Pergamon

Tetrahedron Letters, Vol. 38, No. 17, pp. 3089-3092, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00552-2

Enantioselective Synthesis of the Four Catechin Diastereomer Derivatives

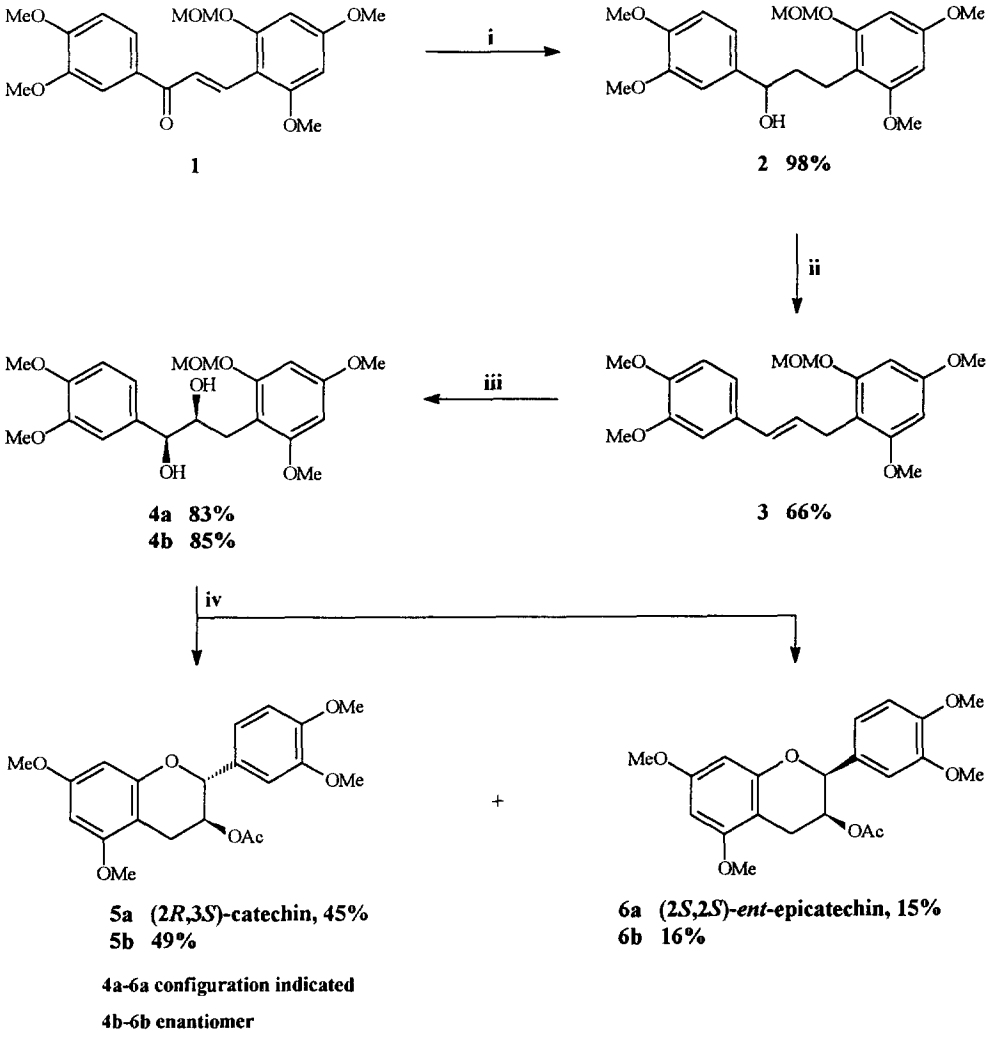
Hendrik van Rensburg, Pieter S. van Heerden, Barend C.B. Bezuidenhoudt and Daneel Ferreira*

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

Abstract: Asymmetric dihidroxylation of (E)-1-(3,4-dimethoxyphenyl)-3-(2-methoxy-methyl-4,6-dimethoxy-phenyl)-propene with AD-mix-α or AD-mix-β in the presence of methanesulfonamide, followed by acid catalysed cyclization, afforded the four catechin diastereomers in high enantiomeric excesses and yields. © 1997 Published by Elsevier Science Ltd.

Flavan-3-ols represents the largest class of naturally occuring monomeric flavanoids, with catechin and epicatechin, occurring almost ubiquitously.[1] These compounds are the most important constituent units of oligomeric proanthocyanidins[1] and also serve as the nucleophilic entities in the semi-synthesis of all catechin-based condensed tannins,[2] oligomers which are becoming increasingly important for their health promoting effects in tea, vegetables, fruits, fruit juices and red wine. Surprisingly, the only synthetic access to the stereochemically simple catechin, incidentally the only flavan-3-ol that is cheaply available commercially, involves the cumbersome process of hydrogenation and reduction of the corresponding (2*R*,3*R*)-2,3-*trans*-dihydroquercetin tetra-*O*-benzylether derivative.[3,4] Owing to the absence of a 5,7,3',4'-tetrahydroxy-dihydroflavonol with 2,3-cis stereochemistry from natural sources, such an approach does not permit synthetic access to epicatechin. In order to address the issue of stereocontrol at C-2 and C-3 of the flavan-3-ol molecular backbone, we have opted for a more direct synthetic route that is based on the asymmetric dihydroxylation of an oxygenated 1,3-diarylpropene (*retro*-deoxodihydrochalcone).

