The first enantioselective synthesis of *trans*- and *cis*-dihydroflavonols

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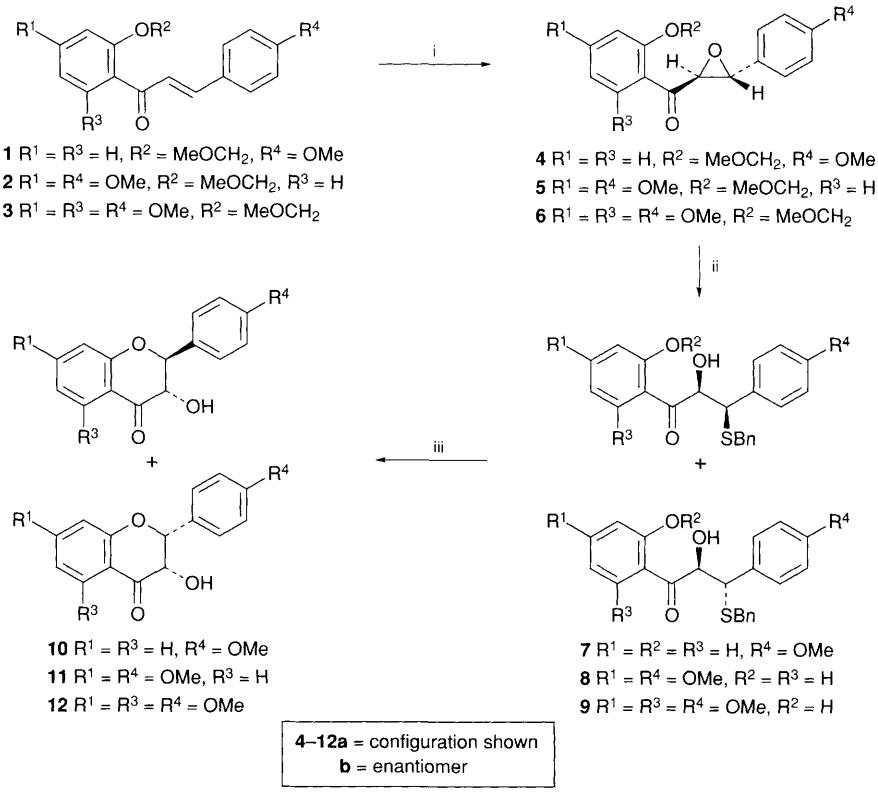
Epoxidation of a series of polyoxygenated chalcones with H_2O_2 in the presence of poly(α-amino acid) catalysts, followed by Lewis acid-catalysed phenylmethanethiol ring-opening and cyclization, afforded *trans*- and *cis*-dihydroflavonols in moderate to high enantiomeric excess and yield.

Dihydroflavonols occur widely in the plant kingdom.[1] Apart from exhibiting fungistatic properties they are used as pharmaceutical and industrial chemicals and are important in both wood preservation and in the paper industry.[2] In addition, these compounds serve as incipient electrophiles in the semi-synthesis of oligomeric proanthocyanidins[3] natural products that are increasingly being recognized for their profound health-promoting effects in tea, fruit juices and red wine (the 'French paradox'). Owing to the absence of synthetically and naturally occurring flavonoid electrophiles with 2,3-*cis* stereochemistry which might be used as precursors to polymeric proanthocyanidins with *e.g.* epicatechin chain extender units, we employed the versatile chemistry of α,β-epoxy ketones to address the issue of stereocontrol at either C-2 or C-3 in the enantioselective synthesis of 2,3-*trans*- and -*cis*-dihydroflavonols.

Thus, epoxidation of (*E*)-chalcones **1–3** ($J_{\alpha,\beta}$ 15.8–16.0 Hz) at *ca* 20 °C with hydrogen peroxide in the triphasic system consisting of aqueous NaOH–poly-L- or -D-alanine–CCl_4 afforded the (−)-*trans*-epoxides **4a**, **5a** and **6a** ($J_{\alpha,\beta}$ 1.5–2.2 Hz) and (+)-*trans*-epoxides **4b**, **5b** and **6b** ($J_{\alpha,\beta}$ 1.5–2.2 Hz) respectively in high yields (97–99%).[4,5] The (−)-chalcone oxiranes exhibited higher optical purities (70–84% ee) than the (+)-isomers (53–74% ee) due to the considerably higher purity of natural L-alanine {$[\alpha]_D^{25}$ +12.57 (*c*, 5.695 in 1 M HCl)} *versus* synthetic D-alanine {$[\alpha]_D^{25}$ −9.71 (*c*, 1.363 in 6 M HCl)} (Table 1). This was reflected in the optical purity of the poly-L-{$[\alpha]_D^{25}$ −142.8 (*c*, 0.671 in CF_3CO_2H)} and poly-D-alanine {$[\alpha]_D^{25}$ +102.0 (*c*, 0.314 in CF_3CO_2H)} catalysts. Subsequent deprotection and cyclization of epoxide **5a** using $MgBr_2$–Et_2O,[6] yielded (2*R*,3*R*)-4′,7-dimethoxydihydroflavonol **11a** ($^3J_{2,3}$ 12.0 Hz) in low yield (20%) but high ee (78%). Similar results were obtained with the Lewis acid BF_3–Et_2O.[7]

