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Stereoselective synthesis of flavonoids. Part 4.[1,2] *Trans*- and *cis*-dihydroflavonols

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Abstract: Epoxidation of a series of poly-oxygenated chalcones with H_2O_2 in the presence of poly-α-aminoacids yielded chiral aromatic oxygenated oxiranes in moderate to high optical yields. Lewis acid-catalysed phenylmethanethiol ringopening of the epoxide functionality and subsequent formation of the pyranone heterocycle, afforded *trans*- and *cis*-dihydroflavonols in moderate to high enantiomeric excess and yield. © 1997 Elsevier Science Ltd.

Flavonoids represent one of the most abundant and ubiquitous groups of natural products.[3] These compounds have attracted considerable interest over the last few years on account of their biological properties[4], e.g. their presumed health promoting effects in the human diet (*cf.* the 'French paradox'). Although important progress has been made in the isolation and identification of oligomeric flavanoids, progress in the study of condensed tannins is still restricted by the limited availability of monomeric precursors exhibiting the aromatic oxygenation patterns of naturally occurring proanthocyanidins. Versatility in the semi-synthetic approach to these complex phenolics is further hampered by the predominant natural occurrence of synthetically useful flavanoid monomers exhibiting only (2*R*,3*R*)-2,3-*trans*-stereochemistry.[5] Owing to the potential of dihydroflavonols as incipient electrophilic, and following two successive reduction steps also as nucleophilic synthons in the semi-synthesis of oligomeric proanthocyanidins, we recently[6] employed the versatile chemistry of α,β-epoxy ketones to target enantiomerically enriched 2,3-*trans*- and the hitherto elusive 2,3-*cis*-dihydroflavonols. These results prompted extension of the protocol to a series of epoxides exhibiting the aromatic oxygenation patterns usually encountered in flavonoid chemistry. We thus now disclose detailed results of relevance to the synthesis of poly-oxygenated chalcone epoxides and their use as chirons for enantiomerically enriched dihydroflavonols.

Thus, the requisite *trans*-(E)-chalcone methyl ethers **1-5** ($J_{\alpha,\beta}$ 15.8 - 16.0 Hz) were prepared as described[1] previously. Subsequent treatment with hydrogen peroxide in the triphase system, aqueous NaOH/ poly-L- or -D-alanine/ CCl_4, afforded the (-)-*trans*- **6a-10a** ($\alpha R,\beta S$) and (+)-*trans*-epoxides **6b-10b** ($\alpha S,\beta R$) ($J_{\alpha,\beta}$=1.5-2.2 Hz), respectively, in high yields (79-99%)(Scheme 1, Table 1).[1,7-9] These conversions proceeded slowly with reaction times varying from 36 to 96 hours. The (-)-chalcone oxiranes exhibited higher optical purities (49-86% ee) than the (+)-isomers (47-75% ee) due to the higher purity of the natural L-alanine {$[\alpha]_D^{25}$ +12.57(*c*, 5.695 in 1M HCl)} *versus* synthetic D-alanine {$[\alpha]_D^{25}$ -9.72 (*c*, 1.363 in 6M HCl)}, which was reflected in the optical purity of the poly-L- {$[\alpha]_D^{25}$ -142.8 (*c*, 0.671 in CF_3COOH)} and poly-D-alanine- {$[\alpha]_D^{25}$ +102.0 (*c*, 0.314 in CF_3COOH)} catalysts (Table 1).[1] The enantiomeric purity of the epoxides was determined by ^1H NMR using $Pr(hfc)_3$ as chiral shift reagent and the absolute stereochemistry assigned by comparison of CD data with those of authentic samples.[1,10] The CD curves of the (-)-*trans*-chalcone oxiranes **6a-10a** exhibited high amplitude sequential negative and positive Cotton effects, respectively, in the 290-310 nm (n,π^* transition) and 240-264 nm (π,π^* transition) regions, with the signs of these Cotton effects being reversed for the (+)-*trans*-epoxychalcones **6b-10b** (*cf* Figure 1 for comparison of epoxides **7a** and **7b**).

