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Enantioselective Synthesis of Flavonoids. Part 5[1]. Poly-oxygenated β-hydroxydihydrochalcones

Reinier J.J. Nel, Pieter S. van Heerden, Hendrik van Rensburg* and Daneel Ferreira*

Department of Chemistry, University of the Orange Free State, P.O. Box 339, Bloemfontein, 9300 South Africa

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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 ringopening, afforded β-hydroxydihydrochalcones in moderate to high enantiomeric excess and yield.

β-Hydroxydihydrochalcones represent a rare group of C_6-C_3-C_6 metabolites presumably sharing a close biogenetic relationship with the α-methyldeoxybenzoins, isoflavonoids and aurones.[2-7] Although several members of this group of natural products have been identified,[8] progress in the chemistry of these compounds is hampered 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. Optically enriched 2',β-dihydroxydihydrochalcones may also serve as important intermediates in the asymmetric synthesis of flavanones, which represent the richest array of compounds in the category of the minor flavonoids.[8,9] Consecutive reduction steps of the flavanones would lead to the flavan-4-ols and flavans which may then serve as electrophilic and nucleophilic synthons, respectively, in the semisynthesis of the 3-deoxy (C-ring) A- and B-type proanthocyanidins, *e.g.* the procassinidins.[10] Our successful conversion of enantiomerically enriched chalcone epoxides to α-hydroxydihydrochalcones[11-13] and to *trans*- and *cis*-dihydroflavonols,[1,14] prompted utilisation of the versatile chemistry of oxiranes in the enantioselective synthesis of oxygenated β-hydroxydihydrochalcones.

Since the Julia[15] asymmetric epoxidation of chalcones often gives disappointing stereoselectivity, we selected the adapted version recently developed by Bentley and Roberts[16,17] and involving a two-phase non-aqueous system for the asymmetric epoxidation of chalcone methyl ethers **1-3** ($J_{\alpha,\beta}$=15.8-16.0Hz)[12]. Thus, treatment of enones **1-3** with immobilised poly-(*L*)-leucine[18] (PLL), urea-hydrogen peroxide complex (UHP)[19] and

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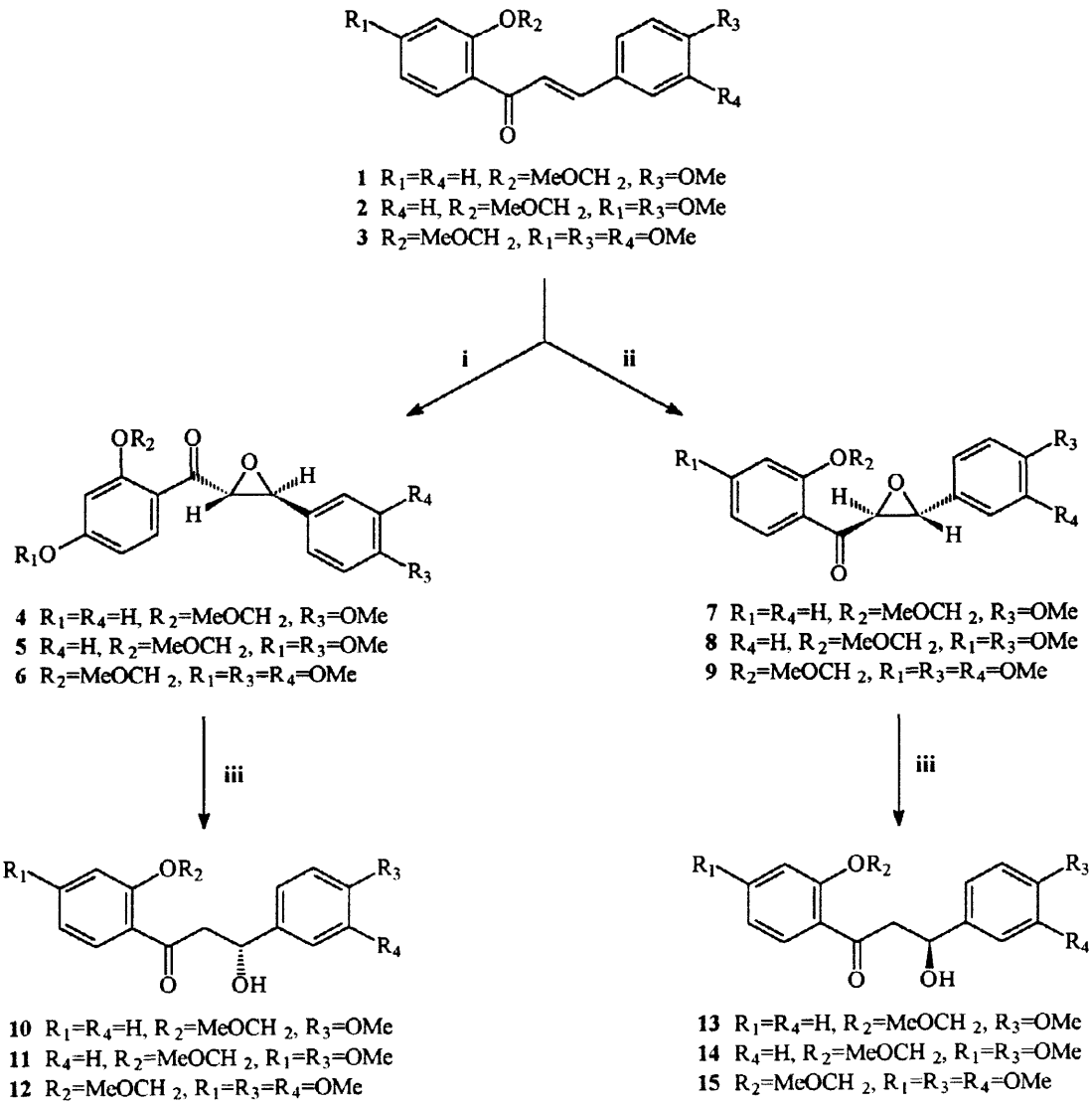
1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry THF, afforded the (-)-(α*R*,β*S*)-*trans*-epoxychalcones **4-6** ($J_{\alpha,\beta}$ 1.5-2.2 Hz) in high yields (64-80%) and improved optical purity (85-95% ee) in comparison with the Julia procedure [1,11] (67-86%). The enantiomeric (+)-(α*S*,β*R*)-*trans*-epoxychalcones **7-9** ($J_{\alpha,\beta}$ 1.5-2.2 Hz) were similarly obtained by using immobilised poly-(*D*)-leucine (PDL) in the same two-phase system (61-76% yield, 81-90% ee) (58-74% for the Julia procedure)[1,11] (Scheme 1, 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.[12,20]



