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Stereoselective Synthesis of Flavonoids. Part 7.[1] Poly-oxygenated β-Hydroxydihydrochalcone Derivatives

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Abstract: Epoxidation of a series of poly-oxygenated chalcones with urea-hydrogen peroxide complex in THF in the presence of DBU and poly-(L)- or -(D)-leucine, followed by TBTH/AIBN catalysed ring opening, afforded β-hydroxydihydrochalcones in moderate to high enantiomeric excess and yield. This represents the first stereoselective route towards this group of flavonoids.

Keywords: Chalcones; Epoxidation; Enantioselection; Flavonoids; Oxiranes; Regioselection.

INTRODUCTION

α- and β-Hydroxydihydrochalcones represent rare groups of flavonoid metabolites which play an important role as insect feeding attractants and deterrents.[2] In addition, certain dihydrochalcone derivatives and related compounds are used as non-nutritional sweeteners in chewing gum, mouthwashes and various brands of candy.[3] The α-hydroxydihydrochalcones are biogenetically related to α-methyldeoxybenzoins and isoflavonoids[4-9] while the β-isomers suggest close biosynthetic ties with β-ketochalcones and flavones.[10,11] Although several members of these groups of natural products have been identified,[4-8,12,13] progress in the chemistry of these compounds is restricted by the lack of synthetic access to both enantiomers and also by absence of a method for determination of the absolute configuration at the single stereogenic centre. The flavanones not only represent one of the most abundant group of compounds in the category of the minor flavonoids,[14] but may be reductively converted into enantiomerically enriched flavan-4-ols and flavans which may then serve as electrophilic[15-17] and nucleophilic synthons, respectively, in the semisynthesis of the 3-deoxy (C-ring) A- and B-type proanthocyanidins, *e.g.* the procassinidins.[18] Previously[9,19] we addressed the problems associated with the stereoselective synthesis of α-hydroxydihydrochalcones utilising catalytic hydrogenation ($Pd/BaSO_4$; Pd/C) of optically enriched chalcone epoxides. We recently[20] adopted this protocol to the first enantioselective synthesis of β-hydroxydihydrochalcones and herein we report the synthesis of a series of analogues exhibiting the characteristic aromatic oxygenation patterns usually encountered in naturally occurring flavonoids.

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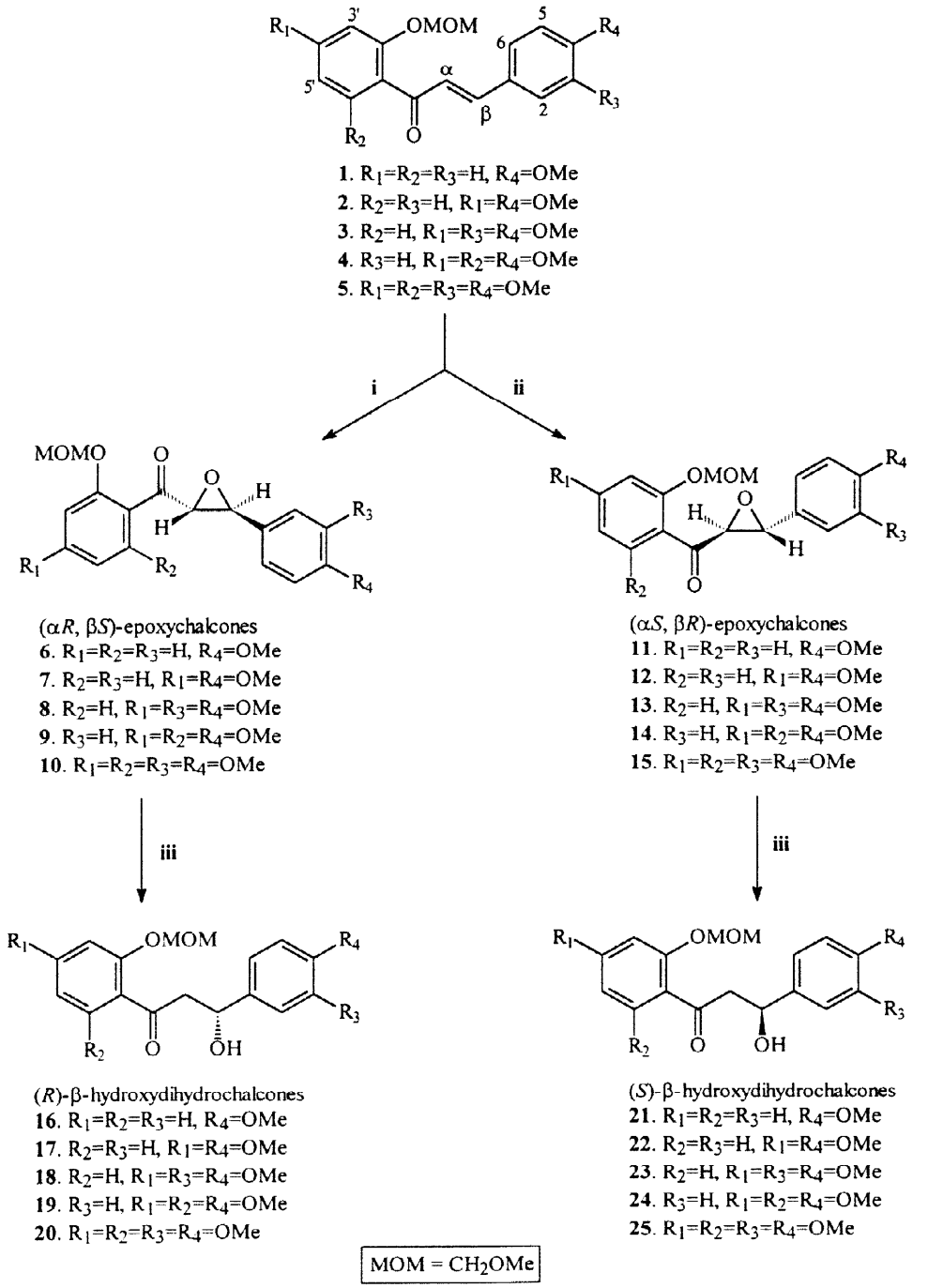
RESULTS AND DISCUSSION