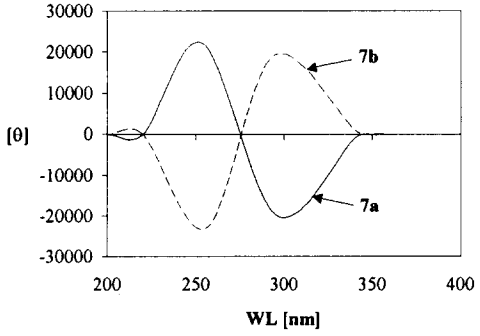
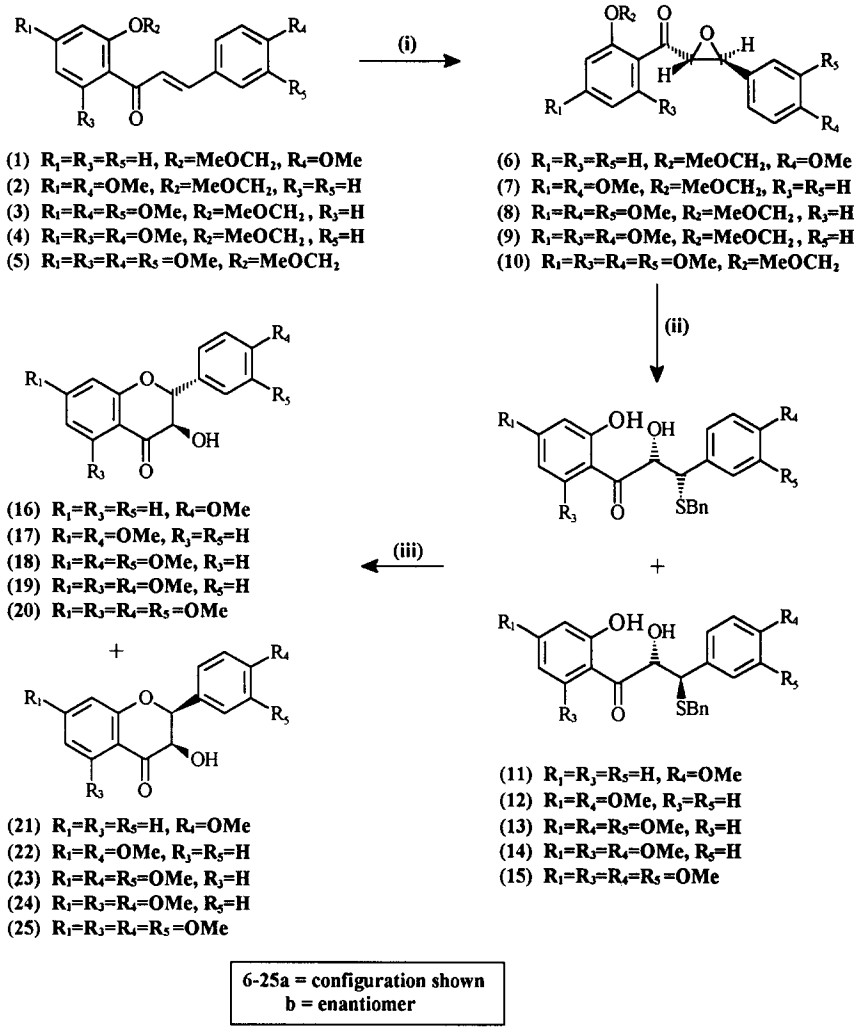


Figure 1 CD curves of the (-)-(αR, βS)-**7a** and (+)-(αS, βR)-**7b** chalcone epoxides.

Initial attempts towards cyclization of the chalcone epoxide **7a** to the corresponding (2*R*,3*R*)-2,3-*trans*-**17a** and (2*S*,3*R*)-2,3-*cis*-dihydroflavonols **22a** using acid catalysis[1], were hampered by two major difficulties, i.e. aroyl migration with formation of the artefact, 4',7-dimethoxyisoflavone **27** in 48% yield, and epimerization/racemization of the thermodynamically less stable (2*S*,3*R*)-2,3-*cis*-4',7-dimethoxydihydroflavonol **22a** (Scheme 2). This resulted in low yield (38%) and ee (50%) of only the (2*R*,3*R*)-2,3-*trans*-dihydroflavonol **17a** ($^3J_{2,3}$ 12.0 Hz). Formation of the isoflavone **27** may be attributed to acid-catalyzed cleavage of the highly reactive oxirane functionality prior to deprotection (Scheme 2).

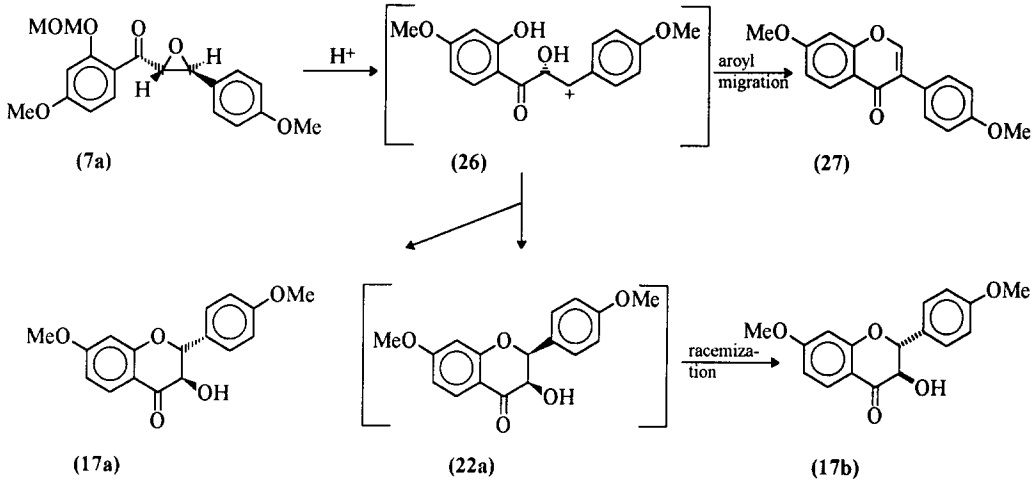


Scheme 1 *Reagents and conditions*: i 30% H_2O_2 : 6 M NaOH 1:0.32 (v/v), poly-L- or poly-D-alanine : chalcone 1:1 (m/m), CCl_4, room temp., 36-96h; ii, BnSH (4 equiv.), $SnCl_4$ (0.2 equiv.), -20 to 0°C; iii, $AgBF_4$ (5 equiv.), CH_2Cl_2, 0°C.

