The first enantioselective synthesis of *trans*- and *cis*-dihydroflavonols

Hendrik van Rensburg, Pieter S. van Heerden, Barend C. B. Bezuidenhoudt and Daneel Ferreira*

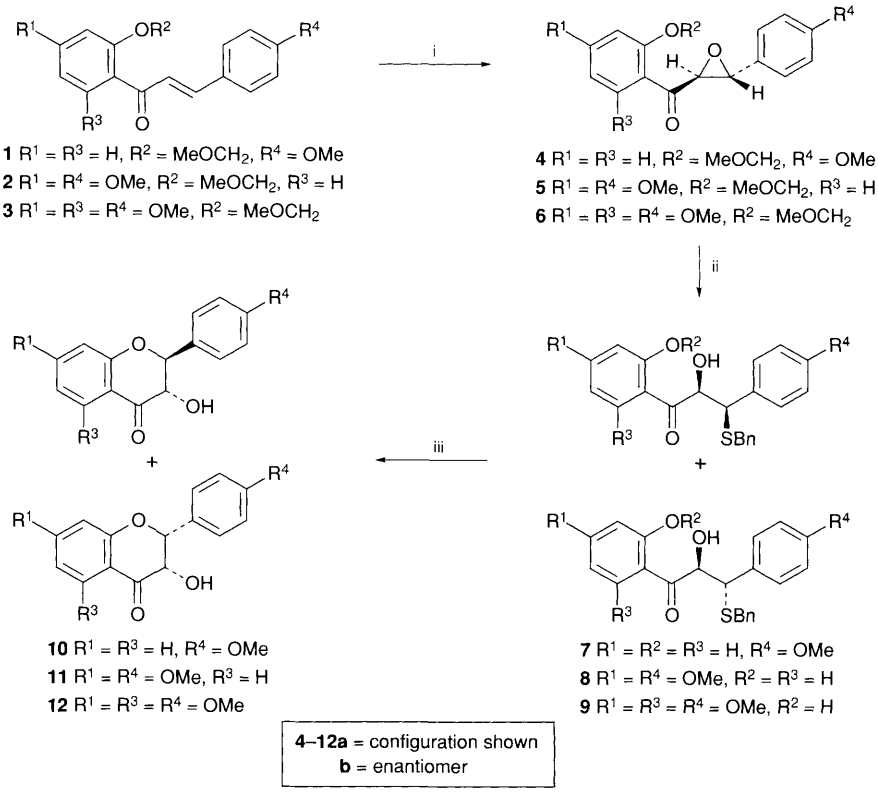
Department of Chemistry, University of the Orange Free State, PO Box 339, Bloemfontein, 9300 South Africa

Epoxidation of a series of polyoxygenated chalcones with H_2O_2 in the presence of poly(α-amino acid) catalysts, followed by Lewis acid-catalysed phenylmethanethiol ring-opening and cyclization, afforded *trans*- and *cis*-dihydroflavonols in moderate to high enantiomeric excess and yield.

Dihydroflavonols occur widely in the plant kingdom.[1] Apart from exhibiting fungistatic properties they are used as pharmaceutical and industrial chemicals and are important in both wood preservation and in the paper industry.[2] In addition, these compounds serve as incipient electrophiles in the semi-synthesis of oligomeric proanthocyanidins[3] natural products that are increasingly being recognized for their profound health-promoting effects in tea, fruit juices and red wine (the 'French paradox'). Owing to the absence of synthetically and naturally occurring flavonoid electrophiles with 2,3-*cis* stereochemistry which might be used as precursors to polymeric proanthocyanidins with *e.g.* epicatechin chain extender units, we employed the versatile chemistry of α,β-epoxy ketones to address the issue of stereocontrol at either C-2 or C-3 in the enantioselective synthesis of 2,3-*trans*- and -*cis*-dihydroflavonols.

Thus, epoxidation of (*E*)-chalcones **1–3** ($J_{\alpha,\beta}$ 15.8–16.0 Hz) at *ca* 20 °C with hydrogen peroxide in the triphasic system consisting of aqueous NaOH–poly-L- or -D-alanine–CCl_4 afforded the (−)-*trans*-epoxides **4a**, **5a** and **6a** ($J_{\alpha,\beta}$ 1.5–2.2 Hz) and (+)-*trans*-epoxides **4b**, **5b** and **6b** ($J_{\alpha,\beta}$ 1.5–2.2 Hz) respectively in high yields (97–99%).[4,5] The (−)-chalcone oxiranes exhibited higher optical purities (70–84% ee) than the (+)-isomers (53–74% ee) due to the considerably higher purity of natural L-alanine {$[\alpha]_D^{25}$ +12.57 (*c*, 5.695 in 1 M HCl)} *versus* synthetic D-alanine {$[\alpha]_D^{25}$ −9.71 (*c*, 1.363 in 6 M HCl)} (Table 1). This was reflected in the optical purity of the poly-L-{$[\alpha]_D^{25}$ −142.8 (*c*, 0.671 in CF_3CO_2H)} and poly-D-alanine {$[\alpha]_D^{25}$ +102.0 (*c*, 0.314 in CF_3CO_2H)} catalysts. Subsequent deprotection and cyclization of epoxide **5a** using $MgBr_2$–Et_2O,[6] yielded (2*R*,3*R*)-4′,7-dimethoxydihydroflavonol **11a** ($^3J_{2,3}$ 12.0 Hz) in low yield (20%) but high ee (78%). Similar results were obtained with the Lewis acid BF_3–Et_2O.[7]