The Julia[21,22] asymmetric epoxidation, consisting of H_2O_2 in the triphasic system, aqueous NaOH, poly-*L*- or *D*-alanine and CCl_4, was the first successful method towards optically enriched chalcone epoxides.[9,19] Since this protocol is not without limitations, *i.e.*, disappointing stereoselectivity and continuous addition of oxidant and base,[23] we selected the adapted version of Bentley and Roberts,[24,25] involving a two-phase non-aqueous system for the asymmetric epoxidation of chalcone methyl ethers. Thus, the *trans*-chalcone methyl ethers **1-5** ($J_{\alpha,\beta}$= 15.8-16.0 Hz)[9], accessible *via* base-catalysed aldol condensation of the appropriate oxygenated acetophenones and benzaldehydes,[9,26] were epoxidised with immobilised poly-*L*- or –*D*-leucine[27] (PLL or PDL), urea-hydrogen peroxide complex (UHP)[28] and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry THF. This afforded the (-)-(α*R*, β*S*)- **6-10** and (+)-(α*S*, β*R*)-*trans*-epoxychalcones **11-15** ($J_{\alpha,\beta}$ 1.5-2.2 Hz) in moderate to high yields (19-80%) and improved optical purity (50-95% ee) in comparison with the Julia procedure [29,30] (49-86% ee) (Scheme, Table 1). The enantiomeric purity of the epoxides was determined by ^{1}H NMR using $Eu(tfc)_3$ as chiral shift reagent and the absolute stereochemistry assigned by comparison of CD data with those of authentic samples.[9,31]

Several procedures, using reagents such as samarium diiodide,[32] aluminium amalgam/ultrasound,[33] metallic lithium in liquid ammonia[34] and sodium hydrogen telluride[35] have been used for the reductive ring opening of α,β-epoxy ketones. The excellent results reported by Hasegawa *et. al.*[36] for the regioselective reductive conversion of α,β-epoxyketones into β-hydroxyketones with tributyltin hydride (TBTH) under both photochemical (irradiate at 254 nm) and thermal conditions [addition of azoisobutyronitrile (AIBN)], prompted evaluation of these procedures for reduction of the aromatic oxygenated chalcone epoxides. Owing to the *ca.* 50% improved yields obtained using the thermal reaction (reflux for 1 h in benzene) with excess TBTH (3 equiv.) in the presence of catalytic amounts of AIBN (0.1 equiv.), this method was employed for the selective C_α-O bond cleavage of (-)-(α*R*, β*S*)- **6-10** and (+)-(α*S*, β*R*)-*trans*-epoxychalcones **11-15**, affording the (*R*)- **16-20** and (*S*)-2'-*O*-methoxymethyl-β-hydroxydihydrochalcones **21-25**, respectively, in excellent yields (70-90%, Table 1).