Table 1 Intermediate products in the conversion of chalcones **1-5** to dihydroflavonols **16-25**

Chalcone Epoxide	Yield (%)	ee[a] (%)	Dihydro-chalcone	Yield (%)	Dihydro-flavonol	Yield (%)	ee[b] (%)	*trans:cis*
6a	99	84	**11a**	86	**16a/21a**	86	83	93:7
6b	98	69	**11b**	90	**16b/21b**	83	69	94:6
7a	98	86	**12a**	93	**17a/22a**	71	84	79:21
7b	98	74	**12b**	90	**17b/22b**	72	75	83:17
8a	99	67	**13a**	89	**18a/23a**	81	68	85:15
8b	98	58	**13b**	91	**18b/23b**	79	58	86:14
9a	97	70	**14a**	89	**19a/24a**	65	69	78:22
9b	97	53	**14b**	89	**19b/24b**	64	53	84:16
10a	79	49	**15a**	91	**20a/25a**	61	47	82:18
10b	76	49	**15b**	88	**20b/25b**	63	44	80:20

[a] Determined with $Pr(hfc)_3$ as chiral shift reagent. [b] Determined with $Eu(tfc)_3$ as chiral shift reagent.



Scheme 2 Proposed route to the formation of dihydroflavonol **17a** and isoflavone **27**.

Lewis acids such as $MgBr_2$ and BF_3-OEt_2 smoothly cleave alkoxymethyl ethers and acetals under mild conditions.[11,12] It was thus anticipated that deprotection of the 2'-*O*-methoxymethyl group with concomitant cyclization would enhance the preservation of optical integrity. Treatment of (-)-(α*R*,β*S*)-chalcone epoxide **7a** (86% ee) with $MgBr_2$-etherate indeed afforded (2*R*,3*R*)-2,3-*trans*-4',7-dimethoxydihydroflavonol **17a** with virtually no loss of optical purity but in a modest 20% chemical yield, as well as 4',7-dimethoxyisoflavone **27** (4%). Similar results were obtained with BF_3-OEt_2.[13] In order to circumvent the problem of isoflavone formation, we investigated methods aimed at the initial nucleophilic opening of the oxirane functionality, followed by deprotection and cyclization. Owing to the excellent nucleophilic and nucleofugic properties of mercaptans, evaluation of thiols in the presence of Lewis acids resulted in the selection of the phenylmethanethiol (BnSH)-tin(iv) chloride ($SnCl_4$)[14] system as the reagent of choice for oxirane cleavage. Thus, treatment of the series of methoxymethylchalcone epoxides **6a/b-10a/b** with BnSH/$SnCl_4$ selectively cleaved the C_β-O bond of the oxirane functionality at -20°C and effectively deprotected the methoxymethyl group at 0°C to give the corresponding α,2'-dihydroxy-β-benzylsulfanyldihydrochalcones **11a/b-15a/b** as diastereomeric mixtures (*syn*:*anti ca.* 2.3:1) in 86-93% yield. The ^{1}H NMR data of the dihydrochalcones **11a/b-15a/b** were compatible with either a β-substituted α-hydroxy- or an α-substituted β-hydroxydihydrochalcone. Deuterium exchange, however, proved that the OH-group is on the carbon bearing the proton resonating at δ 5.12-5.40, i.e. the chemical shift of the α-hydrogen in α-hydroxydihydrochalcones[2].

Treatment of α-hydroxy-β-benzylsulfanyldihydrochalcones **11a/b-15a/b** with the thiophilic Lewis acid, silver tetrafluoroborate ($AgBF_4$)[15] in CH_2Cl_2 at 0°C, gave the 2,3-*trans*-dihydroflavonols **16-20** ($^3J_{2,3}$ 12.0 Hz) in good yields (48-80%) and, albeit in low proportions (5-15%), for the first time also the 2,3-*cis*-analogues **21-25** ($^3J_{2,3}$ 6.1 Hz)(Table 1). Despite the fact that the substituted dihydrochalcones **11-15** exhibited a high aptitude towards aroyl migration due to the *o*- and/or *o*-/*p*-hydroxylation of their A-rings, isoflavone formation (10-25%) was restricted to analogues **14** and **15**.

Assessment of optical purity of the dihydroflavonols was done by ^{1}H NMR using $Eu(hfc)_3$ as chiral shift reagent. These results indicated that, within standard experimental deviation, the dihydroflavonols exhibited the same enantiopurities than the parent epoxides, thus unequivocally confirming the fact that optical integrity was being preserved in the transformation of the epoxides **6a/b-10a/b** to the corresponding *trans*-**16a/b-20a/b** and *cis*-dihydroflavonols **21a/b-25a/b** (Table 1). The absolute stereochemistry of the 2,3-*trans*-derivatives **19a** and **20a** was assigned by comparison of their CD data with those of the same derivatives of authentic dihydroquercetin[16,17] and dihydrokaempferol.[18-21] The absolute configuration of the remaining *trans*-isomers **16a-18a** was then assigned assuming that the stereochemistry of the reactions leading to those compounds is the same as for products **19a-20a**. The mirror-image relationship of the two sets of *trans*-isomers (Figure 2), confirmed the enantiomeric connection between these series and hence proof of the 2*S*,3*S*

absolute configuration for analogues **16b-20b**. The (2*R*,3*R*)-2,3-*trans*-dihydroflavonols **16a-20a** exhibited positive and negative Cotton effects, respectively, in the 330-340 nm (n,π^* transition) and 285-315 nm (π,π^* transition) regions, with these Cotton effects being reversed in these regions for the (2*S*,3*S*)-2,3-*trans*-isomers **16b-20b** (*cf* Figure 2 for comparison of **17a** and **17b**). The *cis*-dihydroflavonols **21a/b-25ab** accompanying the corresponding *trans*-isomers exhibited negative (340-345 nm) and positive (295-320nm) Cotton effects for the (2*S*,3*R*)-2,3-*cis* analogues **21a-25a** and opposite sequential positive and negative Cotton effects for the (2*R*,3*S*)-2,3-*cis* isomers **21b-25b** (*cf* Figure 3 for comparison of **22a** and **22b**). Their absolute configurations then follow from the fact that optical integrity was preserved at C-3 in the transformation epoxide → dihydrochalcone → *cis*-dihydroflavonol.

