



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 H₂O₂ 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 properties⁴, 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 recently⁶ 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 described¹ previously. Subsequent treatment with hydrogen peroxide in the triphase system, aqueous NaOH/poly-L- or -D-alanine/ CCl₄, 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 {[α]_D²⁵ +12.57(c, 5.695 in 1M HCl)} *versus* synthetic D-alanine {[α]_D²⁵ -9.72 (c, 1.363 in 6M HCl)}, which was reflected in the optical purity of the poly-L- {[α]_D²⁵ -142.8 (c, 0.671 in CF₃COOH)} and poly-D-alanine- {[α]_D²⁵ +102.0 (c, 0.314 in CF₃COOH)} 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**).

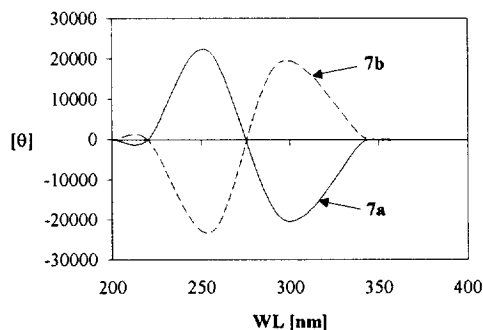
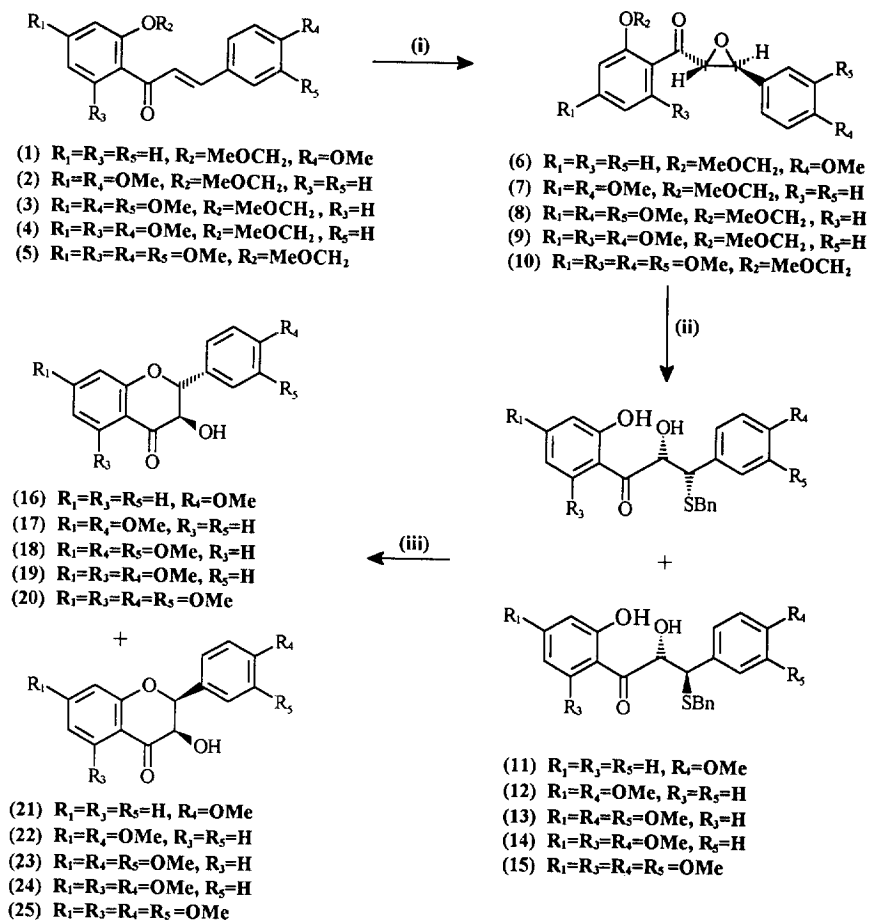


Figure 1 CD curves of the (-)-(α*R*, β*S*)-**7a** and (+)-(α*S*, β*R*)-**7b** chalcone epoxides.

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 catalysis¹, 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** (³*J*_{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).