The ^{1}H NMR data of the β-hydroxydihydrochalcones **16-25** show, besides the expected aromatic protons, two geminally coupled protons (δ 3.51-3.21 and 3.44-3.08, J = ±18.0, 9.1 and 3.1 Hz) as the AB portion of a vicinal ABMX system, where the M proton appears as a diffuse doublet (J = ±3.0 Hz) at δ 3.74-3.59 and the X proton at δ 5.27-5.21 as a diffuse multiple resonance. Addition of D_2O eliminates the M proton (indicating M to be OH) while the X proton refines to a doublet of doublets (J = ±8.7 and 3.6 Hz). These data, however, are consistent with either an α- or β-hydroxydihydrochalcone. Comparison of this NMR data with those published for similar oxygenated α-hydroxydihydrochalcones,[19] shows that the geminal methylene protons of compounds **16-25** occur at a lower field than the same protons of the α- hydroxydihydrochalcones (δ 3.51-3.21 *vs* 3.20-2.96 and δ 3.44-3.08 *vs* 2.80-2.65) while the hydroxyl proton occurs at higher field (δ 3.74-3.60 *vs* 3.94-3.70). These

spectral differences and the selective benzylic coupling of the β-H resonance of the β-hydroxydihydrochalcones, permitted distinction between the two series of closely related compounds. Unequivocal differentiation was however effected with HMBC experiments, where association of 2- and 6-H with the β-C and also the α-methylene protons with the carbonyl carbon were observed for compounds **16-25**.



Scheme *Reagents and conditions*: i, poly-(*L*)-leucine, urea-hydrogen peroxide complex, DBU, THF, rt; ii, poly-(*D*)-leucine, urea-hydrogen peroxide complex, DBU, THF, rt; iii, TBTH, AIBN, benzene, reflux.

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

Chalcone	Poly-(amino acid)[a]	Chalcone epoxide	% Yield (% Conversion)	ee[b] (%)	β-Hydroxydi-hydrochalcone	% Yield	ee[b] (%)
1	PLL	**6**	71	85	**16**	73	85
1	PDL	**11**	69	81	**21**	70	80
2	PLL	**7**	80	95	**17**	83	91
2	PDL	**12**	76	90	**22**	90	88
3	PLL	**8**	64 (89)	88	**18**	78	84
3	PDL	**13**	61 (86)	87	**23**	81	85
4	PLL	**9**	36 (51)	60	**19**	79	55
4	PDL	**14**	33 (52)	61	**24**	76	61
5	PLL	**10**	21 (39)	53	**20**	83	48
5	PDL	**15**	19 (33)	50	**25**	78	47

[a] PLL: poly-(*L*)-leucine; PDL: poly-(*D*)-leucine. [b] Determined with $Eu(tfc)_3$ as chiral shift reagent.

The ee's of the β-hydroxydihydrochalcones **16-25** were determined by ^1H NMR, again using $Eu(tfc)_3$ as chiral shift reagent and as anticipated, these conversions proceeded without loss in optical purity (Table 1). Since the optical integrity had been preserved in the reductive transformation, epoxide → dihydrochalcone, the absolute configuration of the β-hydroxydihydrochalcones **16-25** could be deduced from the known configuration of the epoxides **6-15**. All attempts to confirm such a conjecture *via* transformation into the corresponding MTPA esters,[37] however, resulted in elimination to the more stable, conjugated, chalcones **1-5**.

The CD spectra of the (*R*)-series of compounds, *e.g.* **17**, exhibit strong negative and positive Cotton effects in the 320 and 240 nm regions, respectively, with the signs of these CE's being reversed for the (*S*)-enantiomers *e.g.* **22** (Figure). The chiroptical information should be useful in the assignment of the absolute configuration of this class of simple flavonoid.

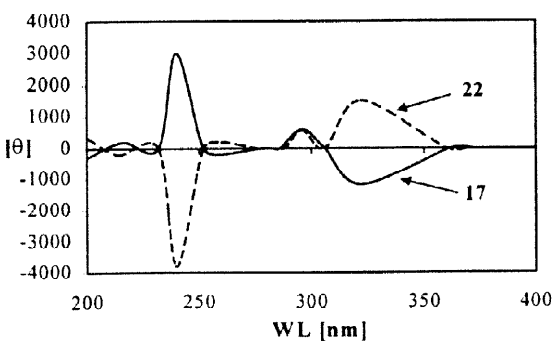


Figure. CD curves of the (*R*)-**17** and (*S*)-**22**-β-hydroxydihydrochalcones.

We have thus effected the first stereoselective synthesis of β-hydroxydihydrochalcones. This protocol should contribute substantially towards eliminating the high degree of confusion[38] regarding differentiation between the closely related α- and β-hydroxydihydrochalcones. These results should additionally provide stereoselective access towards flavanones and flavans, and eventually proanthocyanidins with C-3 deoxy chain extender and terminating units. We are currently exploring these and will report the results elsewhere.