The data for the 2,3-*cis*-dihydroflavonols respesent the first systematic compilation of the circular dichroic properties of this rare class of C6-C3-C6-type polyphenols[22-24] and should hence contribute substantially towards elucidation of the absolute configuration of naturally occurring analogues.

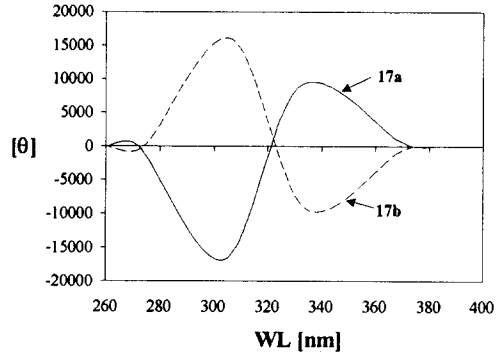


Figure 2: CD curves of the (2R,3R)-**17a** and (2S,3S)-**17b** -2,3-*trans*-dihydroflavonols

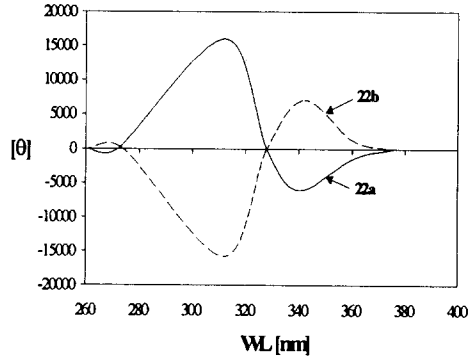


Figure 3: CD curves of the (2S,3R)-**22a** and (2R,3S)-**22b** -2,3-*cis*-dihydroflavonols

We have thus developed the first enantioselective route towards both *trans*- and *cis*-dihydroflavonols. These results demonstrate the considerable potential of this protocol especially in view of the amount of research[25] focussing on the development of improved asymmetric epoxidation of enones. These results should contribute significantly towards a general synthesis of oligomeric proanthocyanidins with 2,3-*trans* and also 2,3-*cis*-flavanoid chain extender units in order to assess the physical and chemical properties that determine their health promoting properties in the human diet.

EXPERIMENTAL

^{1}H NMR spectra were recorded at ambient temperature on a Bruker AM-300 spectrometer for solutions in $CDCl_3$ with solvent as internal standard. High and low resolution EI-mass spectra were obtained on a VG70-70E mass spectrometer. Melting points were measured on a Reichert hot-stage apparatus and are uncorrected. CD measurements were obtained for solutions in MeOH on a Jasco J-710 spectropolarimerer. Thin layer chromatography (TLC) was preformed on DC-Alufolien Kieselgel 60 F_{254} (0.25) plates with visualisation by ultraviolet light and/or formaldehyde-sulphuric acid spray. Preparative plates (PLC) [Kieselgel PF_{254} (1.0mm)] were air-dried and used without prior activation. Flash column chromatography (FLC) was done on Merck Kieselgel 60 (230-400 mesh) under a positive pressure by means of compressed nitrogen. The chalcones **1-5** and chalcone epoxides **6a/b-10a/b** were prepared according to standard procedures.[7]

General procedure for preparation of α,2'-dihydroxy-β-benzylsulfanyldihydrochalcones 11a/b-15a/b

To a dry solution of the chalcone epoxides **6-10** (0.10-0.35 mmol) in CH_2Cl_2 (1-3ml) was added benzylmercaptan (0.4-1.4 mmol, 4 equiv.) and the mixture was stirred at -20°C for 10 min. A solution of $SnCl_4$ (0.02-0.07 mmol, 0.2 equiv.) in CH_2Cl_2 (0.5ml) was added and stirring was continued for 10-16h (progress was monitored by TLC) at 0°C. The product was directly purified by PLC (hexane-benzene-acetone 5:4:1) to give a diastereomeric mixture of the desired dihydrochalcones **11-15.**

4-Methoxy-α,2'-dihydroxy-β-benzylsulfanyldihydrochalcone **11a/b** (mixture of *syn* and *anti* isomers). R_f 0.50 (hexane-benzene-acetone 5:4:1); ^{1}H NMR δ 11.50* (s, 2'-OH), 11.18 (s, 2'-OH), 7.50-7.43 (m, Ph), 7.39-7.23 (m, Ph), 7.14 (dd, J 8.0 and 2.0, Ph), 7.05-6.85 (m, Ph), 6.80-6.70 (m, Ph), 5.27 (dd, J 6.8 and 2.5, H-α), 5.25* (dd, J 8.0 and 2.5, H-α), 4.04 (d, J 2.5, H-β), 3.93* (d, J 8.0, α-OH), 3.92* (d, J 2.5, H-β), 3.81*, 3.76 (2 x s, 2 x OMe), 3.76 (d, J 6.8, α-OH), 3.70 (d, J 14.0) and 3.48 (d, J 14.0)(S$\underline{CH_2}$Ph), 3.45* (d, J 14.0) and 3.29* (d, J 14.0)(S$\underline{CH_2}$Ph); *m/z* 394 (M^+, 0%), 253(26), 243(48), 153(5), 121(100) (Found M^+, 394.1229. $C_{23}H_{22}O_4S$ requires M^+, 394.1239).