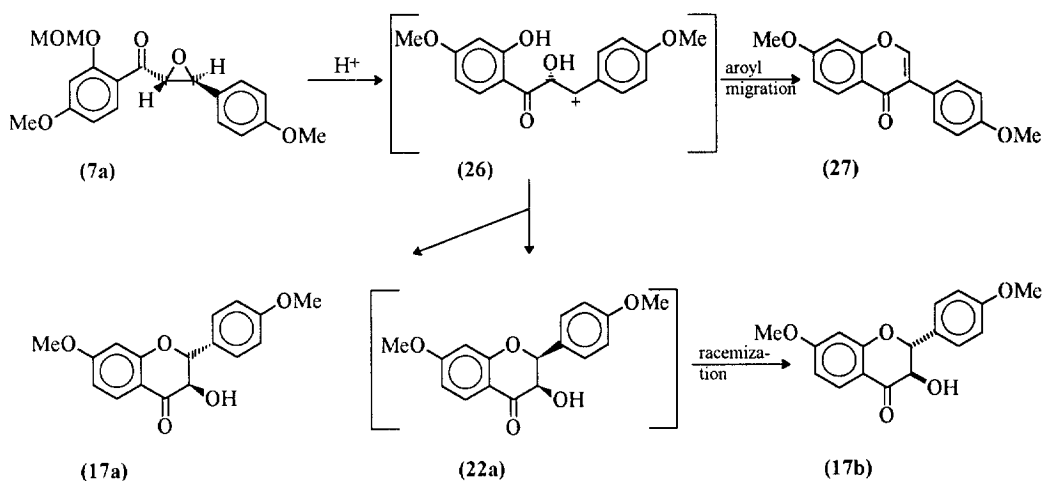


Scheme 1 Reagents and conditions: i 30% H_2O_2 : 6 M NaOH 1:0.32 (v/v), poly-L- or poly-D-alanine : chalcone 1:1 (m/m), CCl_4 , room temp., 36-96h; ii, BnSH (4 equiv.), $SnCl_4$ (0.2 equiv.), -20 to $0^\circ C$; iii, $AgBF_4$ (5 equiv.), CH_2Cl_2 , $0^\circ C$.

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 (%)	<i>trans:cis</i>
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 $\text{BF}_3\cdot\text{OEt}_2$ 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 (-)-($\alpha R, \beta S$)-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 $\text{BF}_3\cdot\text{OEt}_2$.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 C₈-O bond of the oxirane functionality at -20°C and effectively deprotected the methoxymethyl group at 0°C to give the corresponding $\alpha, 2'$ -dihydroxy- β -benzylsulfanyldihydrochalcones **11a/b**-**15a/b** as diastereomeric mixtures (*syn:anti ca.* 2.3:1) in 86-93% yield. The ¹H 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 -hydroxydihydrochalcones².

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** (³*J*_{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** (³*J*_{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 ¹H NMR using $\text{Eu}(\text{hfc})_3$ 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 $\rightarrow$ dihydrochalcone $\rightarrow$ *cis*-dihydroflavonol.

The data for the 2,3-*cis*-dihydroflavonols represent the first systematic compilation of the circular dichroic properties of this rare class of C6-C3-C6-type polyphenols²²⁻²⁴ and should hence contribute substantially towards elucidation of the absolute configuration of naturally occurring analogues.

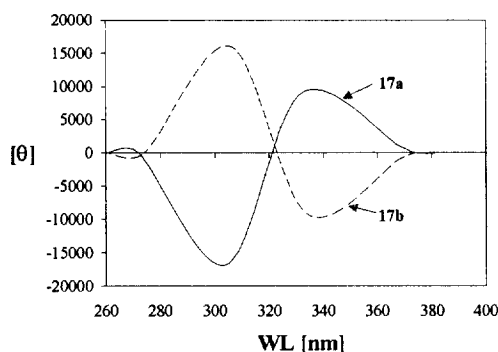


Figure 2: CD curves of the (2*R*,3*R*)-**17a** and (2*S*,3*S*)-**17b** -2,3-*trans*-dihydroflavonols

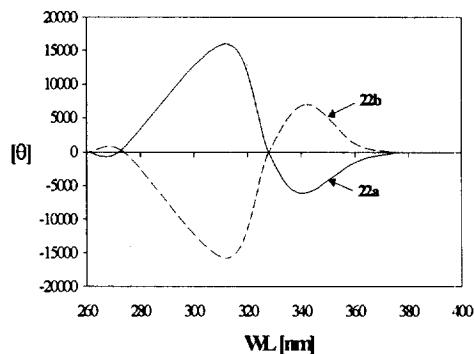


Figure 3: CD curves of the (2*S*,3*R*)-**22a** and (2*R*,3*S*)-**22b** -2,3-*cis*-dihydroflavonols

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 research²⁵ 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

^1H 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 spectropolarimeter. Thin layer chromatography (TLC) was performed on DC-Alufolien Kieselgel 60 F₂₅₄ (0.25) plates with visualisation by ultraviolet light and/or formaldehyde-sulphuric acid spray. Preparative plates (PLC) [Kieselgel PF₂₅₄ (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 $\alpha,2'$ -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- $\alpha,2'$ -dihydroxy- β -benzylsulfanyldihydrochalcone **11a/b*** (mixture of *syn* and *anti* isomers). R_f 0.50 (hexane-benzene-acetone 5:4:1); ^1H 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)(SCH_2Ph), 3.45* (d, J 14.0) and 3.29* (d, J 14.0)(SCH_2Ph); m/z 394 (M^+ , 0%), 253(26), 243(48), 153(5), 121(100) (Found M^+ , 394.1229. $\text{C}_{23}\text{H}_{22}\text{O}_4\text{S}$ requires M^+ , 394.1239).