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 spectropolarimeter and infrared spectra were recorded in $CHCl_3$ on a Hitachi infrared model 270-50 spectrophotometer. Thin layer chromatography (TLC) was performed 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. The chalcones **1-5** were prepared according to standard procedures.[8]

General procedure for the preparation of asymmetric chalcone epoxides 6-15

To 'activated' immobilised poly-(*L*)- or poly–(*D*)-leucine (800 mg)[24,25] was added THF (7.5 ml), urea-hydrogen peroxide (1.2 *eq*) and DBU (1.4 *eq*). Chalcone (400 mg) was added to the slurry and the mixture stirred for 48-96 h. The catalyst was removed by filtration, rinsed with Et_2O and the filtrate washed with water. Drying (Na_2SO_4) of the solvent and evaporation at reduced pressure gave the crude product, which was purified by PLC and crystallised from ethanol. Immobilised poly-(*L*)-leucine afforded the (-)-(α*R*,β*S*)-2'-*O*-methoxymethylchalcone epoxides **6-10** (21-80% yield, 53-95% ee) while immobilised poly-(*D*)-leucine afforded the (+)-(α*S*,β*R*)-2'-*O*-methoxymethylchalcone epoxides **11-15** (19-76% yield, 50-90% ee) (Table 1).

(-)-(α*R*,β*S*)-4-Methoxy-2'-*O*-methoxymethylchalcone epoxide 6.

Reaction time, 48 h; yield, 71%; ee = 85%; Mp 78°C (lit.[9] 75-78°C); R_f 0.53 (hexane:benzene:Me_2CO, 5:4:1); ^{1}H NMR ($CDCl_3$) δ 7.79 (dd, J 7.9 and 1.9, H-6'), 7.46 (ddd, J 8.8, 8.8 and 1.9, H-4'), 7.27 (d, J 9.0, H-2,6), 7.13 (dd, J 8.8 and 1.0, H-3'), 7.07 (ddd, J 8.8, 7.9 and 1.0, H-5'), 6.90 (d, J 9.0, H-3,5), 4.92, 4.85 (2 x d, J 7.0, O$\underline{CH_2}$OCH$_3$), 4.29 (d, J 1.9, H-α), 3.95 (d, J 1.9, H-β), 3.80 (s, OCH_3), 3.12 (s, $OCH_2O\underline{CH_3}$); CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = -22.2x10^3 (307), +9.1x10^3 (240).

(+)-(α*S*,β*R*)-4-Methoxy-2'-*O*-methoxymethylchalcone epoxide 11.

Reaction time, 48 h; yield, 69%; ee = 81%; CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = +21.5x10^3 (306), -8.4x10^3 (240); The R_f and ^{1}H NMR data corresponded to those of **6**.

(-)-(α*R*,β*S*)-4,4'-Dimethoxy-2'-*O*-methoxymethylchalcone epoxide 7.

Reaction time, 48 h; yield,80%; ee = 95%; Mp 63-65°C (lit.[9] 59-62°C); R_f 0.42 (hexane:benzene:Me_2CO, 5:4:1); ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J 8.9, H-6'), 7.27 (d, J 9.0, H-2,6), 6.90 (d, J 9.0, H-3,5), 6,63 (d, J 2.0, H-3'), 6.60 (dd, J 8.9 and 2.0, H-5'), 4.87, 4.80 (2 x d, J 7.0, $O\underline{CH_2}OCH_3$), 4.29 (d, J 1.9, H-α), 3.91 (d, J 1.9, H-β), 3.82, 3.81 (2 x s, 2 x OCH_3), 3.11 (s, $OCH_2O\underline{CH_3}$); CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = -12.0x10^3 (296), +10.3x10^3 (252).

(+)-(α*S*,β*R*)-4,4'-Dimethoxy-2'-*O*-methoxymethylchalcone epoxide 12.

Reaction time, 48 h; yield,76%; ee = 90%; CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = +11.0x10^3 (294), -9.7x10^3 (255); The R_f and ^{1}H NMR data corresponded to those of **7**.

(-)-(α*R*,β*S*)-3,4,4'-Trimethoxy-2'-*O*-methoxymethylchalcone epoxide 8.

Reaction time, 48 h; yield, 64%; ee = 88%; Mp 62-64°C (lit.[9] amorphous solid); R_f 0.19 (hexane:benzene:Me_2CO, 5:4:1); ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J 8.8, H-6'), 6.98 (dd, J 8.3 and 2.0, H-5), 6.89 (d, J 8.3, H-6), 6.85 (d, J 2.0, H-2), 6.67 (d, J 2.2, H-3'), 6.64 (dd, J 8.8 and 2.2, H-5'), 4.93, 4.85 (both d, J 7.0, $O\underline{CH_2}OCH_3$), 4.33 (d, J 2.0, H-α), 3.95 (d, J 2.0, H-β), 3.92, 3.90, 3.86 (3 x s, 3 x OCH_3), 3.16 ($OCH_2O\underline{CH_3}$); CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = -24.6x10^3 (306), +27.6x10^3 (260).

(+)-(α*S*,β*R*)-3,4,4'-Trimethoxy-2'-*O*-methoxymethylchalcone epoxide 13.

Reaction time, 48 h; yield, 61%; yield, 61%; ee = 87%, CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = +25.9x10^3 (307), -17.8x10^3 (260); The R_f and ^{1}H NMR data corresponded to those of **8**.