*Major diastereoisomer.

4,4'-Dimethoxy-α,2'-dihydroxy-β-benzylsulfanyldihydrochalcone **12a/b** (mixture of *syn* and *anti* isomers). R_f 0.41 (hexane-benzene-acetone 5:4:1); ^{1}H NMR δ 11.98* (s, 2'-OH), 11.68 (s, 2'-OH), 7.34 (d, J 8.8, H-2,6), 7.25* (d, J 8.8, H-2,6), 7.08-6.94 (m, 2 x S$\underline{CH_2}$Ph), 6.87* (d, J 8.8, H-3,5), 6.75 (d, J 8.8, H-3,5), 6.44* (d, J 2.5, H-3'), 6.38 (d, J 2.5, H-3'), 6.28* (dd, J 9.0 and 2.5, H-5'), 6.24 (dd, J 9.0 and 2.5, H-5'), 5.17 (dd, J 7.9 and 3.0, H-α), 5.14* (dd, J 7.9 and 3.0, H-α), 3.98 (d, J 3.0, H-β), 3.95* (d, J 7.9, α-OH), 3.88* (d, J 3.0, H-β), 3.86*, 3.84, 3.80*, 3.79 (4 x s, 4 x OMe), 3.70 (d, J 13.2) and 3.48 (d, J 13.2)(S$\underline{CH_2}$Ph), 3.48 (d, J 7.9, α-

OH), 3.43* (d, J 13.2) and 3.27* (d, J 13.2)(S$\underline{CH_2}$Ph); *m/z* 424 (M^+, 0%), 301(25), 283(16), 243(31), 181(4), 151(100), 121(22) (Found M^+, 424.1340. $C_{24}H_{24}O_5S$ requires M^+, 424.1345).
*Major diastereoisomer.

3,4,4'-Trimethoxy-α,2'-dihydroxy-β-benzylsulfanyldihydrochalcone **13a/b** (mixture of *syn* and *anti* isomers). R_f 0.24 (hexane-benzene-acetone 5:4:1); ^1H NMR δ 11.98* (s, 2'-OH), 11.68 (s, 2'-OH), 7.30-7.25 (m, Ph), 6.98-7.14 (m, Ph), 6.83 (dd, J 8.0 and 2.5, H-6), 6.76 (d, J 8.0, H-5), 6.73 (d, J 2.5, H-2), 6.67 (d, J 8.0, H-5), 6.49 (dd, J 8.0 and 2.5, H-6), 6.43* (d, J 2.5, H-3'), 6.38 (d, J 2.5, H-3'), 6.30* (dd, J 9.0 and 2.5, H-5'), 6.25 (dd, J 9.0 and 2.5, H-5'), 5.18* (dd, J 7.8 and 3.0, H-α), 5.18 (dd, J 7.8 and 3.0, H-α), 3.98 (d, J 3.0, H-β), 3.97* (d, J 7.8, α-OH), 3.87* (d, J 3.0, H-β), 3.85*, 3.83, 3.76 (3 x s, 6 x OMe), 3.70 (d, J 14.0) and 3.46 (d, J 14.0) (S$\underline{CH_2}$Ph), 3.48* (d, J 14.0) and 3.33* (d, J 14.0) (S$\underline{CH_2}$Ph), 3.52 (d, J 7.8, α-OH); *m/z* 454 (M^+, 0%), 331(24), 313(37), 273(25), 181(6), 151(100) (Found M^+, 454.1446. $C_{25}H_{26}O_6S$ requires M^+, 454.1450).
*Major diastereoisomer.

4,4'6'-Trimethoxy-α,2'-dihydroxy-β-benzylsulfanyldihydrochalcone **14a/b** (mixture of *syn* and *anti* isomers). R_f 0.40 (hexane-benzene-acetone 5:4:1); ^1H NMR δ 13.03* (s, 2'-OH), 12.70 (s, 2'-OH), 7.34* (d, J 9.0, H-2,6), 7.25-6.90 (m, Ph), 6.87* (d, J 9.0, H-3,5), 6.77 (d, J 9.0, H-3,5), 6.11* (d, J 2.5, H-3'), 6.04 (d, J 2.5, H-3'), 5.76 (d, J 2.5, H-5'), 5.75* (d, J 2.5, H-5'), 5.38 (dd, J 9.0 and 2.1, H-α), 5.32* (dd, J 9.0 and 2.1, H-α), 4.30* (d, J 8.0, α-OH), 4.06 (d, J 2.0, H-β), 3.79* (d, J 2.0, H-β), 3.64 (d, J 9.0, α-OH), 3.86, 3.83, 3.81, 3.77, 3.55, 3.37 (6 x s, 6 x OMe), 3.57 (d, J 14.0) and 3.18 (d, J 14.0) (S$\underline{CH_2}$Ph), 3.45* (d, J 14.0) and 3.24* (d, J 14.0) (S$\underline{CH_2}$Ph); *m/z* 454 (M^+, 0%), 331(45), 313(100), 303(14), 243(9), 209(25), 181(53), 155(13), 149(15), 124(30), 121(94) (Found M^+, 454.1445. $C_{25}H_{26}O_6S$ requires M^+, 454.1450).
*Major diastereoisomer.