Since the low yields may be attributed to cleavage of the highly reactive oxirane functionality prior to deprotection, we attempted to increase dihydroflavonol yields *via* initial opening of the epoxide by an external nucleophile, followed by deprotection and cyclization. The Lewis acid, tin tetrachloride ($SnCl_4$), in the presence of the powerful nucleophile phenylmethanethiol (BnSH) was utilized for selective cleavage of the C_β–O bond of the oxirane functionality (−20 °C) and subsequent removal of the methoxymethyl group (0 °C) to give the dihydrochalcones **7–9** (86–93%: *syn*:*anti* *ca.* 2.3:1). Selective crystallization and X-ray crystallographic analysis of (2*S*,3*S*)-*syn*-2,2′-dihydroxy-3-benzylsulfanyldihydrochalcone **9a** confirmed the predominant *syn*-orientations of products



1 $R^1 = R^3 = H$, $R^2 = MeOCH_2$, $R^4 = OMe$
2 $R^1 = R^4 = OMe$, $R^2 = MeOCH_2$, $R^3 = H$
3 $R^1 = R^3 = R^4 = OMe$, $R^2 = MeOCH_2$

4 $R^1 = R^3 = H$, $R^2 = MeOCH_2$, $R^4 = OMe$
5 $R^1 = R^4 = OMe$, $R^2 = MeOCH_2$, $R^3 = H$
6 $R^1 = R^3 = R^4 = OMe$, $R^2 = MeOCH_2$

10 $R^1 = R^3 = H$, $R^4 = OMe$
11 $R^1 = R^4 = OMe$, $R^3 = H$
12 $R^1 = R^3 = R^4 = OMe$

7 $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
8 $R^1 = R^4 = OMe$, $R^2 = R^3 = H$
9 $R^1 = R^3 = R^4 = OMe$, $R^2 = H$

4–12a = configuration shown
b = enantiomer

Scheme 1 *Reagents and conditions*: i, 30% H_2O_2 : 6 M NaOH 1 : 0.32 (v/v), poly-D- or poly-L-alanine : chalcone 1 : 1 (m/m), CCl_4, room temp., 24 H; ii, BnSH (4 equiv.), $SnCl_4$ (0.2 equiv.), −20 to 0 °C; iii, $AgBF_4$ (5 equiv.), CH_2Cl_2, 0 °C

Table 1 Intermediate products[a] in the conversion of chalcones **1–3** to dihydroflavonols **10–12**

Chalcone Epoxide	Yield (%)	ee[b] (%)	Dihydro-chalcone	Yield (%)	Dihydro-flavonols	Yield (%)	Ee[c] (%)	*trans* : *cis*
4a	99	84	**7a**	86	**10a**	86	83	93 : 7
4b	98	69	**7b**	90	**10b**	83	69	94 : 6
5a	98	86	**8a**	93	**11a**	71	84	79 : 21
5b	98	74	**8b**	90	**11b**	72	75	83 : 17
6a	97	70	**9a**	89	**12a**	65	69	78 : 22
6b	97	53	**9b**	89	**12b**	64	53	84 : 16

[a] All new compounds were fully characterized by spectroscopic methods, elemental composition being established by accurate mass measurement or microanalysis. [b] Determined with $Pr(hfc)_3$ as chiral shift reagent. [c] Determined with $Eu(tfc)_3$ as chiral shift reagent.

7–9.[8] Owing to the thiophilicity of tin and the highly polarised tin–chloride bonds, and active Lewis acid species, *i.e.* $Cl_xSn(SBn)_y$,[9] presumably permits delivery of the thiolate moiety intramolecularly *via* an S_N2 mechanism. Intermolecular S_N2 attack by BnSH may account for *anti*-product formation.

Treatment of α,2′-dihydroxy-β-benzylsulfanyldihydrochalcones **7–9** with the thiophilic Lewis acid silver tetrafluoroborate ($AgBF_4$)[10] in CH_2Cl_2 at 0 °C gave the 2,3-*trans*- and, albeit in low yields, for the first time also 2,3-*cis*-dihydroflavonols ($^3J_{2,3}$ 6.1 Hz) in good yields (64–86%) without loss of optical purity. Although either an S_N1 or S_N2 mechanism may explain the formation of the 2,3-*trans*- and -*cis*-dihydroflavonols **10–12**, the mechanism remains obscure and is currently being investigated more fully. The absolute stereochemistry of the predominant enantiomers of the *trans*-dihydroflavonols was accessed by circular dichroism (CD)[11] of the *O*-acetyl derivatives. The absolute configuration of the *cis*-dihydroflavonols accompanying the *trans*-isomers then follows from the fact that optical integrity was preserved in the transformation epoxide → dihydrochalcone → *cis*-dihydroflavonol.

We have thus developed the first enantioselective route towards both *trans*- and *cis*-dihydroflavonols. This protocol should contribute substantially towards a general synthesis of oligomeric proanthocyanidins with 2,3-*trans*- and, for the first time, also 2,3-*cis*-flavan-3-ol chain extender units in order to assess the physical and chemical properties that determine their health promoting properties in the human diet.

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