(-)-(α*R*,β*S*)-4,4',6'-Trimethoxy-2'-*O*-methoxymethylchalcone epoxide 9.

Reaction time, 96 h; yield, 36%; ee = 60%; Mp 66°C (lit.[39] oil); R_f 0.14 (hexane:benzene:Me_2CO, 5:4:1); ^{1}H NMR ($CDCl_3$) δ 7.25 (d, J 8.9, H-2,6), 6.90 (d, J 8.9, H-3,5), 6.35 (d, J 2.0, H-3'), 6.14 (d, J 2.0, H-5'), 5.11 (s, $O\underline{CH_2}OCH_3$), 3.97 (d, J 1.9, H-β), 3.93 (d, J 1.9, H-α), 3.83, 3.82, 3.77, (3 x s, 3 x OCH_3), 3.39 (s, $OCH_2O\underline{CH_3}$); CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = -17.9x10^3 (298), +21.0x10^3 (250).

(+)-(αS,β*R*)-4,4',6'-Trimethoxy-2'-*O*-methoxymethylchalcone epoxide 14.

Reaction time, 96 h; yield, 33%; ee = 61%; CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = +17.5x10^3 (295), -14.8x10^3 (252); The R_f and ^{1}H NMR data corresponded to those of **9**.

(-)-(α*R*,β*S*)-3,4,4',6'-Tetramethoxy-2'-*O*-methoxymethylchalcone epoxide 10.

Reaction time, 96 h; yield, 21%; ee = 53%; Mp 114°C (lit.[9] not stable enough for crystallization); R_f 0.14 (hexane:benzene:Me_2CO, 5:4:1); ^1H NMR ($CDCl_3$) δ 6.94 (dd, J 2.0 and 8.3, H-6), 6.86 (d, J 8.3, H-5), 6.79 (d, J 2.0, H-2), 6.35 (d, J 2.1, H-3'), 6.16 (d, J 2.1, H-5), 5.12 (s, $O\underline{CH_2}OCH_3$), 3.98 (d, J 1.9, H-β), 3.93 (d, J 1.9, H-α), 3.90, 3.89, 3.83, 3.77, (4 x s, 4 x OCH_3), 3.39 (s, $OCH_2O\underline{CH_3}$); CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = -10.5x10^3 (300), +8.7x10^3 (260).

(+)-(α*S*,β*R*)-3,4,4',6'-Tetramethoxy-2'-*O*-methoxymethylchalcone epoxide 15.

Reaction time, 96 h; yield,19%; ee = 45%; CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = +8.1x10^3 (300), -7.3x10^3 (262); The R_f and ^1H NMR data corresponded to those of **10**.

General procedure for the synthesis of optically enriched β-hydroxydihydrochalcones 16-25.

A solution of optically enriched chalcone epoxide **6-15** (50 mg) and AIBN (0.1 *eq*) in dry benzene (10 ml) was purged with N_2 for 15 min. TBTH (3 *eq*) was added and the mixture refluxed for 1 h. Evaporation of the solvent at reduced pressure gave the crude product, which was purified by PLC to afford the β-hydroxydihydrochalcones **16-25** as clear oils (70-90% yield) with retention of configuration (Table 1).

(*R*)-β-Hydroxy-4-methoxy-2'-*O*-methoxymethyldihydrochalcone 16.

Yield,73%; ee = 85%; R_f 0.25 (hexane:benzene:Me_2CO, 5:4:1); ^1H NMR ($CDCl_3$) δ 7.74 (dd, J 7.9 and 1.8, H-6'), 7.47 (ddd, J 8.6, 7.9 and 1.8, H-4'), 7.36 (d, J 9.0, H-2,6), 7.20 (dd, J 8.6 and 1.1, H-3'), 7.08 (ddd, J 8.6, 8.6 and 1.1, H-5'), 6.91 (d, J 9.0, H-3,5), 5.27 (m, H-β), 5.26 (s, $O\underline{CH_2}OCH_3$), 3.83 (s, OCH_3), 3.47 (dd, J 18.1 and 3.9) and 3.39 (dd, J 18.1 and 8.5)(α-CH_2), 3.47 (s, $OCH_2O\underline{CH_3}$); CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = -1.1x10^3 (319), +1.4x10^3 (243); *m/z* 316 (M^+, 35%), 253(28), 165(32), 135(70), 121(20), 76(86) (Found; M^+, 316.1311. $C_{18}H_{20}O_5$ requires M^+, 316.1311); IR ($CHCl_3$) ν_{max} :1666(CO), 1612, 1600 cm^{-1}

(*S*)-β-Hydroxy-4-methoxy-2'-*O*-methoxymethyldihydrochalcone 21.

Yield,70%; ee = 80%; CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = +1.0x10^3 (318), -1.5x10^3 (244); The R_f, ^1H NMR, MS and IR data corresponded to those of **16**.

(*R*)-β-Hydroxy-4,4'-dimethoxy-2'-*O*-methoxymethyldihydrochalcone 17.