3,4,4'6'-Trimethoxy-α,2'-dihydroxy-β-benzylsulfanyldihydrochalcone **15a/b** (mixture of *syn* and *anti* isomers). R_f 0.21 (hexane-benzene-acetone 5:4:1); ^1H NMR δ 13.04* (s, 2'-OH), 12.66 (s, 2'-OH), 7.31-7.04 (m, Ph), 6.96-6.77 (m, Ph), 6.70 (d, J 8.5, H-5), 6.55 (dd, J 8.5 and 2.0, H-6), 6.12* (d, J 2.2, H-3'), 6.03 (d, J 2.5, H-3'), 5.78 (d, J 2.5, H-5'), 5.76* (d, J 2.0, H-5'), 5.40 (dd, J 8.5 and 2.0, H-α), 5.35* (dd, J 8.0 and 2.0, H-α), 4.32* (d, J 7.5, α-OH), 4.05 (d, J 2.5, H-β), 3.86*, 3.85, 3.82, 3.80, 3.55*, 3.40 (6 x s, 8 x OMe), 3.78* (d, J 2.0, H-β), 3.72 (d, J 7.5, α-OH), 3.57 (d, J 14.0) and 3.21 (d, J 14.0) (S$\underline{CH_2}$Ph), 3.44* (d, J 14.0) and 3.28* (d, J 14.0) (S$\underline{CH_2}$Ph); *m/z* 484 (M^+, 0%), 361(34), 343(38), 273(24), 211(5), 181(100), 151(57), 124(18) (Found M^+, 484.1551. $C_{26}H_{28}O_7S$ requires M^+, 484.1556).
*Major diastereoisomer.

General procedure for conversion of dihydrochalcones 11a/b-15a/b into dihydroflavonols 16a/b-25a/b.

A solution of the dihydrochalcone (0.05-0.18 mmol) **11a/b-15a/b** in CH_2Cl_2 (5-10ml) was treated with $AgBF_4$ (0.25-0.9mmol, 5 equiv) at 0°C for 12 h. Preparative PLC (hexane-benzene-acetone 5:4:1) afforded the corresponding 2,3-*trans*- and 2,3-*cis*-dihydroflavonol derivatives **16a/b-25a/b.**

(2R,3R)-2,3-trans-4'-methoxydihydroflavonol **16a**[26] Mp 167°C Rf (hexane-benzene-acetone 5:4:1); ^{1}H NMR δ 7.91 (dd, J 7.8 and 1.8, H-5), 7.54 (ddd, J 7.8, 7.8 and 1.8, H-7), 7.50 (d, J 8.8, H-2',6'), 7.09 (ddd, J 7.8, 7.8 and 1.1, H-6), 7.02 (dd, J 7.8 and 1.1, H-8), 6.98 (d, J 8.8, H-3'5'), 5.07 (d, J 12.5, H-2), 4.65 (dd, J 12.5 and 2.0, H-3), 3.83 (s, OMe), 3.64 (d, J 2.0, 3-OH); *m/z* 270 (M^+, 12%), 241(21), 150(54), 135(12), 133(18), 121(100), 120(5), 107(6) (Found M^+, 270.08924. Calculated for $C_{16}H_{14}O_4$, 270.08912) CD: $\Delta\varepsilon_{max}[\lambda(nm)] = +8.8x10^3$ (340), $-14.0x10^3$ (310).

(2S,3S)-2,3-trans-4'-methoxydihydroflavonol **16b** mp 167°C CD: $\Delta\varepsilon_{max}[\lambda(nm)] = -9.0x10^3$ (340), $+14.4x10^3$ (312); The R_f, ^{1}H NMR and MS data corresponded to those reported for **16a**.

(2S,3R)-2,3-cis-4'-methoxydihydroflavonol **21a** R_f 0.37 (hexane-benzene-acetone 5:4:1); ^{1}H NMR (3-*O*-acetyl derivative) δ 7.89 (dd, J 7.8 and 1.9, H-5), 7.52 (ddd, J 7.8, 7.8 and 1.9, H-7), 7.34 (d, J 9.0, H-2',6'), 7.05 (ddd, J 7.8, 7.8 and 1.1, H-6), 7.04 (dd, J 7.8 and 1.1, H-8), 6.86 (d, J 9.0, H-3',5'), 5.81 (d, J 3.8, H-2), 5.60 (d, J 3.8, H-3), 3.77 (s, OMe), 2.04 (s, OAc); *m/z* 270 (M^+, 19%), 241(29), 150(23), 135(43), 133(19), 121(100), 120(6), 107(21) (Found M^+, 270.08916. $C_{16}H_{14}O_4$ requires M^+, 270.08912) CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ $-5.8x10^3$ (344), $+16.0x10^3$ (316).