*Major diastereoisomer.

*4,4'-Dimethoxy- $\alpha,2'$ -dihydroxy- β -benzylsulfanyldihydrochalcone **12a/b*** (mixture of *syn* and *anti* isomers). R_f 0.41 (hexane-benzene-acetone 5:4:1); ^1H 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 SCH_2Ph), 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)(SCH_2Ph), 3.48 (d, J 7.9, α -

OH), 3.43* (d, J 13.2) and 3.27* (d, J 13.2)(SCH₂Ph); *m/z* 424 (M⁺, 0%), 301(25), 283(16), 243(31), 181(4), 151(100), 121(22) (Found M⁺, 424.1340. C₂₄H₂₄O₅S 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) (SCH₂Ph), 3.48* (d, J 14.0) and 3.33* (d, J 14.0) (SCH₂Ph), 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. C₂₅H₂₆O₆S 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) (SCH₂Ph), 3.45* (d, J 14.0) and 3.24* (d, J 14.0) (SCH₂Ph); *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. C₂₅H₂₆O₆S 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) (SCH₂Ph), 3.44* (d, J 14.0) and 3.28* (d, J 14.0) (SCH₂Ph); *m/z* 484 (M⁺, 0%), 361(34), 343(38), 273(24), 211(5), 181(100), 151(57), 124(18) (Found M⁺, 484.1551. C₂₆H₂₈O₇S 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**.

(2*R*,3*R*)-2,3-*trans*-4'-methoxydihydroflavonol **16a**²⁶ Mp 167°C R_f (hexane-benzene-acetone 5:4:1); ^1H 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 $\text{C}_{16}\text{H}_{14}\text{O}_4$, 270.08912) CD: $\Delta\epsilon_{\text{max}}[\lambda(\text{nm})] = +8.8 \times 10^3$ (340), -14.0×10^3 (310).

(2*S*,3*S*)-2,3-*trans*-4'-methoxydihydroflavonol **16b** mp 167°C CD: $\Delta\epsilon_{\text{max}}[\lambda(\text{nm})] = -9.0 \times 10^3$ (340), $+14.4 \times 10^3$ (312); The R_f, ^1H NMR and MS data corresponded to those reported for **16a**.

(2*S*,3*R*)-2,3-*cis*-4'-methoxydihydroflavonol **21a** R_f 0.37 (hexane-benzene-acetone 5:4:1); ^1H 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. $\text{C}_{16}\text{H}_{14}\text{O}_4$ requires M^+ , 270.08912) CD: $\Delta\epsilon_{\text{max}}[\lambda(\text{nm})] = -5.8 \times 10^3$ (344), $+16.0 \times 10^3$ (316).

(2*R*,3*S*)-2,3-*cis*-4'-methoxydihydroflavonol **21b** CD: $\Delta\epsilon_{\text{max}}[\lambda(\text{nm})] = +7.0 \times 10^3$ (344), -14.1×10^3 (318); The R_f, ^1H NMR and MS data corresponded to those reported for **21a**.

(2*R*,3*R*)-2,3-*trans*-4',7-dimethoxydihydroflavonol **17a**²⁷ mp 124°C R_f 0.24 (hexane-benzene-acetone 5:4:1); ^1H 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. $\text{C}_{17}\text{H}_{16}\text{O}_5$ requires M^+ , 300.09967) CD: $\Delta\epsilon_{\text{max}}[\lambda(\text{nm})] = +9.0 \times 10^3$ (332), -16.8×10^3 (304).

(2*S*,3*S*)-2,3-*trans*-4',7-dimethoxydihydroflavonol **17b** mp 126°C CD: $\Delta\epsilon_{\text{max}}[\lambda(\text{nm})] = -9.2 \times 10^3$ (334), $+16.0 \times 10^3$ (306); The R_f, ^1H NMR and MS data corresponded to those reported for **17a**.