Yield, 83%; ee = 91%; R_f 0.26 (hexane:benzene:Me_2CO, 5:4:1); ^1H NMR ($CDCl_3$) δ 7.82 (d, J 8.9, H-6'), 7.32 (d, J 9.0, H-2,6), 6.87 (d, J 9.0, H-3,5), 6.67 (d, J 2.3, H-3'), 6.57 (dd, J 8.9 and 2.3, H-5'), 5.21 (m, H-β), 5.21 (s, $O\underline{CH_2}OCH_3$), 3.82, 3.78 (2 x s, 2 x OCH_3), 3.43 (s, $OCH_2O\underline{CH_3}$), 3.40 (dd, J 18.1 and 3.3) and 3.30 (dd, J 18.1 and 9.1)(α-CH_2); ^{13}C NMR ($CDCl_3$) δ 52.45 (α-C), 55.68, 56.00, 56.91, 70.41 (β-C), 94.86,

101.29, 101.56, 114.20 (x2), 121.38 (x2), 127.49, 132.94, 136.04, 159.20, 159.30, 165.12, 200.53 (CO); CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = -1.2x10^3 (322), +3.0x10^3 (241); *m/z* 346 (M^+, 27%), 283(22), 195(23), 165(25), 151(28), 121(12) 106(8) (Found; M^+, 346.1416. $C_{19}H_{22}O_6$ requires M^+, 346.1416); IR ($CHCl_3$) ν_{max} :1652(CO), 1602, 1576 cm^{-1}

(*S*)-β-Hydroxy-4,4'-dimethoxy-2'-*O*-methoxymethyldihydrochalcone 22.

Yield, 90%; ee = 88%; CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = +1.5x10^3 (322), -3.8x10^3 (242); The R_f, ^{1}H NMR, ^{13}C NMR, MS and IR data corresponded to those of **17**.

(*R*)-β-Hydroxy-3,4,4'-trimethoxy-2'-*O*-methoxymethyldihydrochalcone 18.

Yield, 78%; ee = 84%; R_f 0.10 (hexane:benzene:Me_2CO, 5:4:1); ^{1}H NMR ($CDCl_3$) δ 7.86 (d, J 9.0, H-6'), 7.04 (d, J 2.0, H-2), 6.95 (dd, J 8.3 and 2.0, H-6), 6.87 (d, J 8.3, H-5), 6.71 (d, J 2.3, H-3'), 6.62 (dd, J 9.0 and 2.3, H-5'), 5.25 (m, H-β), 5.25 (s, O$\underline{CH_2}$OCH$_3$), 3.92, 3.90, 3.87 (3 x s, 3 x OCH$_3$), 3.47 (s, OCH$_2$O$\underline{CH_3}$), 3.45 (dd, J 18.3 and 4.0) and 3.33 (dd, J 18.3 and 9.1)(α-CH$_2$); ^{13}C NMR ($CDCl_3$) δ 52.52 (α-C), 56.02, 56.26, 56.32, 56.92, 70.62 (β-C), 94.89, 101.31, 107.57, 109.50, 111.37, 118.34, 121.34, 132.95, 136.52, 148.65, 159.22, 165.17, 200.56 (CO); CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = -1.0x10^3 (310), +4.3x10^3 (242); *m/z* 376 (M^+, 29%), 313(18), 195(25), 165(34), 151(46), 106(60) (Found; M^+, 376.1523. $C_{20}H_{24}O_7$ requires M^+, 376.1522); IR ($CHCl_3$) ν_{max} :1654(CO), 1600, 1576 cm^{-1}

(*S*)-β-Hydroxy-3,4,4'-trimethoxy-2'-*O*-methoxymethyldihydrochalcone 23.

Yield, 81%, ee = 85%; CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = +1.3x10^3 (310), -4.5x10^3 (243); The R_f, ^{1}H NMR, ^{13}C NMR, MS and IR data corresponded to those of **18**.

(*R*)-β-Hydroxy-4,4',6'-trimethoxy-2'-*O*-methoxymethyldihydrochalcone 19.

Yield, 79%, ee = 55%; R_f 0.25 (hexane:EtOAc, 8:2); ^{1}H NMR ($CDCl_3$) δ 7.34 (d, J 9.0, H-2,6), 6.35 (d, J 2.1, H-3'), 6.16 (d, J 2.1, H-5'), 6.89 (d, J 9.0, H-3,5), 5.25 (m, H-β), 5.15 (s, O$\underline{CH_2}$OCH$_3$), 3.82, 3.81, 3.79 (3 x s, 3 x OCH$_3$), 3.47 (s, OCH$_2$O$\underline{CH_3}$), 3.23 (dd, J 19.3 and 3.6) and 3.13 (dd, J 19.3 and 9.1)(α-CH$_2$); ^{13}C NMR ($CDCl_3$) δ 53.84 (α-C), 55.69, 55.92, 56.26, 56.79, 70.38 (β-C), 92.63, 93.73, 95.24, 110.01, 114.15, 114.24, 114.29, 127.49, 135.68, 156.37, 158.65, 159.35, 162.97, 204.78 (CO); CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = -1.4x10^3 (306), +0.8x10^3 (245); *m/z* 376 (M^+, 22%), 313(15), 225(25), 195(22), 181(35), 136(98) 121(9) (Found; M^+, 376.1522. $C_{20}H_{24}O_7$ requires M^+, 376.1522); IR ($CHCl_3$) ν_{max} :1692(CO), 1608, 1590 cm^{-1}

