed by reductive removal of the chiral auxiliary and cyclization, for establishing the isoflavan framework. Owing to the excellent results obtained by Evans *et al.*,[4] the commercially available (±)-4-benzyl-2-oxazolidinones **1** were utilized as chiral auxiliaries in these reactions. Thus, the phenylacetyl chlorides[5] **2**, **3** and **4** were reacted with (+)- and (−)-4-benzyl-2-oxazolidinone and the *N*-acylated compounds treated with lithium isopropylcyclohexylamide (LICA). The resultant enolate was trapped with 2-*O*-methoxymethylbenzyl bromide[6] leading to the α-benzylated products. These reactions, however, were hampered by low yields (13–30%), which could be substantially improved (*ca.* 45%) by the addition of hexamethylphosphoric triamide (HMPA) in the alkylation step, albeit with a severe decrease in stereoselectivity (*ca.* 20% d.e.).

Since the low yields could be attributed to considerable ketene formation in the deprotonation step, the chiral auxiliaries were changed to the (4*S*,5*R*)-(+)- and (4*R*,5*S*)-(−)-imidazolidin-2-ones,[7,8] **5a** and **5b**, with poorer nucleofugic properties relative to **1**, and the basicity of these compounds decreased by utilizing them as trimethylsilyl ethers **6a** and **6b**. Optimum reproducibility and yields for the alkylation step were obtained in a mixture of CH_2Cl_2–THF (2 : 3) as solvent.[9]

The *N*-acyl imidazolidinones **7–9** could accordingly be alkylated in excellent yields with only one diastereoisomer detectable by NMR (Table 1). The alkylated products **10–12** were smoothly converted into the 2,3-diarylpropan-1-ols **13–15** by reduction with LAH followed by quantitative deprotection with 3 mol dm^{-3} HCl in methanol to afford the phenolic propan-1-ols **16–18**. Activation of the primary hydroxy group by brosylation (*p*-bromobenzenesulfonyl chloride–pyridine) followed by treatment with sodium hydride gave disappointing yields (45–60%) in the cyclization step. The isoflavans **19–21** were, however, formed in excellent yields by employing Mitsunobu conditions[10] (Ph_3P–diethyl azodicarboxylate).

The stereochemistry of the alkylation step is explicable in terms of the preferential formation of a *Z*-enolate.[11] Attack of the electrophile is then directed to the face of the enolate opposite the phenyl moiety on the chiral auxiliary. Our results are in agreement with those of Evans *et al.*[11] who reported that the chiral auxiliary having a 4*S*-configuration led to propanols exhibiting positive optical rotations, and those from 4*R*-*N*-acyloxazolidinones showing negative $[\alpha]_D$ values. Alkylation of (4*S*,5*R*)-(+)-*N*-phenylacetylimidazolidinones therefore resulted in (+)-propanols and (3*S*)-isoflavans and (4*R*,5*S*)-(−)-*N*-phenylacetylimidazolidinones in (−)-propanols and (3*R*)-isoflavans. The signs of rotation of the oxygenated isoflavans (**20** and **21**) are in agreement with those of (3*R*)- and (3*S*)-2′,7-di-*O*-methylvestitol, respectively, obtained by hydrogenolysis of (6a*R*, 11a*R*)-(−)-homopterocarpin and (6a*S*, 11a*S*)-(+)-medicarpin.[12]

We have thus developed the first and highly efficient enantioselective route towards isoflavans. The potential of this protocol in the chemistry of the isoflavonoids is evident and it should contribute substantially in establishing chirality also at C-2 and C-4 of the 3-phenylchroman system in the full range of isoflavonoids.



Scheme 1 *Reagents and conditions*: i, BuLi (1.0 equiv.), Ph_3CH (catalytic), THF, 0 °C; then Me_3SiCl, −78 °C → room temp., ii, tetrabutylammonium fluoride, MeCN, room temp., iii, LICA (1.4 equiv.), 2-*O*-methoxymethylbenzyl bromide (1.5 equiv.), THF–CH_2Cl_2, −40 °C; iv, $LiAlH_4$ (2 equiv. THF solution), −24 °C → room temp.; v, 3 mol dm^{-3} HCl, MeOH, reflux; vi, BrsCl (1.05 equiv.), pyridine (1.5 equiv.), CH_2Cl_2 room temp., then NaH (excess), 0 °C → room temp. vii, PPh_3 (9 equiv.), diethyl azodicarboxylate (4.5 equiv.), THF, room temp.

Table 1 Products[a] of the reactions of *N*-acylimidazolidinones **7–9**

N-Acylimid-azolidinone (Yield %)	Alkylation product (Yield %)	Propanol[b] (Yield %)	Hydrolysis product (Yield %)	Isoflavan (Yield %)	e.e.[c] (%)	*R/S*
7a (91)	**10a** (90)	**13a** (84)	**16a** (97)	**19a** (92)	96	*S*
7b (90)	**10b** (86)	**13b** (77)	**16b** (98)	**19b** (87)	94	*R*
8a (75)	**11a** (84)	**14a** (89)	**17a** (94)	**20a** (85)	99	*S*
8b (80)	**11b** (92)	**14b** (85)	**17b** (85)	**20b** (80)	99	*R*
9a (72)	**12a** (88)	**15a** (90)	**18a** (85)	**21a** (73)	98	*S*
9b (73)	**12b** (90)	**15b** (76)	**18b** (95)	**21b** (75)	99	*R*

[a] All new compounds were fully characterized by spectroscopic methods, elemental composition being established by accurate mass measurement or microanalysis. [b] Propanols **13a**, **14a** and **15a** gave positive and **13b**, **14b** and **15b** gave negative $[\alpha]_D$ values. [c] E.e. values were determined by HPLC using a chiral adenine glycoprotein column with 18–20% isopropanol in a pH 7 phosphate buffer as eluent.

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