THE FIRST ENANTIOSELECTIVE SYNTHESIS OF POLY-OXYGENATED α-HYDROXYDIHYDRO-CHALCONES AND CIRCULAR DICHROIC ASSESSMENT OF THEIR ABSOLUTE CONFIGURATION Barend C.B. Bezuidenhoudt, Annelie Swanepoel, Jan A.N. Augustyn, and Daneel Ferreira* Department of Chemistry, University of the Orange Free State, P.O. Box 339, Bloemfontein, 9300 South Africa

<u>Abstract</u>: Epoxidation of 4-methoxy-2',4'-dimethoxymethyl-(<u>E</u>)-chalcone with H_2O_2 in the presence of poly- α -aminoacid catalysts afforded chiral aromatic oxygenated chalcone epoxides. These were transformed into the corresponding α -hydroxydihydrochalcones and their absolute configurations determined by c.d. spectroscopy. One of these was proved to be identical to a novel αR -analogue from *Pericopsis elata*.

Despite the availability of non- and mono-oxygenated chalcone epoxides in high optical yields,¹⁻⁸ utilisation of these versatile precursors in synthesis of flavonoids and isoflavonoids is restricted to a single fortuitous transformation³ into an aromatic deoxy α -hydroxydihydrochalcone. Although several members⁹⁻¹³ of the latter rare group of natural products, with their close biogenetic relationship to isoflavonoids, have been identified since the isolation¹³ of racemic nubigenol, progress in the chemistry of these compounds is hampered by lack of synthetic access to both enantiomers and also by absence of a method for determination of the absolute configuration at the single chiral centre. Our present characterisation¹⁴ of 4-methoxy- α ,2',4'-trihydroxydihydrochalcone <u>4</u> from the heartwood of *Pericopsis elata* initiated efforts towards its enantioselective synthesis and also definition of the absolute stereochemistry at C- α .

Epoxidation of 4-methoxy-2',4'-dimethoxymethyl-(<u>E</u>)-chalcone <u>1</u> with H_2O_2 in the triphase system aqueous NaOH, poly-L-alanine and CCl_4 ,⁶ afforded the (-)-trans-epoxide (<u>2</u>, $J_{\alpha,\beta}$ 2.0 Hz), the enantiomeric purity (70% ee) of which was assessed by ¹H NMR in CDCl₃ using Pr(hfc)₃ as chiral shift reagent. The αR , βS absolute configuration of <u>2</u> was confirmed by comparison of its c.d. data with those of the aromatic deoxy (-)-trans-epoxychalcone {[α]²⁵₅₇₈ -198^O; 90% ee} with known³ αR , βS stereochemistry. Similar treatment of chalcone <u>1</u>, but with poly-D-alanine⁶ gave the (+)-trans-epoxide <u>3</u> in 36% ee¹⁵ and a presumed αS , βR absolute configuration. These oxiranes <u>2</u> and <u>3</u> were separately subjected to hydrogenolysis (H₂/Pd-BaSO₄) to give the respective α -hydroxydihydrochalcones <u>6</u> and <u>8</u> with 65% and 32% ee [Pr(hfc)₃ as chiral shift reagent]. The presumed αR configuration for <u>6</u> and αS for <u>8</u> were confirmed by adoption of the c.d. exciton chirality approach of Nakanishi *et al.*^{16,17} The u.v. spectra of the 4-methoxybenzoate esters <u>7</u> and <u>9</u> indicate intramolecular CT or ¹L_a transitions in the 260 nm region. The c.d. curve of ester <u>7</u> (73% ee) exhibits intense sequential negative and positive Cotton effects (λ_{ext} 283 nm, θ - 11000 and 245 nm, θ + 14000, A = $\theta_1 - \theta_2 = -25000$) which presumably indicates exciton interaction between the benzoate and benzoyl chromophores. The negative sign of the A-value is in agreement with negative



<u>Reagents and Conditions</u>: (i) <u>1</u> (400 mg), poly-L-alanine (200 mg), CCl₄ (4.8 g), soln. of NaOH in 30% H_2O_2 (6 ml; 0.08 g/ml), r.t., 72 h; (ii) H_2 , Pd-BaSO₄, EtOH; (iii) *p*-MeO·C₆H₄COCl, pyridine; (iv) similar to (i) except for replacement of poly-L- by poly-D-alanine.



chirality between the two long axes of these chromophores [presentation <u>11</u> based on preferred conformation <u>10</u> (Dreiding models)], thus confirming the αR absolute configuration for <u>7</u>. The intense positive first and negative second Cotton effects (λ_{ext} 282 nm, θ + 6400 and 245 nm, θ - 10000, A = + 16400) for the benzoate <u>9</u> (38% ee) similarly defines its αS configuration. Removal of the protecting groups in the synthetic analogue <u>6</u> and subsequent acetylation afforded the triacetate <u>5</u> of the αR -hydroxydihydrochalcone which exhibited an identical c.d. spectrum than that of the natural product.

The above strategy could, in principle, be expanded to include the full range of naturally occurring α -hydroxydihydrochalcones. These and other results regarding utilisation of chalcone epoxides as chirons for enantiomerically enriched dihydroflavonols will be the subject of full publication.

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- 14. ¹H NMR $[(CD_3)_2CO 300 \text{ MHz}] \& 10.29(s, OH), 7.55(d, J 9.0 Hz, H-6'), 7.03(d, J 9.0 Hz, H-2,6), 6.79(d, J 9.0 Hz, H-3,5), 6.40(d, J 2.5 Hz, H-3'), 6.40(dd, J 2.5, 9.0 Hz, H-5'), 5.20(ddd, J 4.0, 7.0, 7.0 Hz, H-\alpha), 3.76(s, OMe), 3.61(d, J 7.0 Hz, <math>\alpha$ -OH), 3.13(dd, J 4.0, 14.0 Hz) and 2.90(dd, J 7.0, 14.0 Hz)(β -CH₂). The position of the single methoxy function was defined by n.O.e. association of these protons with the H-3,5 doublet.
- 15. The reduced enantiomeric purity of the (+)-trans-epoxide <u>3</u> is partially attributable to optical impure D-alanine $\{[\alpha]_D^{20} 9.71^{\circ}(c, 1.363 \text{ in 6N} \text{ HCl});\]$ literature $[\alpha]_D^{30} 14.61^{\circ}(c, 1.344 \text{ in 6N HCl}) \text{R.C. Weast, M.J.}$ Astle and W.H. Beyer, CRC Handbook of Chemistry and Physics, CRC Press Inc., Boca Raton, Florida, 1984, 64, C 720 $\}$.
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