(*S*)-β-Hydroxy-4,4',6'-trimethoxy-2'-*O*-methoxymethyldihydrochalcone 24.

Yield, 76%, ee = 61%; CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = +1.9x10^3 (306), -1.3x10^3 (245); The R_f, ^{1}H NMR, MS and IR

data corresponded to those of **19**.

(*R*)-β-Hydroxy-3,4,4',6'-tetramethoxy-2'-*O*-methoxymethyldihydrochalcone 20.

Yield, 83%, ee = 48%;R_f 0.10 (hexane:benzene:Me_2CO, 5:4:1); ^{1}H NMR ($CDCl_3$) δ 7.00 (d, J 2.1, H-2), 6.92 (dd, J 8.4 and 2.1, H-5), 6.84 (d, J 8.4, H-6), 6.35 (d, J 2.1, H-3'), 6.17 (d, J 2.1, H-5'), 5.24 (m, H-β), 5.15 (s, $O\underline{CH_2}OCH_3$), 3.91, 3.88, 3.82, 3.80 (4 x s, 4 x OCH_3), 3.47(s, $OCH_2O\underline{CH_3}$), 3.24 (dd, J 17.8 and 3.2) and 3.14 (dd, J 17.8 and 9.1)(α-CH_2); CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = -0.6x10^3 (310), +0.7x10^3 (241); *m/z* 406 (M^+, 32%), 343(18), 225(17), 195(21), 181(38), 136(88) 151(6) (Found; M^+, 406.1629. $C_{21}H_{26}O_8$ requires M^+, 406.1628); IR ($CHCl_3$) ν_{max} :1690(CO), 1608, 1589 cm^{-1}.

(*S*)-β-Hydroxy-3,4,4',6'-tetramethoxy-2'-*O*-methoxymethyldihydrochalcone 25.

Yield, 78%, ee = 47%; CD: $\Delta\varepsilon_{max}[\lambda(nm)]$ = +1.1x10^3 (310), -1.2x10^3 (242); The R_f, ^{1}H NMR, MS and IR data corresponded to those of **20**.

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REFERENCES

1. Nel, R.J.J.; Mthembu, M.; Coetzee, J.; Van Rensburg, H.; Malan, E.; Ferreira, D. *Phytochemistry*, **1999**, submitted, paper, PHYTO99-06100NA.
2. Harborne, J.B.; Grayer, R.J. in *The Flavonoids-Advances in Research since 1986*, ed. J.B. Harborne, Chapman & Hall, London, **1994**, 599-601.
3. Horowitz, R.M. in *Plant Flavonoids in Biology and Medicine*, eds. V. Cody, E. Middleton and J.B. Harborne, Alan R. Liss, New York, **1986**, 163-175.
4. Bhakuni, D.; Bittner, M.; Silva, M.; Sammes, P.G. *Phytochemistry*, **1973**, *12*, 2777-2779.
5. Shukla, Y.N.; Tandon, J.S.; Dhar, M.M. *Indian J. Chem.*, **1973**, *11*, 720-722.
6. Bezuidenhoudt, B.C.B.; Brandt, E.V.; Roux, D.G. *J. Chem. Soc., Perkin Trans. I*, **1981**, 263-269.
7. Beltrami, E.; De Bernardi, M.; Fronza, G.; Mellerio, G.; Vidari, G.; Vita-Vinzi, P. *Phytochemistry*, **1982**, *21*, 2931-2933.
8. Ferrari, F.; Botta, B.; Alves de Lima, R. *Phytochemistry*, **1983**, *22*, 1663-1664.
9. Augustyn, J.A.N.; Bezuidenhoudt, B.C.B.; Ferreira, D. *Tetrahedron*, **1990**, *46*, 2651-2660.
10. Banerji, A.; Goomer, N.C. *Indian J. Chem.*, **1986**, *25B*, 304-305.
11. Bhardwaj, D.K.; Chand, G.; Jain-Munjal, A.; Srivastava, N. *Indian J. Chem.*, **1986**, *25B*, 1165-1166.
12. Manners, G. D.; Jurd, L. *Phytochemistry*, **1979**, *18*, 1037-1042.
13. Bohm, B.A. in *The Flavonoids - Advances in Research*, eds. Harborne, J.B. and Mabry, T.J.; Chapman & Hall, London, **1982**, 348-349.
14. Bohm, B.A. in *The Flavonoids - Advances in Research since 1980*, ed. Harborne, J.B.; Chapman & Hall,

London, **1988**, 348-372.