Scheme 1 *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[a] in the conversion of chalcones **1-3** to β-hydroxydihydrochalcones **10-15**

Chalcone	Poly-(amino acid)[b]	Chalcone Epoxide	% Yield (% Conversion)	ee[c] (%)	β-Hydroxydi-hydrochalcone	% Yield	ee[c] (%)
1	PLL	**4**	71	85	**10**	73	85
1	PDL	**7**	69	81	**13**	70	80
2	PLL	**5**	80	95	**11**	83	91
2	PDL	**8**	76	90	**14**	90	88
3	PLL	**6**	64 (72)	88	**12**	78	84
3	PDL	**9**	61 (71)	87	**15**	81	85

[a] All new compounds were fully characterized by spectroscopic methods, elemental composition being established by accurate mass measurement or microanalysis. [b] PLL: poly-(L)-leucine; PDL: poly-(D)-leucine. [c] Determined with $Eu(tfc)_3$ as chiral shift reagent.

Owing to the excellent results reported by Hasegawa *et. al.*[21] for the regioselective reductive conversion of α,β-epoxyketones into β-hydroxyketones, the series of chalcone epoxides **4-9** were next treated with tributyltin hydride (TBTH) and azoisobutyronitrile (AIBN) in refluxing benzene, to give the (*R*)- **10-12** and (*S*)-2'-*O*-methoxymethyl-β-hydroxydihydrochalcones **13-15** in excellent yields (70-90%) and without loss of optical purity. The ee's were determined by ^1H NMR, again using $Eu(tfc)_3$ as chiral shift reagent. The absolute configuration of the β-hydroxydihydrochalcones then follows from the fact that optical integrity had been preserved in the reductive transformation, epoxide → dihydrochalcone. All attempts to confirm such a conjecture *via* transformation into the corresponding MTPA esters,[22] however, resulted in elimination to form the parent chalcones. The CD spectra of the (*R*)-series of compounds, *e.g.* **11**, exhibit strong negative and positive Cotton effects in the 320 and 240 nm

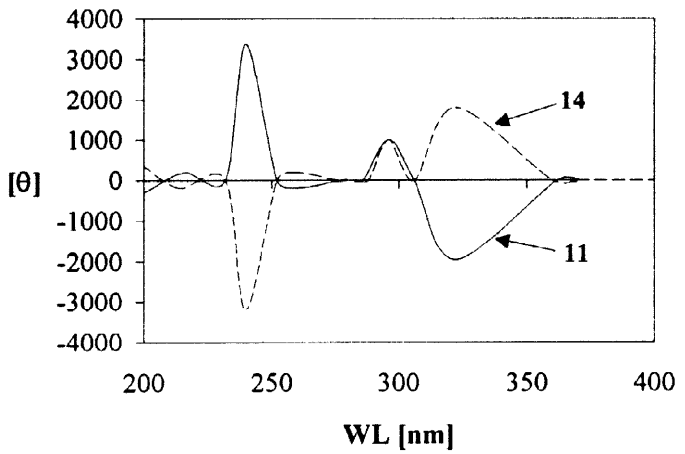


Figure 1 CD curves of the (*R*)-**11** and (*S*)-**14** β-hydroxydihydrochalcones.

regions, respectively, with the signs of these CE's being reversed for the (*S*)-enantiomers *e.g.* **14** (Figure 1).

In conclusion, we have effected the first enantioselective synthesis of β-hydroxydihydrochalcones. This protocol should contribute substantially towards eliminating the high degree of confusion[23] regarding differentiation between the closely related α- and β-hydroxydihydrochalcones. In addition, the CD data should usefully contribute towards assessment of the absolute configuration of this class of flavonoids.

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