Thus, the protected (E)-propene **3** was prepared *via* reduction (Pd/H_2 and $NaBH_4$) of the (E)-*retro*-chalcone **1** and elimination ($SOCl_2$ and DBU) of the ensuing alcohol **2** according to the sequence in scheme 1. Subsequent asymmetric dihydroxylation[5-8] of **3** at 0°C with AD-mix-α or AD-mix-β in the two phase system *t*-BuOH:H_2O (1:1), afforded the (S,S)-*syn*- **4a** and (R,R)-*syn*-diol **4b**, respectively, in high yields (83-85%) and



Scheme 1 *Reagents and Conditions*: i, Pd/H_2, EtOH, then $NaBH_4$, EtOH; ii, $SOCl_2$, CH_2Cl_2, then DBU, CH_2Cl_2, reflux; iii, AD-mix-α or AD-mix-β, *t*-BuOH:H_2O 1:1 ($^v/_v$), $CH_3SO_2NH_2$, 0°C; iv, 3M HCl, MeOH:H_2O 3:1 ($^v/_v$), then $(CH_3CO)_2O$, piridine.

optical purity (>99% ee). The enantiomeric excesses of the diols were determined by ^{1}H NMR analysis of the corresponding bis-MTPA esters[9] and their absolute configuration tentatively assigned according to the Sharpless model[5,6] for AD-mix.

Simultaneous deprotection and cyclization of diols **4a,b** under acidic conditions, followed by acetylation, yielded a *trans:cis* (*ca* 3:1) mixture of the 3',4',5,7-tetramethoxyflavan-3-ol acetate derivates **5a,b** and **6a,b** in moderate yields (60-65%) and excellent enantiomeric excesses (>99%) (Scheme 1). The ee's were determined by ^{1}H NMR using Eu(hfc)$_3$ as chiral shift reagent and absolute stereochemistry assigned by comparison of CD data with those of authentic samples.[10] Unambiguous confirmation of the absolute configuration of the corresponding diols then follows from the fact that optical integrity was preserved in the *trans*- and *cis*-flavan-3-ol acetates. Formation of both the catechin **5a,b** and epicatechin **6a,b** derivatives is explicable in terms of the generation of an incipient C-1 carbocation *via* protonation of the benzylic alcohol functionality, and subsequent S_N1 cyclization that leads to predominant formation of the thermodynamically more stable *trans*-isomer.[11]

We have thus developed the first direct and highly efficient enantioselective route towards the permethylarylether acetates of the two enantiomers of catechin and epicatechin. The potential of this protocol in the chemistry of the flavan-3-ols in particular and of the oligomeric proanthocyanidins in general is evident, especially in view of its aptitute to the synthesis of free phenolic analogues, a study with is currently being undertaken in this laboratory.

Financial support by the Foundation for Research Development, Pretoria and by the 'Sentrale Navorsingsfonds' of this University is acknowlegded.

REFERENCES

1. Porter, L.J. in *The Flavonoids, Advances in Research since 1980*, ed. Harborne, J.B., Chapman & Hall, London, 1988, p. 27; and in *The Flavonoids, Advances in Research since 1986*, ed. Harborne, J.B., Chapman & Hall, London, 1994, p. 23.
2. Botha, J.J.; Ferreira, D.; Roux, D.G. *J. Chem. Soc., Perkin Trans I*, **1981**, 1235; and Delcour, J.A.; Ferreira, D.; Roux, D.G. *J. Chem. Soc., Perkin Trans I*, **1983**, 1711.
3. Weinges, K. *Annalen*, **1958**, *615*, 203.
4. Freudenberg, K.; Weinges, K. *Annalen*, **1958**, *613*, 61.

5. Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.; Kwong, H.; Morikawa, K.; Wang, Z.; Xu, D.; Zhang, X. *J. Org. Chem.*, **1992**, *57*, 2768.
6. Jeong, K.; Sjo, P.; Sharpless, K.B. *Tetrahedron Lett.*, **1992**, *33*, 3833.
7. Wang, Z.; Zhang, X.; Sharpless, K.B. *Tetrahedron Lett.*, **1993**, *34*, 2267.
8. Kolb, H.C.; VanNieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.*, **1994**, *94*, 2483.
9. Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.*, **1973**, *95*, 512.
10. Barrett, M.W.; Klyne, W.; Scopes, P.M.; Fletcher, A.C.; Porter L.J.; Haslam, E. *J. Chem. Soc., Perkin Trans. I*, **1979**, 2375.
11. Kiatgrajai, P.; Wellons, J.D.; Gollob, L.; White, J.D. *J. Org. Chem.*, **1982**, *47*, 2910, 2913.

(*Received in UK* 10 *February* 1997; *accepted* 21 *March* 1997)