15. Malan, E.; Sireeparsad, A.; Swinny, E.; Ferreira, D. *Phytochemistry*, **1997**, *44*,529-531.
16. Hatano, T.; Yamashita, A.; Hashimoto, T.; Ito, H.; Kubo, N.; Yoshiyama, M.; Shimura, S.; Itoh, Y.; Okuda, T.; Yoshida, T. *Phytochemistry*, **1997**, *46*,893-900.
17. Coetzee, J.; Mciteka, L.; Malan, E.; Ferreira, D. *Phytochemistry*, **1999**, in the press, paper 2433.
18. Porter, L.J.; in *The Flavonoids - Advances in Research since 1980*, ed. Harborne, J.B.; Chapman & Hall, London, **1988**, 21-62; Porter, L.J. in *The Flavonoids-Advances in Research Since 1986*, ed. J.B. Harborne, Chapman & Hall, London, **1994**, 23-55.
19. Augustyn, J.A.N.; Bezuidenhoudt, B.C.B.; Swanepoel, A.; Ferreira, D. *Tetrahedron*, **1990**, *46*, 4429-4442.
20. Nel, R.J.J.; Van Heerden, P.S.; Van Rensburg, H.; Ferreira, D. *Tetrahedron Lett.*, **1998**, *39*, 5623-5626.
21. Julia, S.; Masana, J.; Vega, J.C. *Angew. Chem. Int. Ed. Engl.*, **1980**, *19*, 929-931.
22. Colonna, S.; Molinan, H.; Banfi, S.; Julia, S.; Masana, J.; Alvarez, A. *Tetrahedron*, **1983**, *39*, 1635-1641.
23. Van Rensburg, H.; Van Heerden, P.S.; Bezuidenhoudt, B.C.B.; Ferreira, D., *Chem. Commun.*, **1996**, 2747-2748.
24. Bentley, P.A.; Bergeron, S.; Cappi, M.W.; Hibbs, D.E.; Hursthouse, M.B.; Nugent, T.C.; Pulido, R.; Roberts, S.M.; Wu, L.E. *Chem. Commun.*, **1997**, 739-740.
25. Lasterra-Sanchez, M.E.; Felfer, U.; Mayon, P.; Roberts, S.M.; Thornton, S.R.; Todd, C.J. *J. Chem. Soc., Perkin Trans. I*, **1996**, 343-348.
26. Auerbach, J.; Weinreb, S.M. *J. Chem. Soc., Chem. Commun.*, **1974**, 298-299.
27. Itsuno, S.; Sakakura, M.; Ito, K. *J. Org. Chem.*, **1990**, *55*, 6047-6047.
28. Heaney, H. *Aldrichim. Acta*, **1993**, *26*, 35-45; Cooper, M.S.; Heaney, H.; Newbold, A.J.; Sanderson, W.R. *Synlett.*, **1990**, 533-535.
29. Bezuidenhoudt, B.C.B.; Swanepoel, A.; Augustyn, J.A.N.; Ferreira, D. *Tetrahedron Lett.*, **1987**, *28*, 4857-4860.
30. Van Rensburg, H.; Van Heerden, P.S.; Bezuidenhoudt, B.C.B.; Ferreira, D. *Tetrahedron*, **1997**, *53*, 14141-14152
31. Marsman, B.; Wynberg, H. *J. Org. Chem.*, **1979**, *44*, 2312-2314.
32. Molander, G.A.; Hahn, G.L. *J. Org. Chem.*, **1986**, *51*, 2596-2599.
33. Mirinda-Moreno, M.J.S.; Sa e Melo, M.L.; Neves, C. A. S. *Tetrahedron Lett.*, **1993**, *34*, 353-356.
34. McChesney, J.D.; Thompson, T. N. *J. Org. Chem.*, **1985**, *50*, 3473-3481.
35. Osuka, A.; Takaoka, K.; Suzuki, H. *Chem. Lett.*, **1984**, 271-272
36. Hasegawa, E.; Ishiyama, K.; Kato, T.; Horaguchi, T.; Shimizu, T.; Tanaka, S.; Yamashita, Y. *J. Org. Chem.*, **1992**, *57*, 5352-5359.
37. Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.*, **1973**, *95*, 512-519.
38. Bezuidenhoudt, B.C.B.; Brandt, E.V.; Ferreira, D. *Phytochemistry*, **1987**, *26*, 531-535.
39. Takahashi,H., Kubota, Y., Fang, L., Li, S., Onda, M. *Chem. Pharm. Bull.*, **1986**, 34, 4597-4604.