(2*S*,3*R*)-2,3-*cis*-4',7-dimethoxydihydroflavonol **22a** mp 78°C R_f 0.21 (hexane-benzene-acetone 5:4:1); ¹H 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. C₁₇H₁₆O₅ requires M⁺, 300.09967) CD: Δε_{max}[λ(nm)] = -6.1x10³ (340), +16.0x10³ (312).

(2*R*,3*S*)-2,3-*cis*-4',7-dimethoxydihydroflavonol **22b**; mp 80°C CD: Δε_{max}[λ(nm)] = +7.0x10³ (342), -15.8x10³ (312); The R_f, ¹H NMR and MS data corresponded to those reported for **22a**.

(2*R*,3*R*)-2,3-*trans*-3',4',7-trimethoxydihydroflavonol **18a**²⁷ mp 141°C R_f 0.14 (hexane-benzene-acetone 5:4:1); ¹H 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 C₁₈H₁₈O₆, 330.11022) CD: Δε_{max}[λ(nm)] = +9.6x10³ (332), -18.0x10³ (304).

(2*S*,3*S*)-2,3-*trans*-3',4',7-trimethoxydihydroflavonol **18b** mp 142°C CD: Δε_{max}[λ(nm)] = -9.0x10³ (334), +17.3x10³ (306); The R_f, ¹H NMR and MS data corresponded to those reported for **18a**.

(2*S*,3*R*)-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); ¹H 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. C₁₈H₁₈O₆ requires M⁺, 330.11022) CD: Δε_{max}[λ(nm)] = -7.0x10³ (340), +18.0x10³ (308).

(2*R*,3*S*)-2,3-*cis*-3',4',7-trimethoxydihydroflavonol **23b** mp (3-*O*-acetyl derivative) 114°C CD: Δε_{max}[λ(nm)] = +6.5x10³ (340), -16.5x10³ (310); The R_f, ¹H NMR and MS data corresponded to those reported for **23a**.

(2*R*,3*R*)-2,3-*trans*-4',5,7-trimethoxydihydroflavonol **19a**²⁸ mp 143°C *R*_f 0.09 (hexane-benzene-acetone 5:4:1); ¹H 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 C₁₈H₁₈O₆, 330.11034) CD: Δ*ε*_{max}[λ(nm)] = +6.0×10³ (332), -17.0×10³ (294).

(2*S*,3*S*)-2,3-*trans*-4',5,7-Trimethoxydihydroflavonol **19b** mp 145°C CD: Δ*ε*_{max}[λ(nm)] = -5.9×10³ (330), +16.0×10³ (292); The *R*_f, ¹H NMR and MS data corresponded to those reported for **19a**.

(2*S*,3*R*)-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); ¹H 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. C₁₈H₁₈O₆ requires *M*⁺, 330.11034) CD: Δ*ε*_{max}[λ(nm)] = -6.5×10³ (342), +16.7×10³ (296).

(2*R*,3*S*)-2,3-*cis*-4',5,7-trimethoxydihydroflavonol **24b** mp (3-*O*-acetyl derivative) 78°C CD: Δ*ε*_{max}[λ(nm)] = +6.5×10³ (340), -17.8×10³ (294); The *R*_f, ¹H NMR and MS data corresponded to those reported for **24a**.

(2*R*,3*R*)-2,3-*trans*-3',4',5,7-tetramethoxydihydroflavonol **20a** mp 154°C *R*_f 0.07 (hexane-benzene-acetone 5:4:1); ¹H 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. C₁₉H₂₀O₇ requires *M*⁺, 360.12091) CD: Δ*ε*_{max}[λ(nm)] = +5.2×10³ (332), -16.0×10³ (290).

(2*S*,3*S*)-2,3-*trans*-3',4',5,7-tetramethoxydihydroflavonol **20b** mp 158°C CD: Δ*ε*_{max}[λ(nm)] = -6.0×10³ (330), +16.6×10³ (288); The *R*_f, ¹H NMR and MS data corresponded to those reported for **20a**.

(2*S*,3*R*)-2,3-*cis*-3',4',5,7-tetramethoxydihydroflavonol **25a** *R*_f 0.07 (hexane-benzene-acetone 5:4:1); ¹H 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: $\Delta\epsilon_{\max}[\lambda(\text{nm})] = -5.0 \times 10^3$ (344), $+17.0 \times 10^3$ (298).

(2*R*,3*S*)-2,3-*cis*-3',4',5,7-tetramethoxydihydroflavonol **25b** CD: $\Delta\epsilon_{\max}[\lambda(\text{nm})] = +6.0 \times 10^3$ (344), -17.6×10^3 (296); The R_f , ^1H NMR and MS data corresponded to those reported for **25a**.

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