Since the low yields may be attributed to cleavage of the highly reactive oxirane functionality prior to deprotection, we attempted to increase dihydroflavonol yields *via* initial opening of the epoxide by an external nucleophile, followed by deprotection and cyclization. The Lewis acid, tin tetrachloride ($SnCl_4$), in the presence of the powerful nucleophile phenylmethanethiol (BnSH) was utilized for selective cleavage of the C_β–O bond of the oxirane functionality (−20 °C) and subsequent removal of the methoxymethyl group (0 °C) to give the dihydrochalcones **7–9** (86–93%: *syn*:*anti* *ca.* 2.3:1). Selective crystallization and X-ray crystallographic analysis of (2*S*,3*S*)-*syn*-2,2′-dihydroxy-3-benzylsulfanyldihydrochalcone **9a** confirmed the predominant *syn*-orientations of products



Scheme 1 *Reagents and conditions*: i, 30% H_2O_2: 6 M NaOH 1 : 0.32 (v/v), poly-D- or poly-L-alanine : chalcone 1 : 1 (m/m), CCl_4, room temp., 24 H; 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[a] in the conversion of chalcones **1–3** to dihydroflavonols **10–12**

Chalcone Epoxide	Yield (%)	ee[b] (%)	Dihydro-chalcone	Yield (%)	Dihydro-flavonols	Yield (%)	Ee[c] (%)	*trans* : *cis*
4a	99	84	**7a**	86	**10a**	86	83	93 : 7
4b	98	69	**7b**	90	**10b**	83	69	94 : 6
5a	98	86	**8a**	93	**11a**	71	84	79 : 21
5b	98	74	**8b**	90	**11b**	72	75	83 : 17
6a	97	70	**9a**	89	**12a**	65	69	78 : 22
6b	97	53	**9b**	89	**12b**	64	53	84 : 16

[a] All new compounds were fully characterized by spectroscopic methods, elemental composition being established by accurate mass measurement or microanalysis. [b] Determined with $Pr(hfc)_3$ as chiral shift reagent. [c] Determined with $Eu(tfc)_3$ as chiral shift reagent.

7–9.[8] Owing to the thiophilicity of tin and the highly polarised tin–chloride bonds, and active Lewis acid species, *i.e.* $Cl_xSn(SBn)_y$,[9] presumably permits delivery of the thiolate moiety intramolecularly *via* an S_N2 mechanism. Intermolecular S_N2 attack by BnSH may account for *anti*-product formation.

Treatment of α,2′-dihydroxy-β-benzylsulfanyldihydrochalcones **7–9** with the thiophilic Lewis acid silver tetrafluoroborate ($AgBF_4$)[10] in CH_2Cl_2 at 0 °C gave the 2,3-*trans*- and, albeit in low yields, for the first time also 2,3-*cis*-dihydroflavonols ($^3J_{2,3}$ 6.1 Hz) in good yields (64–86%) without loss of optical purity. Although either an S_N1 or S_N2 mechanism may explain the formation of the 2,3-*trans*- and -*cis*-dihydroflavonols **10–12**, the mechanism remains obscure and is currently being investigated more fully. The absolute stereochemistry of the predominant enantiomers of the *trans*-dihydroflavonols was accessed by circular dichroism (CD)[11] of the *O*-acetyl derivatives. The absolute configuration of the *cis*-dihydroflavonols accompanying the *trans*-isomers then follows from the fact that optical integrity was preserved in the transformation epoxide → dihydrochalcone → *cis*-dihydroflavonol.

We have thus developed the first enantioselective route towards both *trans*- and *cis*-dihydroflavonols. This protocol should contribute substantially towards a general synthesis of oligomeric proanthocyanidins with 2,3-*trans*- and, for the first time, also 2,3-*cis*-flavan-3-ol chain extender units in order to assess the physical and chemical properties that determine their health promoting properties in the human diet.

Support by the Foundation for Research Development, Pretoria, the 'Sentrale Navorsingsfonds' of this University and the Marketing Committee, Wattle Bark Industry of South Africa, Pietermaritzburg, is acknowledged.

References

1 B. A. Bohm, in *The Flavonoids-Advances in Research since 1986*, ed. J. B. Harborne, Chapman & Hall, London, 1994, p. 419.
2 B. A. Bohm, in *The Flavonoids*, eds. J. B. Harborne, T. J. Mabry and H. Mabry, Chapman & Hall, London, 1975, pp. 560–562.
3 J. A. Delcour, D. Ferreira and D. G. Roux, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1711.
4 S. Colonna, H. Molinari, S. Banfi, S. Julia, J. Masana and A. Alvarez, *Tetrahedron*, 1983, **39**, 1635.
5 J. A. N. Augustyn, B. C. B. Bezuidenhoudt and D. Ferreira, *Tetrahedron*, 1990, **46**, 2651.
6 S. Kim, Y. H. Park and I. S. Kee, *Tetrahedron Lett.*, 1991, **32**, 3099.
7 C. Moberg, L. Rakos and L. Tottie, *Tetrahedron Lett.*, 1992, **33**, 2191.
8 D. Ferreira, unpublished data.
9 M. Pereyre, J. P. Quitard and A. Rahm, *Tin in Organic Synthesis*, Butterworth, London, 1987, pp. 4–14.
10 A. G. M. Barrett, B. C. B. Bezuidenhoudt, A. R. Howell and A. C. Lee, *J. Org. Chem.*, 1989, **54**, 2275.
11 W. Gaffield, *Tetrahedron*, 1970, **26**, 4093.

Received, 16th September 1996, Com. 6/06342J