(2R,3S)-2,3-cis-4'-methoxydihydroflavonol **21b** CD: $\Delta\varepsilon_{max}[\lambda(nm)] = +7.0x10^3$ (344), $-14.1x10^3$ (318); The R_f, ^{1}H NMR and MS data corresponded to those reported for **21a.**

(2R,3R)-2,3-trans-4',7-dimethoxydihydroflavonol **17a**[27] mp 124°C R_f 0.24 (hexane-benzene-acetone 5:4:1); ^{1}H NMR δ 7.83 (d, J 8.8, H-5), 7.49 (d, J 9.0, H-2',6'), 6.98 (d, J 9.0, H-3',5'), 6.65 (dd, J 8.8 and 2.5, H-6), 6.46 (d, J 2.5, H-8), 5.05 (d, J 12.0, H-2), 4.56 (dd, J 12.0 and 2.0, H-3), 3.83 (s, 2 x OMe), 3.70 (d, J 2.0, OH); *m/z* 300 (M^+, 19%), 271(71), 270(1), 243(7), 163(26), 151(100), 150(39), 135(16), 121(39), 107(8), 91(13) (Found M^+, 300.09921. $C_{17}H_{16}O_5$ requires M^+, 300.09967) CD: $\Delta\varepsilon_{max}[\lambda(nm)] = +9.0x10^3$ (332), $-16.8x10^3$ (304).

(2S,3S)-2,3-trans-4',7-dimethoxydihydroflavonol **17b** mp 126°C CD: $\Delta\varepsilon_{max}[\lambda(nm)] = -9.2x10^3$ (334), $+16.0x10^3$ (306); The R_f, ^{1}H NMR and MS data corresponded to those reported for **17a**.

(2S,3R)-2,3-cis-4',7-dimethoxydihydroflavonol **22a** mp 78°C R_f 0.21 (hexane-benzene-acetone 5:4:1); ^{1}H NMR δ 7.75 (d, J 8.5, H-5), 7.24 (d, J 9.0, H-2',6'), 6.79 (d, J 9.0, H-3',5'), 6.58 (dd, J 8.5 and 2.0, H-6), 6.45 (d, J 2.0, H-8), 5.72 (d, J 6.1, H-2), 4.86 (dd, J 6.1 and 3.0, H-3), 3.83, 3.74 (2 x s, 2 x OMe), 3.40 (d, J 3.0, OH); *m/z* 300 (M^+, 19%) 271(65), 270(6), 243(9), 163(45), 151(100), 150(61), 135(23), 121(34), 107(3), 91(23) (Found M^+, 300.09935. $C_{17}H_{16}O_5$ requires M^+, 300.09967) CD: $\Delta\varepsilon_{max}[\lambda(nm)] = -6.1x10^3$ (340), $+16.0x10^3$ (312).

(2R,3S)-2,3-cis-4',7-dimethoxydihydroflavonol **22b**; mp 80°C CD: $\Delta\varepsilon_{max}[\lambda(nm)] = +7.0x10^3$ (342), $-15.8x10^3$ (312); The R_f, ^{1}H NMR and MS data corresponded to those reported for **22a**.

(2R,3R)-2,3-trans-3',4',7-trimethoxydihydroflavonol **18a**[27] mp 141°C R_f 0.14 (hexane-benzene-acetone 5:4:1); ^{1}H NMR δ 7.83 (d, J 8.8, H-5), 7.11 (dd, J 8.0 and 2.1, H-6'), 7.08 (d, J 2.1, H-2'), 6.94 (d, J 8.0, H-5'), 6.56 (dd, J 8.8 and 2.1, H-6), 6.48 (d, J 2.1, H-8), 5.04 (d, J 12.0, H-2), 4.57 (d, J 12.0, H-3), 3.92, 3.90, 3.83 (3 x s, 3 OMe); *m/z* 330 (M^+, 34%), 301(58), 180(41), 163(25), 151(100), 150(4), 137(8), 107(7) (Found M^+, 330.11023. Calculated for $C_{18}H_{18}O_6$, 330.11022) CD: $\Delta\varepsilon_{max}[\lambda(nm)] = +9.6x10^3$ (332), $-18.0x10^3$ (304).

(2S,3S)-2,3-trans-3',4',7-trimethoxydihydroflavonol **18b** mp 142°C CD: $\Delta\varepsilon_{max}[\lambda(nm)] = -9.0x10^3$ (334), $+17.3x10^3$ (306); The R_f, ^{1}H NMR and MS data corresponded to those reported for **18a**.

(2S,3R)-2,3-cis-3',4',7-trimethoxydihydroflavonol **23a** mp (3-*O*-acetyl derivative) 115°C R_f 0.13 (hexane-benzene-acetone 5:4:1); ^{1}H NMR δ 7.75 (d, J 8.8, H-5), 6.89 (dd, J 8.8 and 2.0, H-6'), 6.85 (d, J 2.0, H-2'), 6.73 (d, J 8.8, H-5'), 6.57 (dd, J 8.8 and 2.0, H-6), 6.47 (d, J 2.0, H-8), 5.70 (d, J 6.5, H-2), 4.87 (dd, J 6.5 and 3.0, H-3), 3.83, 3.81, 3.77 (3 x s, 3 OMe), 3.40 (d, J 3.0, OH); *m/z* 330 (M^+, 23%), 301(45), 180(56), 163(12), 151(100), 150(8), 137(9), 107(12) (Found M^+, 330.11013. $C_{18}H_{18}O_6$ requires M^+, 330.11022) CD: $\Delta\varepsilon_{max}[\lambda(nm)] = -7.0x10^3$ (340), $+18.0x10^3$ (308).

(2R,3S)-2,3-cis-3',4',7-trimethoxydihydroflavonol **23b** mp (3-*O*-acetyl derivative) 114°C CD: $\Delta\varepsilon_{max}[\lambda(nm)] = +6.5x10^3$ (340), $-16.5x10^3$ (310); The R_f, ^{1}H NMR and MS data corresponded to those reported for **23a**.

(2R,3R)-2,3-trans-4',5,7-trimethoxydihydroflavonol **19a**[28] mp 143°C R_f 0.09 (hexane-benzene-acetone 5:4:1); ^{1}H NMR (3-*O*-acetyl derivative) δ 7.38 (d, J 8.8, H-2',6'), 6.93 (d, J 8.8, H-3',5'), 6.11 (d, J 2.0, H-6), 6.09 (d, J 2.0, H-8), 5.67 (d, J 12.0, H-2), 5.28 (d, J 12.0, H-3), 3.87, 3.83, 3.80 (3 x s, 3 x OMe), 2.01 (s, OAc); *m/z* 330 (M^+, 1%), 312(96), 311(40), 301(2), 283(18), 281(15), 266(20), 193(2), 181(100), 150(11) (Found M^+, 330.11079. Calculated for $C_{18}H_{18}O_6$, 330.11034) CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = $+6.0x10^3$ (332), $-17.0x10^3$ (294).

(2S,3S)-2,3-trans-4',5,7-Trimethoxydihydroflavonol **19b** mp 145°C CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = $-5.9x10^3$ (330), $+16.0x10^3$ (292); The R_f, ^{1}H NMR and MS data corresponded to those reported for **19a**.

(2S,3R)-2,3-cis-4',5,7-trimethoxydihydroflavonol **24a** mp (3-*O*-acetyl derivative) 71°C R_f 0.08 (hexane-benzene-acetone 5:4:1); ^{1}H NMR (3-*O*-acetyl derivative) δ 7.34 (d, J 8.8, H-2',6'), 6.86 (d, J 8.8, H-3',5'), 6.14 (d, J 2.5, H-6), 6.06 (d, J 2.5, H-8), 5.64 (d, J 3.8, H-3), 5.52 (d, J 3.8, H-2), 3.86, 3.82, 3.78 (3 x s, 3 x OMe), 1.99 (s, OAc); *m/z* 330 (M^+, 6%), 312(78), 311(45), 301(8), 283(34), 281(28), 266(39), 193(9), 181(100), 150(28) (Found M^+, 330.11087. $C_{18}H_{18}O_6$ requires M^+, 330.11034) CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = $-6.5x10^3$ (342), $+16.7x10^3$ (296).

(2R,3S)-2,3-cis-4',5,7-trimethoxydihydroflavonol **24b** mp (3-*O*-acetyl derivative) 78°C CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = $+6.5x10^3$ (340), $-17.8x10^3$ (294); The R_f, ^{1}H NMR and MS data corresponded to those reported for **24a**.

(2R,3R)-2,3-trans-3',4',5,7-tetramethoxydihydroflavonol **20a** mp 154°C R_f 0.07 (hexane-benzene-acetone 5:4:1); ^{1}H NMR δ 7.10 (dd, J 8.8 and 2.0, H-6'), 7.06 (d, J 2.0, H-2'), 6.93 (d, J 8.8, H-5'), 6.12 (d, J 2.1, H-8), 6.10 (d, J 2.1, H-6), 4.96 (d, J 12.0, H-2), 4.45 (dd, J 12.0 and 2.0, H-3), 4.05 (d, J 2.0, OH), 3.93, 3.92, 3.89, 3.81 (4 x s, 4 x OMe); *m/z* 360 (M^+, 3%), 331(60), 193(15), 181(100), 180(37), 165(18), 151(33), 137(11) (Found M^+, 360.11971. $C_{19}H_{20}O_7$ requires M^+, 360.12091) CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = $+5.2x10^3$ (332), $-16.0x10^3$ (290).

(2S,3S)-2,3-trans-3',4',5,7-tetramethoxydihydroflavonol **20b** mp 158°C CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = $-6.0x10^3$ (330), $+16.6x10^3$ (288); The R_f, ^{1}H NMR and MS data corresponded to those reported for **20a**.

(2S,3R)-2,3-cis-3',4',5,7-tetramethoxydihydroflavonol **25a** R_f 0.07 (hexane-benzene-acetone 5:4:1); ^{1}H NMR (3-*O*-acetyl derivative) δ 6.97 (dd, J 8.0 and 2.0, H-6'), 6.96 (d, J 2.0, H-2'), 6.82 (d, J 8.0, H-5'), 6.17 (d, J 2.1, H-8), 6.08 (d, J 2.1, H-6), 5.64 (d, J 3.9, H-3), 5.51 (d, J 3.8, H-2), 3.87, 3.85 3.82 (3 x s, 4 x OMe),

1.99 (s, OAc); *m/z* 360 (M^+, 5%), 331(59), 193(49), 181(100), 180(48), 165(27), 151(33), 137(36) (Found M^+, 360.11913. $C_{19}H_{20}O_7$ requires M^+, 360.12091) CD: $\Delta\varepsilon_{max}[\lambda(nm)] = -5.0x10^3$ (344), $+17.0x10^3$ (298).

(2R,3S)-2,3-cis-3',4',5,7-tetramethoxydihydroflavonol **25b** CD: $\Delta\varepsilon_{max}[\lambda(nm)] = +6.0x10^3$ (344), $-17.6x10^3$ (296); The R_f, ^1H NMR and MS data corresponded to those reported for **25a**.

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